

# Nutrient Vitamins and Minerals

## Handling/Processing

### Identification of the Petitioned Substances

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This technical report reviews “nutrient vitamins and minerals,” the term which currently appears on the National List at 7 CFR 205.605(b), “Synthetics allowed.” §205.605 relates to “Nonagricultural (nonorganic) substances used as ingredients in or on processed products labeled as “organic” or “made with organic (specified ingredients or food group(s))”.

The actual “substances used as ingredients in or on processed products” to provide “nutrient vitamins and minerals” are those substances approved or allowed by the Food and Drug Administration (FDA) for addition to food that provide a nutrient in a biologically available form. These are the substances reviewed in this report.

The U.S. federal organizations responsible for identifying the vitamins and minerals required by humans are the Institute of Medicine (IOM) and the National Research Council (NRC), which periodically review human nutritional science and issue authoritative reports. Between 1997 and 2005, the Food and Nutrition Board and Institute of Medicine published comprehensive reviews of human nutritional requirements, including vitamins and minerals, in the series “Dietary Reference Intakes (DRI)” (Institute of Medicine 1997; National Research Council 1998, 2000, 2001, 2005; Institute of Medicine 2011). Consequently, this technical report covers the thirty-plus nutrient vitamins and nutrient minerals mentioned in the DRI reports, as well as inositol, a water-soluble nutrient vitamin required in infant formula, which was reviewed earlier (Food and Nutrition Board 1989).

In 2012, the National Organic Program (NOP) published a proposed rule<sup>1</sup> requesting comments on a change to the annotation for “nutrient vitamins and minerals” to: “For food – vitamins and minerals identified as essential in 21 CFR 101.9. For infant formula – vitamins and minerals as required by 21 CFR 107.100 or §107.10.” The listing of vitamins and minerals cited in 21 CFR 101.9, 21 CFR 107.10, and 21 CFR 107.100 is identical with that in the DRI series published by the IOM and NRC, except for the “other carotenoids”- lutein, lycopene, and zeaxanthin – which NRC reviewed but FDA does not cite in its regulations.

Nutrient vitamins and minerals can be divided into five groupings to facilitate review:

- Fat-soluble vitamins
- Water-soluble vitamins
- Trace mineral elements
- Major minerals in bone
- Major electrolyte minerals

**Table 1a – Generally Recognized as Safe (GRAS) Substances with Fat-Soluble Vitamin Activity** (Institute of Medicine 1997; National Research Council 2000, 2001)

Vitamin	GRAS Substance with Vitamin Activity			
	Substance name(s)	Chemical (IUPAC) name	CAS No.	E/INS <sup>2</sup>
Vitamin A	Vitamin A (retinol)	(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraen-1-ol	68-26-8	

<sup>1</sup> 77 FR 1980  
<sup>2</sup> E/INS European/International Numbering System

	Vitamin A acetate (retinyl acetate)	[(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenyl] acetate	127-47-9	
	Vitamin A palmitate (retinyl palmitate)	[(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenyl] hexadecanoate	79-81-2	
	Beta-carotene	1,3,3-trimethyl-2-[(1E,3E,5E,7E,9E,11E,13E,15E,17E)-3,7,12,16-tetramethyl-18-(2,6,6-trimethylcyclohexen-1-yl)octadeca-1,3,5,7,9,11,13,15,17-nonaenyl]cyclohexene	7235-40-7	E160a
Vitamin D	Vitamin D2 (ergocalciferol)	(1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-1-[(E,2R,5R)-5,6-dimethylhept-3-en-2-yl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol	50-14-6	
	Vitamin D3 (cholecalciferol)	(1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol	67-97-0	
	Vitamin D2 resin	(1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-1-[(E,2R,5R)-5,6-dimethylhept-3-en-2-yl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol	n/a	
	Vitamin D3 resin	(1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol	n/a	
Vitamin E	Tocopherols	(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol	1406-66-2	E306
	Alpha-tocopherol acetate	[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-yl] acetate	58-95-7	E307
Vitamin K	Phylloquinone (Vitamin K1) (phytomenadione) (phytonadione)	2-methyl-3-[(E)-3,7,11,15-tetramethylhexadec-2-enyl]naphthalene-1,4-dione	84-80-0	
	Menaquinone 4 (Vitamin K2) (MK-4) (menatetrenone)	2-methyl-3-[(2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl]naphthalene-1,4-dione	863-61-6	
	Menaquinone 6 (Vitamin K2) (MK-6)	2-[(2E,6E,10E,14E,18E)-3,7,11,15,19,23-hexamethyltetracos-2,6,10,14,18,22-hexaenyl]-3-methylnaphthalene-1,4-dione	84-81-1	
	Menaquinone 7 (Vitamin K2) (MK-7)	2-[(2E,6E,10E,14E,18E,22E)-3,7,11,15,19,23,27-heptamethyloctacos-2,6,10,14,18,22,26-heptaenyl]-3-methylnaphthalene-1,4-dione	2124-57-4	
Other carotenoids	Lutein	(1R)-4-[(1E,3E,5E,7E,9E,11E,13E,15E,17E)-18-[(1R,4R)-4-hydroxy-2,6,6-trimethylcyclohex-2-en-1-yl]-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethylcyclohex-3-en-1-ol	127-40-2	E161b

	Lycopene	(6E,8E,10E,12E,14E,16E,18E,20E,22E,24E,26E)-2,6,10,14,19,23,27,31-octamethyldotriacont-2,6,8,10,12,14,16,18,20,22,24,26,30-tridecaene	502-65-8	E160d
	Zeaxanthin	(1R)-4-[(1E,3E,5E,7E,9E,11E,13E,15E,17E)-18-[(4R)-4-hydroxy-2,6,6-trimethylcyclohexen-1-yl]-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethylcyclohex-3-en-1-ol	144-68-3	E161h

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41 A few of these substances with fat-soluble vitamin activity are included in the International Numbering  
42 System (INS) for Food Additives. The carotenoids are listed in the category “colors” and the tocopherols  
43 are listed in the category “antioxidants.”  
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45 **Table 1b – GRAS Substances with Water-Soluble Vitamin Activity** (National Research Council 1998, 2000)  
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Vitamin	GRAS Substance with Vitamin Activity			
	Substance name(s)	Chemical (IUPAC) name	CAS No.	E/INS
Vitamin C	Ascorbic acid	(2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one	50-81-7	E300
	Ascorbyl palmitate	[(2S)-2-[(2R)-3,4-dihydroxy-5-oxo-2H-furan-2-yl]-2-hydroxyethyl] hexadecanoate	137-66-6	E304
	Calcium ascorbate	calcium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate;dihydrate	5743-27-1	E302
	Sodium ascorbate	sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate	134-03-2	E301
Thiamin (Vitamin B1)	Thiamine hydrochloride	2-[3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium-5-yl]ethanol;chloride;hydrochloride	67-03-8	
	Thiamine mononitrate	2-[3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium-5-yl]ethanol;nitrate	532-43-4	
Riboflavin (Vitamin B2)	Riboflavin	7,8-dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypentyl]benzo[g]pteridine-2,4-dione	83-88-5	E101
	Riboflavin-5 phosphate sodium salt	Sodium [(2R,3S,4S)-5-(7,8-dimethyl-2,4-dioxobenzo[g]pteridin-10-yl)-2,3,4-trihydroxypentyl] dihydrogen phosphate	130-40-5	E101
Niacin	Niacin (nicotinic acid)	pyridine-3-carboxylic acid	59-67-6	
	Niacinamide (nicotinamide)	pyridine-3-carboxamide	98-92-0	
	Aluminum nicotinate	aluminum;pyridine-3-carboxylate	1976-28-9	
	Nicotinamide-ascorbic acid complex (niacinamide ascorbate)	(2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one;pyridine-3-carboxamide	1987-71-9	
Vitamin B6	Pyridoxine hydrochloride	4,5-bis(hydroxymethyl)-2-methylpyridin-3-ol hydrochloride	58-56-0	
Folate	Folic acid (folacin)	N-[4-[(2-amino-1,4-dihydro-4-oxo-6-pteridiny]methylamino)benzoyl]-L-glutamic acid	59-30-3	
Vitamin B12	Vitamin B12	cobalt(3+);[(2R,3S,4R,5S)-5-(5,6-	68-19-9	

	(cyanocobalamin) (cobalamin)	dimethylbenzimidazol-1-yl)-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl] [(2R)-1-[3-[(1R,2R,3R,5Z,7S,10Z,12S,13S,15Z,17S,18S,19R)-2,13,18-tris(2-amino-2-oxoethyl)-7,12,17-tris(3-amino-3-oxopropyl)-3,5,8,8,13,15,18,19-octamethyl-2,7,12,17-tetrahydro-1H-corrin-24-id-3-yl]propanoylamino]propan-2-yl] phosphate; cyanide		
Pantothenic acid	Calcium pantothenate	calcium;3-[[[(2R)-2,4-dihydroxy-3,3-dimethylbutanoyl]amino]propanoate	137-08-6	
	Calcium pantothenate calcium chloride double salt	calcium;3-[[[(2R)-2,4-dihydroxy-3,3-dimethylbutanoyl]amino]propanoate; calcium chloride	6363-38-8	
	D-pantothenamide	N-(3-amino-3-oxopropyl)-2,4-dihydroxy-3,3-dimethylbutanamide	7757-97-3	
Biotin	Biotin	5-[(3aS,4S,6aR)-2-oxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-d]imidazol-4-yl]pentanoic acid	58-85-5	
Choline	Choline bitartrate	2-hydroxyethyl(trimethyl)azanium;(2R,3R)-2,3,4-trihydroxy-4-oxobutanoate	87-67-2	
	Choline chloride	2-hydroxyethyl(trimethyl)azanium chloride	67-48-1	
Inositol	Inositol ( <i>myo</i> -inositol)	cyclohexane-1,2,3,4,5,6-hexol	87-89-8	

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48 A few of these substances with water-soluble vitamin activity are included in the International Numbering  
49 System (INS) for Food Additives. Ascorbic acid and ascorbate compounds are listed in the category  
50 “antioxidants” and the riboflavin forms are listed in the category “colors.” Again, the INS system has no  
51 “nutrients” category.

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53 **Table 1c - GRAS Substances with Trace Mineral Activity** (National Research Council 2000, 2001)  
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Mineral nutrient	GRAS Substance with Bioavailable Nutrient Mineral Content			
	Substance name(s)	Chemical (IUPAC) name	CAS Number	E/INS No.
Chromium	Chromium picolinate (chromium tripicolinate)	Chromium(3+) pyridine-2-carboxylate	14639-25-9	
	Chromium (III) chloride (chromic chloride) hexahydrate	Trichlorochromium hexahydrate	10060-12-5	
Copper	Copper gluconate (cupric gluconate)	Copper (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoate	527-09-3	
(Copper & Iodine)	Cuprous iodide	Iodocopper	7681-65-4	
(Copper & Sulfate)	Copper sulfate (cupric sulfate)	Copper sulfate	7758-98-7	
Iodine	Potassium iodide	Potassium iodide	7681-11-0	
Iron	Ferric ammonium citrate (ammonium	Azane 2-hydroxypropane-1,2,3-tricarboxylate, iron(3+)	1185-57-5 1333-00-2	381

	ferric sulfate)			
(Iron & Chloride)	Ferric chloride	Trichloroiron	7705-08-0	
	Ferric citrate	2-hydroxypropane-1,2,3-tricarboxylate, iron(3+)	2338-05-8	
(Iron & Phosphorus)	Ferric phosphate	Iron(3+) phosphate	10045-86-0	
(Iron & Phosphorus)	Ferric pyrophosphate	Iron(3+) phosphonato phosphate	10058-44-3	
	Ferric sulfate	Iron(3+) trisulfate	10028-22-5	
(Iron & Vitamin C)	Ferrous ascorbate	(2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one, iron(2+)	24808-52-4	
	Ferrous carbonate	Iron(2+) carbonate	563-71-3	
	Ferrous citrate	2-hydroxypropane-1,2,3-tricarboxylic acid, iron(2+)	23383-11-1	
	Ferrous fumarate	(E)-but-2-enedioate;iron(2+)	141-01-5	
	Ferrous gluconate	Iron(2+) 2,3,4,5,6-pentahydroxyhexanoate;dihydrate	6047-12-7	E579
	Ferrous lactate	Iron(2+) 2-hydroxypropanoate	5905-52-2	E585
	Ferrous sulfate	Iron(2+) trisulfate	7782-63-0	
	Elemental iron	Iron	7439-89-6	
Manganese	Manganese chloride	Dichloromanganese	7773-01-5	
	Manganese citrate	2-hydroxypropane-1,2,3-tricarboxylate manganese(2+)	5968-88-7	
	Manganese gluconate	Manganese(2+) (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanoate	6485-39-8	
(Manganese & Sulfate)	Manganese sulfate	Manganese(2+) sulfate monohydrate	7785-87-7	
Molybdenum	Ammonium heptamolybdate	Hexaazanium dioxido(dioxo)molybdenum	12027-67-7	
	Sodium molybdate	Disodium dioxido(dioxo)molybdenum	7631-95-0	
Selenium	Sodium selenate	Disodium selenate	13410-01-0	
	Sodium selenite	Disodium selenite	10102-18-8	
Zinc	Zinc sulfate	Zinc sulfate	7733-02-0	
(Zinc & Chloride)	Zinc chloride	Dichlorozinc	7646-85-7	
	Zinc gluconate	Zinc 2,3,4,5,6-pentahydroxyhexanoate	4468-02-4	
	Zinc oxide	Oxozinc	1314-13-2	
	Zinc stearate	Zinc octadecanoate	557-05-1	

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56 In addition to the mineral nutrients in these tables, the Food and Nutrition Board of IOM reviewed five  
57 other trace mineral elements which will not be evaluated in this report: "In the case of arsenic, boron,  
58 nickel, silicon, and vanadium, there is evidence that they have a beneficial role in some physiological  
59 processes in some species. For boron, silicon, and vanadium, measurable responses of human subjects to  
60 variations in dietary intake have also been demonstrated. However, the available data are not as extensive  
61 (e.g., dose-response data are absent) and the responses are not as consistently observed as they are for the  
62 vitamins and other minerals. Thus, data are insufficient to determine an Estimated Average Requirement  
63 (EAR) for any of these minerals." (National Research Council 2001)

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**Table 1d - GRAS Substances with Major Mineral in Bone Activity** (Institute of Medicine 1997)

Mineral nutrient(s)	GRAS Substance with Bioavailable Nutrient Mineral Content			
	Substance name	Chemical (IUPAC) name	CAS Number	E/INS No.
Calcium	Calcium carbonate	Calcium carbonate	471-34-1	E170
(& Chloride)	Calcium chloride	Calcium dichloride	10035-04-8	E509
	Calcium citrate	Tricalcium 2-hydroxypropane-1,2,3-tricarboxylate	813-0994-095	E333
(& Phosphorus)	Calcium glycerol phosphate	Calcium 2,3-dihydroxypropyl phosphate	27214-00-2	
	Calcium hydroxide	Calcium dihydroxide	1305-62-0	E526
	Calcium lactate (not GRAS for infants)	Calcium 2-hydroxypropanoate	814-80-2	E327
	Calcium oxide	Oxocalcium	1305-78-8	E529
(& Sulfate)	Calcium sulfate, anhydrous	Calcium sulfate	7778-18-9	E516
(& Sulfate)	Calcium sulfate, dehydrate (gypsum)	Calcium sulfate dihydrate	10101-41-4	E516
(& Phosphorus)	Calcium phosphate, dibasic	Calcium hydrogen phosphate	7757-93-9	E341
	Calcium phosphate, monobasic	Calcium dihydrogen phosphate	7758-23-8	E341
	Calcium phosphate, tribasic	Tricalcium diphosphate	7758-87-4	E341
(& Phosphorus)	Calcium pyrophosphate	Dicalcium phosphonato phosphate	7790-76-3	
Phosphorus	Phosphoric acid	Phosphoric acid	7664-38-2	E338
Magnesium	Magnesium carbonate	Magnesium carbonate	546-93-0	E504
(& Chloride)	Magnesium chloride hexahydrate	Magnesium dichloride hexahydrate	7791-18-6	E511
	Magnesium hydroxide	Magnesium dihydroxide	1309-42-8	E528
	Magnesium oxide	Oxomagnesium	1309-48-4	E530
(& Phosphorus)	Dibasic magnesium phosphate	Magnesium hydrogen phosphate trihydrate	7782-75-4	E343
(& Phosphorus)	Magnesium phosphate, tribasic	Trimagnesium diphosphate	7757-87-1	E343
(& Sulfate)	Magnesium sulfate heptahydrate (Epsom salts)	Magnesium sulfate heptahydrate	10034-99-8	518
Fluorine	Sodium fluoride	Sodium fluoride	7681-49-4	

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GRAS substances known to be bioavailable sources of the nutrients calcium, phosphorus, and magnesium are allowed by FDA in foods as a “nutrient supplement,” “firming agent,” “pH control agent,” “processing aid,” and/or for other recognized uses. These “non-nutrient” uses are the reason that these substances have INS numbers.

73 Many of the commonly used calcium sources are individually listed at §205.605. Four less common GRAS  
 74 calcium sources are not listed at § 205.605. Three magnesium sources are listed at §205.605, but important  
 75 magnesium sources for certain infant formulas and nutritional supplements currently are not individually  
 76 listed.

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 78 Fluoride is an essential nutrient that concentrates in bone. Fluoridated water, either bottled or as drinking  
 79 water, is permitted as an ingredient in foods. Fluoride salts, however, are not permitted by FDA as a  
 80 specifically added substance in foods. Thus fluorine and fluoride salts are outside the scope of this  
 81 evaluation.

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 83 **Table 1e - GRAS Substances with Major Electrolyte Mineral Activity** (National Research Council 2005)  
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Mineral nutrient(s)	GRAS Substance with Bioavailable Nutrient Mineral Content			
	Substance name	Chemical (IUPAC) name	CAS Number	E/INS No.
Potassium	Potassium acid tartrate	Potassium 2,3,4-trihydroxy-4-oxobutanoate	868-14-4	E336
	Potassium bicarbonate	Potassium hydrogen carbonate	298-14-6	E501
	Potassium carbonate	Dipotassium carbonate	584-08-7	E501
(& Chloride)	Potassium chloride	Potassium chloride	7447-40-7	E508
	Potassium citrate	Tripotassium 2-hydroxypropane-1,2,3-tricarboxylate	866-84-2	E332
	Potassium hydroxide	Potassium hydroxide	1310-58-3	E525
(& Phosphorus)	Dipotassium phosphate	Dipotassium hydrogen phosphate	7758-11-4	E340
Sodium	Sodium bicarbonate	Sodium hydrogen carbonate	144-55-8	E500
	Sodium carbonate	Disodium carbonate	497-19-8	E500
(& Chloride)	Sodium chloride (salt)	Sodium chloride	7647-14-5	
	Sodium citrate dihydrate	Trisodium 2-hydroxypropane-1,2,3-tricarboxylate	6132-04-3	E331
	Sodium hydroxide	Sodium hydroxide	1310-73-2	E524
(& Phosphorus)	Sodium acid phosphate (monosodium phosphate)	Sodium dihydrogen phosphate dihydrate	7558-80-7	E339
(& Phosphorus)	Disodium phosphate, heptahydrate	Disodium hydrogen phosphate heptahydrate	7782-85-6	E339
(& Phosphorus)	Sodium phosphate, tribasic	Trisodium phosphate	7601-54-9	E339
Chloride	Hydrochloric acid	Chlorane	7647-01-0	E507

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 86 With one minor exception (potassium bicarbonate), all of the GRAS sources of the major electrolyte  
 87 minerals are either currently listed individually at §205.605 or preemptively allowed by the Organic Foods  
 88 Production Act of 1990 [7 U.S.C 6510] in the case of sodium chloride (salt). With one exception (salt), all of  
 89 these GRAS sources have INS numbers.

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## Summary of Petitioned Use

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93 “Nutrient vitamins and minerals” currently are listed as “Synthetics allowed” at §205.605(b) with the annotation:  
94 “in accordance with 21 CFR 104.20, Nutritional Quality Guidelines for Foods.” Nutrient vitamins and minerals  
95 are added to organic food to change the nutritional profile of the product.

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## Characterization of Petitioned Substances

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### Composition of the Substances:

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101 Vitamins and minerals are differentiated by their behavior when combusted. Vitamins, with one exception,  
102 are carbon-based and thus are totally combusted to carbon dioxide and other volatile substances; they  
103 leave no ash. The exception is the Vitamin B12 molecule, which contains an atom of cobalt. In contrast,  
104 when nutritionally essential minerals are combusted, there is substantial ash. The ash normally contains  
105 the oxide of the metallic mineral element.

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107 Traditionally, vitamins are categorized based on their solubility properties. Most of the substances used to  
108 contribute Vitamin C and the B-vitamin complex group compounds are water-soluble. Vitamins A, D, E, and K  
109 substances are fat-soluble.

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111 Traditionally, minerals are categorized into “trace minerals,” those mineral elements that our bodies require in  
112 microgram and low-digit milligram amounts, and “major minerals,” those mineral elements that our bodies  
113 require in gram amounts. Discussion of “major minerals” sometimes ignores the essential electrolyte elements, so  
114 in this report the “major minerals” are subdivided into those minerals found primarily in bone – calcium,  
115 phosphorus, magnesium, and fluorine – and the major electrolytes found mainly in body fluids and soft tissues,  
116 particularly blood – sodium, potassium, and chloride.

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### Source or Origin of the Substances:

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119 Vitamins can be extracted from foods, created by chemical synthesis, produced by fermentation, or  
120 produced by a combination of two or more of these processes. For example, alpha-tocopherol acetate can  
121 be produced by isolating alpha-tocopherol from molecular distillates of vegetable oil and then reacting the  
122 tocopherol with acetic anhydride to form the acetate. Similarly, Vitamin A acetate can be produced by  
123 isolating retinol from cold-water fish livers and acetylating the retinol to form the acetate. The most  
124 efficient chemical synthesis of ascorbic acid has two steps performed by fermentation. Fermentation  
125 methods are desirable because many of the vitamins must have a precise stereochemistry to possess  
126 vitamin activity, and the enzymes in microorganisms produce the correct stereoisomers.

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129 Newer biological fermentation processes being developed are more sustainable, efficient, and economic. A  
130 growing number of the methods for fermentative production of individual vitamin compounds utilize  
131 genetically modified organisms (GMOs) (Roseboro 2008). Vitamin B12, for example, is produced  
132 commercially from cultures of *Streptomyces griseus*, *Pseudomonas denitrificans*, and *Propionibacterium*  
133 *freudenreichii* subsp. *shermanii*. Some manufacturers use microorganisms altered by classical mutation-  
134 generating techniques whereas others use genetically engineered microorganisms (Kanga et al. 2012).

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136 The ultimate source of nutrient minerals is the environment. Electrolyte minerals – sodium, potassium,  
137 chloride – are isolated from brines or salt deposits. The major bone minerals come from mineral ores such  
138 as limestone (calcium) and phosphate rock (phosphorus) and natural brines (magnesium). Most of the trace  
139 minerals are extracted by treating ores with sulfuric acid, or by smelting ores and then dissolving the metal  
140 or metal oxide in sulfuric acid.

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### Physical and Chemical Properties of the Substances:

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144 The physical and chemical properties of vitamins were summarized in a recent 2013 Technical Report as  
 145 follows: "As a result of the structural diversity among the vitamin compounds, there is great variability in  
 146 the physical and chemical properties of vitamins as a chemical class. Vitamins are organic (i.e., carbon-  
 147 containing) compounds and are typically grouped depending on their solubility in water vs. organic  
 148 solvents. The more hydrophilic vitamin compounds tend to have multiple polar functionalities (i.e.,  
 149 hydroxyl groups, amino groups, carboxylic acids, alkoxy groups, and/or salts of carboxylic acids). Due to  
 150 their enhanced aqueous solubility, molecules not metabolized by the organism are rapidly excreted.  
 151 Alternatively, more lipophilic vitamins are primarily comprised of aliphatic and aromatic carbon  
 152 frameworks and are stored in animal fat tissues upon consumption of an excess of the vitamin. As a class of  
 153 substances, vitamins have a relatively low vapor pressure." (Pesticide Research Institute 2013)

154  
 155 Substances providing nutrient minerals vary greatly in their solubility in water, ranging from highly  
 156 soluble salts such as calcium chloride to practically insoluble bone ash (tricalcium phosphate). None are  
 157 volatile with respect to the metallic element. However, heating at relatively low temperatures (< 100°C) can  
 158 drive off the water of hydration of hydrated salts, the carbon dioxide from bicarbonates and some  
 159 carbonates, and the ammonia from ammonium salts.

160  
 161 In the following tables, solubility is expressed in grams per 100 mL of water, generally at room temperature  
 162 (20°-30°C) where such data are available. A melting point ("MP") with the letter "d" indicates that the  
 163 substance decomposes upon "melting." The data are drawn from the Merck Index (Budavari 1996), the  
 164 Handbook of Chemistry and Physics, 40<sup>th</sup> Edition, (Hodgman, Weast, and Selby 1959) and U.S. government  
 165 internet sources (e.g., PubChem Compound).

166

167 **Table 2a - Properties of GRAS Substances with Fat-Soluble Vitamin Activity**

168

Substance	Properties	Solubility	MP °C
Vitamin A (retinol)	Solvated crystals from polar solvents, such as methanol or ethyl formate; practically insoluble in water or glycerol; soluble in absolute alcohol, methanol, chloroform, ether, fats and oils	0.067	63.5
Vitamin A acetate	Pale yellow prismatic crystals; more stable to oxidation than is retinol	insoluble	57-58
Vitamin A palmitate	Amorphous or crystalline; more stable to oxidation than is retinol	insoluble	28-29
Beta-carotene	Deep-purple hexagonal prisms or red, rhombic leaflets; absorbs oxygen from the air, yielding colorless inactives	Insoluble	183
Vitamin D2	White or colorless, odorless crystals, with a metallic or bitter taste	0.005	116.5
Vitamin D3	White or colorless, odorless crystals (fine needles)	insoluble	84.5
Vitamin D2 resin	Not a single substance	insoluble	n/a
Vitamin D3 resin	Not a single substance	insoluble	n/a
Tocopherols	Pale yellow viscous oil; boils at 516.3°C; ignites at 204.7°C	insoluble	2.5-3.5
Alpha-tocopherol acetate	Pale yellow viscous liquid; practically unaffected by the oxidizing influence of air, light, and ultraviolet light	insoluble	- 27.5
Phylloquinone (K1)	Yellow viscous oil; odorless; stable to air, moisture; decomposes in sunlight	insoluble	- 20
Menaquinone 4 (K2)	Yellow crystals	insoluble	35
Menaquinone 6 (K2)	Yellow crystals	insoluble	50
Menaquinone 7 (K2)	Light yellow microcrystalline plates	insoluble	54
Lutein	Yellow prisms with metallic luster	insoluble	183-196
Lycopene	Long, deep red needles	insoluble	~ 105
Zeaxanthin	Yellow rhombic plates with steel-blue metallic luster	insoluble	207-215

169

170 Vitamin E, alpha-tocopherol, is the best known antioxidant vitamin. Tocopherols are a common ancillary  
 171 substance in commercial sources of Vitamin A and other carotenoids, Vitamin D and Vitamin K2, because  
 172 these highly unsaturated molecules with four to thirteen carbon-to-carbon double bonds are very prone to  
 173 oxidation and thus loss of vitamin activity. In turn, the naturally occurring plant colorants carotene, lutein,  
 174 lycopene, and zeaxanthin, can be used as 'self-sacrificing' antioxidants to protect other fats, in addition to  
 175 being used as "nutrients."

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178 **Table 2b - Properties of GRAS Substances with Water-Soluble Vitamin Activity**  
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Substance	Properties	Solubility	MP °C
Ascorbic acid	White to slightly yellow crystals or powder, odorless, with a pleasant, sharp, acidic taste; auto-ignition at 380°C	33	190-192
Ascorbyl palmitate	White or yellowish white powder with a citrus-like odor	0.002	112
Calcium ascorbate	White crystalline powder, odorless	50	n/a
Sodium ascorbate	Minute white to yellow crystals, odorless	62	218
Thiamine hydrochloride	Crystals from water, with a slight characteristic thiazole odor and a bitter taste	50 - 100	164
Thiamine mononitrate	White to yellow-white crystals; practically non-hygroscopic; more stable than the hydrochloride	2.7	196-200 d*
Riboflavin	Orange to yellow crystals or needles with a slight odor and a bitter taste	0.010 - 0.013	280 d*
Riboflavin-5 phosphate, sodium	Yellow crystals	11.2	> 210 d*
Niacin	Colorless, odorless needles with a sour taste, non-hygroscopic	1.8	236.6
Niacinamide	White, odorless, crystalline powder with a sour taste	50 - 100	130
Aluminum nicotinate	No data available		
Nicotinamide-ascorbic acid complex (Niacinamide ascorbate)	Yellow crystals, practically odorless	40	141-145
Pyridoxine hydrochloride	White to practically white crystals or crystalline powder; stable in air and slowly affected by sunlight; bitter taste	22	207
Folic acid (folacin)	Yellowish-orange crystals; extremely thin platelets; odorless or almost odorless; tasteless	0.00016	250 d*
Vitamin B12 (cyanocobalamin)	Dark red crystals or an amorphous or crystalline red powder; odorless and tasteless	12.5 mcg	> 300
Calcium pantothenate	Minute needles with a sweetish taste and slightly bitter aftertaste; moderately hygroscopic	36	195-196 d*
Calcium pantothenate calcium chloride double salt	No data available		
D-pantothenamide	No data available		
Biotin	Long, thin, colorless needles crystallized from water	0.022	232 d*
Choline bitartrate	White crystalline powder; odorless or with a faint trimethylamine-like odor; acid taste	10	149-153
Choline chloride	White hygroscopic crystals; strong trimethylamine odor	> 100	305 d*
Inositol ( <i>myo</i> -inositol)	Anhydrous; non-hygroscopic crystals with a sweet taste	14	225-227

180 \*d = decomposes

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183**Table 2c - Properties of GRAS Substances with Trace Mineral Activity**

Substance	Properties	Solubility	MP °C
Chromium picolinate	Violet-red crystalline powder	0.025	137
Chromium chloride hexahydrate	Green or violet crystalline powder; deliquescent in air	58.5	83
Copper gluconate	Light blue to bluish-green odorless crystals or powder, with an astringent taste	30	155-157
Cuprous iodide	Dense white or red-brown powder or cubic crystals	0.0008	588-606
Copper sulfate	Grayish-white to greenish white rhombic crystals or amorphous powder	14.3	560 d*
Potassium iodide	Colorless or white cubic crystals, white granules, or powder; slightly deliquescent in moist air; becomes yellow with age due to liberation/loss of iodine (I <sub>2</sub> )	127.5	723
Ferric ammonium citrate	Brown form: reddish-brown granules, garnet-red transparent scales, or brownish-yellow powder; green form: green transparent, scales, pearls, granules, or powder; ferruginous taste; very deliquescent; decomposes when heated, emitting acrid smoke and irritating fumes	Very soluble	d*
Ferric chloride	Hexagonal red by transmitted light, green by reflected light; sometimes appears brownish-black; dark leaflets or plates; very hygroscopic	64.4	~ 300
Ferric citrate	Small thin transparent reddish-brown crystalline, or crystalline powder; chars when heated strongly	Soluble	d*
Ferric phosphate	White, grayish-white, or light pink; orthorhombic or monoclinic crystals or amorphous powder; dihydrate salt loses water above 140°C.	Very slightly soluble	d*
Ferric pyrophosphate	Yellowish-white powder	insoluble	n/a
Ferric sulfate	Grayish-white powder, or rhombic or rhombohedral crystals; slowly soluble in water	soluble	480 d*
Ferrous ascorbate	Blue-violet powder	soluble	n/a
Ferrous carbonate	Greenish amorphous powder; begins to decompose when heated to 200°C	0.00067	d*
Ferrous citrate	White microscopic rhombic, orthorhombic crystals; decomposes at 350°C in hydrogen	0.05	d*
Ferrous fumarate	Reddish-orange to reddish brown granular powder; odorless; almost tasteless	0.14	> 280 d*
Ferrous gluconate	Yellowish-gray or pale greenish-yellow powder; slight odor of caramel	10	188 d*
Ferrous lactate	Greenish-white powder or crystalline masses; slight characteristic odor; mild, sweet and ferruginous taste; on exposure to air it becomes darker and incompletely soluble	2.1	d*
Ferrous sulfate heptahydrate	Blue-green, monoclinic, odorless crystals or granules; efflorescent; loses 3 water at 56.6°C, 6 water at 65°	48.6	65 d*
Elemental iron	Black to dark gray powders; magnetic	0	1535
Manganese chloride	Cubic pink deliquescent crystals	62.2	650
Manganese citrate	White to white-reddish powder; decomposes at 350°C	very slightly soluble	d*
Manganese gluconate	Slightly pink powder or coarse pink granules, soluble in water	soluble	n/a

Manganese sulfate	Monoclinic pale pink slightly efflorescent crystals; loses all water at 400-500°C	98	700
Ammonium heptamolybdate	Monoclinic; colorless to yellowish crystals	40	d*
Sodium molybdate	White rhombohedral crystals	84	687
Sodium selenate	White crystals; decomposes at high temperature to selenium and disodium oxide fumes	58.5	d*
Sodium selenite	White tetragonal crystals or white powder	89.8	710 d*
Zinc sulfate	Colorless, orthorhombic hygroscopic crystals	57.7	680 d*
Zinc chloride	White, very deliquesce granules, or fused pieces or rods	432	~ 290
Zinc gluconate	White powder or granules	insoluble	144-145
Zinc oxide	White, odorless amorphous powder	0.00016	> 1800
Zinc stearate	Fine, soft, light white powder; repels water	insoluble	130

\*d = decomposes

**Table 2d - Properties of GRAS Substances with Major Mineral in Bone Activity**

Substance	Properties	Solubility	MP °C
Calcium carbonate	Odorless, tasteless powder or crystals; decomposes at 825°C into calcium oxide (quicklime)	0.0015	825 or 1339
Calcium chloride	Dihydrate; hygroscopic granules, flakes, or powder; loses all of its water at 260°C	76.8	772
Calcium citrate	Tetrahydrate; odorless powder; loses most of its water at 100°C and all of it at 120°C	0.85	n/a
Calcium glycerol phosphate	Fine, odorless, almost tasteless powder; decomposes at >170°C	2	> 170 d*
Calcium hydroxide	White powder; loses water at 580°C to form calcium oxide	0.185 (0°)	580 d*
Calcium lactate (not GRAS for infants)	Pentahydrate; odorless, white, slightly efflorescent granules or powder; loses water of hydration at 120°C	7.9	n/a
Calcium oxide	Crystals, white lumps or powder; forms calcium hydroxide when dissolved in water	slightly soluble	2572
Calcium sulfate, anhydrous	White crystals or powder; high affinity for water, absorbs water to form the dihydrate (gypsum)	0.209	1450
Calcium sulfate, dehydrate (gypsum)	Lumps or powder; loses part of its water at 100-150°C to form plaster of Paris	0.241	1450
Calcium phosphate, dibasic	White crystals; loses water of hydration at 109°C; upon ignition at 900°C forms calcium pyrophosphate	0.02	900 d*
Calcium phosphate, monobasic	Crystalline; loses water of hydration at 100°C; decomposes at 200°C	1.8	200 d*
Calcium phosphate, tribasic	Amorphous, odorless, tasteless powder	insoluble	1670
Calcium pyrophosphate	Polymorphous crystals or powder	insoluble	1353
Phosphoric acid	85% solution; clear syrupy liquid; pH (0.1N solution) is 1.5	309	42
Magnesium carbonate	White, odorless, crystalline powder; decomposes to magnesium oxide at 662°C	insoluble	662
Magnesium chloride hexahydrate	Deliquescent crystals; loses some water at 100°C, begins to lose some hydrochloric acid at 110°C, decomposes at 117°C	167	117 d*
Magnesium hydroxide	Amorphous powder; decomposes at 350°C to form magnesium oxide	0.0009	350 d*
Magnesium oxide	White, very fine powder; available in "light" or "heavy" (dense) forms	0.00062	2800
Magnesium phosphate, dibasic	Trihydrate; white crystalline powder	slightly soluble	145 d*

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Magnesium phosphate, tribasic	Anhydrous, white powder	0.02	1184
Magnesium sulfate heptahydrate	Efflorescent crystals or powder; bitter, saline cooling taste; loses the last molecule of water at ~250°C	71	1124
Sodium fluoride	Cubic or tetragonal crystals; aqueous solutions etch glass	4.22	980-997

\*d = decomposes

**Table 2e - Properties of GRAS Substances with Major Electrolyte Mineral Activity**

Substance	Properties	Solubility	MP °C
Potassium acid tartrate	Colorless crystals or white crystalline powder	0.37	burns
Potassium bicarbonate	Colorless, transparent crystals, white granules or powder, begins to lose carbon dioxide above 100°C	22.4	100-200 d*
Potassium carbonate	Hygroscopic, odorless granules or granular powder	260	891
Potassium chloride	White crystals or crystalline powder	34.7	776
Potassium citrate	Anhydrous, white powder; odorless; cooling, saline taste	154	180 d*
Potassium hydroxide	Very caustic! White or yellowish lumps, rods, or pellets	107	360-380
Dipotassium phosphate	Anhydrous; white, somewhat hygroscopic granules; converted into potassium pyrophosphate by ignition	167	d*
Sodium bicarbonate	White crystals or granules; begins to lose carbon dioxide at about 50°C and is converted to sodium carbonate at 100°C	7.1	d*
Sodium carbonate	Soda ash: odorless hygroscopic powder; alkaline taste; begins to lose carbon dioxide at 400°C	7.1	851
Sodium chloride	Cubic white crystals, granules, or powder; colorless	35.7	801
Sodium citrate dihydrate	White odorless crystals, granules, or powder; cool, saline taste; becomes anhydrous at 150°C	72	d*
Sodium hydroxide	Very corrosive; sold as lumps, sticks, pellets, chips, etc.	42	318
Sodium acid phosphate	Anhydrous; colorless	~100	204 d*
Disodium phosphate heptahydrate	Crystals or granular powder; stable in air; loses five (5) waters at 48°C	104	d*
Sodium phosphate, tribasic	Colorless or white crystals, melts at ~75°C if heated rapidly	14.5	1583
Hydrochloric acid	A solution of hydrogen chloride in water (38% HCl)	>62% water	liquid

d\* = decomposes

**Specific Uses and Approved Legal Uses of the Substances:**

Each of the substances listed in this report is generally recognized as safe (GRAS) for use in food and provides an essential nutrient. For those determined to be GRAS by FDA, the specific Paragraph in CFR Title 21 or the FDA GRAS Notice (GRN) is listed in Evaluation Question #4. Other substances were self-affirmed as GRAS after GRAS affirmation by the European Food Safety Authority (EFSA), which published its “GRAS-equivalent” determination of safety in the EFSA Journal. The EFSA citations are entered in Evaluation Question #4. Additional substances are otherwise established as GRAS as indicated in Evaluation Question #4.

With few exceptions, the substances listed in the tables above lacking an INS number have only one purpose in foods: they are “nutrient supplements,” defined by FDA at 21 CFR 170.3(o)(20) as “Substances which are necessary for the body’s nutritional and metabolic processes.” The exceptions, listed in Title 21, Parts 182 and 184, are mineral substances: copper gluconate is also allowed as a “synergist”; copper sulfate

208 is also allowed as a “processing aid”; potassium iodide is also allowed in table salt as a source of iodine;  
 209 and ferrous lactate is also allowed as a “processing aid.”

210  
 211 As indicated in the comments on the fat-soluble vitamins and the water-soluble vitamins, the substances  
 212 with an antioxidant function in the body – Vitamin E, Vitamin C, the carotenoids – are used as  
 213 “antioxidants” in other vitamins, and in fats and oils. Highly colored vitamins, such as the carotenoids and  
 214 riboflavin – are permitted by FDA to be used as “colors.”

215  
 216 Example of multipurpose GRAS substances are calcium hydroxide, which has no FDA-limitation on its  
 217 uses, and calcium sulfate, which FDA allows as an anticaking agent, drying agent, firming agent, flour-  
 218 treating agent, formulation aid, leavening agent, nutrient supplement, pH control agent, stabilizer and  
 219 thickener, synergist, and texturizer.

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 221 **Action of Nutrient Vitamins and Minerals:**

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 223 The major physiological effects of nutrient vitamins and minerals are as follows (Institute of Medicine 1997,  
 224 2011; National Research Council 1998, 2000, 2001, 2005; Food and Nutrition Board 1989):

225

Major physiological effects and Effects of deficiency
<b>Vitamin A</b> is important for normal vision, gene expression, reproduction, embryonic development, growth and immune function. Human deficiency causes xerophthalmia (night blindness, conjunctival and corneal xerosis) and ultimately blindness.
<b>Vitamin D</b> actually is a fat-soluble steroid hormone that humans produce in their skin when exposed to solar ultraviolet radiation, which converts a cholesterol intermediate into Vitamin D3. Its major function is to maintain calcium and phosphorus homeostasis, by enhancing the efficiency of the small intestine to absorb these minerals from the diet. Deficiency of Vitamin D leads to inadequate skeletal mineralization (rickets in infants and small children) or skeletal demineralization (osteomalacia in adults). Vitamin D deficiency may be associated with an increased risk of colon, breast, and prostate cancer.
<b>Vitamin E</b> is the body’s main fat-soluble antioxidant. Its primary role is to prevent propagation of lipid peroxidation. Vitamin E deficiency in humans is rare. Symptoms include peripheral neuropathy, muscle weakness, and ataxia (discoordination).
<b>Vitamin K</b> is involved in blood coagulation and bone metabolism. Osteocalcin is a vitamin K-dependent bone protein. Low Vitamin K intakes are associated with osteoporosis, hip fracture, and arterial atherosclerotic plaque. Deficiency causes hypoprothrombinemia and, in severe cases, hemorrhage.
<b>Lutein</b> (and <b>zeaxanthin</b> ) are carotenoids contained in the macula lutea, a bright yellow spot in the center of the retina that functions to maintain acute central vision. Low intakes of lutein (and zeaxanthin) increase the risk of age-related macular degeneration, the most common cause of irreversible blindness in people over 65 years of age.
<b>Lycopene</b> , the carotenoid responsible for the red color of tomatoes and watermelon, has antioxidant properties. Men with high intakes of lycopene have a significantly lower risk of prostate cancer.
<b>Zeaxanthin</b> – see <b>Lutein</b> . These two polar carotenoids are likely to be biochemically interchangeable.
<b>Vitamin C</b> functions physiologically as a water-soluble antioxidant. It is a cofactor for enzymes involved in the biosynthesis of collagen, carnitine, and neurotransmitters. It scavenges reactive oxidants and diminishes lipid peroxidation. The historical Vitamin C deficiency disease is scurvy, symptoms of which include inflamed and bleeding gums, bruising, impaired wound healing, dry eyes and mouth, weakness, fatigue, depression, and death.
<b>Thiamin</b> functions as a coenzyme in the metabolism of carbohydrates and branch-chained amino acids. Lack of thiamin causes the deficiency disease called beriberi. Alcoholics deficient in thiamin develop Wernike-Korsakoff syndrome. The clinical signs of deficiency include anorexia, weight loss, muscle weakness, mental changes such as apathy, decrease in short-term memory, confusion and irritability and cardiovascular effects such as an enlarged heart.
<b>Riboflavin</b> is an integral part of two coenzymes involved in redox reactions in numerous metabolic

<p>pathways and energy metabolism. The signs of riboflavin deficiency include sore throat; hyperemia and edema of the pharyngeal and oral mucous membranes; cheilosis; angular stomatitis; glossitis (magenta tongue); seborrheic dermatitis; and normochromic, normocytic anemia.</p>
<p><b>Niacin</b> functions as a cosubstrate or coenzyme for transfer of the hydride ion with numerous dehydrogenase enzymes. Pellagra is the classic manifestation of a severe niacin deficiency and was once prevalent in the Southeastern U.S. Pellagra is characterized by a pigmented rash that develops symmetrically in areas exposed to the sun; digestive tract changes that are associated with vomiting, diarrhea, or constipation, and a bright red tongue; and neurological symptoms including depression, apathy, fatigue, headache, and loss of memory.</p>
<p><b>Vitamin B6</b>, provided in food as pyridoxine and related compounds, is present in tissues primarily as pyridoxal phosphate (PAP) and pyridoxamine phosphate. PAP is a coenzyme for more than 100 enzymes involved in amino acid metabolism. The symptoms of Vitamin B6 deficiency are seborrheic dermatitis, microcytic anemia, epileptiform convulsions, and depression and confusion.</p>
<p><b>Folate</b> functions as a coenzyme in single-carbon transfers in the metabolism of nucleic and amino acids. Inadequate folate intakes lead to a rise in the plasma homocysteine concentration and megaloblastic changes in the bone marrow and other tissues with rapidly dividing cells. The risk of spina bifida and other neural tube defects has been reduced by folate fortification of grain products since 1998.</p>
<p><b>Vitamin B12</b> functions as a coenzyme for a critical methyl transfer reaction that converts homocysteine to methionine, and has other functions as well. About 10% to 30% of older people may be unable to absorb naturally occurring Vitamin B12. Vitamin B12 deficiency symptoms include “pernicious anemia,” a pallor of the skin, megaloblastic anemia, diminished energy and exercise tolerance, shortness of breath, and palpitations, and neurological signs such as tingling and numbness of the extremities, vibratory and position sense impairment, motor disturbances, and cognitive changes, including memory loss, disorientation, and dementia.</p>
<p><b>Pantothenic acid</b> is a component of coenzyme A, which is involved in fatty acid metabolism. Pantothenic acid deficiency has only been observed in individuals fed diets devoid of this vitamin. The symptoms include irritability, fatigue, apathy, malaise, sleep disturbances, nausea, vomiting, numbness, etc.</p>
<p><b>Biotin</b> functions as a coenzyme in bicarbonate-dependent carboxylation reactions. Individuals who consume raw egg white over long periods or those on total parenteral nutrition can develop biotin deficiency. The symptoms are dermatitis, conjunctivitis, alopecia, and neurological changes (depression, lethargy, hallucinations, and paresthesia of the extremities).</p>
<p><b>Choline</b> functions as a precursor for acetylcholine, the phospholipid lecithin, and the methyl donor betaine. A choline-deficient diet damages the liver. Fatty liver is a sign of choline deficiency.</p>
<p><b>Inositol</b> is an integral part of the phospholipid phosphatidylinositol. In biologic membranes, phosphatidylinositol mediates cellular responses to external stimuli, nerve transmission, and regulation of enzyme activity. Inositol metabolism is altered in human diabetes mellitus, chronic renal failure, galactosemia, and multiple sclerosis. Administration of <i>myo</i>-inositol to patients with diabetic neuropathy increases nerve conduction velocity. (Food and Nutrition Board 1989)</p>
<p><b>Chromium</b> potentiates the action of insulin. Chromium deficiency has been reported in patients receiving total parenteral nutrition lacking this mineral. Symptoms were weight loss, peripheral neuropathy, and a low respiratory quotient, indicating poor utilization of carbohydrate. Chromium supplements normalized glucose tolerance and insulin action.</p>
<p><b>Copper</b> is part of many copper metalloenzymes, such as the amine oxidases involved in histamine, serotonin and psychoactive drug degradation. Copper deficiency occurs in infants fed cows’ milk. The symptoms are anemia, low white blood cell and neutrophil counts, and osteoporosis.</p>
<p><b>Iodine</b> is an essential component of the thyroid hormones that regulate basal metabolism. Iodine deficiency causes thyroid enlargement (goiter), mental retardation that can be severe (cretinism in 10% of the population), and hypothyroidism. The developing brain is the most sensitive organ; iodine deficiency reduces IQ by 13.5 points. Iodization of salt completely eliminated new cases of cretinism in Switzerland.</p>
<p><b>Iron</b> is an essential component of hemoglobin, enzymes involved in energy metabolism, and other enzymes. Hemoglobin transports oxygen to body tissues. Iron deficiency leads to anemia, poor work performance and endurance, persistent cognitive and developmental impairment, increased maternal perinatal mortality and a greater rate of premature labor and delivery, and depressed immune function.</p>

<p><b>Manganese</b> is involved in the formation of bone and in amino acid, lipid, and carbohydrate metabolism. Inadequate intakes of manganese lead to scaly dermatitis, reduced cholesterol levels, possibly osteoporosis, and increased pain during the premenstrual phase of the estrous cycle in young women.</p>
<p><b>Molybdenum</b> is a cofactor in several enzymes. Only one case of molybdenum deficiency has been reported in the medical literature. The symptoms included tachycardia, headache, and night blindness.</p>
<p><b>Selenium</b> is an essential part of selenoproteins, some of which are oxidant defense enzymes. Infants born to mothers who are both iodine and selenium deficient are at increased risk of cretinism. Keshan disease, a cardiomyopathy, occurs only in selenium-deficient children in response to another stress.</p>
<p><b>Zinc</b> is a component of enzymes in the maintenance of protein structural integrity and regulation of gene expression. Zinc deficiency is more like to occur in individuals with malabsorption syndromes. Symptoms are impaired growth velocity, skin lesions, poor appetite, diarrhea, and slow wound healing.</p>
<p><b>Calcium</b> represents 1% to 2% of body weight, &gt;99% of which is in the bones and teeth. The rest is in soft tissue, involved in vascular contraction, vasodilation, muscle contraction, nerve transmission, and glandular secretion. Inadequate calcium intake leads to reduced bone mass and osteoporosis, which in turn leads to fractures of the hip, vertebrae, distal forearm (wrist, ulna and radius), etc.</p>
<p><b>Phosphorus</b> is important in both bone and soft tissue. Phospholipids are a major component of most biological membranes. Inadequate phosphorus intake is expressed as hypophosphatemia, the effects of which include anorexia, anemia, muscle weakness, bone pain, rickets and osteomalacia, general debility, increased susceptibility to infection, ataxia, confusion, and even death.</p>
<p><b>Magnesium</b> is distributed about half in bone and half in soft tissue. Magnesium is a required cofactor for over 300 enzyme systems, including anaerobic and aerobic energy metabolism. Severe magnesium deficiency is rare but habitually low intakes are commonplace. Magnesium depletion has cardiovascular effects, including increased blood pressure, atrial fibrillation, ventricular tachycardia and fibrillation, and increased risk of cardiac ischemia.</p>
<p><b>Sulfate</b> is required for synthesis of many important sulfur-containing compounds, such as chondroitin sulfate and cerebroside sulfate. The major source of sulfate is the biodegradation of sulfur-containing amino acids. Sulfate deficiency has only been produced experimentally, by restricting the intake of both sulfate and sulfur-containing amino acids.</p>
<p><b>Fluorine</b>, in the form of fluoride, is mainly associated with calcified tissues. An inadequate intake of fluoride is associated with an increased risk of dental caries. Providing a nutritionally appropriate intake of fluoride inhibits the development of dental caries. Too much fluoride causes fluorosis.</p>
<p><b>Potassium</b>, the major intracellular cation in the body, is required for normal cellular function. Severe potassium deficiency is characterized by hypokalemia. The adverse consequences of hypokalemia include cardiac arrhythmias, muscle weakness, and glucose intolerance. Moderate potassium deficiency is characterized by increased blood pressure, increased salt sensitivity, an increased risk of kidney stones, and increased bone turnover. An inadequate intake of potassium may also increase the risk of cardiovascular disease, especially stroke.</p>
<p><b>Sodium</b> and <b>Chloride</b> are required to maintain extracellular volume and plasma osmolality. The body can adapt to extremely low and extremely high intakes of sodium, and thus chloride, since salt (sodium chloride) is the source of most of the chloride in the diet. Chloride depletion can occur with severe vomiting, due to loss of hydrochloric acid from the stomach, resulting in hypochloremic metabolic alkalosis, or from consumption of infant formula deficient in chloride, resulting in hypochloremia. Symptoms of hypochloremia are growth failure, lethargy, irritability, anorexia, gastrointestinal symptoms, and weakness.</p>

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### **Combinations of the Substances:**

### **Ancillary Substances**

All of the substances with fat-soluble vitamin activity are extremely susceptible to oxidation (Budavari 1996) and loss of vitamin activity. Moreover, these substances are oily, fat-soluble materials used in very small amounts, so their incorporation and uniform dispersion into food can be problematic, especially in a dry-blended formulation (Bauernfeind 1973).



235

236 The oxidation problems of fat-soluble vitamin substances are overcome by incorporating compatible fat-  
237 soluble antioxidants with vitamin activity, such as tocopherols, fat-soluble ascorbic acid (ascorbyl  
238 palmitate), and carotenoids, and GRAS synthetic chemical antioxidants (BHT, BHA, PG, and TBHQ<sup>3</sup>). Fat-  
239 soluble vitamin materials usually can be obtained free of BHT, BHA, PG, or TBHQ (see below).

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241 The major “physiologically friendly” antioxidants are the tocopherols, ascorbyl palmitate, and beta-  
242 carotene. Ascorbic acid itself can be used with tocopherols synergistically as an antioxidant (Ismail et al.  
243 2009). The tocopherol acts as the primary antioxidant, reacting with and repairing free radicals, and then is  
244 regenerated by the ascorbic acid (Golumbic and Mattill 1941). Citric acid may be used to chelate trace  
245 amounts of reactive pro-oxidant metals such as iron and copper (Lindsay 1996).

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247 The fat-soluble vitamins A, D, and K are required in very small amounts, ranging from 10 micrograms (400  
248 International Units) a day for vitamin D3 to 625 micrograms a day for Vitamin A. Most oily forms of these  
249 vitamins are standardized with vegetable oil to provide a useful product ingredient. An example is shown  
250 in the table below: Vitamin D3 containing 1 million IU per gram in corn oil that comprises more than 95%  
251 corn oil and no less than 2.5% cholecalciferol.

252

253 The dispersion problem in fat-containing processed foods, such as infant formula, which provides half of  
254 food energy as a blend of fats and oils, can be overcome by dissolving the fat-soluble vitamin ingredients  
255 and an emulsifier, usually lecithin, in the fat blend prior to homogenization (Rule 1988). This ensures  
256 uniform distribution of vitamin activity.

257

258 In other foods, the dispersion problem is overcome by micro-encapsulating the fat-soluble vitamins into  
259 beadlets using matrices of starch, gums, gelatin, casein, and/or other GRAS substances compatible with the  
260 vitamin (Bauernfeind 1973). Micro-encapsulation provides a barrier against chemical reactions and  
261 improves vitamin activity retention. Micro-encapsulation provides an adequate dilution of the vitamins in  
262 a form that has good distribution properties (Bauernfeind 1973).

263

264 Fat-soluble vitamins can be micro-encapsulated by spray-drying an emulsion of the fat-soluble vitamin,  
265 optionally dissolved in an oil phase, in a matrix material. The matrix material typically is a protein, for  
266 example gum arabic, sodium caseinate or gelatin, in combination with a carbohydrate, for example  
267 maltodextrin, sucrose or lactose. The matrix material is optionally coated with starch or modified starch.  
268 (Grandia, Sibeijn, and Zoet 2012)

269

270 U.S. Patent Application 2003/0170324 (Tritsch, Yu, and Mazzaro 2003) discloses micro-encapsulation of 25-  
271 hydroxy-cholecalciferol, a form of vitamin D3. The vitamin is first dissolved in oil and the resulting oil  
272 composition is then encapsulated in an encapsulation agent selected from starches, protein, pectin,  
273 alginate, agar, maltodextrins, lignin sulfonates, cellulose derivatives, saccharides, sugars, sorbitols, or  
274 gums.

275

276 A cold-water dispersible (CWD) vitamin D beadlet produced in India is a gelatin-free product containing  
277 90,000 to 110,000 IU per gram of Vitamin D3. The beadlet contains Vitamin D3, sucrose, an undisclosed  
278 emulsifier, and DL-alpha-tocopherol as antioxidant (Fermenta Biotech Ltd 2011)

279 The formulated fat-soluble vitamin offerings of one U.S. supplier<sup>4</sup> and the percentage compositions  
280 provided on the Material Safety Data Sheet (MSDS) of each are listed in the following table.

281

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<sup>3</sup> BHT (butylated hydroxytoluene), BHA (butylated hydroxyanisole), PG (Propyl Gallate), and TBHQ (Tertiary Butyl Hydroquinone).

<sup>4</sup>

[http://worldaccount.basf.com/wa/NAFTA~en\\_US/Catalog/HumanNutrition/pi/BASF/StartingPoint/productgroup\\_top](http://worldaccount.basf.com/wa/NAFTA~en_US/Catalog/HumanNutrition/pi/BASF/StartingPoint/productgroup_top). Accessed 19 November 2014.

282 Table 3: Fat soluble vitamin product ingredients listing on MSDSs of one U.S. supplier

Fat-soluble Vitamin Product	Percentage Composition
Dry Vitamin A-Acetate 250 DC/GFP	20% - 40% Sucrose; 20% - 40% Gum Arabic; 10% - 30% starch; 5% - 10% Vitamin A Acetate; 1% - 5% Water
Dry Vitamin A-Acetate 325 GFP/E	20% - 40% Sucrose; 20% - 40% starch; 10% - 30% Gum Arabic; 10% - 20% Vitamin A Acetate; 1% - 5% Water
Dry Vitamin A-Acetate 500, 40 Mesh	20% - 40% Sucrose; 10% - 30% Gelatin; 10% - 30% Vitamin A Acetate; 10% - 30% Starch; 1% - 5% Water; 1% - 5% BHT
Dry Vitamin A-Acetate 500, 60 Mesh	20% - 40% Sucrose; 15% - 30% Gelatin; 15% - 30% starch; 15% - 30% Vitamin A Acetate; 5% - 10% Water; 1% - 5% BHT
Dry Vitamin A Palmitate 250 MS CWD	35% - 45% Modified Corn Starch; 15% - 25% Dextrin; 7% - 15% Vitamin A palmitate; 7% - 13% Sucrose; 3.0% - 7.0 % Water
Dry Vitamin A-Palmitate 250 Food Grade	20% - 40% Sucrose; 20% - 40% Gum Arabic; 10% - 30% starch; 10% - 30% Vitamin A palmitate; 1% - 5% Water; 1.0% - 5.0 % Tricalcium phosphate
Dry Vitamin A-Palmitate 500	20%- 40% Vitamin A palmitate; 15% - 30% Sucrose; 15% - 30% starch; 15% - 30% Gelatin; 1% - 5% Water; 1% - 5% BHT
Dry Vitamin AD2 Acetate 500/50, 60 Mesh	20% - 40 % Sucrose; 15% - 30% starch; 15% - 30% Gelatin; 15% - 30% Vitamin A Acetate; 1% - 5% Water; 1% - 5% BHT; 0.1% - 1.5 % Vitamin D2
Dry Vitamin AD3K1	30% -50% starch; 20% - 40% Gum Arabic; 10% - 20% Sugar; 5% - 10% sodium ascorbate (Vitamin C); 1% - 5% Vitamin A palmitate; 1% - 5% Water; 0.5% - 1.5% Tricalcium phosphate; Vitamins K1, D3
Vitamin A-Acetate 1.5 Million IU/G stabilized with BHT	30% - 60% Vitamin A Acetate; 30% - 60% Sunflower oil; 1.0% - 5.0 % BHT
Vitamin A-Palmitate 1.0 Million IU/G stabilized with BHT	30% - 60% Vitamin A palmitate; 30% - 60 % Sunflower oil; 1.5% % BHT
Vitamin A-Palmitate 1.0 Million IU/G stabilized with Tocopherol	40% - 60% Vitamin A palmitate; 30% - 50% Sunflower oil; D,L-alpha-Tocopherol
Vitamin A-Palmitate 1.7 Million IU/G stabilized with BHT	80% - 100% Vitamin A palmitate; 1% - 5 % BHT
Vitamin A-Palmitate 1.7 Million IU/G stabilized with Tocopherol	80% - 100% Vitamin A palmitate; 1% - 5% D,L-alpha-Tocopherol
Vitamin A-Palmitate 1.7 Million IU/G unstabilized	80% - 100% Vitamin A palmitate; 1% - 5% Sunflower oil
Dry Vitamin D3 100 GFP HP	15% - 40% sucrose; 10% - 30% starch; 10% - 30% gum Arabic; 7% - 13% glycerides; 3% - 7% water; 0.1% - 1.0% calcium phosphate; 0.1% - 1.0% cholecalciferol (vitamin D3); < 0.1% D,L-alpha-tocopherol
Dry Vitamin D3 100 HP	29% - 39% Sucrose; 16% - 26% Gelatin; 16% - 26% starch; 14% - 24% Glycerides; 0% - 5% Water; 0.1% - 1.0% Vitamin D3; 0 - 1% BHT; 0 - 1% Sodium aluminosilicate
Vitamin D3 1.0 Mio IU/G	80% - 100% Glycerides; 1% - 5% Vitamin D3
Vitamin D3 1.0 Mio IU/G in Corn Oil	95% - 99% Corn oil; 1% - 5% Vitamin D3
Dry Vitamin E-Acetate 50% DC	40% - 60% Tocopheryl Acetate; 15% - 30% Corn starch; 15% - 30% Gelatin; 3% - 7% Sucrose; 3% - 7% Water; 0.5% - 1.5% Sodium aluminosilicate
Dry Vitamin E-Acetate 50% DC/GFP	40% - 60% Tocopheryl Acetate; 10% - 30% Sucrose; 10% - 30% Modified Corn Starch; 5% - 15% starch; 1% - 5% Water

Vitamin A/E Blend 1R	40% - 60% Vitamin A palmitate; 10% - 20% Soybean oil
Vitamin E 500 BG Vitamin E 500 FG	40% - 60% dl-alpha Tocopheryl Acetate; 30% - 50% Starch modified (hydrogen 2-(octen-1-yl)butanedioate, sodium salt); 1% - 5% Silicon dioxide
Dry Vitamin K1 1% GFP	50 - 70 % hydrolyzed starch syrups, dehydrated; 20 - 40% Gum Arabic; 5 - 10% Water; 0.1 - 1.0 % Vitamin K1; 0.5 - 1.5 % Tricalcium phosphate
Dry Vitamin K1 5% GFP	50% - 70% Glucose; 15% - 30% Gum Arabic; 3% - 7% Water; 3% - 7% Vitamin K1

283 [http://worldaccount.basf.com/wa/NAFTA~en\\_US/Catalog/HumanNutrition/pi/BASF/StartingPoint/  
284 productgroup\\_top](http://worldaccount.basf.com/wa/NAFTA~en_US/Catalog/HumanNutrition/pi/BASF/StartingPoint/productgroup_top)  
285

286 A technique often used to encapsulate water-soluble vitamins such as vitamin C is dispersion of the water-  
287 soluble vitamin in molten fat or wax, followed by spray-cooling or spray-chilling of the dispersion. Patent  
288 GB 922,697, for example, discloses coating of water-soluble vitamin with a mixture of saturated C14-C18  
289 fatty acids having a melting point of at least 45 °C. The coating process involves suspension of the vitamin  
290 in the molten fatty material followed by the production of solid spheroidal particles by means of spray-  
291 chilling of the suspension. (Grandia, Sibeijn, and Zoet 2012)  
292

293 Iron salts, particularly ferrous sulfate, are sometimes encapsulated to prevent the iron from catalyzing  
294 oxidation reactions that lead to rancidity, color and taste changes, or other undesirable effects (Hurrell  
295 1985). The encapsulation agent is usually hydrogenated vegetable fat, with lecithin as an optional  
296 ingredient (Zlotkin et al. 2001). Encapsulation of iron compounds may reduce iron bioavailability,  
297 depending upon the particle size of the iron source. Heating a food containing encapsulated iron above the  
298 melting point of the encapsulating fat can cause the undesired color changes.  
299

300 Several water-soluble vitamins are typically used in low dosages that can be difficult to distribute  
301 homogeneously in food or feed products. For example, the requirement for vitamin B12 is very small – a  
302 few micrograms per day – compared to requirements of several milligrams per day for most of the other  
303 water-soluble vitamins. To facilitate dispersion of vitamin B12 in a dry vitamin premix, a powder  
304 preparation of Vitamin B12 is customarily used. For example, 1% cyanocobalamin (vitamin B12) is  
305 dispersed over dicalcium phosphate dihydrate and microcrystalline cellulose matrix as a carrier. Calcium  
306 phosphate is currently listed at § 205.605, but the synthetic substance microcrystalline cellulose is not.  
307 Other commercial sources of vitamin B12 provide 0.1% or 1% cyanocobalamin with maltodextrin as the  
308 carrier<sup>3</sup>.  
309

310 These ancillary substances are GRAS. Good manufacturing practice (GMP) requires that they be used at  
311 levels that avoid unacceptable environmental, human health, and toxicological effects. For example, the  
312 synthetic antioxidants BHA and BHT are carcinogenic at high levels but anti-carcinogenic at current levels  
313 of food additive use (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) 2012;  
314 Williams, Iatropoulos, and Whysner 1999), protecting against chemical carcinogens (Williams, Iatropoulos,  
315 and Jeffrey 2002) and the liver cancer caused by aflatoxin (Williams 2003).  
316

317 Some individuals are sensitive to these two antioxidants. Two patients with chronic idiopathic urticaria  
318 (hives or nettle rash) who experienced remissions with a dye- and preservative-elimination diet had  
319 exacerbations of their urticaria when they were challenged under double-blind, placebo-controlled  
320 conditions with BHT and BHA (Goodman et al. 1990).  
321

322 Protein is the cause of most allergies, and, as noted above, one or more proteins are used in many  
323 encapsulated vitamin preparations. Gelatin, a partially hydrolyzed protein of limited antigenicity, is the  
324 protein most commonly used in vitamin and mineral formulation.  
325

**Status**

327

328 **Historic Use:**

329  
330 The current annotation for nutrient vitamins and minerals in handling was proposed and adopted by the  
331 National Organic Program (NOP) in its initial rulemaking to convert the recommendations of the National  
332 Organic Standards Board (NOSB) into a Federal regulation.

333  
334 The first of two 1995 NOSB recommendations for “nutrient vitamins and minerals” included an annotation that  
335 read: “Accepted for use in organic foods for enrichment or fortification when required by regulation or  
336 recommended by an independent professional organization.” The final NOSB recommendation was:

337  
338 “Upon implementation of the National Organic Program (NOP), the use of synthetic vitamins, minerals,  
339 and/or accessory nutrients in products labeled as organic must be limited to that which is required by  
340 regulation or recommended for enrichment and fortification by independent professional associations.”

341  
342 The current annotation in the USDA organic regulations reads: “in accordance with 21 CFR 104.20,  
343 Nutritional Quality Guidelines for Foods.”

344  
345 In 2011, recognizing that the current annotation was not consistent with the final 1995 recommendation of  
346 the NOSB, the NOSB Handling Committee recommended the following annotation:

347  
348 Proposed Amended Annotation: “Materials required or allowed by law for the purpose of  
349 enrichment, supplementation or fortification of foods, including infant formula, and materials the  
350 use of which is supported by the FDA or the Institute of Medicine of the National Academies.”

351  
352 In 2012, NOP (77 FR 1980) proposed modifying the annotation for “nutrient vitamins and minerals” to:

353  
354 “For food – vitamins and minerals identified as essential in 21 CFR 101.9. “

355 “For infant formula – vitamins and minerals as required by 21 CFR 107.100 or § 107.10.”

356 However, this proposal has not been implemented; the current annotation remains in force (77 FR 59287).

357  
358 Responding to 2010 questions from the NOP about FDA regulation 21 CFR 104.20, the FDA clarified its  
359 meaning (Schneeman 2011 APR 14). First of all, 21 CFR 104.20 is a guidance document expressing FDA  
360 food fortification policy, aimed at avoiding indiscriminate fortification. Moreover, 21 CFR 104.20(f)  
361 recognizes existing regulations in Chapter 1 of CFR Title 21, which includes Subchapter B, “Food for  
362 Human Consumption,” (Parts 100 to 199), and Subchapter E, “Animal Drugs, Feeds, and Related  
363 Products,” (Parts 500-502 and 582-589, relating to animal feed), the Subchapters pertaining to food and feed  
364 fortification. Some of the specific standards of identity in Subchapter B are identified in the following table.

365  
366 The current NOP regulation also allows the use of vitamins and trace elements in organic livestock  
367 production for enrichment or fortification when FDA approved, at § 205.603, Synthetic Substances Allowed  
368 for Use in Organic Livestock Production. The Organic Foods Production Act (OFPA) mentions use of  
369 vitamins and minerals with regard to organic production, but is silent as to organic handling.

370  
371 **International**

372  
373 **The Canadian General Standards Board Permitted Substances List**

374 “Minerals, vitamins and similar isolated ingredients” are permitted by the following entry: “Vitamins and  
375 minerals: Minerals (including trace elements), vitamins and similar isolated ingredients shall not be used  
376 except where legally required or a dietary or nutritional deficiency can be demonstrated and shall be  
377 documented. Vitamins shall not be derived from organisms from genetic engineering.”

378  
379 **The CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and  
380 Marketing of Organically Produced Foods (GL 32-1999)**

381 “Minerals, vitamins, essential fatty and amino acids, and other nitrogen compounds” are permitted by the  
382 CODEX guidelines, which reads “3.5 Minerals (including trace elements), vitamins, essential fatty and

383 amino acids, and other nitrogen compounds. Only approved in so far as their use is legally required in the  
384 food products in which they are incorporated.”

385

### 386 **European Economic Community (EEC) Council Regulation**

387 “Minerals (trace elements included), vitamins, aminoacids, and micronutrients” are permitted by EC  
388 Regulation No. 889/2008, Article 27, entitled “Use of certain products and substances in processing of  
389 food,” which reads “1.For the purpose of Article 19(2)(b) of Regulation (EC) No 834/2007, only the  
390 following substances can be used in the processing of organic food, with the exception of wine:” . . . “(f)  
391 minerals (trace elements included), vitamins, aminoacids, and micronutrients, only authorised as far their  
392 use is legally required in the foodstuffs in which they are incorporated.”

393

### 394 **The Japan Agricultural Standard (JAS) for Organic Production**

395 Vitamins and minerals are not permitted by Notification No. 1606 of the Ministry of Agriculture, Forestry  
396 and Fisheries of October 27, 2005) (the last revision March, 2012)<sup>5</sup>. There is no entry for nutrient vitamins  
397 and minerals as an approved food additive in Table 1 or as a chemical agent in Table 2.

398

### 399 **The International Federation of Organic Agriculture Movements (IFOAM) Standard<sup>6</sup>**

400 “Minerals, vitamins, essential fatty and amino acids, and other isolated nutrients” are permitted by the  
401 IFOAM Standard, which reads “8.3 Processing and Handling: Organic processing only uses minerals  
402 (including trace elements), vitamins, essential fatty and amino acids, and other isolated nutrients when  
403 their use is legally required or strongly recommended in the food products in which they are  
404 incorporated.”

405

406 Unlike the current NOP regulation and the latest NOP proposal, the other four international regulations  
407 only permit nutrient vitamin and mineral addition when legally required. The European Union standard  
408 and CODEX guidelines restrict vitamin and mineral addition to those uses legally required. The Canadian  
409 and IFOAM standards use language quite similar to that of the 1995 NOSB Final Board Recommendation  
410 in describing permitted uses other than those legally required.

411

412 Each international regulation permitting nutrient addition uniquely defines the classes of nutrients that are  
413 allowed. The Final NOSB Board Recommendation 13 from 1995 is included for illustration purposes.

414

415	NOSB FBR13	Synthetic vitamins, minerals, and/or accessory nutrients
416	Canada:	Minerals (including trace elements), vitamins and similar isolated ingredients
417	IFOAM:	Minerals (including trace elements), vitamins, essential fatty, amino acids, and 418 other isolated nutrients
419	Codex:	Minerals (including trace elements), vitamins, essential fatty and amino acids, and 420 other nitrogen compounds
421	EEC	Minerals (trace elements included), vitamins, amino acids, and micronutrients

422

## 423 **Evaluation Questions for Substances to be used in Organic Handling**

424

425 **Evaluation Question #1: Describe the most prevalent processes used to manufacture or formulate the**  
426 **petitioned substance. Further, describe any chemical change that may occur during manufacture or**  
427 **formulation of the petitioned substance when this substance is extracted from naturally occurring plant,**  
428 **animal, or mineral sources (7 U.S.C. § 6502 (21)).**

429

430 According to Vandamme (Vandamme 1992), “vitamins are now either prepared chemically or  
431 biotechnologically via fermentation or bioconversion processes. Several vitamins and related biofactors are  
432 now (1992) only or mainly produced chemically (vitamin A, cholecalciferol (D3), tocopherol (E), vitamin  
433 K2, thiamine (B1), niacin (PP or B3), pantothenic acid (B5), pyridoxine (B6), biotin (H or B8), folic acid (B9))

<sup>5</sup> [http://www.maff.go.jp/e/jas/specific/pdf/834\\_2012-3.pdf](http://www.maff.go.jp/e/jas/specific/pdf/834_2012-3.pdf). Accessed 3 November 2014.

<sup>6</sup> <http://www.ifoam.org/standard/norms/cover.html>

434 or via extraction processes ( $\beta$ -carotene or provitamin A, provitamin D3, tocopherol, vitamin F-group).  
 435 However, for several of these compounds microbiological or algal methods also exist or are rapidly  
 436 emerging. Other vitamins are produced practically exclusively via fermentation (ergosterol or provitamin  
 437 D2, riboflavin (B2), cyanocobalamin (B12), orotic acid (B13), vitamin F-group<sup>7</sup>, ATP, nucleosides,  
 438 coenzymes, etc.] or via microalgal culture ( $\beta$ -carotene, E, F). Both chemical and microbial processes are run  
 439 industrially for vitamin B2, while vitamin C (ascorbic acid) is produced via a combination of chemical  
 440 reactions and fermentation processes.”

441  
 442 In the past twenty-five years, numerous patents have been issued disclosing fermentations by genetically  
 443 modified microorganisms to produce various water-soluble vitamins (see below).  
 444

445 **Fat-Soluble Vitamins**

446

	Substance	Manufacturing Description
Vitamin A	Vitamin A (retinol)	Vitamin A (retinol) is extracted from fish liver oils or produced by total synthesis from [beta]-ionone and a propargyl halide. [21 CFR 184.1930(a)(1)]
	Vitamin A acetate	Vitamin A acetate is the acetate ester of retinol. It is prepared by esterifying retinol with acetic acid. [21 CFR 184.1930(a)(2)]
	Vitamin A palmitate	Vitamin A palmitate is the palmitate ester of retinol. It is prepared by esterifying retinol with palmitic acid. [21 CFR 184.1930(a)(3)]
	Beta-carotene	Beta-carotene is synthesized by saponification of vitamin A acetate. The resulting alcohol is either reacted to form vitamin A Wittig reagent or oxidized to vitamin A aldehyde. Vitamin A Wittig reagent and vitamin A aldehyde are then reacted together to form beta-carotene. [21 CFR 184.1245]
Vitamin D	Vitamin D2	Crystalline vitamin D2 is produced by ultraviolet radiation of ergosterol isolated from yeast and related fungi and is purified by crystallization. [21 CFR 184.1950(a)(1)]
	Vitamin D3	Crystalline vitamin D3 occurs in, and is isolated from, fish liver oils. It is also manufactured by ultraviolet radiation of 7-dehydrocholesterol produced from cholesterol. It is purified by crystallization. Vitamin D3 is the vitamin D form that is produced endogenously in humans through sunlight activation of 7-dehydrocholesterol in the skin. [21 CFR 184.1950(a)(2)] Vitamin D3 also appears to be biosynthesized by lichen (Wang et al. 2001).
	Vitamin D2 resin	Vitamin D2 resin is the concentrated form of radiated ergosterol (D2) that is separated from the reacting materials produced by ultraviolet radiation of ergosterol. The resulting product is sold as a food source of vitamin D without further purification. [21 CFR 184.1950(a)(3)]
	Vitamin D3 resin	“7-dehydrocholesterol is radiated with ultraviolet light to give pre vitamin D3. Some isomers of vitamin D are formed during ultraviolet radiation (tachysterol and lumisterol), resulting in a mixture of the pre vitamin D, these isomers and 7-dehydrocholesterol (80%). The 7-dehydrocholesterol is removed by crystallization from methanol; the methanol is removed leaving a mixture of pre vitamin D, lumisterol and tachysterol. The mixture is heated to convert the pre vitamin to vitamin D. This material is in the form of a resin that melts at about room temperature and usually has a potency of 25,000,000 to 30,000,000 International Units per gram.” (AGD Nutrition)
Vitamin E	Tocopherols	Mixed tocopherols are isolated from edible vegetable oils through molecular distillation, solvent extraction, or absorption chromatography, obtained by vacuum steam distillation of edible vegetable oil products [21 CFR 184.1890], or isolated from wheat germ (Budavari 1996).

<sup>7</sup> Omega-3 and omega-6 essential fatty acids.

	Alpha-tocopherol acetate	The natural d form of alpha-tocopherol is more active than its synthetic dl-alpha-tocopherol racemic mixture. [21 CFR 182.8892] Alpha-tocopherol and alpha-tocopherol acetate can be synthesized <i>de novo</i> by cyclocondensation of trimethylhydroquinone with phytol or isophytol in the presence of an acid catalyst and of an inert solvent, with subsequent acetylation to form the acetate ester (Lowack et al. 1996).
Vitamin K	Phylloquinone (Vitamin K1)	Plants naturally produce phylloquinone. Phylloquinone was first synthesized in 1939. The starting materials were menadione or menadiol as the aromatic component, and natural phytol or one of its derivatives. In the 1950s, it was found that monoacylated menadiols (e.g., the monoacetate or the monobenzoate) could be used in the alkylation step and that natural phytol could be replaced by isophytol, which is easy to synthesize. A later improvement was to react 2-methyl-1,4-naphthohydroquinone with phytol to form the critical intermediate (Wendler 1958). In the major commercial process, menadione is first subjected to a Diels-Alder reaction with cyclopentadiene. After treatment with a strong base, the resulting enolate is alkylated with phytol bromide. On heating in toluene, it decomposes rapidly into vitamin K1 and cyclopentadiene. The cyclopentadiene can be recovered by distillation and reused.
	Menaquinone(s) (Vitamin K2)	Vitamins K2 (menaquinones) can be synthesized according to the same scheme as phylloquinone.
	Menaquinone 4	Different microorganisms produce Vitamin K2 (menaquinones) in fermentation, with various side-chain lengths (MK-4, MK-5, MK-7, etc.).
	Menaquinone 6	
	Menaquinone 7	Synthetic menaquinone 7 ("MK-7") is produced as described above. The richest dietary source of natural Vitamin K2 is "natto," a traditional Japanese food made from soybeans fermented with <i>Bacillus subtilis var. natto</i> . A proprietary multistep process of purification, condensation and crystallization of fermentation-derived K2 yields a Vitamin K2 product that is more than 95% pure natural menaquinone-7, customarily referred to as "MK-7" (Nattopharma ASA 2014).
Other carotenoids	Lutein	Lutein is the yellow pigment in marigolds. Lutein is obtained from marigold ( <i>Tagetes erecta</i> ) flowers that are dried, milled, and subjected to solvent extraction and filtration, and subsequent crystallization from alcohol. [GRN 140] Another process for obtaining lutein also starts with dried marigold ( <i>Tagetes erecta</i> ) flowers. The flowers are subjected to solvent extraction with hexane to isolate an oleoresin. The oleoresin is then subjected to saponification with potassium hydroxide and 1-propanol. Following saponification, the contents are washed with ethyl acetate, extracted with hexane, and then filtered. The wet cake is washed with ethanol, filtered, and dried under vacuum to remove the remaining organic solvents. The resulting dried concentrate consists of lutein and zeaxanthin. [GRN 385] Tocopherols are added as antioxidants in all carotenoid materials to prevent oxidation and loss of biological activity.
	Lycopene	Lycopene is the red pigment of tomatoes. A crystallized tomato lycopene extract can be prepared from tomatoes by a patented ethyl acetate extraction process. [GRN 156] Lycopene can be produced by fermentation of <i>Blakeslea trispora</i> , through a co-fermentation process using the two sexual mating types of the organism. Lycopene is extracted from the fungal cells and crystallized. [GRN 173] Lycopene can be produced synthetically in a three-stage process. Stage one produces an organic solution of C15 phosphonium methanesulfonate in dichloromethane (DCM). Stage two produces an organic solution of C10 dialdehyde in toluene. In stage three, the intermediates produced in stages

		one and two are gradually combined with sodium methoxide solution and undergo a condensation reaction to form crude lycopene. Glacial acetic acid and deionized water are added, the mixture is stirred vigorously, the aqueous and organic phases are allowed to separate, and the organic phase containing DCM and crude lycopene is extracted with water. Methanol is added to the organic phase, DCM is removed via distillation under reduced pressure, the crude methanolic lycopene solution is heated and then cooled to form a crystalline slurry that is filtered and washed with methanol. The lycopene crystals are then recrystallized and dried under heated nitrogen. [GRN 119] Tocopherols are added as antioxidants in all carotenoid materials to prevent oxidation and loss of biological activity.
	Zeaxanthin	Zeaxanthin is the yellow pigment of corn ("Zea mays"). The manufacturing process for zeaxanthin starts with dried marigold ( <i>Tagetes erecta</i> ) flowers, which are washed with water, dried, ground, and then pelletized with steam. These pellets are extracted with hexane. The hexane is removed by evaporation under vacuum, yielding an oleoresin. The oleoresin is washed with an alkali solution, followed by dilute acid solutions to remove impurities, such as fatty acids, waxes, gums, and other plant materials. The oleoresin is then saponified using aqueous potassium hydroxide to free the xanthophylls and initiate the isomerization of lutein to zeaxanthin. The pH of the isomerized extract is adjusted and the product is washed with water and then further extracted with a solvent blend (hexane, acetone, and methanol). The solvents are removed using evaporation under vacuum and heat. [GRN 481] The synthetic all-trans isomer of zeaxanthin is produced by the Wittig condensation from synthetic intermediates commonly used in the production of other carotenoids with application in foods (Stankovic and Valente Soares 2006). Tocopherols are added as antioxidants in all carotenoid materials to prevent oxidation and loss of biological activity.

447  
448  
449

**Water-soluble Vitamins**

	Substance	Manufacturing Description
Vitamin C	Ascorbic acid	Ascorbic acid produced by major American manufacturers is synthesized by the Reichstein process, a six-step process. D-glucose is hydrogenated to D-sorbitol. D-sorbitol is oxidized by microbiological fermentation to produce L-sorbose. L-sorbose is reacted with acetone to form the 2,3:4,6-bis-diacetone-L-sorbose, which is oxidized to di-acetone-ketogulonic acid (2-KLGA) and then rearranged by treatment with hydrogen chloride to yield ascorbic acid. [1995 Tap review]  In a two-stage process developed in China, the chemical reactions of the Reichstein process that convert L-sorbose to 2-KLGA are replaced by a second fermentation (Ning et al., 1988; Yin et al., 2001). The 2-KLGA is then chemically processed to L-AA. This process is used by all Chinese producers (Bremus et al., 2006).  Total fermentation processes involving GM organisms are being studied but apparently have not yet been commercialized (Soetaert and Vandamme 2006).
	Ascorbyl palmitate	Ascorbic acid is esterified with sulfuric acid. The product of that reaction is esterified with palmitic acid. In practice, equimolar concentrations of ascorbic acid and palmitic acid are combined in a sulfuric acid solution and left at room temperature for 16-24 hours. The resulting ascorbyl palmitate is recovered and purified through a recrystallization process. (ICF International 2012)
	Calcium ascorbate	Ascorbic acid and calcium carbonate are reacted in water. Calcium ascorbate is precipitated by adding acetone or alcohol (Budavari 1996).



	Sodium ascorbate	Ascorbic acid is dissolved in water and an equivalent amount of sodium bicarbonate is added. After cessation of effervescence, the sodium ascorbate is precipitated by the addition of isopropyl alcohol (Budavari 1996).
Thiamin (B1)	Thiamine hydrochloride	Thiamine hydrochloride is prepared by linking the preformed thiazole and pyrimidine ring systems. [21 CFR 184.1875] 5-(beta-hydroxyethyl)-4-methylthiazole is reacted with 2-methyl-4-amino-5-bromomethylpyrimidine, hydrogen bromide salt. The resulting thiamine bromide hydrobromide is converted to thiamine hydrochloride by treatment with silver chloride in methanol, an ion-exchange resin, or hydrochloric acid.
	Thiamine mononitrate	Thiamine mononitrate is prepared from thiamine hydrochloride by dissolving the hydrochloride salt in alkaline solution followed by precipitation of the nitrate half-salt by adding a stoichiometric amount of nitric acid. [21 CFR 184.1878] Thiamine also can be produced by GM bacterial fermentation (Goese, Perkins, and Schyns 2010).
Riboflavin (B2)	Riboflavin	Riboflavin may be prepared by chemical synthesis from 3,4-xylydine, D-ribose, and barbituric acid; biosynthetically by the microorganisms <i>Bacillus subtilis</i> , the ascomycetes <i>Eremothecium ashbyii</i> and <i>Ashbya gossypii</i> , and the yeasts <i>Candida flareri</i> and <i>Saccharomyces cerevisiae</i> ; or isolated from natural sources. The majority of the riboflavin produced by fermentation is used in animal feeds (Moine et al. 2011). High purity riboflavin for human use once was chemically synthesized. Chemical riboflavin production is being replaced by microbial processes to reduce the cost by half, reduce waste and energy requirements, and use renewable resources like sugar or plant oil. Three microorganisms are currently in use for industrial riboflavin production. Some of these are genetically engineered (Stahmann, Revuelta, and Seulberger 2000). Riboflavin produced by GM organisms has a 40% lower production cost than riboflavin produced by chemical synthesis (Soetaert and Vandamme 2006).
	Riboflavin-5 phosphate sodium salt	Riboflavin-5'-phosphate (sodium) is prepared by phosphorylation of riboflavin with chlorophosphoric acid, pyrophosphoric acid, metaphosphoric acid, or pyrocatechol cyclic phosphate. [21 CFR 184.1697]
Niacin	Niacin (nicotinic acid)	Nicotinic acid is formed by the oxidation of nicotine. [21 CFR 184.1535] Other production processes include preparation by oxidation of alkyl beta-substituted pyridines (the raw materials 5-ethyl-2-methylpyridine and 3-methylpyridine (3-picoline)); oxidation of nicotine, quinoline, or 2-methyl-5-ethylpyridine (from ammonia and formaldehyde or acetaldehyde); decarboxylation of isocinchomeric acid; base-catalyzed hydrolysis of nicotinonitrile; nitric acid oxidation of 5-ethyl-2-methylpyridine; and the reaction of paraldehyde with ammonia to form 5-ethyl-2-methylpyridine and subsequent oxidation with nitric acid.
	Niacinamide	Niacinamide is the amide of nicotinic acid. [21 CFR 184.1537] It is formed by esterifying nicotinic acid with methanol, followed by reaction with ammonia.
	Aluminum nicotinate	Aluminum nicotinate is prepared by dissolving nicotinic acid in hot water and adding aluminum hydroxide. The precipitate is separated and dried (Miale 1961).
	Nicotinamide-ascorbic acid complex	A mixture of equimolar amounts of nicotinamide and ascorbic acid is moistened with suitable solvents such as water, acetone, or various alcohols to accomplish the reaction. The solvents are removed to reduce the resulting product to the dry form (Fox and Paterson 1947).

Vitamin B6	Pyridoxine hydrochloride	Pyridoxine hydrochloride is prepared by chemical synthesis. [21 CFR 184.1676] Ethyl pyruvate, sodium bisulfite, sodium cyanide and ethyl glycinate are reacted to form ethyl- $\alpha$ -carbethoxy methylamino- $\alpha$ -methylcyanoacetate, which is reacted with 1,4-dimethoxybutanone-2 to form 2- methyl-3-hydroxy-4,5-bismethoxymethyl-6-carbethoxypyridine. This latter compound is acidified with dilute hydrochloric acid and heated in an autoclave at elevated temperatures to form pyridoxine hydrochloride (Pollak 1962). Other processes involve condensation of cyanoacetamide and ethoxyacetylacetone or synthesis from 2-butanone-1,4-diol and $\alpha$ -methyliminopropionitrile (Stevens 1954).
Folate	Folic acid (folacin)	Folic acid consists of a pteridine nucleus (containing two rings), conjugated with para-aminobenzoic acid and glutamic acid. A ten-step reaction sequence starting with 1,2-dihalo-1,3,3-trialkoxy propanes, 1,2-dihalo-1,3,3-triaryloxy propanes, and a 2,4,5-triamino pyrimidine substituted in the 6 position with a hydroxyl, alkoxy, aryloxy, or araloxy radical, form the 2-amino-5,6-dihydropteridine portion of folic acid that is reacted with N-(p-aminobenzyl) glutamic acid (Sletzinger and Tishler 1958). GM microorganisms are being developed for complete synthesis of folic acid from glucose and salts (Zhu et al. 2005).
Vitamin B12	Vitamin B12 (cyano-cobalamin)	Virtually all dietary vitamin B12 originates from microbial synthesis in the rumen of herbivores (Underwood 1977). Microbial production has become the sole method for producing vitamin B12 (Kanga et al. 2012). Vitamin B12 is produced commercially from cultures of <i>Streptomyces griseus</i> , <i>Pseudomonas denitrificans</i> , and <i>Propionibacterium freudenreichii</i> subsp. <i>shermanii</i> . Some manufacturers use microorganisms altered by classical mutation-generating techniques whereas others use genetically engineered microorganisms (Kanga et al. 2012). Cobalamins (cobalt-containing compounds) in the fermentation broth are converted to the more stable “cyanocobalamin” by adding potassium cyanide in the presence of sodium nitrite and heat during the extraction process.
Pantothenic acid	Calcium pantothenate	Commercial calcium pantothenate is prepared synthetically from isobutyraldehyde and formaldehyde via 1,1-dimethyl-2-hydroxy-propionaldehyde and pantolactone. [21 CFR 184.1212] Calcium pantothenate also can be prepared by the reaction of $\beta$ -alanine, calcium oxide and $\alpha$ -hydroxy- $\beta$ , $\beta$ -dimethyl- $\gamma$ -butyrolactone (Brooks 1960). Pantothenic acid can be produced by fermentation of a GM bacterium (Lothar and Hermann 2002).
	Calcium pantothenate-calcium chloride double salt	Calcium pantothenate and calcium chloride are separately dissolved in methanol. The two solutions are mixed and heated to reflux temperature for two hours. The double-salt precipitate is separated and dried (Lekberg 1977).
	D-pantothenamide	$\alpha$ , $\gamma$ -dihydroxy- $\beta$ , $\beta$ -dimethyl- $\gamma$ -butyrolactone is mixed with $\beta$ -alaninamide at room temperature, the reaction mixture is allowed to stand for sufficient time to complete formation of pantothenamide, and the product thus formed is recovered (Bentel 1965).
Biotin	Biotin	Biotin is synthesized chemically by a 14-step chemical synthesis involving the gas phosgene (Goldberg 1949). A commercially important goal for vitamin manufacturers serving the general market is applying genetic engineering technology to achieving an improvement in biotin production by microorganisms (Brown and Kamogawa 1991).
Choline	Choline bitartrate	The dominating industrial process for choline is reacting ethylene oxide with trimethylamine and water, or an acid if one of its salts is desired, in a batch or continuous manufacturing process (Atwater 2003). The tartaric acid salt is formed by neutralizing choline base or its carbonate with tartaric acid.

	Choline chloride	Choline chloride is synthesized from ethylene oxide, hydrochloric acid, and trimethylamine (Budavari 1996).
Inositol	Inositol	Inositol ( <i>myo</i> -inositol) occurs naturally and is prepared from corn steep liquor by precipitation of crude phytate, which is enzymatically hydrolyzed to <i>myo</i> -inositol. [21 CFR 184.1370]

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**Trace Mineral Elements**

Substance	Manufacturing Description
Chromium (III) picolinate	Chromium picolinate is obtained synthetically from the combination of picolinic acid and potassium chromium sulfate in an aqueous solution. The starting chromium (III) material product is controlled for the presence of chromium (VI) and of other contaminants. No chromium (VI) is detected (European Food Safety Authority 2010a). Note: Picolinic acid is a natural metabolite of the essential amino acid tryptophan. Picolinic acid is an isomer of nicotinic acid (the vitamin “niacin”).
Chromium (III) chloride	The primary chromium ore is the mixed metal oxide chromite, FeCr <sub>2</sub> O <sub>4</sub> . Chromite ore is heated with a mixture of calcium carbonate and sodium carbonate in the presence of air. The chromium is oxidized to the hexavalent chromate (VI) form, while the iron forms iron (III) oxide. Subsequent leaching at higher temperatures dissolves the chromate and leaves the insoluble iron oxide. The chromate is treated with hydrochloric acid and methanol to produce hydrated chromium (III) chloride. (Papp and Lipin 2006)
Copper gluconate	Copper gluconate is prepared from gluconic acid and basic cupric carbonate (Budavari 1996). Basic cupric carbonate is prepared by mixing a solution of copper sulfate with a solution of sodium carbonate (Budavari 1996).
Cuprous iodide	Copper (I) iodide is prepared by heating iodine and copper in concentrated hydriodic acid. [21 CFR 184.1265]
Copper sulfate	Copper (II) sulfate is produced industrially by treating copper metal with hot concentrated sulfuric acid or copper oxides with dilute sulfuric acid. [21 CFR 184.1261]
Potassium iodide	Nonsynthetic: Potassium iodide occurs naturally in sea water and in salt deposits. Synthetic: Potassium iodide can be produced by reacting hydriodic acid with potassium bicarbonate or by electrolysis of hydriodic acid and potassium bicarbonate or, industrially, by treating potassium hydroxide with iodine. [21 CFR 184.1634]
Ferric ammonium citrate	Ferric ammonium citrate is prepared by adding ferric hydroxide to an aqueous solution of citric acid and ammonia (Perry 2011). [21 CFR 184.1296]
Ferric chloride	Ferric (III) chloride can be prepared from iron and chlorine, or from ferric oxide and hydrogen chloride. [21 CFR 1184.1297]
Ferric citrate	Ferric citrate can be produced by the reaction of ferric hydroxide with citric acid. [21 CFR 184.1298] Commercial ferric citrate is a combination of iron and citric acid of indefinite composition (Budavari 1996).
Ferric phosphate	Ferric phosphate can be prepared by the reaction of sodium phosphate with ferric chloride or ferric citrate. [21 CFR 184.1301] Pharmaceutical-grade ferric citrate can be produced by mixing solid citric acid and a solid ferric salt to form a mixture, adding alcohol to the mixture, and filtering the mixture to obtain solid pharmaceutical-grade ferric citrate (Hsiao et al. 2005).
Ferric pyrophosphate	Ferric pyrophosphate is produced by adding an aqueous solution of sodium pyrophosphate to an aqueous solution of ferric chloride or ferric citrate. [21 CFR 184.1304] The precipitate is insoluble ferric pyrophosphate, which is

	separated and dried.
Ferric sulfate	Iron (III) sulfate is produced on a large scale by reacting sulfuric acid, a hot solution of ferrous sulfate, and an oxidizing agent such as nitric acid or hydrogen peroxide, or by treating ferric oxide or ferric hydroxide with sulfuric acid [21 CFR 184.1307].
Ferrous ascorbate	Ferrous ascorbate is formed by reacting ferrous hydroxide and ascorbic acid. [21 CFR 184.1307a]
Ferrous carbonate	Ferrous carbonate is prepared by treating solutions of iron (II) salts with alkali carbonate salts (e.g., sodium carbonate). [21 CFR 184.1307b]
Ferrous citrate	Ferrous citrate can be prepared by reacting iron and citric acid, or ferrous sulfate and sodium citrate. [21 CFR 184.1307c]
Ferrous fumarate	Ferrous fumarate is prepared by adding a hot aqueous solution of sodium fumarate to a hot ferrous sulfate solution. Ferrous fumarate precipitates. The resulting slurry is separated by filtration. [21 CFR 184.1307d]
Ferrous gluconate	Ferrous gluconate is prepared by reacting barium gluconate and ferrous sulfate. The insoluble barium sulfate precipitates, yielding a ferrous gluconate solution, which is dried. It also can be prepared by heating freshly prepared ferrous carbonate with gluconic acid in aqueous solution. [21 CFR 184.1308]
Ferrous lactate	Ferrous lactate is prepared by interaction of calcium lactate or sodium lactate with ferrous sulfate, or by direct action of lactic acid on iron filings. [21 CFR 184.1311]
Ferrous sulfate	Ferrous sulfate is made by reacting sulfuric acid with iron. [21 CFR 184.1315]
Elemental iron Three kinds of elemental iron are used for food fortification: reduced iron; electrolytic iron; and carbonyl iron.	<b>Reduced iron</b> is made by reduction of ground iron oxide with hydrogen or carbon monoxide at an elevated temperature. <b>Electrolytic iron</b> powder is produced by electrolytic deposition using chemically pure iron anodes, a ferrous sulfate bath, and thin stainless steel cathode sheets onto which the iron migrates. <b>Carbonyl iron</b> is produced by treating iron with carbon monoxide to produce iron pentacarbonyl, which is subsequently decomposed under controlled conditions to yield an iron powder and carbon monoxide (Patrick 1973).
Manganese chloride	Manganese (II) chloride is produced by treating manganese (IV) oxide with concentrated hydrochloric acid. [21 CFR 184.1446]
Manganese citrate	Manganese citrate is produced by the action of citric acid on manganese hydroxide or manganese carbonate. [21 CFR 184.1449]
Manganese gluconate	Manganese gluconate is formed by reacting manganese carbonate with gluconic acid. [21 CFR 184.1452]
Manganese sulfate	Manganese sulfate is produced by treating manganese compounds with sulfuric acid. [21 CFR 184.1461]
Ammonium heptamolybdate	Ammonium heptamolybdate is prepared by dissolving molybdenum trioxide in an excess of aqueous ammonia and evaporating the solution at room temperature (Sax and Lewis 1987).
Sodium molybdate dihydrate	Sodium molybdate is produced by dissolving molybdenum (IV) oxide in sodium hydroxide at 50–70 °C and crystallizing the filtered product (Braithwaite and Haber 1994).
Sodium selenate	The primary method of isolating sodium selenate is to dissolve metallic selenium in nitric acid, producing selenious acid. The selenious acid is then treated with sodium hydroxide or sodium carbonate to form sodium selenite. Next, the selenite is oxidized in a basic environment with hydrogen peroxide to form sodium selenate (Bjornberg, Martensson, and Paulsson 1986).
Sodium selenite	Sodium selenite can be prepared by evaporating an aqueous solution of sodium hydroxide and selenious acid between 60 and 100 °C; by heating a mixture of sodium chloride and selenium oxide; and by neutralizing

	selenious acid with sodium carbonate (Bjornberg, Martensson, and Paulsson 1986).
Zinc sulfate	Zinc sulfate is produced by treating zinc (including zinc-bearing ore) with aqueous sulfuric acid. Pharmaceutical grade zinc sulfate is produced by reacting high purity zinc oxide with sulfuric acid.
Zinc chloride	Zinc chloride is readily prepared similarly by treating zinc metal with hydrochloric acid or by reacting zinc oxide or zinc sulfide with hydrochloric acid.
Zinc gluconate	Zinc gluconate can be produced by reacting gluconic acid with zinc oxide or by reacting sodium, ammonium, or calcium gluconate with zinc oxide.
Zinc oxide	The most common process for producing zinc oxide involves melting metallic zinc in a graphite crucible where the zinc vaporizes at temperatures above 907 °C (typically around 1000 °C). Zinc vapor reacts with the oxygen in the air to produce zinc oxide. The zinc oxide particles are transported through a cooling duct and collected.
Zinc stearate	Zinc stearate is prepared by adding a hot solution of zinc chloride to a hot solution of the sodium salt of the fatty acid stearic acid (Budavari 1996). The insoluble zinc stearate separates out.

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**Major Minerals in Bone: Calcium, Phosphorus, Magnesium, and Fluoride**

Substance	Manufacturing Description
Calcium carbonate	Calcium carbonate is prepared by three common methods of manufacture: (1) as a byproduct in the "Lime soda process" (adding lime (calcium oxide) and sodium carbonate to hard water precipitates calcium as the carbonate); (2) by precipitation of calcium carbonate from calcium hydroxide in the "Carbonation process"; or (3) by precipitation of calcium carbonate from calcium chloride in the "Calcium chloride process." [21 CFR 184.1191]
Calcium chloride	Calcium chloride may be commercially obtained as a byproduct in the ammonia-soda (Solvay) process, and as a joint product from natural salt brines, or it may be prepared by substitution reactions with other calcium and chloride salts. [21 CFR 184.1193]
Calcium citrate	Calcium citrate is prepared by neutralizing citric acid with calcium hydroxide or calcium carbonate. [21 CFR 184.1195]
Calcium glycerol phosphate	Calcium glycerol phosphate is prepared by neutralizing glycerophosphoric acid with calcium hydroxide or calcium carbonate. [21 CFR 184.1201]
Calcium hydroxide	Calcium hydroxide is produced by the hydration of lime (calcium oxide). [21 CFR 184.1205]
Calcium lactate (not GRAS for infants)	Calcium lactate is prepared commercially by the neutralization of lactic acid with calcium carbonate or calcium hydroxide. [21 CFR 184.1207]
Calcium oxide	Calcium oxide is produced from calcium carbonate, limestone, or oyster shells by calcination at temperatures of 1,700-2,450 °F. [21 CFR 184.1210]
Calcium sulfate, anhydrous	Calcium sulfate, also known as plaster of Paris, anhydrite and gypsum, occurs naturally and exists as a fine, white to slightly yellow-white odorless powder. The anhydrous form is prepared by complete dehydration of gypsum, below 300 °C, in an electric oven. [21 CFR 184.1195]
Calcium sulfate, dihydrate	
Calcium phosphate	Monocalcium phosphate [Ca(H <sub>2</sub> PO <sub>4</sub> ) <sub>2</sub> ], food grade, is produced by treating calcium hydroxide with phosphoric acid. Dicalcium phosphate [CaHPO <sub>4</sub> ] is produced by the reaction of phosphoric acid, calcium chloride, and sodium hydroxide. Calcium carbonate can be used in place of the calcium chloride and sodium hydroxide.

	<p>Tricalcium phosphate [Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>] occurs naturally in several forms, but purified material appropriate for food use is prepared from phosphoric acid and calcium hydroxide.</p> <p>Tricalcium phosphate has an “excellent” calcium-to-phosphorus ratio of almost 2:1, but is extremely insoluble in water. In liquid nutritional formulations, added calcium phosphate quickly settles out in mix tanks, in piping, and ultimately in the final package, resulting in substantial quantitative loss of calcium phosphate during processing, and formation of a poorly dispersible layer of mineral at the bottom of the final container. To avoid these problems, calcium phosphate is formed <i>in situ</i> as a colloidal, hydrated gel, by adding concentrated phosphoric acid to a dilute solution of calcium hydroxide at a uniform and slow enough rate so that the pH of the reaction mixture is maintained above about 7 (Lin and Cho 1987).</p>
Calcium pyrophosphate	Calcium pyrophosphate is prepared by ignition of dicalcium phosphate (Budavari 1996).
Phosphoric acid	Phosphoric acid is produced by treating phosphate rock (tricalcium phosphate) with sulfuric acid, forming phosphoric acid and calcium sulfate (Budavari 1996).
Magnesium carbonate	Magnesium carbonate is also known as magnesium carbonate hydroxide. It is a white powder formed either by adding an alkaline carbonate (such as sodium carbonate) to a solution of magnesium sulfate, or by carbonation of a slurry of magnesium hydroxide followed by boiling of the resulting magnesium carbonate. [21 CFR 184.1425]
Magnesium chloride	Magnesium chloride occurs naturally as the mineral bischofite. It is recovered from natural brines, especially Great Salt Lake brines, and sea water brines by concentration (evaporation), followed by fractional crystallization. It is prepared synthetically by dissolving magnesium oxide, hydroxide, or carbonate in aqueous hydrochloric acid solution and crystallizing out magnesium chloride hexahydrate. [21 CFR 184.1426]
Magnesium hydroxide	Magnesium hydroxide occurs naturally as the colorless, crystalline mineral brucite. It is prepared synthetically by the addition of sodium hydroxide to a water-soluble magnesium salt or by hydration of reactive grades of magnesium oxide. [21 CFR 184.1428]
Magnesium oxide	Magnesium oxide occurs naturally as the colorless, crystalline mineral periclase. It is produced synthetically either as a bulky white powder (light) or a relatively dense white powder (heavy) by heating magnesium hydroxide or carbonate. Heating these magnesium salts under moderate conditions (400° to 900 °C for a few hours) produces light magnesium oxide. Heating the salts under more rigorous conditions (1200 deg. C for 12 hours) produces heavy magnesium oxide. Light magnesium oxide is converted to heavy magnesium oxide by sustained heating at high temperatures. [21 CFR 184.1431]
Magnesium phosphate, dibasic	Magnesium phosphate, dibasic, occurs naturally as the white, crystalline mineral newberyite. It is prepared commercially as a precipitate formed by treating a solution of magnesium sulfate with disodium phosphate under controlled conditions. [21 CFR 184.1434]
Magnesium phosphate, tribasic	Magnesium phosphate, tribasic, may contain 4, 5, or 8 molecules of water of hydration. It is produced as a precipitate from a solution of magnesite with phosphoric acid. [21 CFR 184.1434]
Magnesium sulfate	Magnesium sulfate occurs naturally as the mineral epsomite. It is prepared synthetically by neutralizing magnesium oxide, hydroxide, or carbonate with sulfuric acid and evaporating the solution to crystallization. [21 CFR 184.1443]

Sodium fluoride	Sodium fluoride is prepared by fusing the mineral cryolite (sodium hexafluoroaluminate) with sodium hydroxide, or by adding sodium hydroxide or sodium carbonate to concentrated hydrofluoric acid.
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**Major Electrolyte Minerals**

Substance	Manufacturing Description
Potassium acid tartrate	Potassium bitartrate, known as ‘cream of tartar,’ is obtained naturally from the lees of wine (Budavari 1996).
Potassium bicarbonate	Potassium bicarbonate is made by treating a solution of either potassium hydroxide or potassium carbonate with carbon dioxide. [21 CFR 184.1613]
Potassium carbonate	Potassium carbonate is produced by the following methods of manufacture: (1) by electrolysis of potassium chloride followed by exposing the resultant potassium to carbon dioxide; (2) by treating a solution of potassium hydroxide with excess carbon dioxide to produce potassium carbonate; and (3) by treating a solution of potassium hydroxide with carbon dioxide to produce potassium bicarbonate, which is then heated to yield potassium carbonate. [21 CFR 184.1619]
Potassium chloride	Potassium chloride is a white, odorless solid prepared from source minerals by fractional crystallization or flotation. [21 CFR 184.1622]
Potassium citrate	Potassium citrate is prepared by neutralizing citric acid with potassium hydroxide or potassium carbonate. [21 CFR 184.1625]
Potassium hydroxide	Potassium hydroxide is obtained commercially from the electrolysis of potassium chloride solution in the presence of a porous diaphragm. [21 CFR 184.1631]
Dipotassium phosphate	All of the orthophosphate derivatives of potassium can be generated by neutralization of phosphoric acid with potassium hydroxide (Budavari 1996).
Sodium bicarbonate	Sodium bicarbonate is prepared by treating a sodium carbonate or a sodium carbonate and sodium bicarbonate solution with carbon dioxide. As carbon dioxide is absorbed, a suspension of sodium bicarbonate forms. The slurry is filtered, forming a cake which is washed and dried. [21 CFR 184.1736]
Sodium carbonate	Sodium carbonate is produced (1) from purified trona ore that has been calcined to soda ash; (2) from trona ore calcined to impure soda ash and then purified; or (3) synthesized from limestone by the Solvay process. [21 CFR 184.1742]
Sodium chloride (salt)	Sodium chloride is produced from seawater evaporation or from salt mines.
Sodium citrate dihydrate	Sodium citrate is prepared by neutralizing citric acid with sodium hydroxide or sodium carbonate. [21 CFR 184.1751]
Sodium hydroxide	Sodium hydroxide is prepared commercially by electrolyzing a sodium chloride solution or by reacting calcium hydroxide with sodium carbonate. [21 CFR 184.1763]
Sodium acid phosphate	All of the orthophosphate derivatives of sodium can be generated by neutralizing phosphoric acid with sodium hydroxide (Budavari 1996).
Disodium phosphate	
Sodium phosphate, tribasic	
Hydrochloric acid	Hydrogen chloride is produced by the action of sulfuric acid on salt (sodium chloride) or by reacting salt, sulfur dioxide, oxygen, and water. Dissolving hydrogen chloride (gas) in water forms hydrochloric acid (Budavari 1996).

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460 **Evaluation Question #2: Discuss whether the petitioned substances are formulated or manufactured by**  
 461 **a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)). Discuss**  
 462 **whether the petitioned substance is derived from an agricultural source.**  
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464 As the above descriptions detail, most vitamin and mineral nutrients are synthetic substances, even  
 465 including some with natural or agricultural origins.  
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467 The compound *myo*-Inositol is derived from the phytic acid of corn. Phytic acid is present in sulfited corn  
 468 steep liquor. Phytic acid can be precipitated and treated with phytase enzyme to free the inositol of  
 469 phosphoric acid. Some commercial preparations of lutein and zeaxanthin are commercially produced by  
 470 solvent extraction of marigold petals. Similarly, some commercial preparations of lycopene are extracted  
 471 from tomato pulp. Mixed tocopherols are stripped from vegetable oils during oil refining, by a molecular  
 472 distillation. At elevated temperature and under high vacuum during deodorization, the tocopherols  
 473 become volatile and can be recovered from the distillate. Conversion of tocopherols to tocopherol acetate or  
 474 palmitate is a synthetic process. Similarly, retinol (Vitamin A) isolated from fish liver oil is converted to  
 475 retinol acetate or retinol palmitate by chemical processes. However, much of the retinol for human use is  
 476 produced by total chemical synthesis.  
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478 Fermentation by non-GM microorganisms can be the source of certain vitamins. Vitamin K2 is produced by  
 479 the bacterium *Bacillus subtilis natto* that is used to produce natto from soybeans (Berenjian et al. 2013).  
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481 All the commercial supplies of Vitamin B12 are produced by fermentation of microorganisms (Kanga et al.  
 482 2012). Some manufacturers use microorganisms altered by classical mutation-generating techniques  
 483 whereas others use genetically engineered microorganisms (Kanga et al. 2012).. The extraction process  
 484 involves sodium cyanide and various synthetic solvents. Most riboflavin used in animal feeds is produced  
 485 by fermentation, but riboflavin for human use was usually produced synthetically and now probably by  
 486 GMO fermentation.  
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488 **Evaluation Question #3: If the substance is a synthetic substance, provide a list of nonsynthetic or**  
 489 **natural source(s) of the petitioned substance (7 CFR § 205.600 (b) (1)).**  
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491 Most vitamins and minerals are not available from nonsynthetic sources. See above for more details about  
 492 manufacturing processes. As a broad class, "Nutrient vitamins and minerals" is listed on the National List  
 493 at §205.605(b), "Synthetics allowed." In contrast, potassium iodide and several other substances with  
 494 nutrient activity (see listing below) are on the National List at §205.605(a), "Nonsynthetics allowed." This  
 495 reflects the regulatory response in drafting the organic regulations taken by USDA to implement the  
 496 specific NOSB recommendations that these several nonorganic, nonagricultural substances must be from  
 497 nonsynthetic sources, which is what §205.605(a) lists, and must **NOT** be from synthetic sources.  
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499 The current National List listings creates confusion for those nutrient vitamins and minerals specifically  
 500 listed at §205.605(a), which requires a nonsynthetic source, whereas "Nutrient vitamins and mineral" are a  
 501 class of "allowed synthetics." For example, the producer of a nutritional product may not be sure if  
 502 supplemental magnesium as magnesium sulfate is restricted to a nonsynthetic source.  
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504 Eliminating the listing of these substances from §205.605(a) would permit synthetic forms of these  
 505 substances to be used, since "Nutrient vitamins and mineral" are listed at §205.605(b) "Allowed  
 506 synthetics." This is not consistent with the recommendation of the NOSB for those nutrient-containing  
 507 substances listed at §205.605(a).  
 508

509 The following nonsynthetic sources of nutrient vitamins and minerals are currently listed at § 205.605(a).  
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Substance name	CAS Number	FDA citation(s)
Potassium iodide	7681-11-0	21 CFR 184.1634
Calcium sulfate anhydrous	7778-18-9 (	21 CFR 184.1230



Calcium sulfate dihydrate	10101-41-4	
Magnesium sulfate heptahydrate	10034-99-8 (	21 CFR 184.1443
Potassium chloride	7447-40-7	21 CFR 184.1622
Sodium bicarbonate	144-55-8	21 CFR 184.1736
Sodium carbonate	497-19-8	21 CFR 184.1742

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**Evaluation Question #4: Specify whether the petitioned substance is categorized as generally recognized as safe (GRAS) when used according to FDA’s good manufacturing practices (7 CFR § 205.600 (b)(5)). If not categorized as GRAS, describe the regulatory status.**

All of the substances listed in this Technical Report are generally recognized as safe (“GRAS”). The FDA citations in 21 CFR (Parts 182, 184, or elsewhere) are presented below. GRAS Notices from FDA are identified by “GRN Number.” The European Food Safety Authority published a “GRAS-like” safety review for several of these substances, one<sup>8</sup> of which apparently prompted the supplier’s withdrawal of a submission to FDA (GRN 245) for menaquinone 7, a form of Vitamin K2, given that a positive GRAS determination from an “official” source had been published. Sodium selenate and sodium selenite, used in FDA-regulated fortified foods and nutritional supplements, are cited in an NIH Selenium Dietary Supplement Fact Sheet. Monographs for the molybdate salts are included in the Food Chemicals Codex.

The subparagraph of §205.605 is cited for those substances individually present on the National List as allowed ingredients in or on processed foods labeled as “organic” or “made with organic (specified ingredients or food group(s)).”

**Fat-Soluble Vitamins**

Vitamin	Substance name (s)	CAS No.	FDA citation(s)	National List
Vitamin A	Vitamin A (retinol)	68-26-8	21 CFR 184.1930(a)(1)	
	Vitamin A acetate (retinyl acetate)	127-47-9	21 CFR 184.1930(a)(2)	
	Vitamin A palmitate (retinyl palmitate)	79-81-2	21 CFR 184.1930(a)(3)	
	Beta-carotene	7235-40-7	21 CFR 184.1245	
Vitamin D	Vitamin D2 (ergocalciferol)	50-14-6	21 CFR 184.1950(a)(1)	
	Vitamin D3 (cholecalciferol)	67-97-0	21 CFR 184.1950(a)(2) 21 CFR 172.380	
	Vitamin D2 resin	n/a	21 CFR 184.1950(a)(3)	
	Vitamin D3 resin	n/a	21 CFR 184.1950(a)(3)	
Vitamin E	Tocopherols	1406-66-2	21 CFR 182.8890	205.605(b)
	Alpha-tocopherol acetate	58-95-7	21 CFR 182.8892	205.605(b)
Vitamin K	Phylloquinone (Vitamin K1) (phytomenadione) (phytonadione)	84-80-0	21 CFR 100.107(c)	
	Menaquinone 4 (Vitamin K2) (MK-4)	863-61-6	(European Food Safety Authority 2008)	
	Menaquinone 6 (Vitamin K2) (MK-6)	84-81-1		
Menaquinone 7 (Vitamin K2) (MK-7)	2124-57-4			
Other carotenoids	Lutein	127-40-2	GRN 110, 140, 221, 291, 385, 390, 532	
	Lycopene	502-65-8	GRN 119, 156, 173,	

<sup>8</sup> [http://www.efsa.europa.eu/en/scdocs/doc/nda\\_op\\_ej822\\_vit\\_k2\\_en.pdf?ssbinary=true](http://www.efsa.europa.eu/en/scdocs/doc/nda_op_ej822_vit_k2_en.pdf?ssbinary=true)

			185	
	Zeaxanthin (meso-Zeaxanthin)	144-68-3	GRN 481	

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**Water-Soluble Vitamins**

Vitamin	Substance name(s)	CAS Number	FDA citation(s)	National List
Vitamin C	Ascorbic acid	50-81-7	21 CFR 182.3013 21 CFR 182.8013	205.605(b)
	Ascorbyl palmitate	137-66-6	21 CFR 182.3149	
	Calcium ascorbate	5743-27-1	21 CFR 182.3189	
	Sodium ascorbate	134-03-2	21 CFR 182.3731	
Thiamin (B1)	Thiamine hydrochloride	67-03-8	21 CFR 184.1875	
	Thiamine mononitrate	532-43-4	21 CFR 184.1878	
Riboflavin (B2)	Riboflavin	83-88-5	21 CFR 184.1695	
	Riboflavin-5 phosphate sodium	130-40-5	21 CFR 184.1697	
Niacin	Niacin (nicotinic acid)	59-67-6	21 CFR 184.1535	
	Nicotinamide	98-92-0	21 CFR 184.1537	
	Aluminum nicotinate	1976-28-9	21 CFR 172.310	
	Nicotinamide-ascorbic acid complex (Niacinamide ascorbate)	1987-71-9	21 CFR 172.315	
Vitamin B6	Pyridoxine hydrochloride	58-56-0	21 CFR 184.1676	
Folate	Folic acid (folacin)	59-30-3	21 CFR 172.345	
Vitamin B12	Vitamin B12 (cyanocobalamin)	68-19-9	21 CFR 184.1945	
Pantothenic acid	Calcium pantothenate	137-08-6	21 CFR 184.1212	
	Calcium pantothenate-calcium chloride double salt	6363-38-8	21 CFR 172.330	
	D-pantothenamide	7757-97-3	21 CFR 172.335	
Biotin	Biotin	58-85-5	21 CFR 182.8159	
Choline	Choline bitartrate	87-67-2	21 CFR 182.8250	
	Choline chloride	67-48-1	21 CFR 182.8252	
Inositol	Inositol	87-89-8	21 CFR 184.1370	

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**Trace Mineral Elements**

Mineral Nutrient(s)	Substance name	CAS Number	FDA citation(s)	National List
Chromium	Chromium picolinate (chromium tripicolinate)	14639-25-9	(European Food Safety Authority 2010a)	
	Chromium (III) chloride hexahydrate	10060-12-5	(European Food Safety Authority 2010b)	
Copper	Copper gluconate	527-09-3	21 CFR 184.1260	
(& Iodine)	Cuprous iodide	7681-65-4	21 CFR 100.155 21 CFR 184.1265	
(& Sulfate)	Copper sulfate	7758-98-7	21 CFR 184.1261	

Iodine	Potassium iodide	7681-11-0	21 CFR 100.155 21 CFR 184.1634	205.605(a)
Iron	Ferric ammonium citrate	1185-57-5 1333-00-2	21 CFR 184.1296	
(& Chloride)	Ferric chloride	7705-08-0	21 CFR 184.1297	
	Ferric citrate	2338-05-8	21 CFR 184.1298	
(& Phosphorus)	Ferric phosphate	10045-86-0	21 CFR 184.1301	
(& Phosphorus)	Ferric pyrophosphate	10058-44-3	21 CFR 184.1304	
	Ferric sulfate	10028-22-5	21 CFR 184.1307	
(& Vitamin C)	Ferrous ascorbate	24808-52-4	21 CFR 184.1307a	
	Ferrous carbonate	563-71-3	21 CFR 184.1307b	
	Ferrous citrate	23383-11-1	21 CFR 184.1307c	
	Ferrous fumarate	141-01-5	21 CFR 184.1307d	
	Ferrous gluconate	6047-12-7	21 CFR 184.1308	
	Ferrous lactate	5905-52-2	21 CFR 184.1311	
	Ferrous sulfate	7782-63-0	21 CFR 184.1315	205.605(b)
	Elemental iron	7439-89-6	21 CFR 184.1375	
Manganese	Manganese chloride	7773-01-5	21 CFR 184.1446	
	Manganese citrate	5968-88-7	21 CFR 184.1449	
	Manganese gluconate	6485-39-8	21 CFR 184.1452	
(& Sulfate)	Manganese sulfate	7785-87-7	21 CFR 184.1461	
Molybdenum	Ammonium heptamolybdate	12027-67-7	EC Directive 2002/46/EC, OJ L 183, 12.7.2002, p. 51. Food Chemicals Codex 8 <sup>th</sup> Ed., 2012	
	Sodium molybdate (IV)	7631-95-0		
Selenium	Sodium selenate	13410-01-0	NIH	
	Sodium selenite	10102-18-8	NIH	
Zinc	Zinc sulfate	7733-02-0	21 CFR 182.8997	
(& Chloride)	Zinc chloride	7646-85-7	21 CFR 182.8985	
	Zinc gluconate	4468-02-4	21 CFR 182.8988	
	Zinc oxide	1314-13-2	21 CFR 182.8991	
	Zinc stearate	557-05-1	21 CFR 182.8994	

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**Major Minerals in Bone: Calcium, Phosphorus, Magnesium, and Fluoride**

Mineral Nutrient(s)	Substance name	CAS Number	FDA citation(s)	National List
Calcium	Calcium carbonate	471-34-1	21 CFR 184.1191	205.605(a)
(& Chloride)	Calcium chloride	10035-04-8	21 CFR 184.1193	205.605(a)
	Calcium citrate	813-0994-095	21 CFR 184.1195	205.605(b)
(& Phosphorus)	Calcium glycerophosphate	27214-00-2	21 CFR 184.1201	
	Calcium hydroxide	1305-62-0	21 CFR 184.1205	205.605(b)
	Calcium lactate (not GRAS for infants)	814-80-2	21 CFR 184.1207	

	Calcium oxide	1305-78-8	21 CFR 184.1210	
(& Sulfate)	Calcium sulfate, anhydrous	7778-18-9	21 CFR 184.1230	205.605(a)
(& Sulfate)	Calcium sulfate, dihydrate	10101-41-4	21 CFR 184.1230	205.605(a)
(& Phosphorus)	Calcium phosphate	various	21 CFR 182.1217	205.605(b)
(& Phosphorus)	Calcium pyrophosphate	7790-76-3	21 CFR 182.8223	
Phosphorus	Phosphoric acid	7664-38-22	21 CFR 182.1073	205.605(b) <sup>9</sup>
Magnesium	Magnesium carbonate	546-93-0	21 CFR 184.1425	205.605(b)
(& Chloride)	Magnesium chloride hexahydrate	7791-18-6	21 CFR 184.1426	205.605(b)
	Magnesium hydroxide	1309-42-8	21 CFR 184.1428	
	Magnesium oxide	1309-48-4	21 CFR 184.1431	
(& Phosphorus)	Magnesium phosphate, dibasic	7782-75-4	21 CFR 184.1434	
(& Phosphorus)	Magnesium phosphate, tribasic	7757-87-1	21 CFR 184.1434	
(& Sulfate)	Magnesium sulfate heptahydrate	10034-99-8	21 CFR 184.1443	205.605(a)
Fluorine	Sodium fluoride (via water only)	7681-49-4	21 CFR 165.110(b)	

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**Major Electrolyte Minerals**

Mineral Nutrient(s)	Substance name	CAS Number	FDA citation(s)	National List
Potassium	Potassium acid tartrate	868-14-4	21 CFR 184.1613	205.605(b)
	Potassium bicarbonate	298-14-6	21 CFR 184.1613	
	Potassium carbonate	584-08-7	21 CFR 184.1619	205.605(b)
(& Chloride)	Potassium chloride	7447-40-7	21 CFR 184.1622	205.605(a)
	Potassium citrate	866-84-2	21 CFR 184.1625	205.605(b)
	Potassium hydroxide	1310-58-3	21 CFR 184.1631	205.605(b)
(& Phosphorus)	Dipotassium phosphate	7758-11-4	21 CFR 182.6285	205.605(b)
Sodium	Sodium bicarbonate	144-55-8	21 CFR 184.1736	205.605(a)
	Sodium carbonate	497-19-8	21 CFR 184.1742	205.605(a)
(& Chloride)	Sodium chloride (table salt)	7647-14-5	21 CFR 182.1	OFPA
	Sodium citrate dihydrate	6132-04-3	21 CFR 184.1751	205.605(b)
	Sodium hydroxide	1310-73-2	21 CFR 184.1763	205.605(b)
(& Phosphorus)	Sodium acid phosphate	7558-80-7	21 CFR 182.6085	205.605(b)
(& Phosphorus)	Disodium phosphate heptahydrate	7782-85-6	21 CFR 182.6290	205.605(b)
(& Phosphorus)	Sodium phosphate, tribasic	7601-54-9	21 CFR 182.6778	205.605(b)
Chloride	Hydrochloric acid	7647-01-0	21 CFR 182.1057	

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**Permitted Legal Uses**

**Standards of Identity in Title 21 CFR that permit or require Nutrient Fortification**

Food class	Regulation	Specific vitamins or minerals required by FDA
Infant formula	21 CFR 107.10 21 CFR 107.100	All nutrients known to be essential and listed therein

<sup>9</sup> Phosphoric acid annotation: “cleaning of food-contact surfaces and equipment only” (i.e., not permitted as a direct “food ingredient”).

Bakery products	21 CFR Part 136	Thiamine, riboflavin, niacin, folic acid, iron*
Cereal flours	21 CFR Part 137	Thiamine, riboflavin, niacin, folic acid, iron*
Macaroni & noodles	21 CFR Part 139	Thiamine, riboflavin, niacin, folic acid, iron*
Margarine	21 CFR 166.110	Vitamin A

549 \*For foods labeled as “enriched.”

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Food class	Regulation	Specific vitamins or minerals optional
Milk	21 CFR Part 131	Vitamins A & D
Bakery products	21 CFR Part 136	Calcium
Cereal flours	21 CFR Part 137	Calcium*; Vitamin D in enriched corn meal, farina, rice
Macaroni & noodles	21 CFR Part 139	Calcium*, Vitamin D* in enriched macaroni & noodle products
Canned fruits	21 CFR Part 145	Ascorbic acid (Vitamin C)
Pineapple juice	21 CFR 146.185	Vitamin C
Prune juice	21 CFR 146.187	Vitamin C
Margarine	21 CFR 166.110	Vitamin D

551 \*For foods labeled as “enriched.”

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554 Another Federal agency, the Food and Nutrition Service of USDA, provides the Federal requirements for  
555 foods eligible for the “Women Infants, and Children” (WIC) federal program. FNS/USDA requirements  
556 for WIC-eligible foods can be found at 7 CFR Part 246.10 These requirements are not within FDA’s  
557 jurisdiction. Nevertheless, some of the WIC regulations refer to standards of identity in 21 CFR. For  
558 example, fluid milks for the WIC program must conform to FDA standards of identity at 21 CFR Part  
559 131.110, 21 CFR Part 131.111, 21 CFR Part 131.112, 21 CFR Part 131.127, 21 CFR Part 131.130 or 21 CFR Part  
560 131.147; must be pasteurized; and must contain 400 IU of Vitamin D per quart and, for reduced fat, low-fat  
561 or nonfat milk, 2000 IU of Vitamin A per quart.

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563 Other WIC regulations are unique (see the following table), such as a very high required level of iron in  
564 infant cereals. This may not be encompassed by the current annotation at 7 CFR 205.605(b) that permits  
565 nutrient addition “in accordance with 21 CFR 104.20, Nutritional Quality Guidelines for Foods” to foods  
566 labeled as “organic.” Moreover, USDA permits State WIC Agencies to exercise certain options (e.g., “At  
567 the State agency’s option, juice fortified with other nutrients may be allowed”).

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Food class	Regulation	Specific vitamins or minerals required for WIC Package Foods
Fruit juice	7 CFR 246.10	Minimum of 30 mg of Vitamin C per 100 mL of juice
Infant cereals	7 CFR 246.10	Minimum of 45 mg of Iron per 100 g of dry cereal
Breakfast cereals	7 CFR 246.10	Minimum of 28 mg of Iron per 100 g of dry cereal
Soy-based beverage (milk alternative)	7 CFR 246.10	Vitamins A & D, calcium, magnesium, phosphorus, riboflavin, vitamin B12

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570 **Evaluation Question #5: Describe whether the primary technical function or purpose of the petitioned**  
571 **substance is a preservative. If so, provide a detailed description of its mechanism as a preservative (7**  
572 **CFR § 205.600 (b)(4)).**

573  
574 Direct human food ingredients may be added to foods for certain defined physical or technical functions.  
575 “Nutrient supplements,” per 21 CFR 170.3(o)(21), are defined by FDA as “Substances which are necessary  
576 for the body’s nutritional and metabolic processes.” All of the substances enumerated in this report  
577 provide vitamins and/or minerals “. . . necessary for the body’s nutritional and metabolic processes.

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579 “Preservatives,” per se, are not defined by FDA, but FDA at 21 CFR 170.3(o)(2) defines “Antimicrobial  
580 agents” as “Substances used to preserve food by preventing growth of microorganisms and subsequent  
581 spoilage, including fungistats, mold and rope inhibitors, and the effects listed by the NAS/NRC under

582 ‘preservatives.’” The NAS/NRC (National Academy of Sciences/National Research Council 1972) defined  
 583 “preservatives” as “including antimicrobial agents, fungistats, mold and rope inhibitors, etc.”

584  
 585 None of the substances enumerated herein are “antimicrobial agents” in this sense. The ingredient “salt”  
 586 has been used since time immemorial to preserve food by reducing the water activity of a food to the point  
 587 that few microorganisms can grow, but salt is not customarily considered a “preservative” as defined by  
 588 NAS/NRC, since it has no direct antimicrobial activity.

589  
 590 Several forms of nutrient vitamins act as “antioxidants,” defined by FDA at 21 CFR 170.3(o)(3) as  
 591 “Substances used to preserve food by retarding deterioration, rancidity, or discoloration due to oxidation.”  
 592 Ascorbic acid, acting as a water-soluble antioxidant, can help prevent enzymatic browning in freshly cut  
 593 fruit (el-Shimi 1993). Tocopherols and other substances with Vitamin E activity delay oxidation and  
 594 rancidity of fats and oils (Becvarova et al. 2005). Oxidative rancidity of fats leads to production of  
 595 hydroxyl-fatty acids and diarrhea (Bhat et al. 1995).

596  
 597 It can be difficult to differentiate between “nutrient” effects and “antioxidant” effects of a substance with  
 598 Vitamin C or Vitamin E activity. Here are several examples:

- 599 • The infant formula regulation at 21 CFR 107.100(b) requires that “Vitamin E shall be present at a level  
 600 of at least 0.7 International Unit of vitamin E per gram of linoleic acid.” Linoleic acid is an essential  
 601 polyunsaturated fatty acid (PUFA) which is prone to oxidation and rancidity, and the infant must  
 602 receive sufficient vitamin E to protect his or her body from *in vivo* oxidation of PUFA. It is not clear  
 603 whether this regulatory mandate classifies the tocopherols providing Vitamin E activity as “nutrient  
 604 supplements” or as “antioxidants.” The biological role of tocopherols is to be the body’s antioxidant.
- 605 • Ascorbyl palmitate is a fat-soluble form of Vitamin C; ascorbic acid comprises 41% of the ascorbyl  
 606 palmitate molecule. A serving of food containing 146 mg of ascorbyl palmitate provides 60 mg of  
 607 Vitamin C, the Reference Daily Intake (RDI) for adults and children four or more years of age. When  
 608 ascorbyl palmitate is added to fat at a level which provides only a milligrams or less of Vitamin C, it is  
 609 reasonable to conclude that its function is as an antioxidant. It is not clear whether ascorbyl palmitate  
 610 should be considered a “nutrient supplement” or an “antioxidant” when the amount added to a food  
 611 provides 12 mg of Vitamin C activity (20% of the RDA) per serving and thus makes the food eligible  
 612 for the claim “an excellent source of Vitamin C” per 21 CFR 101.54(b).
- 613 • It is well recognized that ascorbic acid improves iron bioavailability (Fishman, Christian, and West  
 614 2000; Hallberg, Brune, and Rossander 1989). Ascorbyl palmitate is a fat-soluble form of Vitamin C,  
 615 which survives the baking process better than does water-soluble ascorbic acid. Researchers made  
 616 bread with wheat fortified either with ferrous sulfate alone or with ferrous sulfate plus ascorbyl  
 617 palmitate (AP). Iron absorption from the bread fortified with ferrous sulfate was 10.5%. The addition of  
 618 AP at molar ratios of AP to Fe of 2:1 and 4:1 significantly increased iron absorption, to 14.6% and  
 619 20.2%, respectively (P < 0.001). The authors concluded that ascorbyl palmitate is a strong promoter of  
 620 iron absorption from fortified bread because of its thermoresistant properties (Pizarro et al. 2006),  
 621 suggesting a ‘nutrient supplement’ effect of ascorbyl palmitate.

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 623 **Evaluation Question #6: Describe whether the petitioned substances will be used primarily to recreate**  
 624 **or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law)**  
 625 **and how the substance recreates or improves any of these food/feed characteristics (7 CFR § 205.600**  
 626 **(b)(4)).**

627  
 628 Those foods labeled as “organic” that currently are enriched or fortified with nutrient vitamins and  
 629 minerals are in classes of foods in which the addition of nutrient vitamins and/or minerals is required by  
 630 law or allowed by regulation. Examples of specific regulations include the following.

Food class	Regulation	Specific vitamins or minerals required by the regulation
Iodized salt	21 CFR 100.155	Iodine
Infant formula	21 CFR 107.10 21 CFR 107.10	All nutrients known to be essential
Milk for WIC	7 CFR 246.10	Vitamins A & D

	21 CFR Part 131	
Soy-based beverage (milk alternative)	7 CFR 246.10	Vitamins A & D, calcium, magnesium, phosphorus, riboflavin, vitamin B12
Bakery products	21 CFR Part 136	Thiamine, riboflavin, niacin, folic acid, iron*
Cereal flours	21 CFR Part 137	Thiamine, riboflavin, niacin, folic acid, iron*
Macaroni & noodles	21 CFR Part 139	Thiamine, riboflavin, niacin, folic acid, iron*
Fruit juice for WIC	7 CFR 246.10	Vitamin C
Infant cereals (WIC)	7 CFR 246.10	Iron
Adult cereals (WIC)	7 CFR 246.10	Iron

\*For foods labeled as "enriched."

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Some of these nutrients are added for public health reasons (e.g., vitamin D in milk to avoid rickets; iodine in salt to avoid iodine deficiency/goiter; iron in cereals to avoid iron deficiency anemia; folate in grain-based foods to avoid neural tube birth defects), whereas the other B vitamins are added to milled cereal products to replace what is lost in milling, and vitamin A is added to skim milk to replace what is removed with the milk fat.

**Evaluation Question #7: Describe any effect or potential effect on the nutritional quality of the food or feed when the petitioned substance is used (7 CFR § 205.600 (b)(3)).**

Adding a nutrient vitamin or mineral substance increases the levels or the level of the vitamin or mineral found in the food product. Adding a nutrient substance to a food converts that nutrient from a "Class II" nutrient to a "Class I" nutrient [21 CFR 101.9(g)(3)]. A Class I nutrient is one which is added to a fortified or fabricated food; it must be present at a level at least equal to the label claim. A Class II nutrient is a nutrient naturally occurring in an ingredient in the food and thus its level is subject to normal variation. A Class II nutrient must be present at a level at least equal to 80% of the label claim.

Vitamin C sources are known to increase the bioavailability of iron (Ziegler et al. 2011). Vitamin E and other vitamins with antioxidant properties are known to protect other fat-soluble vitamins and dietary fat from oxidative deterioration (rancidity). Beta-carotene, allowed by FDA as a vitamin A source, also has antioxidant effects that protect fats and other fat-soluble vitamins (Canfield, Forage, and Valenzuela 1992).

**Evaluation Question #8: List any reported residues of heavy metals or other contaminants in excess of FDA tolerances that are present or have been reported in the petitioned substance (7 CFR § 205.600 (b)(5)).**

The GRAS substances providing vitamin and mineral nutrient activity enumerated herein are listed in the Food Chemicals Codex or have undergone safety evaluation by international organizations and comply with accepted reference standards for heavy metals and other contaminants in food ingredients in the U.S.

**Evaluation Question #9: Discuss and summarize findings on whether the manufacture and use of the petitioned substance may be harmful to the environment or biodiversity (7 U.S.C. § 6517 I (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).**

**Vitamin Nutrients**

Few harmful impacts of the manufacture and use of the major form of each vitamin nutrient on the environment and biodiversity have been identified; see below.

**Manufacturing Issues and Use Issues described in the Material Safety Data Sheet for each Nutrient**

Vitamin Nutrient	Manufacturing issues	Use issues
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Vitamin A (retinyl acetate)	The historical process of retinol extraction from fish livers created significant amounts of high BOD (biological oxygen demand) waste streams. The modern synthetic methods are engineered to minimize emissions and energy usage.	Short term degradation products are possibly hazardous, though not likely. However, long term degradation products may arise. The product itself and its products of biodegradation are not toxic.
Vitamin D (D3)	Cholecalciferol is isolated from wool fat, thus utilizing an agricultural input. The solvents used to fractionate the UV-radiated intermediates are recycled to reduce volatile solvent emissions.	Vitamin D3 is a rodenticide at high dosage. Short term degradation products are possibly hazardous, though not likely. However, long term degradation products may arise. The products of biodegradation are more toxic.
Vitamin E (alpha-tocopherol acetate)	Mixed tocopherols are stripped from vegetable oils during deodorization. The acetate ester is produced chemically from alpha-tocopherol. The other tocopherols are used as antioxidants.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The product itself and its products of biodegradation are not toxic.
Vitamin K (MK7)	Menadione 7 is created by fermentation of natto bacteria.	Not considered to be toxic for humans. Stable under normal temperatures and pressures. No toxic effects known.
Lutein, lycopene, zeaxanthin	These three carotenoids are either isolated from plant tissue or synthesized in nature-identical form.	Like the marigold flowers and tomato tissue of their origin, the products and biodecomposition products are not toxic.
Vitamin C (ascorbic acid)	Newer fermentation-facilitated processes that produce ascorbic acid are simpler and use fewer chemicals.	Ascorbic acid is acidic and reduces pH. Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The product and products of biodegradation are not toxic.
Thiamin (thiamine hydrochloride)	The chemical synthesis has been simplified to fewer steps.	Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation (sulfur compounds) are more toxic.
Riboflavin (riboflavin)	The chemical synthesis used to make riboflavin for human use is being replaced by microbial processes. These reduce costs, waste and energy requirements, and use renewable resources like sugar or plant oil.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The products of biodegradation are more toxic.
Niacin (niacin)	The oxidation of nicotine is a very simple and controllable reaction.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The products of biodegradation are more toxic.
Vitamin B6 (pyridoxine hydrochloride)	The standard oxazole-based process uses benzene as a solvent and hydrogen chloride and phosphorus oxychloride as reagents. A newer	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The product itself



	method replaces these agents with safer and less toxic substances (Zou et al. 2013).	and its products of biodegradation are not toxic.
Folate	The synthesis of folic acid involves a series of complex chemical reactions. The commercial attractiveness of GMO fermentation for conventional applications is based on its operational simplicity and lower cost.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The products of biodegradation are more toxic.
Vitamin B12 (cyanocobalamin)	The Vitamin B12 molecule contains an atom of cobalt and an atom of cyanide, which require attention to process safety.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The products of biodegradation are more toxic.
Pantothenic acid (calcium pantothenate)	One commercial synthetic process for pantothenic acid involves formaldehyde.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The product itself and its products of biodegradation are not toxic.
Biotin	Biotin is synthesized chemically by a very complicated 14-step chemical synthesis involving the poisonous gas phosgene.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The products of biodegradation are more toxic.
Choline (choline chloride)	One precursor of choline chloride is trimethylamine. Trimethylamine has a rotten fish odor.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The products of biodegradation are more toxic.
Inositol	Inositol is prepared from corn steep liquor by phytase enzymatic hydrolysis of the phosphates of phytic acid. Corn steep liquor contains residual sulfur dioxide.	Short term degradation products are possibly hazardous, though not likely. However, long term biodegradation products may arise. The product itself and its products of biodegradation are not toxic.

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**Mineral nutrients**

As a general rule, mineral nutrients share the need to be extracted from mined terrestrial ores and then must be refined and converted into food grade substances. The processes of mining, roasting, smelting, and otherwise refining, and subsequent chemical reaction frequently involve mineral acids, such as sulfuric acid, hydrochloric acid, and phosphoric acid, with environmental risks related to the use and misuse of these agents.

Several NOSB recommendations for mineral substances for use as ingredients in processed foods labeled as “organic” were contingent upon using a natural source. These substances are listed at § 205.605(a).

Some nutritionally essential heavy metals pose a risk to the environment. If released to soil, copper sulfate may leach to groundwater, be partly oxidized, or bind to humic materials, clay, or hydrous iron and manganese. In water, it will bind to carbonates as well as humic materials, clay and hydrous oxides of iron and manganese. Copper is accumulated by plants and animals, but it does not appear to biomagnify from plants to animals. This lack of biomagnification appears common with heavy metals. In air, copper aerosols (in general) have a residence time of 2 to 10 days in an unpolluted atmosphere and 0.1 to >4 days in

692 polluted, urban areas (Fisher Science Education 2012). Zinc sulfate is very toxic to aquatic organisms  
 693 (Skidmore 1964).

694 **Use Issues**  
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Mineral Nutrient	Use issues (described in the MSDS)
Chromium (III) (chromium trichloride)	Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, or of inhalation (lung irritant). Not carcinogenic. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation are less toxic than the product itself.
Copper & Sulfur (copper sulfate)	Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, or of inhalation (lung irritant). Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation are less toxic than the product itself.
Iodine (potassium iodide)	Slightly hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, or of inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The product itself and its products of biodegradation are not toxic.
Iron & Sulfur (ferrous sulfate)	Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, or of inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation are less toxic than the product itself.
Manganese & Sulfur (manganese sulfate)	Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, or of inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The product itself and its products of biodegradation are not toxic.
Molybdenum (sodium molybdate)	Causes eye, skin, and respiratory tract irritation; may cause gastrointestinal irritation with nausea, vomiting and diarrhea. This product does not require biodegradability as its components are part of the environment naturally. Product does not pose environmental risk; it is considered a non-dangerous waste.
Selenium (sodium selenite)	Very hazardous in case of skin contact (irritant), eye contact (irritant), ingestion, or inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation are less toxic than the product itself.
Zinc & Sulfate (zinc sulfate)	Causes severe eye irritation and possible eye injury. Causes skin and respiratory tract irritation. May be harmful if swallowed. Very toxic to aquatic organisms. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation are more toxic.
Calcium (calcium carbonate)	Hazardous in case of eye contact (irritant). Slightly hazardous in case of skin contact (irritant), ingestion, or inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The product itself and its products of biodegradation are not toxic.
Phosphorus (tri-calcium phosphate)	Hazardous in case of skin contact (irritant), eye contact (irritant), ingestion, or inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation are as toxic as the original product.
Phosphorus (85% phosphoric acid)	Causes burns by all exposure routes (skin, respiratory system, eyes, gastrointestinal tract). Hygroscopic. [Use personal protective equipment. Ensure

	adequate ventilation. Do not get in eyes, on skin, or on clothing.]
Magnesium (magnesium hydroxide)	Slightly hazardous in case of skin contact (irritant), eye contact (irritant), ingestion, or inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation are as toxic as the original product.
Fluorine (sodium fluoride)	Hazardous in case of skin contact (irritant), eye contact (irritant, corrosive), ingestion, or inhalation. Slightly hazardous in case of skin contact (corrosive). Severe over-exposure can result in death. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The products of biodegradation are less toxic than the product itself.
Potassium & Chloride (potassium chloride)	Slightly hazardous in case of skin contact (irritant), eye contact (irritant), ingestion, or inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The product itself and its products of biodegradation are not toxic.
Sodium & Chloride (table salt)	Slightly hazardous in case of skin contact (irritant), eye contact (irritant), ingestion, or inhalation. Possibly hazardous short term biodegradation products are not likely. However, long term biodegradation products may arise. The product itself and its products of biodegradation are not toxic.
Chloride (Hydrochloric acid; 38% HCl)	Corrosive to metals. Causes burns by all exposure routes. May cause irritation of respiratory tract. Corrosive to the eyes and may cause severe damage including blindness. [Wear personal protective equipment. Do not breathe vapors or spray mist. Do not get in eyes, on skin, or on clothing. Do not ingest.]

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**Ancillary substances**

There is no literature to suggest that the manufacture or use of vitamins and minerals with ancillary substances is harmful to the environment or to biodiversity.

**Evaluation Question #10: Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (ii) and 7 U.S.C. § 6518 (m) (4)).**

Adequate intakes of essential vitamins and minerals are essential for life. Inadequate intakes cause deficiency diseases, which can lead to death. Iodine-fortification of salt, a public health measure introduced in the United States in 1924, eliminated goiter and cretinism and increased IQ in men born in low-iodine areas after an average of 15 points above that of their slightly older peers (Freyer, Weil, and Politi 2013). Fortification of refined grain products, a public health measure implemented during World War II, cured the pellagra due to deficiency of niacin in Southern populations subsistent on milled corn meal (Brooke 1968). Cod liver oil and then milk fortified with vitamin D effectively eliminated rickets in infants and children. Iron deficiency, which was prevalent in infants until about 1970, was largely eliminated by a resurgence of breast-feeding and a prolongation of formula feeding of iron-fortified infant formulas (Fomon 2001).

On the other hand, excessive intakes of individual vitamins or minerals may cause disease or increase the risk of disease, either directly (e.g., hypervitaminosis A or D), or by creating an imbalance (e.g., hemostatic effects of consuming too much sodium when potassium intakes are low (Liu et al. 2011); increased risk of heart failure when calcium or phosphorus intakes are high and magnesium intakes are low (Lutsey et al. 2014)).

The Dietary Reference Intakes provide the average daily nutrient intake level estimated to meet the requirement of half of the healthy individuals in a particular life stage and gender group (the Estimated Average Requirement, or “EAR”), the average daily nutrient intake level sufficient to meet the requirements of nearly all healthy individuals in a particular life stage and gender group (the

728 Recommended Dietary Allowance, or “RDA”), and the highest average daily nutrient intake level that is  
 729 likely to pose no risk of adverse health effects to almost all individuals in the general population (the  
 730 Upper Limit, or “UL”). For those nutrients with insufficient data to estimate an EAR or an RDA, an  
 731 “Adequate Intake” (“AI”) for almost all individuals was estimated. The Dietary Reference Intakes also  
 732 discuss the levels high enough to create direct adverse effects and what those adverse effects might be. The  
 733 following chart summarizes their findings.

734 The Dietary Reference Intakes for calcium and Vitamin D were revised in 2011 (Institute of Medicine 2011).  
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Nutrient & Units	EAR / AI	RDA	UL	Adverse effects at	Adverse ‘nutrient’ effects/Comment
Vitamin A, RAE* (*Retinol Activity Equivalents)	625	900	3,000	≥ 150,000	Acute: nausea, vomiting, headache, vertigo, bulging fontanel in infants
				≥ 30,000	Chronic: liver abnormalities, bone & skin changes; central nervous system effects; beta-carotene turns skin orange (harmless)
Vitamin D, mcg	10	15	100	≥ 250	Hypercalcemia, kidney disease (stones, etc.)
Vitamin E, mg	12	15	1,000	≥ 1,100	In rats, increased hemorrhage & clotting time
Vitamin K, mcg	120		none		Menadione (K3) is NOT allowed for humans
Vitamin C, mg	75	90	2,000	≥ 3,000	Diarrhea, colic, increased oxalate excretion
Thiamin (B1), mg	1.0	1.2	none	none	No reports of adverse effects to oral doses
Riboflavin (B2), mg	1.1	1.3	none	none	No reports of adverse effects to oral doses
Niacin, mg	12	16	35	≥ 50	Flushing (vasodilation)
Vitamin B6, mg	1.4	1.7	100	> 200	Sensory neuropathy
Folate, mcg	320	400	1,000	≥ 5,000	Precipitates the neuropathy of B12 deficiency
Vitamin B12, mcg	2	2.4	none	none	No reports of adverse effects to oral doses
Pantothenate, mg	5		none	none	No reports of adverse effects to oral doses
Biotin, mcg	30		none	none	No reports of adverse effects to oral doses
Choline, mg	550		3,500	≥ 7,500	Fishy body odor, sweating, salivation, hypotension
Inositol, mg					None (Required nutrient for Infant Formula)
Chromium, mcg	35		not estab.		Chromium (III) is <u>not</u> toxic. Chromium (VI) is a well established as a human health concern.
Copper, mcg	700	900	10,000		Gastrointestinal (nausea), liver damage
Iodine, mcg	95	150	1,100	> 18,000	Goiter (enlarged thyroid), thyroid cancer
Iron, mg (men/women)	6 / 8.1	8 / 18	45	20 - 60	Acute: accidental overdose of ferrous sulfate drops is the most common cause of poisoning deaths in children in the U.S.
				≥ 50	Chronic: constipation, nausea, vomiting, iron accumulation in the liver, higher cancer risk; hemochromatosis
Manganese, mg	2.3		11	≥ 15	Manganese dust is toxic; neurological effects
Molybdenum, mcg	34	45	2,000		No toxicity ever noted in humans; UL based on animal studies
Selenium, mcg	45	55	400	≥ 900	Selenosis: hair & nail loss, brittleness. Sodium selenite is very hazardous in case of skin contact (irritant), eye contact (irritant), ingestion, or inhalation. Hazardous in case of skin contact. Severe over-exposure can result

					in death. Eye inflammation is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.
Zinc, mg	9.4	11	40	≥ 50	Epigastric pain, nausea, vomiting; depressed HDL levels
Calcium, mg	800	1000	2,500	≥ 2,500	Kidney stones, soft tissue calcification
Phosphorus, mg	580	700	4,000	10,200	No direct toxicity (but interacts with calcium)
Magnesium, mg	350	420	+ 350		Diarrhea (given as the chloride or citrate)
Sulfate	Not estab.		not estab.		Diarrhea at high intake levels
Fluorine, mg	4		10	> 10	Tooth mottling, skeletal and dental fluorosis
Potassium, g	4.7				Cardiac arrhythmias from supplements
Sodium, g	1.5		2.3	≥ 2.3	Increased blood pressure (from too much salt); hyperchloremia and acidosis from too much chloride; hypernatremia and alkalosis from too much sodium
Chloride, g	2.3		3.6	≥ 3.6	

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The National Research Council considered the knowledge base for the ‘other carotenoid’ nutrients with established health-related roles (e.g., lutein and zeaxanthin are related to age-related macular degeneration and lycopene lowers prostate cancer risk) to be inadequate to justify setting an EAR (“Estimated Average Requirement”) or an AI (“Adequate Intake”).(National Research Council 2001).

All ancillary substances used in combination with vitamins and minerals are GRAS. Good manufacturing practice (GMP) requires that they be used at levels that avoid unacceptable environmental, human health, and toxicological effects. For example, the synthetic antioxidants BHA and BHT are carcinogenic at high levels but anti-carcinogenic at current levels of food additive use (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) 2012; Williams, Iatropoulos, and Whysner 1999), protecting against chemical carcinogens (Williams, Iatropoulos, and Jeffrey 2002) and the liver cancer caused by aflatoxin (Williams 2003).

Some individuals are sensitive to these two antioxidants. Two patients with chronic idiopathic urticaria (hives or nettle rash) who experienced remissions with a dye- and preservative-elimination diet had exacerbations of their urticaria when they were challenged under double-blind, placebo-controlled conditions with BHT and BHA (Goodman et al. 1990).

Protein is the cause of most allergy, and, as noted above, one or more proteins are used in many encapsulated vitamin preparations. Gelatin, a partially hydrolyzed protein of limited antigenicity, is the protein most commonly used in vitamin and mineral formulation.

**Evaluation Question #11: Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).**

One of the alternatives to foods fortified with nutrient vitamins and minerals are unfortified foods that are part of a diverse and balanced diet.

Every five years, the USDA and FDA jointly publish Dietary Guidelines for Americans. The latest report was published in 2010 (U.S. Department of Agriculture and U.S. Department of Health and Human Services 2010). A fundamental premise of the Dietary Guidelines is that nutrients should come primarily from foods. Foods in nutrient-dense, mostly intact forms contain not only the essential vitamins and

771 minerals that are often contained in nutrient supplements, but also dietary fiber and other naturally  
772 occurring substances that may have positive health effects.

773  
774 The Dietary Guidelines stress that Americans should aim to meet their nutrient requirements through a  
775 healthy eating pattern that includes nutrient-dense forms of foods, while balancing calorie intake with  
776 energy expenditure. The Dietary Guidelines acknowledge that dietary supplements or fortification of  
777 certain foods may be advantageous in specific situations to increase intake of a specific vitamin or mineral.  
778 Fortification can provide a food-based means for increasing intake of particular nutrients or providing  
779 nutrients in highly bioavailable forms. The report provides the following three examples.

- 780 • “Vitamin D. For many years, most fluid milk has been fortified with vitamin D to increase calcium  
781 absorption and prevent rickets. Vitamin D-fortified milk is now the major dietary source of vitamin  
782 D for many Americans. Other beverages and foods that often are fortified with vitamin D include  
783 orange juice, soy beverages, and yogurt. Vitamin D also is available as a dietary supplement. As  
784 intake increases above 4,000 IU (100 mcg) per day, the potential risk of adverse effects increases.”
- 785 • “Folic acid. More recently, folic acid fortification of enriched grains was mandated to reduce the  
786 incidence of neural tube defects, which are serious birth defects of the brain and spine.  
787 Subsequently, folate intake has increased substantially. It is recommended that all women who are  
788 capable of becoming pregnant consume 400 mcg per day of folic acid from these fortified foods or  
789 from dietary supplements, in addition to eating food sources of folate.”
- 790 • “Vitamin B12. Foods fortified with the crystalline form of vitamin B12, such as fortified cereals, or  
791 vitamin B12 supplements, are encouraged for individuals older than age 50 years. A substantial  
792 proportion of these individuals may have reduced ability to absorb naturally occurring vitamin  
793 B12, but their ability to absorb the crystalline form is not affected. In addition, vegans should  
794 ensure adequate intake of vitamin B12 through fortified foods or supplements.”  
795 The specific recommendation reads: “Individuals ages 50 years and older - Consume foods  
796 fortified with vitamin B12, such as fortified cereals, or dietary supplements.”  
797

798 The Dietary Guidelines further recommend that soy beverages used to replace milk be fortified to deliver  
799 the calcium, vitamin D, and other nutrients ordinarily provided in the diet by cows’ milk. The vegan dairy  
800 group includes calcium-fortified beverages and foods commonly used as substitutes for milk and milk  
801 products. These vegetarian variations represent healthy eating patterns, but rely on fortified foods for some  
802 nutrients. In the vegan patterns especially, fortified foods provide much of the calcium and vitamin B12,  
803 and either fortified foods or supplements should be selected to provide adequate intake of these nutrients  
804 (p 53). The Dietary Guidelines also encourage selecting more fat-free or low-fat vitamin D-fortified milk or  
805 yogurt than cheese (p. 52).

806 Other alternatives to foods fortified with nutrient vitamins and minerals are nutritional supplements.  
807 Compared to fortified foods, nutritional supplements (“vitamin pills” and “mineral pills”) are more easily  
808 taken in excess and thus much more likely to produce adverse effects, as the Dietary Guidelines indicate  
809 above for Vitamin D.

810  
811 Foods labeled as “organic” are fortified with vitamins and minerals to a lesser extent than conventional  
812 foods. In the UK, for example, under Soil Association standards, organic foods must not be fortified with  
813 added artificial nutrients, unless the fortification is required by law<sup>10</sup>. This is consistent with the consumer  
814 perception that foods labeled as “organic” are more nutritious and contain fewer synthetic chemicals, such  
815 as synthetic vitamins and minerals (Byrne et al. 1991; Anderson, Wachenheim, and Lesch 2006).  
816

817  
818 Some research support the consumer belief that organic foods are more nutritious. For example, organic  
819 potatoes generally contain more ascorbic acid (Hajslova et al. 2005). Several critical reviews of the literature  
820 comparing the nutritional quality of organic and conventional foods have appeared in the past fifteen  
821 years. A universal conclusion is that organic fertilization practices produces leafy vegetables and potatoes

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<sup>10</sup> <http://www.soilassociation.org/frequentlyaskedquestions/yourquestion/articleid/2384/is-organic-food-fortified-with-vitamins-and-minerals>. Accessed 1 February 2015.

822 with higher levels of ascorbic acid (Worthington 1998; Magkos, Arvaniti, and Zampelas 2003), lower levels  
823 of nitrate (Worthington 1998; Magkos, Arvaniti, and Zampelas 2003, 2006), and improved protein quality  
824 (Worthington 1998; Magkos, Arvaniti, and Zampelas 2006). The higher concentration of ascorbic acid and  
825 occasionally of other nutrients may relate to the higher water content of conventional vegetables, which  
826 causes nutrient dilution (Worthington 1998).

827  
828 Williams (Williams 2002) noted that very few studies that have compared animal products (meat, milk and  
829 dairy products) produced under the two agricultural systems, and very few nutritional or other  
830 compositional differences have been reported. Holmboe-Ottesen et al. (Holmboe-Ottesen 2004) noted in  
831 their review that organic foods seem to have a higher content of antioxidants in plant products and a  
832 higher content of fat-soluble vitamins and omega-3 fatty acids in animal products. Humans fed an organic  
833 diet excrete more antioxidants in the urine (Grinder-Pedersen et al. 2003).

834  
835 Health and reproductive performance are improved slightly when animals are organically fed  
836 (Worthington 1998; Magkos, Arvaniti, and Zampelas 2003). Animals (including rabbits and chickens) show  
837 higher fertility and less morbidity in when fed organically. These observations appear relevant to humans.  
838 A Norwegian prospective cohort study of 28,912 women in their first pregnancy (Torjusen et al. 2014)  
839 showed that in those women who reported eating organic vegetables 'often' or 'mostly' (n=2493, 8.8%) had  
840 lower risk of pre-eclampsia than those who reported 'never/rarely' or 'sometimes.' The lower risk  
841 associated with high organic vegetable consumption was evident also when adjusting for overall dietary  
842 quality, assessed as scores on a healthy food pattern derived by principal component analysis. No  
843 associations with pre-eclampsia were found for high intake of organic fruit, cereals, eggs or milk, or a  
844 combined index reflecting organic consumption. Consequently, the improved reproductive performance  
845 related to organic food consumption appears to be unrelated to nutrient composition.

846  
847 Vitamin and mineral fortification and enrichment schemes are the manifestation of certain nutritional and  
848 public health responses to current dietary behaviors and food preferences. Reversion to some pre-  
849 industrial era practices would obviate the need for some forms of vitamin and mineral addition.

850  
851 Iron deficiency is common in infants when they are fed low-iron infant formulas and cows' milk and in  
852 breast-fed infants after four or six months of age. When homes had dirt floors and soap and hot water were  
853 rarely available, the young infant would consume soil and dirt and thus iron (Fomon 1986). Dirt can  
854 provide bioavailable iron, as shown in the differential hemoglobin levels of piglets allowed access to soil  
855 and those raised on concrete (Furugouri 1972).

856  
857 Breast milk contains a small but highly bioavailable amount of iron that normally maintains good iron  
858 status for the first four to six months of life, depending on the infant's growth rate and his or her iron  
859 endowment at birth. Thereafter, either dirt containing bioavailable iron or iron-fortified foods such as  
860 infant cereal are required to maintain iron status (Ziegler, Nelson, and Jeter 2009) (Ziegler et al. 2011).

861  
862 The enrichment scheme for refined grains with iron and B-vitamins was a war-time (1942-1943) public  
863 health response to the observed deficiency diseases seen in populations consuming polished rice (beriberi  
864 from thiamin deficiency) and degermed corn meal (pellagra from niacin deficiency) (Yetley 2000). More  
865 than 75% of the riboflavin and other B-vitamins can be lost during wheat milling, when the bran and the  
866 germ are separated from the endosperm to make flour. Removal of the oil-containing germ from corn,  
867 wheat, and other grains is necessary for our modern food storage and distribution system, since the  
868 unsaturated oil in germ can become rancid upon exposure to air. Whole grain flours do not require  
869 enrichment with the traditional nutrients, but have a shorter shelf-life.

870  
871 In 1991, the Centers for Disease Control (CDC) and in 1992 the U.S. Public Health Service (PHS)  
872 recommended that women get folic acid during pregnancy to prevent neural tube birth defects (spina  
873 bifida, etc.) (Erickson 2002). Three years later, in 1995, when the NOSB made its Final Board  
874 Recommendation that included the phrase "recommended for enrichment and fortification by independent  
875 professional associations," FDA had not taken any action to implement the CDC/PHS recommendation.

876 Folate was added to the cereal and flour enrichment scheme in 1998 (Mathews, Honein, and Erickson  
877 2002), based on the superiority of grain-based products as vehicles for this vitamin (Yetley 2000).  
878

879 Many processed cereal foods labeled as “organic” contain whole grain cereals. The original cereal  
880 enrichment scheme was aimed at replacing the B-vitamins removed by cereal milling, and thus whole  
881 grain cereals did not need this enrichment. In contrast, cereal products were selected as the folate  
882 fortification vehicle based on efficient and safe delivery of folate to the population at risk: women in early  
883 pregnancy who might not yet be aware that they are pregnant (Yetley 2000). Whole grain wheat flour  
884 provides only about 15% as much folate as enriched flour, so fortifying whole grain flour and other whole  
885 grain cereal-based foods with folate would be beneficial to this population.  
886

887 Whole cows’ milk and partially or fully skimmed milk are customarily fortified with Vitamin D to prevent  
888 rickets, a Vitamin D deficiency disease. Ultraviolet radiation of our skin converts a cholesterol metabolite  
889 into active Vitamin D3. Air pollution, dark skin pigmentation, and UV-blocker lotions (Rhodes et al. 2014)  
890 reduce ultraviolet light radiation of the skin. Less use of sunscreen and more outdoor activity would  
891 reduce the need for vitamin D fortification or supplementation, albeit at an increased risk of skin cancer  
892 (Jou and Tomecki 2014).  
893

894 When milk is skimmed to produce non-fat or low-fat milk, both fat and fat-soluble Vitamin A are removed.  
895 Vitamin A is normally added to skimmed milks, to restore the vitamin A level to slightly more than what  
896 whole milk contains. The WIC regulations require vitamin D addition to all “milk” and vitamin A addition  
897 to partially and fully skimmed milk. Consuming more yellow vegetables, such as carrots, winter squash,  
898 and sweet potatoes, would provide beta-carotene, provitamin A, which the body converts into vitamin A  
899 as needed, obviating the need to fortify foods with synthetic vitamin A.  
900

901 **Evaluation Question #12: Describe all natural (nonsynthetic) substances or products which may be used**  
902 **in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances**  
903 **that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).**  
904

905 Vitamins and minerals are normally provided by the foods in our diet. Foods in nutrient-dense, mostly  
906 intact forms contain not only the essential vitamins and minerals that are often contained in nutrient  
907 supplements, but also dietary fiber and other naturally occurring substances that may have positive health  
908 effects. Prior to the identification of vitamins, the particular disease states created by consuming refined  
909 cereal grains, which we now know to be vitamin deficiencies, were treated by feeding nutritious foods such  
910 as yeast, milk, meat, and whole grain cereals.  
911

912 Long before ascorbic acid was identified and synthesized, it was known that scurvy could be cured by  
913 feeding citrus fruit or sauerkraut or tea made from spruce needles. Liver is what was fed to people  
914 suffering from “pernicious anemia,” created by Vitamin B12 deficiency. Cod liver oil was a staple tonic for  
915 children in the last half of the Nineteenth Century and the first half of the Twentieth Century as a rickets  
916 preventative, because of its vitamin D content. It also supplies vitamin A.  
917

918  
919 As described earlier in “Combinations of Substances” the use of synthetic ancillary substances in vitamin  
920 and minerals is common, although some nonsynthetic substances are used as well. As demonstrated, in  
921 certain fat-soluble vitamins, the use of anti-oxidants such as BHA or BHT is preferred and often necessary  
922 to extend shelf-life and ensure appropriate vitamin activity. It is not clear from the literature whether other  
923 synthetic anti-oxidants such as tocopherols (appearing in 205.605(b)) can appropriately replace BHA or  
924 BHT in all of these vitamin formulations.  
925

926 **Potential conflicts between current individual substance § 205.605 listings and annotations and the “nutrient**  
927 **vitamins and minerals” listing and annotation.**  
928

929 Per NOSB request, the following describes the status of potassium iodide and ferrous sulfate and answers  
930 the following questions: Is Potassium Iodide added to food for purposes other than nutrient fortification?



931 Does the annotation for Nutrient Vitamins and Minerals on §205.605(b) allow the use of potassium iodide  
 932 and ferrous sulfate for nutrient fortification? Are the individual listings for potassium iodide and ferrous  
 933 sulfate redundant or superfluous?

934  
 935 **a. Potassium iodide and other “nutrient supplement” substances on the National List at §205.605(a)**  
 936

937 Potassium iodide is allowed in food as a “nutrient supplement” [21 CFR 184.1634(c)] and as an allowable  
 938 ingredient in table salt [21 CFR 184.1634(d)]. In both of these uses, potassium iodide is used as a source of  
 939 the nutrient iodine. No other uses are allowed by FDA in human food. [Some iodate salts are allowed by  
 940 FDA for used in bread making as a “dough strengthener” (calcium iodate, see 21 CFR 184.1206), but iodide  
 941 salts are not.]  
 942

943 Potassium iodide and several other substances (see below) with nutrient activity are present on the  
 944 National List at § 205.605(a). This situation reflects the regulatory approach taken by USDA to implement  
 945 specific NOSB recommendations that these several nonorganic, nonagricultural substances must be from a  
 946 nonsynthetic source, which is what § 205.605(a) lists. Eliminating the listing of these substances from  
 947 §205.605(a) would permit synthetic forms of these substances to be used, since “Nutrient vitamins and  
 948 minerals” are listed at § 205.605(b) “Allowed synthetics.” Allowing the synthetic forms would be  
 949 inconsistent with specific NOSB recommendations.  
 950

Substance name (synonyms)	CAS Number	FDA citation(s)	National List
Potassium iodide	7681-11-0	21 CFR 184.1634	205.605(a)
Calcium sulfate (anhydrous)	7778-18-9	21 CFR 184.1230	205.605(a)
Calcium sulfate (dihydrate)	10101-41-4	21 CFR 184.1230	205.605(a)
Magnesium sulfate heptahydrate	10034-99-8	21 CFR 184.1443	205.605(a)
Potassium chloride	7447-40-7	21 CFR 184.1622	205.605(a)
Sodium bicarbonate	144-55-8	21 CFR 184.1736	205.605(a)
Sodium carbonate	497-19-8	21 CFR 184.1742	205.605(a)

951  
 952 **b. Ferrous sulfate**  
 953

954 In April 1995, the NOSB recommended the addition of the synthetic substance ferrous sulfate to the  
 955 National List with the annotation: “This material is allowed for iron fortification of foods that is required  
 956 by regulation or for iron enrichment by professional recommendation.” In November 1995, the NOSB  
 957 recommended the addition of the synthetic substances “nutrient vitamins and minerals” to the National  
 958 List with the annotation: “Accepted for use in organic foods for enrichment or fortification when required  
 959 by regulation or recommended by an independent professional organization” and also passed final Board  
 960 recommendation addendum number 13, which stated “Upon implementation of the National Organic  
 961 Program, the use of synthetic vitamins, minerals, and/or accessory nutrients in products labeled as organic  
 962 must be limited to that which is required by regulation or recommended for enrichment and fortification  
 963 by independent professional associations.” The example given in the recommendation addendum is infant  
 964 cereal fortified with iron.  
 965

966 It is clear that the NOSB recommended the addition of synthetic ferrous sulfate to the National List with  
 967 the same restrictions that the NOSB later recommended be applied to synthetic “nutrient vitamins and  
 968 minerals,” thus making a separate listing of “ferrous sulfate” for its use for food enrichment or fortification  
 969 superfluous **IF** both annotations are compatible and consistent with the NOSB recommendations.  
 970

971 “Ferrous sulfate” currently is listed at §205.605(b), “Synthetics allowed,” with the annotation “for iron  
 972 enrichment or fortification of foods when required by regulation or recommended (independent  
 973 organizations).” This is consistent with the NOSB recommendation. “Nutrient vitamins and minerals” is  
 974 listed currently at §205.605(b), with the annotation “in accordance with 21 CFR 104.20, Nutritional Quality

975 Guidelines for Foods.” NOP pointed out (77 FR 1980) that this annotation is not consistent with the NOSB  
976 recommendation.

977  
978 **Evaluation Information #13: Provide a list of organic agricultural products that could be alternatives for**  
979 **the petitioned substance (7 CFR § 205.600 (b) (1)).**

980  
981 As described in detail under Question #11, one of the main alternatives to supplementation of synthetic  
982 vitamins and minerals is to obtain these nutrients from organic foods such as fruits, vegetables, and whole  
983 grains. Otherwise, below is a description of other potential additives that can provide specific nutrient or  
984 vitamin value.

985  
986 Organic yeast (*S. cerevisiae*) might be a partial replacement for certain essential vitamins and minerals.  
987 Brewer's yeast, Baker's yeast, and 'nutritional' yeast have been used for many years as nutritional  
988 supplements. They provide B-complex vitamins, chromium, and selenium. The B-complex vitamins in  
989 these yeasts include thiamin, riboflavin, niacin, pantothenic acid, vitamin B6, folate, and biotin.

990  
991 Brewer's yeast and Baker's yeast cannot replace all the B vitamins. The yeast *Saccharomyces cerevisiae* does  
992 not synthesize vitamin B12, a vitamin found naturally only in animal products such as milk and meat, and  
993 in certain bacteria. The National Nutrient Database for Standard Reference<sup>11</sup> value for vitamin B12 in  
994 baker's yeast is 0.03 mcg/100g, dry basis, a nutritionally insignificant amount. Similarly, a distributor of  
995 brewer's yeast reports an absence of vitamin B12 in its "100% pure Brewer's yeast."<sup>12</sup> In contrast, the source  
996 of vitamin B12 in several vegan vitamin products is "nutritional yeast," which also is labeled as "*S.*  
997 *cerevisiae*". The reason that "nutritional yeast" contributes vitamin B12, whereas brewer's yeast and baker's  
998 yeast do not, is that "nutritional yeast" is fortified with synthetic vitamin B12. One step of the five-step  
999 process for manufacture of nutritional yeast is "fortification," described as "vitamins or minerals may be  
1000 added to enhance the nutritional profile of the yeast."<sup>13</sup>

1001  
1002 Another vitamin B12-enriched yeast is derived from cultures of specified strains of *Saccharomyces*  
1003 *cerevisiae* grown in the presence of vitamin B12 (cyanocobalamin). The European Food Safety Authority  
1004 concluded that the bioavailability of vitamin B12 from this vitamin B12-enriched yeast and the safety of this  
1005 vitamin B12-enriched yeast could not be assessed, due to lack of information (European Food Safety  
1006 Authority 2009).

1007  
1008 Brewer's yeast tastes bitter and contains a large amount of tyramine, a biogenic amine substance that can  
1009 interact with monoamine oxidase inhibitor drugs ("MAOIs") and cause a hypertensive crisis. A  
1010 hypertensive crisis is a very fast and dangerous rise in blood pressure that can cause heart attack or stroke.  
1011 MAOIs are used to treat depression. Tyramine also can precipitate migraine attacks in sensitive individuals  
1012 (University of Maryland Medical Center).

1013  
1014 Organic fruit juices may provide vitamin C if the inherent flavor of the fruit juice is compatible with the  
1015 organoleptic characteristics of the product. Moreover, the vitamin C content of fruit juices may be too  
1016 variable to ensure labeled potency (Hallberg, Brune and Rossander 1989).

1017  
1018 Ascorbic acid, the substance with vitamin C activity, separately listed at § 205.605(b), is used as a  
1019 processing aid in organic fruit products, to prevent darkening of cut fruit surfaces, for example. Any  
1020 residual vitamin C activity may or may not be labeled in the Nutrition Facts panel of the food label. In

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<sup>11</sup> Item 18374: Leavening agents, yeast, baker's, compressed. In National Nutrient Database for Standard Reference, Release 27 Software v.2.0b, The National Agricultural Library. Accessed 24 November 2014.

<sup>12</sup> <http://lewislabdirect.com/products/new-brewers-yeast-12-35oz>. Accessed 24 November 2014.

<sup>13</sup> <http://esaffre-yeast.com/five-steps.html>. Accessed 22 November 2014.

1021 some of these situations, organic lemon juice concentrate might replace ascorbic acid without making the  
1022 product taste too 'lemony.'<sup>14</sup> Note that ascorbic acid is not being added as a "nutrient vitamin" in this case.  
1023  
1024

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