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PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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VITAMIN AND MINERAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Establishment of a Monograph, Proposed Rule

[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 345]

[Docket No. 78N-0024]

VITAMIN AND MINERAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Establishment of a Monograph; Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) vitamin and mineral drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products, is part of the Food and Drug Administration's ongoing review of OTC drug products.

DATES: Comments by June 14, 1979, and reply comments by July 16, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on November 1, 1977, a report of the Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products. Additional technical changes were made by the Panel during a telephone conference on December 8, 1977. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC vitamin and mineral drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration (address given above).

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report; the Panel's findings are being issued as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. The report has been prepared independently of the Food and Drug Administration (FDA).

It represents the best scientific judgment of the Panel members but does not necessarily reflect the agency position on any particular matter contained in it. After careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC vitamin and mineral drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC vitamin and mineral drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after April 16, 1979, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address given above).

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (Category I), be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph because they would cause the drug to be not generally recognized as safe and effective or to be misbranded (Category II), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph because the available data are insufficient (Category III) to classify such conditions either as Category I or Category II be permitted to remain on the market, or to be introduced into the market after the date of publication of the final monograph in the FEDERAL REGISTER: *Provided*, That FDA receives notification of testing in accordance with § 330.10(a)(13) (21 CFR 330.10(a)(13)).

The Panel recommended that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I. The Commissioner will review that recommendation as well as all comments on this document, and will determine what time period to permit for Category III testing after that review is completed.

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. In the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), the Commissioner published the final regulations providing for the OTC drug review under § 330.10 which made effective immediately. Pursuant to these regulations, the Commissioner issued in the FEDERAL REGISTER of October 15, 1973 (38 FR 28581) a request for data and information on all active ingredients utilized in OTC vitamin, mineral, and hematinic drug products.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report pursuant to § 330.10(a)(1) on the safety, effectiveness, and labeling of those products:

Irwin H. Rosenberg, M.D., Chairman
Louis V. Avioli, M.D.
George M. Briggs, Ph.D.
Robert S. Goodhart, M.D., D.Med.Sc.
Mary Anne Kimble, Pharm.D.
Carroll M. Leevy, M.D.
Mary Susanne Roscoe, M.D.

The Panel was first convened on December 11, 1973 in an organizational meeting. Working meetings were held on February 17 and 18, April 8 and 9, May 18 and 19, June 16 and 17, July 30 and 31, September 29 and 30, and November 15 and 16, 1974; January 6 and 7, February 16 and 17, April 27 and 28, June 24 and 25, and November 14 and 15, 1975; January 13 and 14, March 22 and 23, July 22 and 23, August 25, 26, and 27, October 17 and 18, and December 14 and 15, 1976; February 14 and 15, June 23 (telephone conference), October 31, November 1, and December 8, 1977 (telephone conference).

Seven nonvoting liaison representatives served on the Panel. Ms. Sandra Zimmerman, nominated by an ad hoc group of consumer organizations, served as the consumer liaison; Joseph M. Pisani, M.D., nominated by the Proprietary Association, served as the industry liaison until August 25, 1976, followed by William W. Bradley; William E. Marshall, Ph.D., nominated by the Council for Responsible Nutrition, also served as an industry liaison until July 1974, followed by Harry Wax, Ph.D. until November 1975, followed by Annette Dickinson. Paul A. Buck, Ph.D., nominated by the National Nutritional Foods Association, also served as an industry liaison.

The following FDA employees served: J. William Boehne served as Executive Secretary. Thomas D. DeCillis, R.Ph., served as Panel Administrator. Lloyd G. Scott, R.Ph., served as Drug Information Analyst until April 1974, followed by Gary P. Trosclair, R.Ph., until October 1974, followed by Thomas H. Gingrich, R.Ph., until June 1975, followed by T. Thomas Clark, R.Ph., until June 1976, followed by Gary P. Trosclair, R.Ph., John T. McElroy, J. D., served as Consumer Safety Officer from June 24, 1975 until March 23, 1976.

The following individuals were given an opportunity to appear before the Panel to express their views:

Ernest Beutler, M.D.
Myron Brin, Ph.D.
Paul A. Buck, Ph.D.
Robert B. Choate
Leon Ellenbogen, Ph.D.
David Herting, Ph.D.
C. J. Jansen, Jr., M.D.
Daniel Marcus, Esq.
L. G. Marviney
Daniel B. Menzel, M.D.
Lowell D. Miller, Ph.D.
Harold Newmark
Billy J. Softly, Ph.D.
William Driscoll

The following individuals were given an opportunity to present their views at the Panel's request:

Leslie Z. Benet, Ph.D.
Gilbert Forbes, M.D.
Linus Pauling, Ph.D.
Daphne A. Roe, M.D.
Leon Rosenberg, M.D.
Harold H. Sandstead, M.D.
H. P. Sarett, Ph.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through December 8, 1977, in arriving at its conclusions and recommendations. The charge to the Panel required the review of three classes of OTC drugs, i.e., vitamins, minerals, and hematinics. However, the Panel concluded early in its deliberations that the review of hematinic drugs as a separate class was in appropriate since this class of drugs could not be considered apart from vitamins and minerals. Hematinics are substances which increase the hemoglobin of the blood and/or increase the number of red blood cells. These effects are discussed by the Panel under the appropriate vitamin or mineral ingredient elsewhere in this document and not as effects of a separate class of drugs. Therefore, the Panel has presented its conclusions and recommendations in only two parts. (See part III. below—VITAMINS, and part IV. below—MINERALS.) Each part covers the submission of data and information discussed below. (See part I. below—SUBMISSION OF DATA AND INFORMATION.)

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC vitamin and mineral drug products are set out in three categories:

Category I. Conditions under which OTC vitamin and mineral drug products are generally recognized as safe and effective and are not misbranded.

Category II. conditions under which OTC vitamin and mineral drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

I. Submission of Data and Information

Pursuant to the notice published in the Federal Register of October 15, 1973 (38 FR 28581) requesting the submission of data and information on OTC vitamin, mineral, and hematinic drugs, the following firms made submissions relating to the indicated products:

A. Submissions by Firms

Firm and Marketed Products

A. H. Robins Co., Richmond, VA 23220—Adabee Multivitamins, Adabee with Minerals Tablets, Allbee Capsules, Allbee-T Multivitamins.

Abbott Laboratories, North Chicago, IL 60064—Daylong Tablets, Fero-Gradumet Filmtab, Fero-Grad-500 Filmtabs, Iberet-500 Liquid, Iberet Filmtab Tablets, Iberet Liquid, Iberol-F Filmtab Tablets, Iberol Filmtab Tablets, Iberet-500 Filmtab Tablets, Optilets-500 Filmtab Tablets, Optilets-M-500 Filmtab Tablets, Surbex Filmtab Tablets, Surbex w/C Filmtab Tablets, Surbex-T Filmtab Tablets.

Ayerst Laboratories, New York, NY 10017—Beminal 500 Tablets, Beminal Forte with Vitamin C Capsules, Beminal Vitamin B Complex with Iron and Liver Capsules, Clusivets Tablets, Clusivol Chew Tablets, Clusivol Syrup, Cyoteferin Tablets.

Central Pharmacal Co., Seymour, IN 47274—Niferex-150, Niferex Elixir, Niferex Tablets.

Cooper Laboratories, Inc., Bedford Hills, NY 10507—Ferronord Tablets, Vitron-C Hematinic Tablets.

Dorsey Laboratories, Lincoln, NE 68501—Neo-Calglucon Syrup.

E. R. Squibb & Sons, Inc., Princeton, NJ 08540—B Complex with Vitamin C Capsules, Iron with Vitamin C Tablets, Natural Vitamin E Capsules 100 I.U., Natural Vitamin E Capsules 400 I. U., Niacin Tablets 50 mg, Niacin Tablets 100 mg, Niacin Tablets 500 mg, Vitamin C Tablets 125 mg, Stress Formula B Complex with Vitamin C Tablets, Theragran Liquid, Theragran-M Tablets, Theragran Tablets, Vitamin A Capsules 10,000 U., Vitamin A from Natural Sources Capsules 10,000 U., Vitamin B-1 50 mg Tablets, Vitamin B-1 100 mg Tablets, Vitamin B-12 Capsules 25 mcg, Vitamin Cmg, Vitamin C Tablets 250 mg, Vitamin C Tablets 500 mg, Vitamin C Orange-Flavored Tablets 250 mg, Vitamin E Capsules 100 I.U., Vitamin E Walnut Flavored Tablets 200 I.U.

ICI America Inc., Wilmington, DE 19899—Ferancee-HP Hematinic Tablets, Ferancee Hematinic Tablets, Mucoplex Tablets, Orexin Therapeutic Vitamin Supplement Tablets, Probec-T Tablets, Probec Tablets, Stuart Hematinic Liquid, Stuart Hematinic Tablets, Stuart Therapeutic Multi-vitamin Tablets, Stuartinic Hematinic Tablets, Theron Tablets.

International Pharmaceutical Corp., Warrington, PA 18976—Calcident Tablets.

J. B. Williams Co., Inc., New York, NY 10022—Geritol Liquid, Geritol Tablets.

Lederle Laboratories, Pearl River, NY 10965—Ferro-Mandets Tablets, Ferro-Sequels Capsules, Filibon OT Prenatal Tablets, Filibon Prenatal Capsule, Gevrabon Vitamin Mineral Supplement, Gevral Capsules, Gevral Protein, Gevral T Capsules, Gevrite Tablets, Incremin with Iron Syrup, Lederplex Capsules, Lederplex Liquid, Lederplex Tablets, Peritinic Tablets, Recoup Tablets, Stresscaps, Stresstabs 600, Vi-magna Capsules.

Mallinckrodt Chemical Works, St. Louis, MO 63160—Toleron Suspension, Toleron Tablets.

Marion Laboratories, Inc., Kansas City, MO 64137—Os-Cal Tablets.

Mead Johnson Laboratories, Evansville, IN 47721—Feminins Tablets.

Merrell-National Laboratories, Cincinnati, OH 45215—Simron Capsules, Simron Plus Capsules.

Pfizer Pharmaceuticals, New York, NY 10017—Crystalets, Stablets, Vitamin A Palmilets.

Plus Products, Los Angeles, CA 90058—Plus Formula 10 Multimineral Tablets, Plus Formula 14 Multi-mins Tablets, Plus Formula 15 Multi-Mins Tablets, Plus Formula 22 Magnesium Oxide Powder, Plus Formula 23 Manganese Tablets, Plus Formula 50 Liver, Iron & B Vitamins Tablets, Plus Formula 49 Vitamin B Complex Tablets, Plus Formula 49A Vitamin B Complex Tablets, Plus Formula 70 Vitamin B complex Tablets, Plus Furmula 71 High Potency Vitamin B Complex with Vitamin C Tablets, Plus Formula 72 Stress Supplement Tablets, Plus Formula 74 Vitamin and Mineral Supplement Perles, Plus Formula 75 B Complex 75 Tablets, Plus Formula 77 Vitamin B complex Syrup with Iron, Plus Formula 78 Vitamin Syrup for

Children, Plus Formula 80A Bone Meal Powder, Plus Formula 85 Natural Bone Meal with Magnesium, Manganese and Zinc Tablets, Plus Formula 86 Zinc 30 mg Tablets (proposed), Plus Formula 87 Zinc Tablets 50 mg (proposed), Plus Formula 92 Granular Soya Lecithin, Plus Formula 93A Lecithin Perles, Plus Formula 98 Vita-Fems tablets (proposed), Plus Formula 100 DFS Perles, Plus Formula 101A Vitamin A Perles, Plus Formula 104A Emulsified A Perles, Plus Formula 122 PABA Tablets 100 mg (proposed), Plus Formula 123 Para-Aminobenzoic Acid (PABA) Tablets 30 mg, Plus Formula 124 Choline Tablets 250 mg, Plus Formula 125A Inositol Tablets 250 mg, Plus Formula 126 Inositol Powder, Plus Formula 127 Choline Tablets 500 mg (proposed), Plus Formula 128 Inositol tablets 500 mg (proposed), Plus Formula 152 Emulsified Vitamin E Complex Perles, Plus Formula 153 Vitamin E Complex Perles, Plus Formula 154A Emulsified Vitamin E Complex Perles, Plus Formula 155 Vitamin E Complex Perles, Plus Formula 156 Vitamin E Complex Perles, Plus Formula 157 Vitamin E Capsules 400 I.U. (proposed), Plus Formula 158 Vitamin E tablets 100 I.U., Plus Formula 159 Vitamin E Perles 100 Units, Plus Formula 160 Vitamin E Capsules 600 I.U. (proposed), Plus Formula 162 Vitamin E Perles 200 I.U., Plus Formula 163 Vitamin E Perles 300 I.U., Plus Formula 164 Vitamin E Perles 400 Units, Plus Formula 165 Vitamin E Perles 500 Units, Plus Formula 166 Vitamin E Capsules 600 I.U. (proposed), Plus Formula 175 Dietary Food Supplement Perles, Plus Formula 180 Potassium & Iodine Tablets, Plus Formula 184 Calcium and Magnesium Tablets, Plus Formula 202A Vitamins A & D Perles, Plus Formula 203A Vitamins A & D Dry Form Tablets, Plus Formula 205A Vitamins A, D & E Perles, Plus Formula 206 A, D & E Drops, Plus Formula 207 Vitamins A & E Perles, Plus Formula 222 High Potency Cod Liver Oil, Plus Formula 234 Vitamin B-1 Tablets 100 mg, Plus Formula 242 Vitamin B-2 Tablets 10 mg, Plus Formula 243 Vitamin B-2 50 mg Tablets (proposed), Plus Formula 244 Vitamin B-2 Tablets 100 mg (proposed), Plus Formula 249 Dried Yeast Tablets, Plus Formula 250 Yeast Plus, Plus Formula 251 Vitamin B-6 Tablets 10 mg, Plus Formula 252 Vitamin B-6 Tablets 25 mg, Plus Formula 253 Vitamin B-6 Tablets 50 mg, Plus Formula 259 Pantothenic Acid Tablets 250 mg (proposed), Plus Formula 260 Niacin Tablets 100 mg, Plus Formula 261 Niacin Tablets 250 mg (proposed), Plus Formula 262 Niacinamide Tablets 250 mg (proposed), Plus Formula 264A Pantothenic Acid Tablets 100 mg, Plus Formula 263 Niacinamide Tablets 200 mg, Plus Formula 265A Acerola Chews Tablets, Plus Formula 266A Chewable Vitamin C Tablets 200 mg, Plus Formula 267A Chewable Vitamin C Tablets 100 mg, Plus Formula 268 Liquid Vitamin C, Plus Formula 272A Vitamin C Tablets 250 mg, Plus Formula 273A Vitamin C Tablets 500 mg, Plus Formula 275 Vitamin C Complex 200 mg, Plus Formula 277 Vitamin C Complex 100 mg, Plus Formula 278 Vitamin C Powder, Plus Formula 279 Vitamin C Powder, Plus Formula 280A Vitamin C Tablets 600 mg, Plus Formula 282 Vitamin C Complex Tablets 200 mg, Plus Formula 290 granular Kelp, Plus Formula 303 Vitamin B-12 Tablets 100 mcg (proposed), Plus Formula 304 Vitamin B-12 Tablets 25 mcg, Plus Formula 333 Dried Yeast and Iron Tablets, Plus Formula 380 Mint-A-Mins Chewable Vitamin Wafers, Plus Formula 450 Instant Brewer's Yeast, Plus Formula 445 Iron Supplement Tablets, Plus Formula 740 Tiger's Milk Cookies, Plus Formula 745 Tiger's Milk Carob Coated Bar, Plus Formula 746 Tiger's Milk Real Peanut Butter Bar, Plus Formula 747 Tiger's Milk Peanut Butter and Honey Bar, Plus Formula 748 Tiger's Milk Peanut Butter and Jelly Bar, Plus Formula 749 Tiger's Milk Calorie Watcher's Snack, Plus Formula 800 Tiger's Milk Nutrition Booster Plain, Plus Formula 825 Tiger's Milk Nutriton Booster Natural Carob Flavor, Plus Formula 850 Tiger's Milk Nutrition Booster Natural Vanilla Flavor, Plus Formula 875 Tiger's Milk Nutrition Booster Natural Cocoa Flavor.

R. L. Gaddy Co., Tallahassee, FL 32302—Vita-Pep Tablets.

Radiance Products Co., Alhambra, CA 91802—Bone Meal Plus Vitamin D and Iron Tablets, Chewable Tasti C with Bioflavanoid Wafers, Dry Aqua-E 200 Int'l Units Tablets, Norwegian Cod Liver Oil with Vegetable Oils Capsules, Proportioned Magnesium 500 mg Tablets, Super B-Complex Plus C Capsules, Super Potency Multiple Vitamins and Minerals Tablets, Vitamin B-6 100 mg Tablets, Vitamin B-12 250 mcgs in a Special Base Tablets.

S. S. S. Co., Atlanta, GA 30302—S. S. S. Tonic Liquid, S. S. S. Tonic Tablets.

Schering Corp., Kenilworth, NJ 07033—Mol-Iron Chronosule Capsules, Mol-Iron Liquid, Mol-Iron Tablets.

Signet Laboratories, Inc., Burbank, CA 91502—Anti-X Tablets, B-12 Tablets 250 Micrograms, Citrex Plus Tablets, Double Absorption B-12 Tablets 500 mcg, Double Absorption B-12 Tablets 25 mcg, Intensive Care B with C Tablets, Mag-Cal Balanced, Neo-Tone Asimicaps Iron with Vitamins and Minerals tablets, Omni Nutrition Plan Tablets, One Plan Multivitamin-Mineral Supplement Tablets, Pantothenic Acid Tablets 100 mg, Premium Nutrition Plan tablets, POWER-B with Paba Tablets, Super Citrex Tablets, Taste-E-Tab 100 I.U., Taste-E-Tab 200 I.U., Taste-E-Tab 400 I.U., Toco E Sol Tablets 100 I.U., Toco E Sol Tablets 200 I.U., Ultra-Vite Multivitamin-Mineral Supplement Tablets, Vitamin B-1 Tablets 50 mg, Vitamin B-1 Tablets 100 mg, Vitamin B-2 Tablets 25 mg, Vitamin B-6 Tablets 25 mg, Vitamin B-6 Tablets 100 mg.

Smith, Kline and French Laboratories, Philadelphia, PA 19101—Feosol Spansule Capsules.

Sterling Drug, Inc., New York, NY 10016—Afaxin Capsules, Betaxin Tablets, Drisdol, Fergon Capsules, Fergon Compound Elixir, Fergon Elixir, Fergon Tablets, Fergon With C Caplets, Ironized Yeast Tablets, Pluravit Capsules, Pluraxin.

TPR Pharmaceuticals, Inc., Indianapolis, IN 46222—B-Tinic Plus Iron.

William H. Rorer, Inc., Fort Washington, PA 19034—Fermalox Tablets.

Wm. T. Thompson Co., Carson, CA 90745—Acerola C Chewable Tablets, B Complex "50" Capsules, B Complex "50" Tablets, B Complex Capsules (proposed), B Complex Plus C Tablets, C-Flavoids "500" Tablets, C Rose Hips Tablets, E & C with A Capsules, Ex-Po 36 Capsules, Ex-Po 36 Capsules (proposed), Flavoid Complex Tablets (proposed), Fluoride 1 mg Tablets, Folic Acid 0.5 mg Tablets (proposed), Iron Hematinic Tablets, Iron Hematinic Tablets (proposed), Multiminerals with Sea Minerals Tablets, Neo-Globin Tablets, Niacin 100 mg Tablets, Niacinamide 250 mg Tablets, Nuplex Tablets, One Gram C Capsules, Pantothenic Acid 100 mg Tablets, Rose Hips C-Flavoids "650" Tablets, Trace Elements Tablets (proposed), Vitamin A 10,000 I.U. Capsules, Vitamin A 10,000 I.U. Tablets, Vitamin A 10,000 I.U. & Vitamin D 400 I.U. Capsules (proposed), Vitamin A 10,000 Unit Tablets, Vitamin A 25,000 I.U. Tablets, Vitamin A & D Capsules, Vitamin B-1 100 mg Tablets, Vitamin B-1 Tablets 100 mg (proposed), Vitamin B-2 100 mg Tablets, Vitamin B-2 100 mg Tablets (proposed), Vitamin B-6 100 mg Tablets, Vitamin B-6 100 mg Tablets (proposed), Vitamin B-12 "250" mg Tablets, Vitamin B-12 250 mcg Tablets (proposed), Vitamin C Tablets 500 mg, Vitamin D 1200 I.U. Tablets (proposed), Vitamin E 400 Capsules (proposed), Vitamin E 400 I.U. Tablets (proposed), Vitamin E 400 Tablets, Vitamin E & C with A Capsules, Vitamin K-1 mg Tablets (proposed), Zinc 30 mg Tablets (proposed).

In addition, the following firms or groups made related data submissions:

Firm and Data Submitted

Abbott Laboratories, North Chicago, IL 60064—Additional Studies on the usefulness of vitamin C in promoting iron absorption, data to demonstrate the clinical efficacy of controlled-release iron preparations.

A. E. Staley Manufacturing Co., Decatur, IL 62525—Inositol (bulk).

Council for Responsible Nutrition, Washington, DC 20036—Reference bibliographies for ascorbic acid, fat-soluble vitamins, niacin and niacinamide, vitamin A and E; proposed labeling of OTC vitamin and mineral products to be used for the prevention of deficiencies.

Eastman Chemical Products, Inc., Kingsport, TN 37662—Supplemental submission of data and views of vitamin E.

General Mills Chemicals, Inc., Minneapolis, MN 55435—Information and abstracts of significant literature on vitamin E.

Hoffman-LaRoche, Inc., Nutley, NJ 07110—Absorption of vitamins, ascorbic acid, biotin, niacin, pantothenic acid, riboflavin, thiamine, vitamin A, vitamin B-6, vitamin E; supplemental submissions on "High Vitamin Dose Levels in man"; summary data on multivitamins; critical review of OTC Panel addendum to vitamin C review; critical review of vitamin C sodium ascorbate: Sodium warning recommended by the OTC VMH Panel; manufacturing overages of vitamins in pharmaceutical products; supplemental submissions on biotin and vitamin E; comments on ascorbyl plamitate and vitamin A.

ICI America, Inc., Wimington, DE 19899—Calcium sulfate as a source of calcium.

J. B. Williams Co., Inc., New York, NY 10022—Statement regarding safety of self-administered iron preparations.

Marion-Laboratories, Inc., Kansas City, MO 64137—Data supporting the safety of oyster shell (OS-CAL); presentation to the FDA Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic drug products on OS-CAL (oyster shell).

Merrell-National Laboratories, Cincinnati, OH 45215—Comments on polysorbate 20.

Paul A. Buck, Ph.D., Ithaca, NY 14850—Presentation to Panel of previously nonreviewed literature.
Philadelphia Dry Yeast Co., Philadelphia, PA 19122—Debittered Brewers Dry Yeast.
Ross Laboratories, Columbus, OH 43216—Alpha tocopheryl polyethylene glycol 1,000 succinate; proposed product for women on oral contraceptives; animal data on water-soluble vitamin E.
Vitaminerals Inc., Glendale, CA 91201—Bioflavonoids; data and views on vitamin A, vitamin D and iron indications, lipotropic substances, magnesium, vitamins, minerals, and hematinics.

B. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS SUBMITTED TO THE PANEL.

Acerola
Activated ergosterol
Alanine
Alcohol
Alfalfa
Algin
p-Aminobenzoic acid
Apricot
Arginine
Ascorbic acid (vitamin C)
Aspartic acid
Beet greens
Betaine
Biotin
Black currants
Bone meal
Brewer's yeast
Buckwheat
Butyl paraben
Cabbage
Calcium
Calcium ascorbate
Calcium carbonate
Calcium caseinate
Calcium citrate
Calcium fluoride
Calcium glubionate
Calcium iodate
Calcium lactate
Calcium pantothenate
Calcium phosphate dibasic anhydrous
Calcium phytate
Calcium sulfate
Carrot powder
Chaparral
Chlorophyll
Chlorophyllins
Cholecalciferol (vitamin D-3)
Choline
Choline bitartrate
Choline citrate
Citrus bioflavonoids
Cobalamin concentrate
Cod liver oil
Comfrey root
Copper
Copper gluconate
Copper oxide
Copper sulfate
Corn oil
Cyanocobalamin (vitamin B-12)
Cystine
Dandelion greens
Date powder
Desiccated liver
Dexpanthenol
Dioctyl sodium sulfosuccinate
Dolomite
Dulse
Duodenal substance
Edible bone phosphate
Egg albumin
Egg shell
Egg yolk
Ergocalciferol (vitamin D-2)
Extract of ox bile
Ferric ammonium citrate
Ferric phosphate
Ferric pyrophosphate
Ferroglycine sulfate complex
Ferrous carbonate stabilized
Ferrous fumarate
Ferrous gluconate
Ferrous sulfate, dried
Fish liver oil
Folic acid
Formic acid
Gelatin
Glutamic acid
Glycine
Green buckwheat
Green pepper powder
Heprofrax (liver fractions A and 2)
Hesperidin
Hesperidin complex
Histidine
Inositol
Iodine
Iron
Irradiated ergosterol
Isoleucine
Kelp
Lactose
Lecithin
Lemon bioflavonoid complex
Lemon grass oil
Lettuce
Leucine
Linoleic acid
Linolenic acid
Liver fraction 1
Liver fraction, insoluble
Liver preparations
Liver substance
Liver substance concentrate
l-Lysine monohydrochloride
Lysine
Magnesium
Magnesium-aluminum hydroxide
Magnesium carbonate
Magnesium chloride
Magnesium hydroxide
Magnesium oxide
Magnesium silicate
Magnesium sulfate
Magnesium trisilicate
Malt extract
Manganese
Manganese chloride
Manganese gluconate
Manganese oxide
Methionine
Mixed bioflavonoids
Molasses
Niacin
Niacinamide
Niacinamide ascorbate
Nicotinic acid
Oyster shell
Pancreatin
Panthenol
Pantothenic acid
d-Pantothenyl alcohol
Papain
Papaya
Parsley
Peas
Pectin
Pepsin
Phenylalanine
Phosphorus
Phytonadione
Polysorbate
Polysorbate 20
Potassium
Potassium gluconate
Potassium iodide
Potassium sulfate
Proline
Protein hydrolysate
Prune concentrate
Pyridoxine hydrochloride (vitamin B-6)
Red bone marrow
Riboflavin
Riboflavin-5-phosphate sodium
Rice bran
Rice oil, cold pressed
Rice polishings
Rose hips powder
Rutin
Safflower oil
Serine
Silica
Silicon
Sodium ascorbate
Sodium benzoate
Sodium saccharin
Sorbitol
Soya lecithin
Soy flower
Soy oil, cold pressed
Spinach powder
Sucrose
Sulfur
Thiamine
Thiamine hydrochloride
Thiamine mononitrate
Threonine
Tillandsia
dl-alpha-Tocopheryl acetate
dl-alpha-Tocopheryl acid succinate
alpha-Tocopheryl polyethylene glycol 1000 succinate
Torula food yeast
Torula yeast
Tricholine citrate
Tryptophan
Turnip greens
Tyrosine
Unsaturated fatty acids (vitamin F)
Valine
Vanilla
Vitamin A
Vitamin A acetate
Vitamin A palmitate
Vitamin B-6
Vitamin B-12
Vitamin C
Vitamin D
Vitamin E
Vitamin K
Watercress
Wheat germ
Wheat germ oil
Wild cherry concentrate
Yeast
Zinc
Zinc gluconate
Zinc lactate
Zinc oxide
Zinc sulfate

The following ingredients have been reviewed in addition to the submitted data:

Ascorbyl palmitate
Calcium gluconate
Choline chloride
Ferric ammonium phosphate
Ferric citrate
Ferric sulfate
Ferric versenate
Ferrocholinate (ferric choline isocitrate)
Ferrous citrate
Ferrous glutamate
Ferrous lactate
Ferrous succinate
Ferrous tartrate

Fluoride (sodium fluoride)
Folacin
Magnesium gluconate
Phylloquinone
Potassium chloride
Retinol
Silicon dioxide (silica, silicon)
alpha-Tocopherol
alpha-Tocopheryl acetate
alpha-Tocopheryl acid succinate
Vitamin K-1
Zinc carbonate
Zinc chloride
Zinc hydroxide
Zinc oxalate
Zinc phytate
Zinc sulfide

C. CLASSIFICATION OF INGREDIENTS.

1. *Active ingredients.* The following ingredients were submitted for Panel review and have been classified into groups identified below according to the vitamin or mineral which these ingredients are intended to provide.

VITAMINS

Vitamin C
  Ascorbic acid
  Ascorbyl palmitate
  Calcium ascorbate
  Niacinamide ascorbate
  Sodium ascorbate
Biotin
  Biotin
Choline
  Choline bitartrate
  Choline chloride
  Choline citrate (tricholine citrate)
Vitamin B-12
  Cyanocobalamin
Folacin
  Folic acid
Niacin
  Niacin (nicotinic acid)
  Niacinamide
  Niacinamide ascorbate
Pantothenic acid
  Calcium pantothenate
  Dexpanthenol (*d*-pantothenyl alcohol, panthenol)
  Pantothenic acid
Vitamin B-6
  Pyridoxine hydrochloride
Riboflavin
  Riboflavin
  Riboflavin-5-phosphate sodium
Thiamine
  Thiamine hydrochloride
  Thiamine mononitrate
Vitamin A
  Vitamin A (retinol)
  Vitamin A acetate
  Vitamin A palmitate
Vitamin D
  Cholecalciferol (vitamin D-3)
  Ergocalciferol (activated ergosterol, irradiated ergosterol, and vitamin D-2)
Vitamin E
  Tocophersolan (alpha-tocopheryl polyethyiene glycol 1,000 succinate)
  apha-Tocopheryl acetate (*dl*-alpha-tocopheryl acetate)
  alpha-Tocopheryl acid succinate (*dl*-alpha-tocopheryl acid succinate)
  Vitamin E (alpha-tocopherol)
Vitamin K
  Phytonadione (phylloquinone, vitamin K-1)

MINERALS

Calcium
  Calcium caseinate
  Calcium citrate
  Calcium glubionate
  Calcium gluconate
  Calcium lactate
  Calcium phosphate dibasic (calcium phosphate dibasic anhydrous)
  Calcium sulfate
  Precipitated calcium carbonate (calcium carbonate)
Copper
  Cupric gluconate (copper gluconate)
  Cupric oxide (copper oxide)
  Cupric sulfate (copper sulfate)
Fluoride
  Calcium fluoride
  Sodium fluoride
Iodine
  Calcium iodate
  Potassium iodide
Iron
  Ferric ammonium citrate
  Ferric ammonium phosphate
  Ferric citrate
  Ferric phosphate
  Ferric pyrophosphate
  Ferric sulfate
  Ferric versenate
  Ferrocholinate (ferric choline isocitrate)
  Ferrohlycine sulfate (ferroglycine sulfate complex)
  Ferrous carbonate (ferrous carbonate stabilized)
  Ferrous citrate
  Ferrous fumarate
  Ferrous glutamate
  Ferrous gluconate
  Ferrous lactate
  Ferrous succinate
  Ferrous sulfate, dried
  Ferrous tartrate
Magnesium
  Magnesium carbonate
  Magnesium chloride
  Magnesium gluconate
  Magnesium hydroxide
  Magnesium oxide
  Magnesium silicate
  Magnesium sulfate
  Magnesium trisilicate
Manganese
  Manganese chloride
  Manganese gluconate
  Manganous oxide (manganese oxide)
Phosphorus
  Calcium phosphate dibasic (calcium phosphate dibasic anhydrous)
Potassium
  Potassium chloride
  Potassium gluconate
  Potassium sulfate
Zinc
  Zinc carbonate
  Zinc chloride
  Zinc gluconate
  Zinc hydroxide
  Zinc lactate
  Zinc oxalate
  Zinc oxide
  Zinc phytate
  Zinc sulfate
  Zinc sulfide

2. *Inactive ingredients.* The Panel has classified the following submitted ingredients as pharmaceutical necessities only.

Alcohol
Butyl paraben
Corn oil
Formic acid
Gelatin
Lactose
Lecithin
Pectin
Polysorbate
Polysorbate 20
Safflower oil
Silicon dioxide (silica, silicon)
Sodium benzoate
Sodium saccharin
Sorbitol
Soya lecithin
Soy oil, cold pressed
Sucrose
Vanilla
Wild cherry concentrate

3. *Miscellaneous ingredients.* The following list of ingredients includes natural sources of vitamins and minerals. Some of these ingredients may have other therapeutic effects (e.g., antacids, enzymes, amino acids) which do not contribute to the effectiveness of vitamins and minerals in treating vitamin or mineral deficiencies. These ingredients have been used in the past as sources for the vitamins and minerals discussed in this document; however, the Panel concludes that these ingredients and/or sources are not appropriate for OTC drug use. It is irrational that any of the following ingredients be included in OTC vitamin and mineral drug products as sources of vitamin or mineral drugs because they are not known to add to the effectiveness or safety of the preparation. For example, magnesium-aluminum hydroxide has been used as an antacid. Betaine hydrochloride and glutamic acid hydrochloride are claimed to be acidifying agents. However, dioctyl sodium sulfosuccinate has been reviewed by another OTC Advisory Review Panel elsewhere as a fecal softener and mild laxative but may be rational when in combination with iron, if testing recommended elsehwere in this document confirms claims of decreased side effects. The use of the above ingredients as separate drugs properly belongs to the review of other FDA Advisory Review Panels. The same restriction applies to the addition of what are supposed to be digestive aids, e.g., duodenal substance, extract of ox bile, pancreating, papain, papaya, and pepsin, to OTC vitamin-mineral preparations. There is no justification for the addition of amino acids or peptides such as histidine, lysine, methionine, or protein hydrolysates in OTC vitamin and mineral preparations, as these compounds make no significant contribution to the vitamin or mineral content or utilization of these products.

Finally, the submissions to the Panel include ingredients of no established nutritional or therapeutic value which are not sources of the vitamins or minerals approved for these combinations. The Panel recognizes no additional nutritional or other benefits from the ad-

dition of these compounds to vitamin and mineral preparations and therefore recommends that their addition not be allowed. Included in this group are such compounds as buckwheat, hesperidin, inositol, lecithin, bioflavonoids, *p*-aminobenzoic acid, rutin, and sulfur.

Acerola
Alanine
Alfalfa
Algin
p-Aminobenzoic acid
Apricot
Arginine
Aspartic acid
Beet greens
Betaine
Black currants
Bone meal
Brewers' yeast
Buckwheat
Cabbage
Calcium phytate
Carrot powder
Chaparral
Chlorophyll
Chlorophyllins
Citrus bioflavonoids
Cobalamin concentrate
Cod liver oil
Comfrey root
Cystine
Dandelion greens
Date powder
Desiccated liver
Dioctyl sodium sulfosuccinate
Dolomite
Dulse
Duodenal substance
Edible bone phosphate
Egg albumin
Egg shell
Egg yolk
Extract of ox bile
Fish liver oil
Glutamic acid
Glycine
Green buckwheat
Green pepper powder
Hesperidin
Hesperidin complex
Histidine
Inositol
Isoleucine
Kelp
Lecithin
Lemon bioflavonoid complex
Lemon grass oil
Lettuce
Leucine
Linoleic acid
Linolenic acid
Liver fraction
Liver fraction, insoluble
Liver fractions A and 2
Liver preparations
Liver substance
Liver substance concentrate
l-Lysine monohydrochloride
Lysine
Magnesium-aluminum hydroxide
Malt extract
Methionine
Mixed bioflavonoids
Molasses
Oyster shell
Pancreatin
Papain
Papaya
Parsley
Peas
Pepsin
Phenylalanine
Proline
Protein hydrolysate
Prune concentrate
Red bone marrow
Rice bran
Rice oil, cold pressed
Rice polishings
Rose hips powder
Rutin
Serine
Soy flower
Spinach powder
Sulfur
Threonine
Tillandsia
Torula food yeast
Torula yeast
Tryptophan
Turnip greens
Tyrosine
Unsaturated fatty acids (vitamin F)
Valine
Watercress
Wheat germ
Wheat germ oil
Yeast

D. REFERENCED OTC VOLUME SUBMISSIONS

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of October 15, 1973 (38 FR 28581). The volumes will be put on public display after April 16, 1979, in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

II. GENERAL STATEMENTS AND RECOMMENDATIONS

A. HISTORICAL FRAMEWORK AND RATIONALE

1. *Background.* No comprehensive review of OTC drugs has previously been carried out by FDA and no detailed review of OTC vitamin and mineral drug products has been undertaken. Vitamin and mineral products first came under the provisions of the Food and Drugs Act of 1906, with subsequent major modifications of the act by Congress in 1912, 1938, 1951, and 1962.

The initial effort by Congress to exert some control over the marketing of foods and drugs was embodied in the Food and Drugs Act of 1906. Under this law, drugs marketed in interstate commerce were required to meet their professed minimal standards of strength, quality, and purity. This act was largely designed to prevent adulteration of foods and drugs and was not directed at the effectiveness or safety of the ingredients themselves.

In 1912 Congress passed the Sherley Amendment to the 1906 Act which defined a drug as misbranded if it included false and fraudulent claims.

In 1938 a comprehensive Federal Food, Drug, and Cosmetic Act was passed with "new drug" provisions which required premarket clearance, i.e., new drugs which were not generally recognized as safe had to be shown to be safe through an approved new drug application (NDA) prior to marketing. "Old" drugs, including vitamins, which were considered safe prior to 1938, were permitted to continue on the market without further review. However, FDA maintained the authority to review these old drugs if possible safety concerns became apparent. In 1951, the Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act was passed. This act formally differentiated between prescription and OTC drugs. It provided that a drug be sold OTC if it is safe and if adequate directions for use can be written which are readily discernible by a layman so that a professional's advice is not required for administration or use of the drug.

In 1962 Congress passed the Kefauver-Harris Bill requiring that all "new drugs," both prescription and OTC, be proven effective as well as safe before marketing. The amendment required an effectiveness review for all new drug products which had been approved for safety between the 1938 Act and the 1962 Amendment. In 1966 FDA contracted with the National Academy of Sciences, National Research Council (NAS/NRC) for an extensive review of 4,000 drugs which had NDA's approved between 1938 and 1962. Some 500 of these drugs were OTC products, and several of them were vitamin and/or mineral preparations. Most OTC vitamins and minerals, however, were marketed without the submission of proof of safety or effectiveness to FDA. Thus, the current OTC drug review of vitamins and minerals is really the first time that FDA has systematically reviewed, in relation to the drug provisions of the Federal Food, Drug, and Cosmetic Act, vitamins and minerals for safety and effectiveness and for the appropriateness of labeled claims for OTC drug use.

2. *Dietary supplement use of vitamins and minerals as compared to OTC drug use of vitamins and minerals.* The Panel accepted the terms of the Federal Food, Drug, and Cosmetic Act in which products are considered drugs if intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (21 U.S.C. 321). The Panel therefore concludes that representation of a vitamine or mineral preparation for use in the "prevention" or for the "treatment" of a vitamin or mineral deficiency is clearly a representation for therapeutic usage, and that such a preparation should be subject to this document and regulat-

ed as a drug, not as a dietary supplement.

A dietary supplement of a vitamin or mineral is a food intended (i.e., purported or represented) to supplement a diet by increasing the total dietary intake of one or more essential vitamins or minerals. The Panel established the philosophy that a vitamin or mineral active ingredient becomes an OTC drug when that vitamin or mineral is used to overcome a probable deficit in the diet (i.e., to prevent the imminent development of a disease condition or for treatment of a vitamin- or mineral-deficiency disease). The Panel concluded that the need for such prevention or treatment should be determined by a physician.

Although a balanced diet provides adequate amounts of essential nutrients, some individuals may not be receiving a balanced diet for various reasons and may wish to supplement their diet. Dietary supplements of vitamins and minerals are marketed for this purpose and are regulated as "foods for special dietary use," as distinguished from OTC drug use. Dietary supplements are regulated by a separate set of regulations which were originally promulgated in 1941 and are clearly outside the purview of this Panel. Efforts to amend the regulations have been ongoing since 1962 and were the subject of hearings from 1968 to 1970, and finally culminated in the publication of final regulations in 1973—the same year this Panel held its first meeting. The 1973 dietary supplement regulations were pertinent to the activities of this Panel in that an "upper limit" on the quantity of vitamins and minerals in a dietary supplement was established (150 percent of the U.S. RDA, in most instances). Products containing vitamins and minerals in excess of the upper limit, as well as those making drug claims, were to be regulated as drugs and therefore were subject to this Panel's review. Due to judicial and legislative developments, the 1973 dietary supplement regulations were never enforced. New regulations were published in the FEDERAL REGISTER of October 19, 1976 (41 FR 46156), and were to take effect in January 1978. Subsequently, the effective date was extended to July 1, 1979. These regulations established "lower limits" (50 percent of the U.S. RDA, in most instances) for the quantity of vitamins and minerals included in dietary supplements. Products intended for use by children or by pregnant or lactating women had to conform to a "standard of identify" specifying which nutrients must be included and the quantity of each that must be present. Products intended for adults other than pregnant or lactating women were not covered by the October 19, 4976 standard of identity, and there were no upper limits on the quantity of vitamins and minerals in such products except when safety limits are established by regulation, e.g., as in the case of food additive regulations limiting the permissible quantities of folic acid and iodine which may be included in any food product, including special dietary foods such as dietary supplements. On February 16, 1978, these regulations were vacated by the United States Court of Appeals for the Second Circuit (*National Nutritional Foods Assn.* v. *Kennedy*, 472 F. 2d 377 (2d Cir. 1978)). They must be re-proposed in conformity with the Court's instructions.

Products subject to the dietary supplement regulations are not subject to the labeling and compositional requirements recommended in this document, which is addressed to OTC vitamin and mineral drug preparations intended for therapeutic use. However, the Panel emphasizes that observations in this document with respect to the safety, effectiveness, and appropriate labeling of vitamins and minerals may be relevant to dietary supplements as well as to drug usage.

3. *Present status.* The Panel viewed its charge according to the OTC drug regulations (21 CFR 330.10) to review all submitted data and the relevant scientific literature in order to make recommendations for the conditions under which vitamins and minerals could be marketed for safe and effective OTC use with appropriate labeling. Thus, for each ingredient reviewed, a determination was made of the conditions under which a vitamin or mineral could be used in the prevention or treatment of a disease or the mitigation of symptoms. In addition, it was necessary to identify those situations under which vitamins, minerals, or combinations of vitamins and minerals could be safely and effectively used as OTC drugs. Thus, for a vitamin or mineral ingredient or combination of vitamins and minerals to be considered Category I, that is safe, effective, and appropriately labeled for OTC drug use, two requisite conditions had to be satisfied: (1) Identification of a disease or condition in a significant target population which could be safely treated or prevented by the OTC ingredient, and (2) instructions to the consumer which are clear, true, and not misleading.

B. LABELING FOR OTC VITAMINS AND MINERALS

After review of all submitted claims and after evaluating pertinent literature, the Panel concluded that the appropriate use for vitamins and minerals as OTC drug products was for the prevention or treatment of vitamin and mineral deficiencies. Since the identification of many conditions which predispose to nutritional deficiency of vitamins and minerals and the identification of the deficiencies require the professional capabilities of a physician, effective instructions to the consumer for the use of vitamins and minerals for the prevention or treatment of vitamin and mineral deficiency can only be given when the need for such prevention and treatment is identified by a physician. Therefore, the formula which has been adopted for labeling use, in the case of each vitamin, mineral, or combination, refers to the use of vitamins and minerals for prevention or treatment "when the need for such therapy has been determined by a physician." This OTC use of vitamins and minerals is to be distinguished clearly from the use of vitamins and minerals by prescription. When vitamins and minerals are being used in doses and combinations which require the persistent and continuing supervision of a physician in order to monitor the therapy for its safety or effectiveness, such therapy must be controlled by prescription. On the other hand, the recommendation of a physician for OTC purchase of vitamins and minerals implies that the patient is not required to see the physician before each purchase of vitamins and minerals. Once the need for prevention or treatment is identified, it is expected that such therapy could be carried out safely and effectively on the basis of labeled directions.

After reviewing all the claims and the date submitted and in keeping with other similar restrictions in the OTC drug review, the indications for use which the Panel recommends will constitute an exclusive list of labeling claims. Claims of special effectiveness or potency (e.g., stress, high or super potency) will not be permitted. In addition, symptoms that may suggest the presence of a specific vitamin or mineral deficiency may not be listed, except as specifically provided in these recommendations. For example, weakness or tiredness may under certain rare circumstances be symptoms indicative of vitamin or mineral deficiency. However, it is not safe or appropriate that vitamins or minerals be taken for weakness or tiredness unless the cause of these symptoms is vitamin or mineral deficiency. The Panel recognizes no symptoms of vitamin or mineral deficiency as so characteristic that they might be recognized by consumers and safely treated under customary conditions of labeling, purchase, and use.

The Panel recommends that FDA consider labeling in its totality. Terms such as "stress," "super potency," and "geriatric" in the brand name are implied claims and do not comply with the labeling recommendations stated within this document.

To avoid confusion, a vitamin present in a product must be identified by its established name as used within this document and the amount present stated in terms of a designated reference form (equivalent). Frequently, more than one source may appropriately supply the active principle of a particular vitamin or mineral, but equal weights of different sources of vitamins or minerals will not always supply equal amounts of biologic activity. For example, 100 milligrams (mg) of vitamin C biologic activity is supplied by 100 mg of *L*-ascorbic acid, but requires 112.5 mg of sodium ascorbate for the same effects. Therefore, a consumer who compares products may be confused if the vitamin content is listed only in terms of the amount of the contributing ingredient and not in terms of the amount required to produce the desired biologic response. When appropriate, the name, formula, and molecular weight of the reference form (equivalent) are given, for each vitamin.

For products containing minerals, each mineral is best described in the labeling by the name of the element, the amount present, and the name and amount of the source of the mineral, e.g., 150 mg ferrous sulfate provides 30 mg elemental iron.

The Panel does object to the designation of a product as "natural" on a label since this may imply an advantage which the Panel rejects as unsupported by evidence.

The Panel also recommends that all ingredients used for formulation be listed in the labeling so that the consumer may be aware of all ingredients, active or inactive. This is particularly important in view of those occasional instances of an allergic or idiosyncratic response of some individuals to ingredients present in a preparation.

Some vitamin-mineral preparations contain as much as, or more than, 17 percent alcohol. This amount of alcohol may be enough to encourage abusive consumption by some persons. In persons using drugs such as disulfiram, acute reactions can be precipated.

C. EVALUATION OF EFFECTIVENESS

In the view of the Panel, the definition of effectiveness of vitamins and minerals as drugs has three major elements: (1) A disease entity or condition which the ingredient is capable of preventing or treating; (2) a dose or dosage range which can be expected to achieve the desired effect on the basis of instructions on the labeling; and (3) assurance that the form and the dose in which the vitamin or mineral is ingested will permit absorption and, therefore, achieve the predicted effect. This latter phenomenon is referred to as bioavailability. (See part II. paragraph D.1. below—Bioavailability.)

In considering the effectiveness of OTC vitamins and minerals, the Panel had to clarify several important issues: (1) The identification of target populations having a need for OTC vitamins and minerals, (2) the questionable added benefit or potential hazard to health by taking higher doses of a vitamin or mineral when lower doses are recognized as adequate, (3) the determination of when dosages of vitamins and minerals sold OTC are appropriate, and (4) the determination of when these drugs should be reserved for use by prescription.

The Panel recognizes that the greatest need for prevention and treatment of vitamin and mineral deficiency will be found largely within certain groups in the population with special nutritional and metabolic needs. A listing of such target groups includes, for example, persons on a restricted diet; persons with intestinal disease which impairs normal dietary intake or absorption; those individuals with known increased requirements for vitamins and minerals, such as pregnant and lactating women; those individuals at increased risk because of increased blood loss, e.g., iron deficiency in women of child-bearing age; and individuals who tend to neglect the adequate intake of vitamins and minerals and in addition have impaired metabolic function, e.g., alcoholics, and individuals who are taking certain drugs which either impair the absorption of vitamins and minerals from the diet or interfere with their normal utilization by the body. Individuals in the above target groups are at greater risk of vitamin and mineral depletion than the general population, which ordinarily can maintain adequate vitamin and mineral status by the regular use of a balanced diet. It is important that the needs of these individuals for prevention or treatment be identified by a physician. In addition, the physician's review of the problem will ensure that a vitamin or mineral deficiency which is attributable to abnormality in diet, intestinal disease, alcoholism, or increased requirements will not be treated without appropriate diagnosis and attention to the underlying cause.

D. ESTABLISHMENT OF ADEQUATE DOSAGE UNITS AND SCHEDULES

For vitamins and minerals, as for other therapeutic agents, effectiveness is not an abstract concept but is operational only in the context of a certain dosage or dosage schedule. A vitamin or mineral ingredient might be judged to be appropriate for Category I when recommended for the prevention of a vitamin or mineral deficiency or recommended for prevention and treatment of vitamin or mineral deficiency. Only when a vitamin or mineral deficiency or a predisposing condition occurs in man in significant numbers and the deficiency is identified by a physician, and then safely treated by OTC medication, are Category I requirements fulfilled. When treatment of deficiency can be safely and effectively carried out only under the specific direction and monitoring of a physician, then such therapy requires the use of prescription vitamins and minerals, and only prevention is recognized as an appropriate Category I definition of effectiveness for OTC use. Such is the case, for example, in vitamin B-12 deficiency, where oral vitamin B-12 may safely prevent the depletion seen in the presence of a completely vegetarian diet. On the other hand, vitamin B-12 deficiency as a manifest clinical syndrome is so commonly associated with absorption abnormalities as to require parenteral therapy or, at least, direct monitoring of oral therapy. Therefore, the Panel concludes that the use of vitamin B-12 sources for the prevention of extrinsic or dietary deficiency is rational but has also concluded that the treatment of vitamin B-12 deficiency is not appropriate for OTC drug use. (See part III. paragraph A.4. below—Vitamin B-12.)

Sometimes an essential vitamin or mineral will have no Category I use because the deficiency state only occurs in the presence of severe disease or with other drug use. In these instances, total medical management is required. Such is the case with potassium deficiency, for example. At times the margin between an effective dose and a toxic dose is so small as to require specific supervision of a physician. Such is also the case for the mineral iodine. In these instances, vitamin or mineral therapy must be prescribed specifically for the unique problem of the individual patient and safety and effectiveness monitored by a physician.

When a vitamin or mineral is recommended for prevention or treatment, the dose requirements are different for these two purposes. In general, a dose range is recommended for each situation. This range encompasses a variety of doses currently in safe use, and extends from a minimum effective dose to an upper dose beyond which no greater benefit is achieved and the benefit-to-risk ratio diminishes. The minimum effective dose for prevention is arrived at on the basis of studies in human subjects of all ages and sexes. The minimum effective dose for treatment is based, when possible, upon successful quantitative therapeutic studies on patients with vitamin and/or mineral deficiencies.

At times, this upper rational limit is based upon known limitations in intes-

tinal absorption, or it is based upon known dangers of higher doses, and at other times upon the concept of implied toxicity. Studies on treating deficiencies have often arbitrarily used doses of vitamins or minerals 5 to 10 times the doses required to prevent deficiency. The rationale for higher doses of vitamins and minerals to treat, as compared to doses needed to prevent, vitamin and mineral deficiency is based on the observations which show that the higher doses more quickly saturate depleted body stores and, therefore, may be expected to initiate a faster reversal of the abnormal metabolic processes which are associated with vitamin and mineral deficiency disease.

The Panel has sought to recommend dosage levels so that a daily dosage unit can generally be taken to achieve the desired effect. The Panel does not object to the mechanism of using multiple dosage units to achieve a fully daily dose. It is understood, however, that a single dosage unit might be recommended for prevention when taken once daily, and for treatment when taken several times daily. However, in view of the advertising campaigns aimed at reinforcing the tendency of consumers to take a single dosage unit of a vitamin or mineral daily and the difficulty encountered in adhering to multidose daily schedules, the Panel does not consider it appropriate for a daily preventive dose to be achieved by multiple dosage units, each of which is below the minimum recommended dose for prevention of vitamin or mineral deficiency. Instead, the Panel recommends that preventive doses whenever possible be given in single daily doeses such that the total quantity of a vitamin and/or mineral will be within the dosage range recommended by the Panel.

Bioavailability. For a vitamin or mineral preparation to be effective, it must be bioavailable, i.e., it must be able to be transported through the intestinal wall in order to enter the blood stream for circulation to the tissues where the biologically active form of the vitamin or mineral will achieve the desired effect of alleviating a deficiency or preventing a deficiency. Bioavailability depends not only on the basic chemical characteristics of the vitamin or mineral and its salts or counterions, but also on the dosage form in which it is administered, e.g., tablet or liquid. It is the requirement of this Panel that all products which are marketed OTC, whether as single ingredients or combination products, be in a form so that all active ingredients are bioavailable to the user. However, to assure that this will be so, the current level of technology in determining the absorption of vitamins and minerals, singly or in combination, must be expanded. We consider it an important responsibility of FDA to ensure that the necessary research is done to form the basis for establishing specific testing requirements for an appropriate degree of bioavailability of all active ingredients in vitamin and mineral products. In the interim, where bioavailability data indicate that a problem exists, requirements for special testing have been included in the appropriate ingredient statements in this document.

E. EVALUATION OF SAFETY

The considerations of paramount importance in the safety of OTC vitamin and mineral preparations are the intrinsic safety of the ingredient or combination, the safety of OTC use of the vitamin and mineral and, most important, the concept of a safe dose range.

Since all the vitamins and minerals considered by the Panel, with the exception of choline, are nutrients which are essential to man, the Panel readily accepts the intrinsic safety of these compounds at the recommended dosages. Therefore, safety was judged largely in the context of the circumstances and dosage under which the vitamin or mineral is taken. As noted above, large amounts of some vitamins and minerals cannot be taken safely as OTC drug preparations even though their use under the direct and continuous care of a physician can be effective. The decision regarding the quantity of a vitamin or mineral which is unsafe at doses above the maximum recommended dose may be based upon unwanted side effects or implied toxicity, i.e., an unsatisfactory ratio of risk to benefit at a given dose, in addition to known or documented toxic effects. The Panel agrees that there is no ingested substance, including water, which is altogether safe at any dose. It is therefore rational to set upper limits of a recommended dose at the point where there is known effectiveness and minimal relative risk of toxicity. A well-established concept in pharmacology is that medication should not be taken in doses beyond those needed to achieve the desired effect, and that to do so increases the risk of unwanted or toxic effects. Each increment of the dose which does not at the same time increase the therapeutic effect of the medication, decreases the therapeutic ratio (benefit to risk) and therefore increases the risk of toxicity. The therapeutic effects of vitamins and minerals are dose-related only to the extent that they replete and saturate the body tissues to prevent or treat deficiency disease. Beyond these saturating doses, which have been taken, in general, as the upper limits of the recommended dosage, some vitamins and minerals may be stored in such a way as to produce abnormal tissue effects, e.g., vitamin A; or they may produce undesirable metabolic effects, e.g., vitamin D; or they may interfere with the physician's ability to diagnose other medical conditions, e.g., high doses of folic acid which mask the diagnosis of pernicious anemia and vitamin B-12 deficiency, and excessive doses of ascorbic acid which may interfere with a commonly use method of testing for urinary sugar in diabetics.

To the concept of a worsening benefit-to-risk ratio caused by doses beyond those of known therapeutic benefit must be added the danger of delayed appearance of toxic symptoms. The toxic effects of excessive doses of vitamins and minerals can be divided roughly into two different types of syndromes. One is the acute toxic reaction which usually occurs in the presence of an excessive vitamin or mineral intake over a short period of time. Such acute intoxication is well described for vitamin A and for most of the known minerals taken in great excess. Second, there is a more chronic or delayed toxic reaction which occurs due to excessive intake over a long period of time. Thus, in the case of vitamin A toxicity, it is possible that the patient may continue to ingest excessive doses of vitamin A without untoward symptoms or recognized side effects until such time as the vitamin has been stored in the liver to such excess that the liver is damaged and scarring and cirrhosis occur. A similar effect of excessive doses of nicotinic acid and even nicotinamide with the delayed development of liver toxicity has been reported and emphasis the contention of the Panel that even water-soluble vitamins such as nicotinic acid or nicotinamide may produce toxic effects which may be recognized only after significant tissue damage has occurred. Although far less well documented as a toxic agent, vitamin C, or ascorbic acid, is known to produce increments in the urinary excretion of oxalate when taken in 1,000 mg or greater daily doses (Ref. 1). Such increases have not been shown clearly to result in an increased incidence of oxalate kidney stones. However, when the theoretical benefits of increasing vitmain C dosage beyond known nutritional benefit are matched against the theoretical dangers of enhancing this metabolic side reaction, the Panel has chosen a safe position of identifying a maximum dose at which all scientifically recognized therapeutic effects can be achieved with a minimum risk of unwanted effects.

There are claims that some individuals in the population require doses of vitamins for maximal health which are 10, 50, or even 100 times the doses which are recognized as needed for nu-

tritional reasons. The Food and Nutrition Board of the National Academy of Sciences (Ref. 2) has stated, "We are aware of no convincing evidence of unique health benefits accruing from consumption of a large excess of any one nutrient." Claims for the effectiveness of high doses of vitamins for the treatment of psychiatric and other medical disorders have been justified by some on the basis of uncontrolled studies of a few practitioners and a theoretical concept called orthomolecular psychiatry. When such claims have been scientifically tested by controlled studies which avoid placebo bias, they have regularly been disproved; these claims have not been reproducible in the hands of other than the original proponents. The claims made for mega-dose therapy are understandably attractive to individuals seeking symptomatic relief or recovery from conditions with no known cure. At the present time, however, there is no scientific documentation for the rational use of mega-quantities of vitamins except for those rare individuals with a specific genetic defect. Until we have obtained adequate evidence of the safety of large doses of vitamins taken for long periods of time or the documentation that high doses of vitamins do have a special health benefit which justifies a worse risk-to-benefit ratio, the Panel has chosen not to venture beyond a recommended dose range which accomplishes the therapeutic goals set out on the label.

Another factor which enters into the decisions to establish an upper dose limit for vitamins or minerals is the theoretical principle of systemic conditioning. This is based on observations which indicate that in the presence of large doses of a vitamin or mineral, certain metabolic responses occur which condition or adapt the body to such large doses. If these large doses are stopped abruptly for one reason or another, the body, conditioned to such large doses, may for a short period of time react as if the tissue is depleted even though the intake is adequate for normal requirements at that point. Shortly thereafter the metabolic machinery of the body adjusts to the new dose of vitamin or mineral and normal functioning is restored. The evidence that such systemic conditioning occurs is still very preliminary. Scurvy has been observed in an individual ingesting 10 to 15 grams (g) ascorbic acid daily when the vitamin was abruptly discontinued. Symptoms abated after vitamin C therapy (Ref. 3). Such a readjustment in metabolic responsiveness may be particularly important in the case of pregnancy. Excessive doses of a vitamin taken by the pregnant woman may pass the placenta and adapt the fetal tissues to a high and excessive vitamin environment. When the infant is delivered and must adjust to normal intakes of a vitamin, a temporary deficiency syndrome may theoretically ensue. A syndrome of vitamin B-6 deficiency in a newborn infant has been reported in one instance when a pregnant woman was taking large doses of vitamin B-6 during the third trimester of pregnancy. No cause-and-effect relationship has been proven. Also in the case of vitamin B-6, there have been cases reported in which the cessation of high-dose vitamin B-6 therapy to pregnant women or women on birth control pills has been followed by sharp exacerbation of symptoms of depression which necessitated reinstitution of high-dose vitamin B-6 therapy (Ref. 4).

The Panel recognizes that there is controversy regarding the applicability of a recommended dose or even a recommended dosage range to a heterogeneous population. Therefore, the Panel has selected an upper dose limit which would satisfy the requirements of the target populations for which the treatment is recommended. The Panel is aware of arguments which suggest that vitamin and mineral requirements may be highly variable on a genetic basis. There are, in fact, rare genetically determined conditions which may be ameliorated with high doses of a specific vitamin. These specific genetic abnormalities tend to appear early in life and produce dramatic clinical presentations. Their diagnosis and management requires intensive and continued involvement of specially skilled clinicians, and management of these conditions with large doses of the special vitamin needed cannot be safety carried out by OTC medication. The presence of such rare genetically determined disorders cannot, however, be extrapolated to suggest that there are wide ranges of genetically determined requirements for vitamins and minerals in the otherwise normal population. There is such a large reserve or safety factor in the normal human system which regulates the utilization of vitamins that small variability in genetic potential is not reflected in substantial variability in individual requirements in the normal population. Thus, a genetic basis for expression of marked individual variability in nutrient requirement is not a tenable concept and constitutes such a small number of consumers with unique requirements as to fall outside the target populations for OTC drug products.

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(3) Dykes, M. H. M., and P. Meier, "Ascorbic Acid and the Common Cold. Evaluation of its Efficacy and Toxicity," *Journal of the American Medical Association*, 231:1073-1079, 1975.

(4) Baumblatt, M. J., and F. Winston, "Pyridoxine and the Pill," *Lancet*, 1:832-833, 1970.

F. COMBINATION POLICY

1. *General statements.* In order to clarify the place of cominations in the marketplace, the Panel applied the OTC drug review regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate direction for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

A special reationale for multiple vitamin and vitamin-mineral preparations is derived from the fact that circumstances of restricted dietary intake, increased requirements, or defective absorption as in pregnancy rarely affect a single nutrient. Thus, combinations of vitamins and minerals may often be the rational means of preventing or treating vitamin and mineral deficiencies in those at special risk.

The Panel concludes, therefore, that multiple vitamin preparations and preparations containing both vitamins and minerals which claim effectiveness for prevention or treatment of vitamin and mineral deficiencies should be formulated on the basis of supplying all those vitamins and minerals whose combined deficiencies may be expected in a significant target population. Preparations of multiple minerals alone, however, are not recommended. (See part II. paragraph F.12.f. below—Preparations of multiple minerals.) When multiple deficiencies are present, or are at increased risk of occurring, it would not be rational or safe to use preparations containing only two or three vitamins and minerals for the observed symptoms or deficiencies and thus unwitingly neglect therapy of other deficiencies. Therefore, a product containing only the fat-soluble vitamins A, D, E, and K is not allowed since the conditions of diet and intestinal disease which may predispose to depletion of some of these vitamins are more rationally treated with preparations which contain all Category I vitamins. Because the water-soluble vitamins (the B-vitamins and vitamin C) are less well stored in the body than the fat-soluble vitamins and may be depleted more

rapidly in the presence of altered intake or disease, and because the several B-vitamins often occur together in the same foods, a preparation containing all B-vitamins with or without vitamin C to prevent or reverse disease in man is recommended.

Minerals pose a different problem. There are few minerals for which a deficiency state in man is recognized which can be safely managed by OTC medication. The conditions leading to deficiency of these few Category I minerals in contrast to the vitamins are not common ones, and thus there is no basis for a multimineral preparation for OTC use. For example, the conditions leading to iron deficiency in women of childbearing age and in pregnant women are distinct from conditions which may result in depletion of either zinc or calcium, the other Category I minerals.

2. *Safety.* In its consideration of active ingredients, the Panel reviewed the safety and effectiveness of all combinations submitted. All combinations that meet the criteria of Category I as set forth below are considered safe. (See part II. paragraph F.7. below—Category I combinations.) In addition, the Panel considered it rational to include both vitamin E and pantothenic acid in multivitamin or vitamin and mineral preparations despite the fact that these two vitamins have no Category I use as single ingredients. (See part III. paragraph A.7. below—Pantothenic acid and part III. paragraph A.13. below—Vitamin E.)

3. *Effectiveness.* Combination products are regarded as effective if each active ingredient is present in the product within the dose range set by the Panel for each Category I active vitamin or mineral ingredient, as discussed within the individual ingredient statements within this document. The Panel deemed unnecessary any attempt to establish the percent of contribution that an active ingredient must make to effectiveness of the product in order for that contribution to be considered significant; the Panel concludes that, where a combination product is permitted, it is sufficient to demonstrate that each active ingredient is present and available in the recommended dosage quantity which would be effective in obtaining the pertinent vitamin or mineral therapeutic result unless interference between two or more vitamins and/or minerals occurs which alters safety or effectiveness as discussed in the individual vitamin and mineral statements within this document.

Combinations claiming effectiveness for prevention of deficiencies should contain doses of the individual vitamins and minerals as recommended for single ingredients for prevention while preparations claiming effectiveness for treatment must use recommended treatment doses for individual ingredients. The Panel recognizes that there may be combinations claiming effectiveness for treatment of deficiency which contain vitamins and/or minerals for which only a preventive dose has been recommended as a single nutrient. Under such circumstances, the maximal permitted preventive dose shall be used in the combination product claiming effectiveness for treatment.

When there is evidence that the combination of ingredients at certain levels may influence bioavailability of any ingredient, testing is required. For example, in solution, zinc may precipitate folic acid; therefore, bioavailability of folic acid must be documented in combinations containing folic acid and zinc.

4. *Active ingredients.* Each claimed active ingredient must be an ingredient that has been reviewed and approved by the Panel. If a product contains ingredients that are in Category II or have not been reviewed and approved by the Panel and consequently not found in this document, such a product is automatically classified as Category II, i.e., not safe and/or not effective.

5. *Panel policy regarding other ingredients in combination preparations.* Inactive ingredients may be present as a vehicle for formulation of biologically active ingredients. Other inactive ingredients may be present in preparations as pharmaceutic aids, as described in the proposed regulations for conditions for use and labeling of inactive ingredients published in the FEDERAL REGISTER of April 12, 1977 (42 FR 19156). The vitamin or mineral preparation must be prepared so that none of its inactive ingredients is present in an amount that exceeds the amount reasonably required to accomplish its intended physical or technical effect, or that impairs the biological availability of the vitamins or minerals.

6. *Review of submitted combination products.* The Panel considered only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of October 15, 1973 (38 FR 28581). The Panel recognizes that other combination products may be in the marketplace but has no knowledge of such products, or insufficient data with respect to such products, to make a judgment of safety and/or effectiveness.

7. *Category I combinations.* Combinations are recommended to meet needs for multiple-vitamin preparations and preparations containing both vitamins and minerals for prevention and therapy for the following special groups when such need has been identified and recommended by a physician: (1) Individuals of all ages on highly restricted diets for whatever reason; (2) pregnant women who have increased nutritional requirements for a variety of vitamins and minerals; and (3) individuals who use alcohol to excess. This latter group is well known to be at increased risk of multiple vitamin and mineral deficiencies and a preparation which addresses itself to the specific needs of this population is strongly recommended. Thus, the Panel recommends that allowable combinations should include and be limited to the following:

a. *Combination for prevention of deficiency.* (1) All Category I vitamins may be combined within the recommended dosage ranges identified within this document for the prevention of deficiency. Although the Panel does not recommend Category I use for either pantothenic acid or vitamin E as single ingredients, either or both of these vitamins may be added to the above combination. (See part III. paragraph A.7. below—Pantothenic acid and part III. paragraph A.13 below—Vitamin E.)

(2) All Category I B-vitamin ingredients (thiamine, riboflavin, pyridoxine, niacin, folic acid, and vitamin B-12) may be combined within the recommended dosage ranges identified within this document for the prevention of deficiency. Although the Panel does not recommend Category I use for pantothenic acid as a single ingredient, this vitamin may be added to the above combination. (See part III. paragraph A.7. below—Pantothenic acid.)

(3) All Category I B-vitamin ingredients (thiamine, riboflavin, pyridoxine, niacin, folic acid, and vitamin B-12) may be combined with vitamin C, all within the recommended dosage ranges identified in this document for the prevention of deficiency. Although the Panel does not recommend Category I use for pantothenic acid as a single ingredient, this vitamin may be added to the above combination. (See part III. paragraph A.7. below—Pantothenic acid.)

(4) Any combination of vitamin ingredients identified in (1) through (3) above may be combined with iron.

(5) Any combination of vitamin ingredients identified in (1) above may be combined with zinc with or without iron and/or calcium.

(6) Any combination of vitamin ingredients identified in (1) above may be combined with calcium with or without iron and zinc.

(7) All Category I vitamins may be combined with zinc for the prevention of deficiency in persons who use alcohol to excess, provided all the ingredients are present at levels provided for treatment of deficiency identified in this document or are at the maximum

dosage level for prevention of deficiency when treatment levels have not been specified. Although the Panel does not recommend Category I use for either pantothenic acid or vitamin E as single ingredients, either or both of these vitamins may be added to the above combination. (See part III. paragraph A.7. below—Pantothenic acid and part III. paragraph A.13. below—Vitamin E.)

(8) Any combination is acceptable for prevention of deficiency in pregnant women provided that dosages of all Category I vitamins that may be combined with iron (zinc and calcium optional) are present and that all ingredients present are within the dosage ranges recommended for pregnancy, or within the prevention dosage ranges if no pregnancy dosage range has been specified.

b. *Combinations for the treatment of deficiency.* (1) All Category I vitamin ingredients within the recommended dosage ranges identified in this document for the treatment of deficiency (niacin, vitamin C, pyridoxine, riboflavin, thiamine, and vitamin A) may be combined with all Category I vitamin ingredients which have no established dosage range for the treatment of deficiency, provided that these ingredients are present at the maximum dosage level identified in this document for the prevention of deficiency (vitamin B-12, folic acid, and vitamin D). Although the Panel does not recommend Category I use for either pantothenic acid or vitamin E as single ingredients, either or both of these vitamins may be added to the above combination. (See part III. paragraph A.7. below—Pantothenic acid and part III. paragraph A.13. below—Vitamin E.)

(2) All Category I B-vitamin ingredients within the recommended dosage ranges identified in this document for the treatment of deficiency (niacin, thiamine, riboflavin, and pyridoxine) may be combined with all Category I B-vitamin ingredients which have no established dosage range for the treatment of deficiency, provided that these ingredients (folic acid and vitamin B-12) are present at the maximum dosage level identified in this document for the prevention of deficiency. Although the Panel does not recommend Category I use for pantothenic acid as a single ingredient, this vitamin may be added to the above combination. (See part III. paragraph A.7. below—Pantothenic acid.)

(3) All Category I B-vitamin ingredients within the recommended dosage ranges identified in this document for the treatment of deficiency (thiamine, riboflavin, pyridoxine, and niacin) may be combined with vitamin C and with all Category I B-vitamin ingredients which have no established dosage range for the treatment of deficiency provided that these ingredients are present at the maximum dosage level identified in this document for the prevention of deficiency (folic acid and vitamin B-12). Although the Panel does not recommend Category I use for pantothenic acid as a single ingredient, this vitamin may be added to the above combination. (See part III. paragraph A.7. below—Pantothenic acid.)

8. *Criteria for determining Category I combinations.* To qualify as a Category I combination, i.e., one that is generally recognized as safe and effective, each of the following conditions must be met: (1) A specific combination of active ingredients as set forth above (See part II. paragraph F.7. above—Category I combinations.), and (2) each ingredient in a combination must be present within the dosage range for a Category I active ingredient as set forth elsewhere in this document within the individual ingredient statements.

9. *Category I combination labeling claims.* The Panel recommends that labeling consist of two parts: (1) A major part in bold type which includes the labeling statements below as they correspond to specific combinations identified above as well as a listing of all the vitamins and minerals and the total quantity of each vitamin and/or mineral contained in the product; and (2) a secondary part of the labeling in smaller type must reflect the name of all inactive ingredients used as pharmaceutic necessities.

The following claims will be acceptable for specific combinations of vitamins and minerals as identified in part II. paragraph F.7.a. above—Combinations for prevention of deficiency and part II. paragraph F.7.b. above—Combinations for the treatment of deficiency:

a. *For prevention*—(1) *For combinations containing only vitamins.* "For the prevention of deficiencies of vitamins named on the label when the need for such therapy has been determined by a physician."

(2) *For combinations containing vitamins and mineral(s).* "For the prevention of deficiencies of vitamins and mineral(s) named on the label when the need for such therapy has been determined by a physician."

(3) *For products identified in paragraph F.7.a.(7) above.* "Useful as an aid in the prevention of deficiency of vitamins named on the label and zinc in persons using alcohol to excess when the need for such therapy has been determined by a physician."

(4) *For products identified in paragraph F.7.a.(8) above.* "For the prevention of deficiency of vitamins named on the label and iron in pregnant women when the need for such therapy has been determined by a physician."

b. *For treatment—For combinations containing only vitamins.* "For the treatment of deficiencies of vitamins named on the label when the need for such therapy has been determined by a physician."

10. *Warnings.* The warnings identified elsewhere in this document for individual vitamin and/or mineral active ingredients are equally applicable to labeling of any combination containing these ingredients.

11. *Category II combination products.* A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe and/or not generally recognized as effective, if any of the following apply:

a. A combination containing any ingredient which is not recommended for inclusion in Category I combinations, either as a Category I vitamin or mineral, as an acceptable source of a vitamin or mineral, or as an inactive ingredient used in formulation as a pharmaceutic necessity.

b. A combination containing any ingredient that is listed elsewhere in this document as a Category II ingredient. The exceptions are pantothenic acid and vitamin E as noted elsewhere. (See part III. paragraph A.7. below—Pantothenic acid and part III. paragraph A.13. below—Vitamin E.)

c. A combination containing any Category I ingredient in excess of the maximum dosage set by the Panel for such ingredient.

d. A combination containing any Category I ingredient which is present at less than the minimum dosage set for each respective ingredient. When more than one source of a vitamin or mineral is present in a combination, the total quantity of the vitamin or mineral from all sources must be present in at least the minimum dosage level established by the Panel.

e. A combination contains any active vitamin or mineral ingredient that has not been reviewed by the Panel and, accordingly, not evaluated in this document.

f. Combinations containing iron must not be labeled for prevention of deficiency in persons who use alcohol to excess.

12. *Miscellaneous Category II combinations*—a. *Vitamin and mineral combinations for infants under 1 year of age.* There are certain circumstances in which infants under 1 year of age may require vitamin and/or mineral supplementation. For example, infants fed other than by human breast milk, e.g., those on cow's milk, may be at risk of vitamin C depletion and vitamin C should be specifically added to the diet in food or as an individual ingredient supplement. Children on a

diet based upon unfortified skim milk may require vitamin A as a single supplement. Vitamin D is rarely required, but may also be supplemented. When special, highly unsaturated fat formulas are used, vitamin E needs should be monitored and therapy prescribed by a physician, Therefore, the Panel concludes that the individual recognized needs for infant use are best handled by individual ingredient supplements or under the advice and supervision of a physician. A combination of vitamins and minerals for infants under 1 year of age does not have a basis for effectiveness and is not recommended by the Panel. The Nutrition Committee of the Academy of pediatrics also does not recommend a combination for infant use (Ref. 1).

b. *Vitamin and mineral combinations for use in children.* The needs of growing children for vitamins and minerals are most appropriately met by an adequate balanced diet, and when the diet is restricted for whatever reason, such needs may be met by combinations of Category I vitamins and minerals. Thus, the preparations recommended in Category I are entirely adequate to the needs of individuals in the pediatric age group from 1 to 12 years of age. The dose range for individual nutrients referred to above under Category I encompasses safe and effective doses for children as well as for adults and therefore no special preparations for pediatric use are recommended and labeling claims specifically for pediatric or childhood use are not recognized as necessary. The Panel does not object to labeling claims on Category I preparations for use by both adults and children except for calcium and iron, where specific dose ranges are indicated for specific age groups. The Panel recognizes that there may be special formulations, such as liquid preparations, that may be specially formulated and marketed for use by children.

c. *The use of vitamins and minerals by the elderly.* Neither the Food and Nutrition Board of the NAS/NRC nor the World Health Organization (WHO) recognizes any need for increasing the vitamin and mineral allowances for healthy elderly individuals above those recommended for young and healthy adults. In fact, the Food and Nutrition Board decreases slightly the recommended dietary allowances for adult males over the age of 51 years for niacin, riboflavin, thiamine, and iodine, and for females over the age of 51 years, it decreases the allowances of niacin, riboflavin, iodine, and iron.

Although requirements for vitamins and minerals are not increased by age, socioeconomic conditions and reduced physical activity among the aged may lead to sharp curtailment in the intake of vitamin- or mineral-containing foods. Under such conditions of dietary restriction, the use of a vitamin and mineral preparation in the prevention or for the treatment of deficiency may be indicated. When such is the case, the doses of vitamins and minerals recommended elsewhere in this document as effective in the prevention and treatment of specific deficiency states or multiple-deficiency states in adults are adequate for use in the elderly population. Therefore, the Panel finds no indication or need for any special OTC vitamin or mineral preparation for geriatric use and any claims referring to such need are false and misleading.

d. *Combinations of folic acid and vitamin B-12 or of folic acid, vitamin B-12, and iron.* The Panel recognizes no justification for a combination containing only vitamin B-12 and folic acid for treatment of a combined deficiency or of megaloblastic anemia. This combination is considered not safe in view of the fact that the situations under which combined folate and vitamin B-12 deficiency occur are likely to be associated with malabsorption of one or both of the vitamins. While malabsorption of folic acid may be overcome by large oral doses of folic acid, vitamin B-12 should be given parenterally in these circumstances. Dietary deficiency of both these vitamins will rarely occur. When such a situation exists, multiple-vitamin deficiencies requiring multiple-vitamin therapy may be expected. Thus, a combination of only folic acid and vitamin B-12 is irrational. The same is true of conditions under which a combination of iron, folic acid, and vitamin B-12 deficiency exists. When all three deficiencies exist due to severe malabsorption, vitamin B-12 should be given parenterally; therefore an oral preparation of the three is irrational. When all three deficiencies exist due to severe dietary depletion, a combination product containing other vitamins and minerals should be employed.

e. *Combinations of fat-soluble vitamins.* The Panel does not recognize any indication for OTC vitamin combinations restricted to the fat-soluble vitamins A, D, E, and K, since depletion of water-soluble vitamins would be expected in clinical situations associated with deficiency of multiple fat-soluble vitamins. In the rare circumstances under which a bile salt deficiency occurs due to obstruction or malabsorption, prevention or treatment of fat-soluble vitamin deficiencies may require doses higher than those recommended for OTC use and will always require careful, continued monitoring by a physician and, therefore, are best handled by prescription.

f. *Preparations of multiple minerals.* As individual ingredients, only iron, zinc, and calcium are considered appropriate for Category I designation. In the case of other minerals, deficiencies in man are recognized only under clinical situations requiring presciption medication and close supervision by a physician because of the severity of the underlying condition or the risk of toxicity from mineral therapy. Unlike the situation with vitamins, multiple-mineral deficiencies rarely occur as a complication of the same condition, e.g., iron deficiency occurs in women of childbearing age from a different cause than would precipitate deficiency of zinc or calcium. Thus, there is no rational basis for a multimineral preparation.

g. *Category II vitamins for users of oral contraceptives.* Recent observations documenting alterations in circulating levels of vitamins as well as clinically detectable vitamin-deficiency states in women taking oral contraceptive preparations obviously bear consideration. Although circulating levels of folic acid, vitamin B-12, vitamin B-6, riboflavin, and vitamin C are lowered in oral contraceptive users, clinical manifestations of vitamin-deficiency syndromes have been adequately described only in women with vitamine B-6 and folic acid deficiency (Ref. 2), although in some instances, i.e., vitamin B-12, drastic reductions in serum levels occur without detectable effects (Ref. 3). It should be emphasized that the data regarding potentially detrimental vitamin-deficiency states in oral contraceptive users derive primarily from studies with contraceptive pills containing 50 micrograms (μg) or more of ethinyl estradiol or mestranol. Studies on patients taking low-dose estrogen pills, i.e., 20 to 30 μg estrogen, are not yet available for evaluation. Despite observations that depression and glucose intolerance apparently result from vitamin B-6 deficiency, and that megaloblastic anemia has been identified in folic acid deficient oral contraceptive users, the causal relationship has not been established. It appears unjustified at this time to recommend that a specific multivitamin preparation, i.e., one containing vitamins C, riboflavin, B-12, B-6, and folic acid, be made available for oral contraceptive users. Since vitamin B-12 levels may be less than 100 nanograms/milliliter (ng/ml) in oral contraceptive users without evidence of clinical deficiency or alteration in circulating hematocrit values (Ref. 3), the need for supplementation is presently unjustified. Similar arguments could be made for vitamins C and riboflavin (Ref. 2). Although the observation that the majority of women taking high estrogen-containing oral contraceptives has been shown to have abnormal tryptophan metabolism with some exhibiting absolute clinical vita-

min B-6 deficiency syndromes (Ref. 4), it appears still unjustified medically to market a combined oral contraceptive-vitamin B-6 product. It may ultimately be totally inappropriate since newer oral contraceptive preparations with lower estrogen content may, in fact, fail to induce the vitamin alterations observed with the high estrogen-containing preparations.

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(1) Committee on Nutrition, "Vitamin K Supplementation for Infants Receiving Milk Substitute Infant Formulas and for Those with Fat Malabsorption," *Pediatrics*, 48:483-487, 1971.

(2) Wyan, V., "Vitamins and Oral Contraceptive Use," *Lancet*, 1:561-564, 1975.

(3) Wertalik, L. F. et al., "Decreased Serum B-12 Levels with Oral Contraceptive Use," *Journal of the American Medical Association*, 221:1371-1374, 1972.

(4) Rose, D. P. et al., "Experimental Vitamin B-6 Deficiency and the Effect of Oestrogen-Containing Oral Contrasceptives on Tryptophan Metabolism and Vitamin B-6 Requirements," *Clinical Science*, 42:465-477, 1972.

G. CATEGORY III TESTING GUIDELINES

Claims for vitamins and minerals for which there are insufficient data for classification in either Category I or Category II are placed in Category III. The inference here is that studies are in process, or are contemplated, that eventually will justify the transfer of the claim, dosage, or product to Category I or Category II. In the meantime, any appropriate Category I claims as well as Category III claims are permitted on the labeling, and the products involved may continue to be marketed until a final disposition is made, assuming there are no other legal obstacles. The problem facing the Panel is the development of testing procedures for the justification of a transfer of Category III claims, dosage, and/or products to Category I in a reasonable period of time. FDA should develop, in conjunction with other workers in the field, whatever criteria are useful in view of the state of the art and in recognition of the ethics of human testing.

In order to do this, and in order to be able to evaluate the results of and claims made for studies conducted, one will have to consider each ingredient and each claim individually for the following reasons:

(1) The various ingredients differ markedly in the degree and duration of their deficiency required before the development of clinical signs and symptoms.

2. The various ingredients differ in the size of the dose necessary to treat a deficiency relative to the dose necessary to prevent deficiency.

3. Generally, deficiency states that develop acutely respond rapidly to the pertinent treatment, while those that develop slowly over a long period of time, either because of previous large body stores or because of a low degree of dietary inadequacy, might well be expected to respond more slowly to treatment.

4. The various diseases and abnormal metabolic and clinical conditions, for which various vitamins and minerals are claimed to be therapeutic in various amounts, also vary widely in their severity, duration, and response to treatment. The natural history of any disease or abnormality for which a therapeutic claim is made must be known.

5. No study can be accepted as disproving any claim made unless that study, while otherwise adequate, employs at least the doses and therapeutic trial periods and regimen advocated by the proponents of a particular ingredient therapy for a specific disease or condition.

III. VITAMINS

A commonly accepted definition of vitamins is that they are chemically unrelated organic substances that are essential in small amounts for the maintenance of normal metabolic functions but are not synthesized within the body and, therefore, must be furnished from exogenous sources (Refs. 1, 2, and 3). Amino acids and essential fatty acids are excluded from this definition. From a clinical point of view, the agents that are generally considered to be vitamins are those organic compounds the absence or inadequacy of which can cause specific metabolic defects (Ref. 2).

This definition has exceptions in that a few organic compounds generally recognized to be vitamins for man can be and are synthesized within the human body and, under suitable conditions, in adequate amounts to support normal metabolic processes. Vitamin D is formed by the activation of 7-dehydrocholesterol in the skin by sunlight. Vitamin A is synthesized within the body from a number of carotenoids with varying degrees of efficiency, and niacin can be made within the body from tryptophan. However, deficiencies of vitamins A, D, and niacin resulting in serious metabolic defects are known to occur and exogenous sources of the preformed vitamins would appear to be essential for most people under most circumstances.

It must also be borne in mind that the exogenous sources referred to are not always foods in the conventional sense. Both vitamin K and biotin are normally synthesized, probably in adequate amounts, by the bacteria of the intestine. The vitamin B-12 formed by bacterial action in the colon is distal to the absorption sites and not normally available to the human host living under modern hygienic conditions.

Vitamins A, D, E, and K are fat soluble and the others are more or less water soluble. This does not imply any other common characteristic among the vitamins within each solubility group other than the fact that, generally, the fat-soluble vitamins are stored better and longer in the body than are the water-soluble vitamins. The dosages for vitamins A, D, and E are usually stated in terms of international units (I.U.) based on standardized bioassays rather than in mg or μg as the other vitamins and minerals discussed in this document.

The dosages recommended in this document for vitamins have been derived from the available data. The Panel is aware of the RDA (Ref. 4) and the dietary supplement regulations published in the FEDERAL REGISTER of October 19, 1976 (41 FR 45156). However, the Panel emphasizes that these considerations were not applicable to the "OTC drug use" recommendations contained in this document.

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(2) Guyton, A. C., "Vitamin and Mineral Metabolism," *in* "Textbook of Medical Physiology," 5th Ed., W. B. Saunders Co., Philadelphia, pp. 979-986, 1976.

(3) Greengard, P., "The Vitamins," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S. and A. Gilman, Macmillan Publishing Co., Inc., New York, pp. 1544-1548, 1975.

(4) "Recommended Dietary Allowances," 8th Ed., National Academy of Sciences, Washington, DC, 1974.

The Panel has classified the following vitamin active ingredients as Category I for OTC drug use for the prevention and/or treatment of deficiency:

Vitamin C
- Ascorbic acid
- Ascorbyl palmitate
- Calcium ascorbate
- Niacinamide ascorbate (Category I only when in combination requiring both niacin and vitamin C activity)
- Sodium ascorbate

Vitamin B-12
- Cyanocobalamin

Folacin
- Folic acid

Niacin
- Niacin
- Niacinamide
- Niacinamide ascorbate (Category I only when in combinations requiring both niacin and vitamin C activity)
- Pantothenic acid (Category I only when in combination)
- Calcium pantothenate
- Dexpanthenol
- Pantothenic acid

Vitamin B-6
- Pyridoxine hydrochloride

Riboflavin
- Riboflavin

Riboflavin-5-phosphate sodium
Thiamine
Thiamie hydrochloride
Thiamine mononitrate
Vitamin A
Vitamin A
Vitamin A acetate
Vitamin A palmitate
Vitamin D
Cholecalciferol
Ergocalciferol
Vitamin E (Category I only when in combination)
Tocophersolan
alpha-tocopheryl acetate
alpha-Tocopheryl acid succinate
Vitamin E

The Panel has classified the following vitamin active ingredients as Category II for OTC drug use for the prevention and/or treatment of deficiency:

Biotin
Biotin
Choline
Choline bitartrate
Choline chloride
Choline citrate
Niacin
Nicotinic acid
Pantothenic acid (Category II as a single ingredient)
Calcium pantothenate
Dexpanthenol
Pantothenic acid
Vitamin D
25-Hydroxylated vitamin D
1, 25-Hydroxylated vitamin D
24, 25-Hydroxylated vitamin D
1-alpha-Vitamin D
5, 6-trans-Vitamin D
Vitamin E (Category II as a single ingredient)
Tocophersolan
alpha-Tocopheryl acetate
alpha-Tocopheryl acid succinate
Vitamin E
Vitamin K
Phytonadione

1. *Vitamin C.* The Panel's statement on vitamin C includes the following ingredients: Ascorbic acid, ascorbyl palmitate, calcium ascorbate, niacinamide ascorbate, and sodium ascorbate.

a. *Reference form.* Dosages recommended in this document for vitamin C are based on the *L*-ascorbic acid equivalent ($C_6H_8O_6$, molecular weight 176.2).

b. *Description.* Vitamin C is present in many foodstuffs, and the average daily consumption in ordinary diets ranges from 30 to 250 mg. The lesser amount is sufficient to prevent the occurrence of scurvy in all persons who are free from specific organic disorders in which the in vivo rate of utilization or destruction of ascorbic acid is adversely affected. In those persons with such disorders as peptic ulcer, achlorhydria, chronic diarrhea, burns, surgical wounds, neoplastic disease, and hyerthyroidism, and also during pregnancy and lactation, ascorbic acid needs are increased but not beyond the ability of a carefully selected diet to meet them (Refs. 1, 2, and 3). Several studies have shown that cigarette smokers have lower plasma/serum and leukocyte ascorbic acid levels than nonsmokers, but the magnitude of differences appears to vary with the level of vitamin C intake (Refs. 4 and 5). In one study, no differences were found between the plasma ascorbic acid levels of smokers and nonsmokers with intakes of about 100 to 500 mg vitamin C daily (Ref. 6). This author attributed his results to the high vitamin C intake of his subjects. The Panel concludes that there is no evidence that oral intake of vitamin C greater than 100 mg daily is necessary to maintain adequate vitamin C status in even heavy smokers. The administration of such drugs as oral contraceptives (Refs. 7, 8, and 9), antibiotics (Refs. 10 and 11), or salicylates (Refs. 12 and 13) has been reported to decrease plasma or platelet ascorbic acid levels and may therefore also increase the vitamin C requirement. There are no data, however, to suggest that these situations require or would benefit from adjunctive therapy with ascorbic acid.

Ascorbic acid functions as a cofactor in specific essential biolgical reactions in the human body for the utilization of absorbed metabolites in maintaining the body economy. It has antioxidant activity and is reversibly oxidized to dehydroascorbic acid, which also has antixcorbutic activity. This oxidation-reduction property of ascorbic acid is important in the extablishment of proper in vivio environments for specific biological reactions involving other reactants, e.g., regulation of intracellular oxidation-reduction potentials and intermidiate conversions of one substrate to another in the process of metabolism. As a cofactor, ascorbic acid acts in concert with other factors and is used up in the process at an average rate of about 3 percent of the existing pool daily so that constant replenishment of the body's pool is essential. Scurvy develops when this pool (approximately 1,500 mg in a well-nourished adult) becomes depleted. Deficiency is usually obvious when the body pool drops below 300 mg and the whole blood level drops below 0.3 mg/100 ml (Refs. 14 and 15). Symptoms include fatigue, spontaneous hemorrhaging and swollen joints, swollen, bleeding guns, follicular hyperkeratosis, muscular aches and pains, and emotional changes. Medical assessment is required to associate these symptoms with measurable biochemical parameters such as ascorbic acid blood levels in order to determine the existence of the ascorbutic syndrome (scurvy).

c. *Safety.* The present clinical and experimental findings indicate that consumption of vitamin C in excess of 1,000 mg daily is not without potential hazard in some individuals, and hence cannot be considered entirely safe (Refs. 16 through 37).

Ingestion of doses of 4 to 15 g daily may cause gastrointestinal disturbances, with nausea followed by diarrhea, due to the high osmolarity and laxative effect (Refs. 16 and 17).

With the administration of greater than 1,000 mg vitamin C, oxalate (Refs. 18 and 19), uric acid (Ref. 20), and calcium (Ref. 21) excretion may be increased, which in turn may enhance the risk of crystal formation in the kidney and bladder. A lowered urinary pH, i.e., increased acidity, resulting from the excreation of large quantities of vitamin C would tend to favor uric acid crystallization (Ref. 22). Recent data defining the supersaturation of normal urine with respect to calcium oxalate (Ref. 23), as well as those citing the mild oxaluria, i.e., increases of urinary oxalate, as little as 20 percent above normal, or patients prone to renal stone formation (Ref. 24) and the formation of renal calculi with relatively small increments in urinary oxalate (Ref. 25), suggest that an increased danger of oxalate crystal formation also exists in persons taking 1 g or more of vitamin C daily.

L-Ascorbic acid serves as a precursor of urinary oxalate in man, normally providing as much as one-third of the oxalate present in urine (Ref. 26). Values reported in the literature for the normal 24-hour urinary oxalate excretion of man range from 14 to 64 mg, with averages of 30 to 38 mg oxalic acid (Ref. 19). Extradietary ascorbic acid is not converted as efficiently, and significant detectable increases of urinary oxalate in a group of normal human subjects were seen only when 4 g or more vitamin C were fed. Increases of from 12 mg oxalate daily with the ingestion of 4 g vitamin C daily, up to 68 mg oxalate daily when ingesting 9 g vitamin C daily, seem modest when compared to the large amounts of ascorbic acid fed (Ref. 19). However, relative to normal urinary oxalate levels, these increases of 40 to 200 percent over normal ranges may result in calcium oxalate precipitation within the urinary tract of potential stone-forming populations (Ref. 25). Increased urinary oxalate upon ingesting as little as 750 mg vitamin C daily has been reported in two patients having iron-overload disorders (Ref. 27).

Moreover, since high oxalate intakes from certain foods, e.g., spinach, rhubarb, chocolate, tea, and/or low calcium intakes also promote increments in urinary oxalate (Ref. 28), vitamin C intakes greater than 1,000 mg daily may prove harmful to individuals with unusual dietary patterns resulting in high oxalate-low calcium intakes. An additional risk factor exists for individuals who reportedly convert ascor-

bic acid to oxalate with considerably greater than normal efficiency (Ref. 29).

In addition to these potential complications in individuals with normal intestinal absorption, others with small intestinal disease (especially those with partial resections) function as a unique population (Refs. 28 and 31). The increased urinary oxalates in these acquired disorders may place these patients at greater risk of forming oxalate stones if they are also subjected to higher doses of vitamin C.

Two clinical problems in making diagnoses involving glycosuria testing have arisen which result from the ingestion of large quantities (more than 1,000 mg daily) of vitamin C. The first is a false-negative glucose oxidase enzyme strip-test, which is given by ascorbic acid concentrations as low as 10 mg/100 ml in the urine (Ref. 34). The second is a false-positive copper reduction test with "Clinitest Tablets" (Ref. 34). Glycosuria testing is important in the monitoring of a diabetic's condition.

Another clinical testing problem resulting from excessive vitamin C ingestion has been the observation of false-negative stool occult blood tests, confirmed by in vitro studies. Fecal examination for occult blood is an important ancillary procedure in the assessment and management of gastrointestinal diseases and gastrointestinal irritation caused by drugs. Amine-dependent occult blood tests such as the Hemoccult test and the Derman test can be inhibited by a fecal excretion of 55 mg ascorbic acid daily, resulting in false-negative indications. A vitamin C intake of 1,000 to 2,000 mg daily has resulted in such false-negative occult blood tests. It has been recommended that no exogenous ascorbic acid should be ingested for 48 to 72 hours prior to conducting amine-dependent stool occult blood tests (Ref. 35).

Sodium comprises approximately 11.6 percent of the weight of sodium ascorbate. Therefore 50 mg sodium ascorbate contains 5.8 mg (0.25 milliequivalent (meq)) sodium, while 1,000 mg of sodium ascorbate will provide 116 mg (5.0 meq) sodium. There is a need for patients on sodium-restricted diets to know the sodium content of the daily dose of an ascorbic acid product which contains sodium ascorbate. This information should be available in the product labeling, to warn patients on severe sodium restriction diets of the potential danger in using high daily dosages of sodium ascorbate products.

Finally, ascorbic acid has been reported to block the anticoagulant effect of heparin in the proportion of about 200 mg ascorbic acid to 100 units (about 1.0 mg) heparin (Ref. 36), and to interfere with the prophylactic use of warfarin sodium (coumadin) in a woman ingesting 16 g ascorbic acid daily (Ref. 37).

In summary, patients prone to recurrent renal calculi (kidney stones), diabetics, patients undergoing stool occult blood tests, and patients on sodium-restricted diets or anticoagulant therapy should be warned of the above effects as a possible consequence of the ingestion of vitamin C products for extended periods in excess of the recommended dosage. The above-mentioned observations also suggest that, because of the possibility that several of the risk factors cited may occur in the same individual, the setting of the upper limit of daily dosage for products marketed for the treatment of vitamin C deficiency at 500 mg would be appropriate to provide an adequate margin of safety when the product is used as directed.

d. *Effectiveness.* The effectiveness of products containing vitamin C is evaluated by the quantitative assay determination of *L*-ascorbic acid by an acceptable, validated method and the determination of ascorbic acid levels in human serum, leukocytes, and urine before and after an appropriate "loading test" (Refs. 38 through 42).

Although as little as 6.5 mg vitamin C daily has been reported to ameliorate symptoms of scurvy, larger doses result in more rapid improvement and in substantial rates of storage in body pools (Ref. 14). In practice, 300 to 500 mg vitamin C daily is often given orally in divided doses of 100 mg for the treatment of vitamin C deficiency. This level of medication is continued until a total of 4,000 mg has been ingested, after which daily doses of 100 mg are used to prevent the recurrence of symptoms. In florid and symptomatic vitamin C deficiency, at which time the patient is under close and careful observation by the physician, larger daily doses, e.g., 1,000 mg, have been recommended until symptoms are controlled (Ref. 1), but such doses have not been shown to be superior to a 500-mg daily dosage and do not provide the margin of safety mentioned in the previous section. Single doses of vitamin C of 100 to 500 mg are effective, i.e., are absorbed and retained by the body, if plasma levels of ascorbic acid are low (Ref. 43). Therefore, the recommended maximum effective daily dose for the treatment of vitamin C deficiency is 500 mg. This dose is considered safe.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that vitamin C, in the dosage and forms identified under Category I conditions below, is safe and effective for use in the prevention and treatment of vitamin C deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which vitamin C is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Acceptance sources of vitamin C activity are ascorbic acid, ascorbyl palmitate, calcium ascorbate, niacinamide ascorbate (for use only in combinations requiring both niacin and vitamin C), and sodium ascorbate. Dosage must be based on the *L*-ascorbic acid equivalent ($C_6H_8O_6$, molecular weight 176.2).

(1) *Dosage*—(i) *For prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 50 to 100 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(ii) *For treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 300 to 500 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.* The Panel recommends the following Category I labeling:

(i) *Indications*—(*a*) *For prevention of deficiency.* "For use in the prevention of vitamin C deficiency when the need for such therapy has been determined by a physician."

(*b*) *For treatment of deficiency.* "For use in the treatment of vitamin C deficiency when the need for such therapy has been determined by a physician."

(ii) *Warnings*—(*a*) *For products containing 0.2 meq (5 mg) or higher of sodium per unit of dose.* The sodium content must be stated per dosage unit (e.g., tablet, teaspoonful) when some or all of the source of vitamin C is sodium ascorbate if the sodium content is 0.2 meq (5 mg) or higher.

(*b*) *For products containing more than 5 meq (125 mg) sodium per unit of dose.* "Do not take this product if you are on a sodium-restricted diet except under the advice and supervision of a physician."

(*c*) *For products containing vitamin C for the treatment of deficiency.* (*1*) "Patients with gout and/or a tendency to form kidney stones may be at increased risk when taking more than the recommended dose."

(*2*) "Diabetics taking more than 500 mg vitamin C daily may obtain false readings in their urinary glucose test."

(iii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) should contain the following additional information: (*a*) "When diabetics ingest large quantities (greater than 500 mg daily) of vi-

tamin C, the following false results may occur when testing for glycosuria: (*1*) False-negatives for glucose oxidase enzyme strip-tests;

(*2*) False-positives for tests based on copper reduction."

(*b*) "The ingestion of daily doses of 1,000 mg or more vitamin C may result in harmful effects due to hyperoxaluria and to increased urinary acidity and uric acid excretion; oxalate and uric acid crystalization may occur in the kidney or bladder, especially in patients prone to renal stone formation. Additional risk factors include consumption of foods containing high levels of oxalate, and small intestinal disease states, e.g., resectioning, evidencing increased urinary oxalate. Persons consuming these excessive amounts of vitamin C should be under a physician's supervision."

(*c*) "No exogenous vitamin C should be ingested for 48 to 72 hours prior to conducting amine-dependent stool occult blood tests, to prevent a false-negative test resulting from a high fecal excretion of ascorbic acid."

g. *Category II conditions under which vitamin C is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC Vitamin C drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The OTC drug use of any source of vitamin C under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning.

The Panel concludes that the following suggested indications appearing in the literature or in the submissions to the Panel for the use of vitamin C sources are presently not supported by adequate controlled clinical studies, or in some instances may require direct supervision by a physican and should not be permitted on the market until scientific testing supports their OTC use:

(i) "Atherosclerosis."

(ii) "Allergy."

(iii) "Mental disease, schizophrenia."

(iv) "Corneal ulcers."

(v) "Idiopathic methemoglobinemia."

(vi) "Thrombosis."

(vii) "Megaloblastic anemia and capillary fragility in the absence of vitamin C deficiency."

(vii) "Adjunctive treatment of iron deficiency anemia in doses less than 200 mg."

(ix) "Treatment of patients on long-term steroid therapy."

(x) "Treatment of immobilized patients and those with pressure sores."

(xi) "Protective or therapeutic effect on the course of the common cold." Although claims have been made for the beneficial effects of 500 to 1,000 mg or more daily of vitamin C for the treatment and/or prevention of the common cold (Ref. 44), double-blind studies have been less than corroborative in this regard (Refs. 45 through 50). Further double-blind studies are required to evaluate fully the validity of the claim. No claims may be made for the use of vitamin C in the treatment of the common cold.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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2. *Biotin.*—a. *Description.* Biotin is a water-soluble vitamin which is found widely distributed in nature in small quantities (Ref. 1). Biotin functions in the body as a cofactor in numerous carboxylation and decarboxylation reactions. It is essential for the intermediate metabolism of carbohydrates, the synthesis of fatty acids, and the interconversions of amino acids.

The potency of the vitamin is reflected in the microgram amounts of normal daily intake which appear to be more than adequate for the body's needs. The average American diet has been estimated to provide 100 to 300 μg biotin daily (Ref. 2). In addition, biotin is synthesized by many of the micro-organisms which normally inhabit the human gastrointestinal tract. In studies of several animal species, the amounts of biotin synthesized in the gut are adequate to meet the host's nutritional needs under normal conditions (Ref. 1). The production of relatively large amounts of biotin in the lower gut of man frequently results in total excretion in urine and feces in excess of dietary intake (Refs. 2 through 6). For this reason, it is unknown whether a dietary requirement for biotin exists in human beings (Ref. 2). Experimental evidence indicates that a clinical biotin deficiency cannot be established by mere removal of the vitamin from the diet (Ref. 2).

Increases in urinary biotin concentration following oral administration of large doses indicates that biotin from the diet is relatively well absorbed (Ref. 3). The mechanism by which this absorption takes place is not known. Absorption at the site of bacterial synthesis, in the large intestine, has also been shown by instillation of an aqueous biotin solution directly into the distal colon. Subsequent increases in blood and urine levels of biotin provide evidence that biotin produced by bacteria in the colon is available for absorption (Ref. 7).

b. *Safety.* Little information regarding toxicity of biotin is available. In the treatment of infantile seborrheic dermatitis (Leiner's disease), infants aged 6-months-old and younger, or their mothers, were given biotin by injection in amounts up to 5 mg daily for as long as 6 to 12 days in some cases. No overt toxic symptoms were noted in mothers or infants in the few studies in which these doses of biotin were administered (Refs. 8, 9, and 10). While animal studies further indicate the biotin is a relatively nontoxic substance (Refs. 1 and 11), the upper human safety limit of biotin intake cannot be estimated from available data.

c. *Effectiveness.* Attempts to produce experimental biotin deficiency in some species of animals and in man have required use of the potent biotin inactivator, avidin, which is present in raw egg whites and is destroyed by heat (Ref. 2). When experimental biotin deficiency has been produced in man by feeding large amounts of raw egg white and additionally limiting biotin intake, deficiency symptoms have occurred after several weeks of the dietary regimen (Refs. 12 and 13). The symptom most characteristic of such a deficiency has been a red, scaly dermatitis which responded rapidly to injected doses of 150 to 300 μg biotin daily for 3 to 5 days. Without such treatment, more sever symptoms involving nerual abnormalities subsequently developed (Refs. 12 and 13). Besides experimentally produced deficiencies, occurrence of clinical biotin deficiency in the human population has been reported in only two individuals. In both cases, the persons affected followed the unusual dietary practice of consuming numerous raw eggs daily, combined with few other nutrient sources, for periods of time ranging from several months to many years. Removal of the raw eggs from the diet, or supplementation with foods containing biotin reversed the deficienty symptoms as seen (Refs. 1, 14, and 15).

Slightly decreased concentrations of biotin have been found in the blood of pregnant women, which suggests the possibility of increased utilization of the vitamin during pregnancy or a dilutional effect caused by increased blood volume which normally accompanies the pregnant state (Ref. 16). If increased demands for biotin exist during pregnancy, there is no evidence that such needs are not met by dietary intake of biotin, coupled with intestinal synthesis of the vitamin.

Two extremely rare genetic biotin dependency syndromes, beta-methylcrotonyl-glycinuria and propionic acidaemia, have been described in man and are caused by genetic occurrence of altered biotin-dependent enzymes with a lowered affinity for biotin. Administration of excess biotin alleviated metabolic symptoms of the disorders in the two cases reported (Refs. 17 and 18). An OTC preparation of biotin is not warranted for use in these disorders, however, because they occur very rarely and would require a physician's diagnosis.

In a limited number of studies, biotin has been claimed to be of value in altering the course of infantile seborrheic dermatitis (Leiner's disease) of breast-fed infants of malnourished mothers (Refs. 8, 9, and 10). However, biotin treatment has not always alleviated the disease symptoms. In addition, the fact that substances besides biotin, such as antibiotics and preparations containing several B-vitamins, have been effective in treating some cases of seborrheic dermatitis (Ref. 10) indicates that biotin deficiency may not be a causal factor in this disease. While some of the cases reported suggest low biotin content of the milk of malnourished mothers to be the cause of the disorder, it has not been demonstrated conclusively that levels of

biotin in human milk are responsive to levels of dietary biotin (Ref. 2). Furthermore, it has been found that seborrheic dermatitis occurs among infants fed formula diets containing larger amounts of biotin than does human milk of healthy individuals (Ref. 10). It is therefore doubtful that biotin deficiency is the cause of seborrheic dermatitis in these instances. In conclusion, it appears from the evidence cited that several factors may be responsible for the onset of infantile seborrheic dermatitis. Further research is therefore needed to elucidate the role of biotin in the development of this disease before a recommendation can be made regarding the effectiveness of biotin in prevention or treatment of infantile seborrheic dermatitis. It should also be noted that if biotin were eventually proven to be valuable in the treatment of infantile seborrheic dermatitis, the disease would still require a physican's diagnosis. In addition, the large amounts used (1 to 5 mg) in attempts to treat the disease indicate the possibility of an individual abnormality of biotin utilization and not a simple deficiency state. It is for these reasons that no recommendation for an OTC preparation of biotin for use in treating infantile seborrheic dermatitis can be made.

A limited number of investigations have been conducted to determine the effect of long-term antimicrobial therapy an microbial biotin synthesis in the intestine (Refs. 13 and 19). Theoretically, if bacterial synthesis of biotin were greatly diminished by administration of antimicrobial agents for sufficiently long periods of time, a deficiency of biotin could develop. However, results have been variable in the few reports available and no conclusion of increased dietary need for biotin under conditions of prolonged antimicrobial therapy can be made at this time.

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that biotin deficiency is virtually nonexistent in the U.S. population and that an OTC preparation of biotin, singly or in conbination, is not warranted.

e. *Category I conditions under which biotin is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which biotin is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC biotin drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that adequate and reliable scientific evidence excludes any basis for claims for the effective use of an OTC drug preparation of biotin, singly or in combination, for prevention or treatment of biotin deficiency. Biotin is available in the diet from numerous plant and animal sources. Synthesis of biotin by intestinal micro-organisms further assures against a biotin deficiency even under conditions of minimal dietary intake.

The Panel further concludes that the use of biotin in the treatment of infantile seborrheic dermatitis (Leiner's disease) is not supported by adequate scientific evidence and that labels purporting such indications are neither truthful nor accurate.

g. *Category III conditions for which the available data are insufficient to permit final classification.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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3. *Choline.* The Panel's statement on choline includes the following ingredients: choline bitartrate, choline chloride, and choline citrate.

a. *Description.* Choline ($C_5H_{15}NO_2$) is a white, water-soluble substance of widespread occurrence, found in abundant quantities in both plant and animal foods (Refs. 1 and 2). Estimates of choline intake in the average American diet range from 150 (Ref. 1) to 900 mg daily (Refs. 1 and 3). Choline is available not only from the diet, but the evidence from a variety of animals and plants studied indicates that choline is synthesized throughout nature (Ref. 4). Choline is synthesized in the human body also by two known pathways. Choline synthesis by transmethylation requires the presence of methyl groups from sources such as methionine. De novo sythesis of methyl groups, requiring adequate amounts of vitamin B-12 and folic acid, can also result in formation of choline in the variety of animal species studied (Ref. 4). Amounts of choline synthesized by these mechanisms in relation to dietary need are not known and appear to depend on a variety of other factors (Refs. 3 and 4). Dietary need for choline, beyond the amount which can be endogenously synthesized, has been demonstrated in a number of animal species (Refs. 1 and 3 through 6). It is possible that a need for dietary choline could also be demonstrated in man under experimental conditions involving systematic removal of choline from the diet (Ref. 3). However, choline deficiency has

not yet been produced in man, and there is no evidence that a dietary need for choline exists for man.

Biochemically, choline functions as a constituent of phospholipids, notably sphingomyelin and lecithin (Refs. 2, 3, and 4). It also serves in the formation of acetylcholine, a substance necessary for neural transmission. Choline further functions as part of a labile methly pool, capable of contributing methyl groups for the synthesis of the amino acid methionine and other methylated compounds necessary for proper growth and cell function (Ref. 4).

Toxic substances known to interfere with choline metabolism in the rat include 2-amino-2-methyl propanol and alpha, alpha-dimethyltriethyl-choline (Refs. 7 and 8). Effects of these inhibitors are overcome by inclusion of excess choline in the diet. Recent research with rats indicates possible interference with choline utilization by phenobarbital (Ref. 9) and by methotrexate, a drug used in treatment of cancer (Ref. 10).

b. *Safety.* Few studies of the toxicity of choline in man are available. However, data concerning various species of animals studied indicate that oral doses are generally less toxic than injected doses (Ref. 1). Choline has been found to be lethal to rabbits when administered subcutaneously in doses of 500 mg/kg of body weight (Ref. 2). Choline chloride is lethal to mice when give interparenterally in doses of 31.3 mg/kg of body weight (Ref. 2). A study of choline toxicity in rats revealed that both the dosage of choline and the vehicle used for its oral administration affected its toxicity. For example, choline chloride fed at 2.7 to 5.0 percent of the diet resulted in decreased growth rate but no deaths among rats studied for 3 to 4 months, while choline chloride fed as 4 percent of the drinking water resulted in the death of all rats studied within 3 months (Ref. 1). It is possible that the greater toxicity seen when choline was fed in the drinking water was an indirect effect of decreased water consumption and not due to the choline itself. The death rate from choline toxicity was found to be comparable between rats and guinea pigs given intraparenteral doses of choline of 45 or 60 mg/100 g of body weight. At the lower dosage, 20 to 29 percent of the animals tested died, while 60 to 74 percent died when the 60 mg dose was injected (Ref. 11).

No reports of choline toxicity in human beings are apparent. Therapeutic doses of choline chloride and of choline dihydrogen citrate, in amounts ranging from 3 to 12 g daily, have been used in the treatment of alcoholic cirrhosis for periods of time ranging from a few days to 4 months as described below, with no toxic effects reported (Refs. 12 through 16). While no data are available regarding the effect of large doses of choline given to normal individuals for indefinite periods of time, there is not evidence from the few cirrhotic patients studied that choline would be toxic at levels several times those commonly ingested in the diet.

c. *Effectiveness.* Bioavailability of choline from any pharmaceutical product can be determined by analysis in plasma and tissues for choline content, using a microbiological assay (Ref. 4). Choline cholride and choline dihydrogen citrate are the forms of choline most frequently used in human studies (Refs. 12, 13, and 14). In addition, choline gluconate and choline phosphate appear to have equal absorptive value (Ref. 1).

Choline deficiency has been induced in a number of animal species, including the rat, guinea pig, dog, pig, monkey, and several species of poultry (Refs. 4, 5, and 6). In most cases the diet used to produce such a deficiency is low in both choline and protein content. Symptoms vary depending on the species studied. However, the most common symptoms found are low growth rate, fatty infiltration of the liver, and hemorrhagic kidney disease.

The fatty liver sign of choline deficiency in animals has received much attention because of its similarity to fatty livers seen in human beings suffering from alcoholism, and to the fatty liver of kwashiorkor. However, animal studies reveal that complex factors are involved in deposition of liver fat. While insufficient amounts of choline is one factor which can bring about fatty infiltration of the liver, other nutritional and physiological factors appear to greatly modify the amount of choline necessary to prevent such liver damage. These influences include the amount of dietary protein (Refs. 17 and 18) and fat (Refs. 4, 5, 19, and 20), type of dietary carbohydrate (Refs. 21 through 24), number of calories fed (Refs. 4, 20, and 25), and possibly the amount of dietary cholesterol (Refs. 6 and 20). In addition, other nutrients, including vitamin B-12 (Refs. 4 and 26) and methionine, threonine, and other amino acids (Refs. 21 and 27) have been shown to prevent or reverse fatty liver symptoms in animals fed low choline diets.

Physiological factors shown to influence choline needs in animals include hormone imbalances, sex, age, and environmental temperature (Refs. 4, 5, 13, and 26). Because of the interplay of these various nutritional and physiological factors, results of studies of choline deficiency in animals have varied widely. It has, therefore, been difficult to assess the importance of dietary choline alone in prevention of fat deposition in the liver. It is likely further that the numerous nutritional and physiological factors influencing the amount of choline required by animals influence choline needs in man.

It is presently believed by the majority of researchers that protein deficiency is the critical element resulting in fat deposition in the liver of children suffering from kwashiorkor (Refs. 4 and 28). The possibility that cirrhosis of chronic alcoholism is a result of inadequate amounts of dietary choline has prompted numerous animal studies, conducted to determine the role of choline and other nutritional factors in ethanol-induced liver damage (Refs. 4, 13, 19, 22, 24, 25, 29, and 30).

As might be expected from results of studies cited concerning choline deficiency alone, results of the effect of choline and other nutritional factors on the fatty liver of cirrhosis are varied. The physiological and nutritional factors determining the need for dietary choline are further complicated by introduction of ethanol.

As a result, it has not yet been determined whether alcoholic cirrhosis in man or animals is caused by one or more nutritional deficiencies, a toxic effect of alcohol itself, an effect of increased calories from alcohol, or a combination of these factors or some other unknown factor (Refs. 4, 13, 19, 22, 24, 25, 29, 30, and 31). In extrapolating animal studies on nutritional factors in alcoholism to human beings, caution must be used for several reasons. In general, it can be said that choline has been shown to have an effect on development of ethanol-induced fatty livers in animals when the choline is supplied at low or marginal amounts in the diet (Ref. 29). However, no relation between dietary choline levels and the occurrence and severity of alcoholic fatty livers in man has ever been demonstrated. In addition, while rats have been used in the majority of ethanol studies in animals, a limited number of enzyme studies suggest possible basic difference between choline metabolism in rats and man and other primates (Refs. 1, 32, 33, and 34). Such differences could, theoretically, reduce the applicability of choline-ethanol relationships in rats to those in man. Furthermore, the correlation between fatty livers in animals and those seen in human beings has not been conclusively established (Ref. 4), nor has the presence of fat in the liver been determined to be causally related to cirrhosis in man (Refs. 15 and 29).

Studies of the effect of choline therapy in alcoholic cirrhosis of human beings are limited and with varying results (Refs. 12 through 15 and 35). In general, such studies often lack ade-

quate controls, employ few numbers of patients, and are carried out over periods of time which are too short in duration to allow for reliable evaluation of results. In addition, most subjects suffering from alcoholism exhibit multiple nutritional deficiencies and vary greatly in response to treatment, making evaluation of any single factor extremely difficult (Refs. 1, 4, and 13).

It does seem quite clear that choline is of no benefit in the treatment of cirrhosis. The majority of the evidence indicates that a diet adequate in all essential nutrients is the most effective in the treatment of cirrhosis. There is no reason to believe that optimal amounts of choline and its precursors are not supplied by such a balanced diet (Refs. 1, 4, 12 through 15, and 35). Also, there is not evidence that alcohol intake increases the need for choline, although, of course, it frequently causes anorexia and decreased food intake (Refs. 1, 4, and 12 through 14).

Choline deficiency has not been demonstrated in man and, in view of the widespread occurrence of choline and methionine in plant and animal foodstuffs, it seems unlikely that is would occur, except possibly in infants or young children with diets severely deficient in protein and rich in highly refined products (Ref. 3). Mixed diets are estimated to provide adults with 400 to 900 mg choline daily (Ref. 3). Such amounts are evidently adequate but, as the quantity of choline synthesized by the body is not known and as mixed diets also provide methionine and probably other methyl donors, these amounts should not be equated with either requirements or dietary allowances (Ref. 3).

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that choline deficiency is virtually nonexistent in the U.S. population and that an OTC drug preparation of choline, singly or in combination, is not warranted.

e. *Category I conditions under which choline is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which choline is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC choline drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that the OTC drug use of choline chloride, choline bitartrate, and choline citrate is not supported by adequate scientific evidence. A choline deficiency syndrome has never been demonstrated in man, and because choline can readily be manufactured within the body from a number of dietary sources of labile methyl groups and there cannot be said to be, for man, a dietary requirement for preformed choline, the Panel concludes that there is no evidence of any drug need for an OTC choline preparation of any kind.

g. *Category III conditions for which the available data are insufficient to permit final classification.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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4. *Vitamin B-12.* The Panel's statement on vitamin B-12 includes the following ingredient: cyanocobalamin.

a. *Reference form.* Dosages recommended in this document are based on the cyanocobalamin equivalent ($C_{63}H_{88}CoN_{14}O_{14}P$, molecular weight 1355.4).

b. *Description.* Vitamin B-12 is a term in common usage to refer to a series of cobalt-containing, nutritionally active corrinoids. The two metabolically active coenzyme forms in man and those found in mammalian tissues are 5-deoxyadenosyl cobalamin (coenzyme B-12) and methyl cobalamin (methyl B-12). The most commonly used oral form of vitamin B-12 is cyanocobalamin. Other semisynthetic forms of vitamin B-12, equipotent with cyanocobalamin for treatment or prevention of vitamin B-12 deficiency, include hydroxycobalamin, aqua cobalamin, and nitritocobalamin. However, the Panel concludes that only cyanocobalamin is acceptable as an OTC drug source of vitamin B-12 activity.

Vitamin B-12 is required for DNA synthesis and cell replication by all mammalian species. As a cofactor in methionine synthesis, vitamin B-12 participates in the conversion to tetrahydrofolate from methyl tetrahydrofolate, thus generating the cofactor for the synthesis of thymidine. In addition, vitamin B-12 is a required cofactor in the interconversion of methyl malonic acid and succinic acid by methyl malonyl CoA mutase (Ref. 1). Vitamin B-12 deficiency is characterized by megaloblastic anemia and similar megaloblastic alterations in other tissues such as the gastrointestinal tract epithelium. Methyl malonic acid or precursors may appear abnormally in urine in vitamin B-12 deficient subjects or in those with genetic defects in vitamin B-12 utilization. Neurologic degeneration may occur when deficiency is prolonged and severe (Ref. 2).

Animal meat including liver, fish, seafood, and eggs are good sources of vitamin B-12. Daily requirements are small, in the range of 0.3 to 2.5 μg (Refs. 3 and 4) and an efficient enterohepatic circulation is capable of conserving several times that amount daily (Ref. 4). The liver can store 1,000 to 1,500 μg in a normal adult, an amount capable of sustaining vitamin B-12 needs for 3 to 5 years.

c. *Safety.* No toxic effects of oral vitamin B-12 have been demonstrated in humans. As a water-soluble substance, excess vitamin B-12 is excreted in urine. Single oral doses ranging from 0.5 to 100 mg have been administered to humans. No apparent side effects were observed (Refs. 5 through 8).

During long-term therapy (3 to 5 years) with weekly oral doses of 1 mg crystalline vitamin B-12, no adverse effects were observed (Ref. 9).

d. *Effectiveness.* Normal absorption of dietary vitamin B-12 occurs by two mechanisms. One mechanism is operative under usual dietary conditions and the other mechanism operates at a significant rate only at vitamin intakes far beyond those in the usual diet. The first absorption mechanism requires the participation of a gastric factor, Intrinsic Factor of Castle (IF), a glycoprotein secreted by the parietal cells of the stomach. The glycoprotein forms a complex with ingested vitamin B-12 in the presence of gastric acid, and the vitamin B-12-IF complex then passes to the distal small intestine or terminal ileum where vitamin B-12 is taken up into the ileal epithelial cells with the aid of specific membrane receptors. This mechanism has an efficiency of about 50 percent when the dose is up to 10 μg. At doses higher than 10 μg the efficiency of absoprtion decreases (Ref. 10). Thus a 10 μg oral dose is considered by this Panel to be an effective dose for the prevention of dietary deficiency because increasing the quantity will produce no additional benefit. The second mechanism of absorption occurs by diffusion at a very low rate with an efficiency of about 1 percent and is quantitatively significant only at oral doses in excess of 100 μg (Ref. 11).

Dietary deficiency of vitamin B-12 is rare. For practical purposes, dietary deficiency occurs in individuals with normal gastrointestinal function only after several years on a very strict vegetarian diet. Dietary deficiency does not occur in ovolacto vegetarians (those who add eggs and milk to a vegetarin diet).

Vitamin B-12 deficiency usually occurs when gastric intrinsic factor is lacking (e.g., pernicious anemia) or when the ileal absorption site is lost or damaged by surgery or disease (Ref. 12). Under these conditions, injected vitamin B-12 is the only entirely reliable means of ensuring an adequate vitamin supply (Ref. 13). Vitamin B-12 deficiency may occur as an acquired condition when the intestine is overgrown abnormally with bacteria or infested with fish tapeworm. In both instances, the deficiency is due to a competition with the offending organism for binding and utilization of vitamin B-12. Therapy consists of eradication of the infestation and treatment of deficiency, if severe, with a single parenteral dose of vitamin B-12.

Vitamin B-12 deficiency may occur due to rare genetic metabolic defects in spite of an adequate amount of dietary intake of vitamin B-12. These metabolic defects include abnormalities in the synthesis of intrinsic factor, ileal receptors, vitamin B-12 transfer proteins (transcobalamins), and enzymes which convert vitamin B-12 to coenzyme forms (Ref. 14). Defective apoenzymes may result in vitamin B-12 requirements 20 to 100 times the usual needs. It should be emphasized that these genetic conditions are rare and require the skill and technology of a sophisticated medical center for diagnosis and managment.

When vitamin B-12 deficiency is due to inadequate absorption, 1 μg parenteral vitamin B-12 daily is adequate (Refs. 10 and 13) and a single 100 μg injection is almost always curtive of all manifestations of deficiency. These conditions are most reliably treated with regular intramuscular vitamin B-12 therapy. The pharmacologic mechanism of absorption could only be utilized safely in therapy if large doses (greater than 100 μg) of oral vitamin B-12 were used under careful medicial supervision to document adequate absorption and utilization. Therapy of the genetic defects requires high dose therapy (20 to 100 times normal) by the intramuscular route under medical care (Refs. 14 and 15).

The documented indications for reliable oral vitamin B-12 therapy are limited to dietary vitamin B-12 deficiency in the rare vegan (an individual adhering to a strict vegetarian diet including no animal products) or in individuals adhering to certain other types of vegetarian diets. Deficiency due to malabsorption associated with diseases of the stomach (e.g., pernicious anemia) and/or the small intestine (e.g., ileal resection, bacterial overgrowth, tropical sprue) or due to rare

genetic defects resulting in malabsorption or block in the metabolic utilization requires parenteral therapy and the careful surveillance of a physician.

The physiologic mechanism of vitamin B-12 absorption has a capacity of 1.5 to 3 μg per dose (Ref. 10). At approximately a 50 percent efficiency, an oral dose of 3 to 10 μg results in an adequate dose of bioavailable vitamin B-12 in the normal individual.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that vitamin B-12, in the dosage and form identified under Category I conditions below, is safe and effective for use in the prevention of vitamin B-12 dietary deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which vitamin B-12 is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Cyanocobalamin is the only acceptable source of vitamin B-12 activity. Dosage must be based on the cyanocobalamin equivalent ($C_{63}H_{88}CoN_{14}O_{14}P$, molecular weight 1355.4.).

(1) *Dosage—For prevention of dietary deficiency.* For adults and children 1 year of age and older, the oral dosage is 3 to 10 μg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.* The Panel recommends the following Category I labeling:

(i) *Indication—For prevention of dietary deficiency. "For use in the prevention of vitamin B-12 dietary deficiency when the need for such therapy has been determined by a physician."*

(ii) *Warnings—(a) For products containing vitamin B-12 as the only active ingredient.* "Caution: This preparation is for the prevention of vitamin B-12 dietary deficiency and cannot be safely used for the treatment of vitamin B-12 dietary deficiency."

(b) For combination products for the treatment of multiple deficiencies which contain a prevention dose of 10 μg. "This product cannot be safely used for the treatment of vitamin B-12 deficiency."

g. *Category II conditions under which vitamin B-12 is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC vitamin B-12 drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that the OTC oral drug use of cyanocobalamin, for the following indications, is not supported by adequate scientific evidence and that labels purporting such indications are neither truthful nor accurate: (1) "For the treatment of vitamin B-12 deficiency secondary to pernicious anemia."

(2) "For vitamin B-12 deficiency secondary to gastrointestinal malabsorption."

(3) "For use in genetic vitamin B-12 or dependency syndromes, e.g., methyl malonic aciduria."

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years by permitted for the completion of studies to support the movement of Category III conditions to Category I.

(1) *Proposed dosage—For prevention of dietary deficiency.* For women taking oral contraceptives, the oral dosage is 3 to 10 μg daily.

(2) *Proposed labeling.* The Panel recommends the following specific labeling for vitamin B-12 for use in women taking oral contraceptives:

Indication—For prevention of dietary deficiency. "For use in the prevention of vitamin B-12 deficiency in women taking oral contraceptives when the need for such therapy has been determined by a physician."

(3) *Evaluation.* Further study is required to document the following: (i) That vitamin B-12 deficiency, characterized by a lowering of serum vitamin B-12 and by morphologic changes in blood or bone marrow, occurs at increased prevalence in women on oral contraceptives relative to appropriate controls.

(ii) That such deficiency is prevented by a daily oral dose of vitamin B-12.

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5. *Folacin.* The Panel's statement on folacin includes the following ingredient: folic acid.

a. *Reference form.* Dosages recommended in this document are based on the pteroyl mono-*L*-glutamic acid equivalent ($C_{19}H_{19}N_7O_6$, molecular weight 441.4).

B. *Description.* Folacin is the generic term for folic acid (pteroylmonoglutamic acid, PGA) and related compounds exhibiting qualitatively the biologic activity of folic acid. Most of the vitamin is present in food as polyglutamates (Ref. 1), which require the action of an intestinal peptidase to free the vitamin for release into the circulation (Ref. 2) Folacin is present in a wide variety of foods, especially liver, leafy vegetables, certain fruit, and yeast.

While dietary folacin consists largely of reduced folates in monoglutamyl or polyglutamyl form, the only synthetic preparation commercially available for oral use is PGA. Once folic acid is absorbed, it must undergo further metabolic conversion to its coenzymatic forms via a series of reduction reactions. The final products, tetrahydrofolates, function primarily in single carbon transfers and along with vitamin B-12 in nucleic acid synthesis. A deficiency characteristically leads to megaloblastic anemia (Ref. 3).

c. *Safety.* Prior to 1973, regulations limited the content of folic acid in multivitamin dietary supplement preparations to 0.1 mg. This limitation was based largely on studies which showed that injections of PGA in doses greater than 0.4 mg could cause remission of the hematologic but not the neurologic complications of pernicious anemia and could, therefore, mask that diagnosis and prevent early intervention and reversal of the neurologic complications of that disease (Refs. 4, 5, and 6). It has also been shown that oral doses of folic acid, at or near the daily requirement of 0.1 to 0.4 mg, would not correct the hematologic complications of vitamin B-12 deficiency anemia (given an absorption efficiency of approximately 50 percent). The effective oral dose required to mask the diagnosis of pernicious anemia would be greater than the 0.4 mg parenteral dose (Ref. 7). Therefore, the case against the widespread use of folic acid in vitamins based on the potential missed diagnosis of pernicious anemia is not substantial and must be weighed against the prevention of folic acid deficiency.

No toxic effects of folic acid are known at doses as high as 15 mg daily. It has been claimed that larger doses of folic acid may reverse effects of anticonvulsants and contribute to seizures (Refs. 8 and 9). These claims are under study.

d. *Effectiveness.* The average daily requirement of crystalline folic acid is based upon hematologic responses to minimal doses of PGA in deficient subjects and a variety of deficiency induction experiments in human volunteers. Evidence exists that daily 0.05 mg PGA orally will induce a complete hematologic remission in most, if not all, patients with folic acid deficiency anemia which is not due to malabsorption (Ref. 4). Similarly, 0.05 mg PGA daily will prevent biochemical evidence of folic acid deficiency in experimental subjects ingesting diets severely deficient in folacin (Ref. 10). Furthermore, the classic time-depletion study in a normal volunteer in whom tissue stores were estimated to be 7.5 mg indicated that about 0.05 mg folic acid were utilized each day (Ref. 11). For normal adults most evidence would place the daily requirement at approximately 0.05 mg crystalline folic acid daily. Doses of 0.1 to 0.2 mg daily are necessary, however, to induce normal serum levels of folic acid in deficient individuals (Refs. 4 and 5).

PGA administered to normal, fasting subjects in doses between 0.2 and 1 mg is absorbed with an efficiency ranging from 45 to 79 percent based upon urinary excretion of labeled folate (Refs. 2 and 12). Disease of the gastrointestinal tract, alcoholism, and drugs such as diphenylhydantoin may depress absorption of the crystalline PGA to 10 to 30 percent (Refs. 2 and 12). Allowing for a wide range of absorption of oral PGA, the recommended upper dose is set at 0.4 mg. For the pregnant and lactating female, the recommendation is for approximately twice that value (1 mg) to insure adequate folate in the presence of increased requirement. Folacin deficiency has been documented in high prevalence among pregnant women (Refs. 10, 13, and 14); patients with diseases affecting the gastrointestinal tract, including celiac disease and other forms of malabsorption, ulcerative colitis, and regional enteritis; patients with intestinal resection; alcoholics; and patients who use certain medications such as anticonvulsants (Ref. 9). Low serum folate levels have been reported in patients taking oral contraceptive pills (Ref. 15). However, an increased incidence of folate deficiency anemia has not been proven and the changes in serum may represent changes in folate binding in serum rather than folate depletion. Initial reports that oral contraceptives interfere with absorption of natural folates are not confirmed (Ref. 16).

Some drugs may cause or contribute to folate deficiency by interfering with either absorption or utilization of folate (Ref. 17). Diagnosis is based on evidence of low serum folate levels and low red cell folate levels, with or without characteristic changes in blood morphology.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that folic acid, in the dosage and form identified under Category I conditions below, is safe and effective for use in the prevention of folic acid deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which folacin is generally recognized as safe and effective and is not misbranded for the prevention of folic acid deficiency.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Folic acid is the only acceptable source of folacin activity. Dosage must be based on the pteroyl mono-*L*-glutamic acid equivalent ($C_{19}H_{19}N_7O_6$, molecular weight 441.4).

(1) *Dosage—For prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 0.1 to 0.4 mg daily. For pregnant and lactating women, the oral dosage is 1.0 mg daily. For those persons who use alcohol to excess, the oral dosage is 1.0 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.* The Panel recommends the following Category I labeling:

(i) *Indication—For prevention of deficiency.* "For use in the prevention of folic acid deficiency when the need for such therapy has been determined by a physician."

(ii) *Warnings—(a) For products containing 1 mg folic acid per unit of dose.* (*1*) "Caution: The use of folic acid for treatment of anemia without the direction of a physician may be dangerous."

(*2*) "Do not exceed the recommended daily dosage."

(*b*) *For combination products for the treatment of multiple deficiencies which contain a prevention dose of 1 mg folic acid.* "This product cannot be safely used for the treatment of folic acid deficiency."

g. *Category II conditions under which folacin is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC folacin drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The OTC drug use of folacin under the following condition is unsupported by scientific data and by sound theoretical reasoning.

The Panel concludes that the use of folacin for the treatment of folic acid deficiency is not supported and can be safely undertaken only under the direct supervision of a physician and therefore requires a prescription mode of therapy.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

(1) *Proposed dosage—For prevention of deficiency.* For women taking oral contraceptives, the oral dosage is 0.1 to 1.0 mg daily.

(2) *Proposed labeling.* The Panel recommends the following specific labeling for folic acid for use with oral contraceptives:

Indication. "For use in the prevention of folic acid deficiency in women taking oral contraceptives when the need for such therapy has been determined by a physician."

(3) *Evaluation.* Further study is required to document the following: (i) That folic acid deficiency, characterized by a lowering of red cell folic acid or by morphological changes in blood or bone marrow (macrocytosis, hyperlobation of polymorphonuclear leukocytes, megaloblastic changes in marrow), occurs at increased preva-

lence with women on oral contraceptives relative to appropriate controls.

(ii) That such deficiency is prevented by a daily oral dose of folic acid from 0.1 to 1.0 mg.

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6. *Niacin.* The Panel's statement on niacin includes the following ingredients: niacin (nicotinic acid), niacinamide, and niacinamide ascorbate.

a. *Reference form.* Dosages recommended in this document for niacin are based on the niacinamide equivalent ($C_6H_6N_2O$, molecular weight 122.1).

b. *Description.* Niacin is the generic descriptor for compounds exhibiting the biologic activity of niacinamide, including niacin (nicotinic acid) and niacinamide. It occurs in biologic materials as nicotinic acid and niacinamide, plus two coenzymatic forms, nicotinamide (niacinamide) adenine dinucleotide (NAD) and nicotinamide adenide dinucleotide phosphate (NADP). These coenzymes act as electron transfer agents and catalyze a variety of basic biochemical reactions involving carbohydrates, amino acids, and fats. Dietary tryptophan is a major precursor of niacin, approximately 60 mg tryptophan being converted into 1 mg niacin (Refs. 1 and 2). Niacin is excreted in urine in a number of forms. In man, the principal metabolites are N'-methylnicotinamide and the N'-methyl-6-pyridone-3-carboxamide. Excretion of niacin metabolites is influenced not only by intake, but also by the need of the body, the amount of methyl donors, the efficiency of the methylating mechanisms, the amount of biosynthesis from tryptophan, and other factors (Ref. 3). On a niacin-deficient diet, urinary levels usually drop rapidly to a low and constant level before any sumptoms of deficiency become evident (Ref. 3).

c. *Safety.* Niacinamide (nicotinamide) is the preferred OTC form of the vitamin because of fewer side effects at higher levels.

(1) *Studies comparing nicotinic acid with nicotinamide.* In a study comparing equal amounts of nicotinic acid and nicotinamide (3 to 7.5 g) in eight subjects, ages 38 to 61, serum cholesterol levels dropped with nicotinic acid treatment lasting 30 weeks (Ref. 4). Symptoms included flushing, dryness of the skin, and irritable bowel symptoms. After 12 weeks of nicotinamide administration, neither the hypolipidemic effect nor other side effects were observed.

Altschul, Hoffer, and Stephen (Ref. 5) administered 1 g nicotinic acid four times daily to 11 healthy young people, and 1 g nicotinic acid daily to 57 patients with various diseases. Nicotinic acid decreased serum cholesterol levels. Similar tests with the same doses of nicotinamide in 20 healthy young adults showed no definite influence on serum cholesterol levels. Flushing and burning of the skin were side effects in the patients receiving nicotinic acid treatment, but no symptoms were noted for those receiving nicotinamide.

Using 3 to 6 mg/100 ml serum uric acid as a normal range, Parsons noted that of 49 patients receiving 3 to 6 g nicotinic acid daily for over 2 years, 38 persons had elevated serum uric acid levels (6.5 mg/100 ml) (Ref. 6). During 12-week therapy with an equal dosage of nicotinamide, in a 10-patient sample, 7 showed average serum uric acid levels of 6.5 mg/100 ml or greater. No gouty arthritis or renal calculi were observed with either drug.

(2) *Nicotinamide tolerance.* There are only a few other studies which help to determine the minimum toxic level of nicotinamide. These few studies, most of which are with animals, confirm the previously cited studies showing that this substance has no observed toxicity up to a range of 3 to 9 g daily. The exact level over a long time is not known. Only one case history appears to have been published showing evidence of toxicity at this level (9 g) in man, so the total evidence is weak.

In this case history, the 35-year-old patient developed severe signs of toxicity after taking 9 g nicotinamide for 7 days, including nausea, vomiting, anorexia, and fatigue (Ref. 7). A liver biopsy revealed portal fibrosis and swollen parenchymal cells. Liver function tests returned to normal 3 weeks after nicotinamide treatment was stopped.

(3) *Nicotinic acid tolerance.* Human studies with nicotinic acid alone show that even relatively small doses give a pharmacological effect. Spies et al. (Ref. 8) noted cutaneous flushing, burning, itching of the skin, and increased sensation of heat in five individuals when 50 mg nicotinic acid in aqueous solution was given as a single oral dose to 100 adult nonpellagrins on an empty stomach. When 100 mg was given under the conditions, about 50 percent of the group exhibited these symptoms. A majority had a reaction when 200 mg was given, and all had some degree of flushing when 500 mg was administered. Four of these 100 adults complained of nausea and cramps after single oral doses of nicotinic acid ranging from 300 to 1,500 mg administered while the stomach was empty.

Goldsmith and Cordill (Ref. 9) administered single oral 50 mg doses of nicotinic acid in aqueous solution to three normal subjects. Responses varied from no skin reaction to severe flushing reaction, with the time of onset from 4 to 23 minutes after administration, and duration of flush from 10 to 90 minutes. When six subjects were given single oral doses of 100 mg, they showed mild to severe flushing reactions. A dose of 200 mg under the same conditions resulted in the same range of response for three persons.

Because of the known serum cholesterol-lowering effect of nicotinic acid, it has been used at relatively high

levels in therapy with hypercholesterolemia. Seventeen female and 31 male patients (ages 35 to 70) with elevated serum cholesterol levels were administered nicotinic acid beginning with 350 or 500 mg doses three times daily, and increasing to 3,000 mg daily if tolerated (Ref. 10). All 48 patients showed flushing. In the period of study from 1 to 10 months, 16 stopped medication because of the severity of the reaction. Forty percent of the patients (19) reported gastrointestinal distress, and 25 percent (12) complained of pruritis. Two individuals suffered from reactivation of peptic ulcers, and six individuals developed "unusual nervousness." Activation of peptic ulcer symptoms in five patients is reported by Parsons at 3 to 7.5 g daily of unbuffered nicotinic acid (Ref. 11). Gastrointestinal symptoms were absent when 1 g buffered nicotinic acid (0.6 g sodium bicarbonate for each g of acid) was administered three times daily for 2 weeks to 12 young adults (Ref. 12). Other human studies with 3 g nicotinic acid confirm these side effects (Refs. 13 through 16). Several individual cases of jaundice and hepatic abnormalities have also been reported with an intake of 3 g nicotinic acid (Refs. 17, 18, and 19).

Of 47 patients (average age 29) who completed at least 24 months of nicotinic acid therapy (3 g daily) for schizophrenia, it was reported that one-third of the subjects developed pigmented hyperkeratosis resembling acanthosis nigricans after several months (Ref. 20).

Glucose intolerance (100 mg glucose load) was demonstrated in five subjects given a 4.5 g treatment of nicotinic acid daily for 4 weeks. Pruritis, nausea, elevated plasma insulin, and elevated plasma uric acid were also side effects which returned to normal within 1 week after nicotinic acid treatment was stopped (Ref. 21). Glucose intolerance was also observed in three diabetics and seven nondiabetics (Ref. 22).

In summary, nicotinic acid produces side effects beginning with single 50 mg oral doses daily, whereas no untoward effects accompany intake of nicotinamide until 3 to 9 g doses are reached.

d. *Effectiveness.* Extra niacin is desirable when taking drugs or chemicals which exhibit antiniacin activity, such as 6-mercaptopurine, or when experiencing conditions which increase the need for the vitamin, such as alcoholism (Ref. 23). A dose of 50 mg daily is recommended under these circumstances.

Body depletion of niacin leads to pellagra with diarrhea, dermatitis, and mental abnormalities. A deficiency state may also be associated with reduced growth, weight loss, loss of appetite, and difficulties in reproduction and lactation (Ref. 24). Pathologic changes include dilation of skin blood vessels, abnormalities of keratinization, ulceration of mucous membranes, and chromatolysis of ganglion cells in the brain. Molecular mechanisms for these manifestations have not been defined. A deficiency state is accompanied by decreased blood and urine levels of niacin and its metabolites, reduced tissue phosphopyridine nucleotides (Ref. 25).

Niacin deficiency, which has been greatly reduced by the enrichment of flour, continues to be a problem among food faddists, alcoholics, and patients with debilitating illness. A survey revealed low circulating levels of niacin in 34 percent of Chinese, 46 percent of Black, 56 percent of Caucasian, and 60 percent of Puerto Rican school children tested in New York City (Ref. 26). Twenty-nine percent of randomly selected hospitalized patients in a municipal hospital in New Jersey had a deficiency of this vitamin (Ref. 27). Dietary histories revealed that this was attributable to a deficient intake of the vitamin in one-third of the patients (Ref. 27).

A variety of methods have been used to test for niacin bioavailability. OTC niacin-containing products should be evaluated with respect to their ability to increase tissue or body fluid niacin levels. Absorbability of niacin in an unknown preparation may be documented by measuring urinary excretion of N'-methylnicotinamide and N'-methyl-6-pyridone-3-carboxamide (Ref. 28). Results are expressed in terms of milligrams per gram (mg/g) creatinine excreted in 24 hours. Alternatively, microbiologic methods may be used to measure blood or urine levels of niacin after a test dose of the vitamin (Ref. 29). Both of these approaches require subjects with no abnormality in intestinal transport or intermediary tryptophan metabolism, and who are not receiving drugs which may influence niacin metabolism. The normal male should excrete approximately 50 percent of a 10 mg dose in the form of niacin metabolites.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that niacin, in the dosage and forms identified under Category I conditions below, is safe and effective for use in the prevention of niacin deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which niacin is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Acceptable sources of niacin activity are niacinamide and niacinamide ascorbate. Dosage must be based on the niacinamide equivalent ($C_6H_6N_2O$, molecular weight 122.1).

(1) *Dosage*—(i) *For prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 10 to 20 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(ii) *For treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 25 to 50 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.* The Panel recommends the following Category I labeling:

Indications—(*a*) *For prevention of deficiency.* "For use in the prevention of niacin deficiency when the neeed for such therapy has been determined by a physician."

(*b*) *For treatment of deficiency.* "For use in the treatment of niacin deficiency when the need for such therapy has been determined by a physician."

g. *Category II conditions under which nicotinic acid as a source of niacin activity is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from nicotinic acid drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that there is no reason for the OTC drug use of nicotinic acid since all the benefits of niacin activity are provided by Category I niacin sources for the prevention and treatment of niacin deficiency. Large doses of nicotinic acid have been used to reduce elevated serum triglycerides, free fatty acids and cholesterol. This quantity of nicotinic acid often causes vasodilation or flushing and may produce hyperglycemia, hyperuricemia, and in some instances liver injury (Ref. 31). Such therapy requires continuous monitoring by a physician so that an OTC dosage is not recommended for this purpose.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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7. *Pantothenic acid.* The Panel's statement on pantothenic acid includes the following ingredients: calcium pantothenate, dexpanthenol, and pantothenic acid.

a. *Reference form.* Dosages recommended in this document for pantothenic acid activity, for use in combination products only and not as a single ingredient, are based on the *D*-pantothenic acid equivalent ($C_9H_{17}NO_5$, molecular weight 219.2).

b. *Description.* Pantothenic acid is a water-soluble vitamin, named for its universal occurrence in nature (pantothenic—from Greek, meaning "from everywhere") (Ref. 1). The vitamin is found in abundant quantities in animal products, whole grains, and vegetables (Refs. 2 through 5). The amount of pantothenic acid found in natural products may vary with maturity of the product, variety of plant or animal, and environmental factors, including soil conditions and diet fed (Ref. 5).

Estimates of the pantothenic acid content of average American diets have been made by a number of researchers (Refs. 2 and 5 through 11) with findings ranging from approximately 5 to 20 mg daily. In addition, biosynthesis of pantothenic acid by intestinal microflora is suspected, but amounts produced and the availability of this source of the vitamin are unknown (Refs. 2, 5, 8, and 12). Bacterial synthesis may further be dependent on adequate sources of folic acid, biotin, ascorbic acid, or other factors (Ref. 4).

Studies of a variety of plant and animal species have revealed the apparently universal function of pantothenic acid as an essential constituent of coenzyme A (Refs. 2, 5, 11, 12, and 13). This important factor, necessary for acyl transfer reactions in living systems, has far-reaching effects on the metabolism of carbohydrate, fat, and protein. Its activity is essential for processes including energy release, gluconeogenesis, fatty acid synthesis, sterol synthesis, and others (Refs. 2, 5, and 11).

c. *Safety* From evidence available, pantothenic acid appears to be a relatively nontoxic substance in humans and several animal species studied (Refs. 5 and 14). For example, an experiment in which humans ingested daily doses of 10 to 20 g pantothenic acid resulted in the relatively mild symptoms of occasional diarrhea and water retention (Ref. 5).

d. *Effectiveness.* Pantothenic acid exists in several forms in nature and in common pharmaceutical products. *D*-Pantothenic acid, calcium pantothenate (calcium *D*-pantothenate), sodium *D*-pantothenate, dexpanthenol (pantothenyl alcohol, which is panthernol commercially), and *D*-pantothenamide are commonly found in pharmaceutical preparations (Ref. 15). These various forms are recognized to be of equal biological value in human beings. The pantothenic acid activity of any pharmaceutical product may be determined by chemical assay (Ref. 15).

Tests of the bioavailability of pantothenic acid have shown that it is well absorbed in man, in any of the above-named forms (Refs. 5, 7, 16, and 17). In these tests, using a microbiological assay, increased amounts of pantothenic acid were found in the blood and urine of individuals following oral administration of the vitamin (Refs. 7 and 15 through 18). In human blood samples, the major amount of pantothenic acid is found as coenzyme A in the erythrocytes, while lesser amounts of free pantothenic acid are found in the serum (Ref. 18). Pantothenic acid in the urine apparently occurs in the free form only (Ref. 18).

Estimates of total pantothenic acid content of human blood, made by a number of researchers, range from 140

to 420 ng/ml (Ref. 4). With slight changes in methods used, average values as high as 464 ng/ml have been found (Refs. 4 and 18). Blood levels of total pantothenic acid in infants and young children appear to be greater than adults (Ref. 19).

In addition, a relatively greater proportion of free pantothenic acid to bound pantothenic acid exists in the serum of infants and children as compared to the serum of adults (Ref. 4). However, considerable variation in these blood parameters exists among individuals. It has been reported that the total concentration of pantothenic acid is decreased in the serum of pregnant women, indicating an increased utilization of the vitamin (Refs. 6 and 20) or a dilutional effect of volume expansion (increased blood volume), which is normal in pregnancy. Supplements of pantothenic acid given late in pregnancy have been shown to elevate the concentration of free pantothenic acid in the serum, but no change was effected in the bulk of the vitamin bound in the erythrocytes until after delivery (Ref. 20). It is possible that the decreases in levels of bound pantothenic acid in the blood occur early in pregnancy. Limited evidence further suggests a decline in pantothenic acid content of the blood as a consequence of aging in women (Ref. 21). However, in each of these studies of pantothenic acid status in pregnancy and in aging, no indications of clinical pantothenic acid deficiency were found. No beneficial effects of pantothenic acid in women taking oral contraceptives have been reported.

Estimates of the normal range of urinary pantothenic acid excretion in healthy individuals of 2 to 7 mg daily (Ref. 2) and 2.5 to 9.6 mg daily (Ref. 22) have been made. Several investigations have shown urinary pantothenic acid excretion to fall within these ranges (Refs. 8, 17, and 18). Slightly lower values appear to be normal for children studied (Refs. 7 and 19). Urinary excretion is generally found to correlate with dietary intake, although individual variation is large (Refs 2, 6, 7, 8, and 17). Urinary excretion of 1 mg pantothenic acid or less per 24 hours has been considered by several investigators to represent a deficient state (Refs. 6, 7, and 17). However, clinical pantothenic acid deficiency has not been reported in conjunction with excretion of this low level of the vitamin.

A number of studies have been conducted in efforts to establish a pantothenic acid deficiency in man (Refs. 23 through 27). In most of these studies, no clinical symptoms of pantothenic acid deficiency were obtained with only the removal of the vitamin from the diet. Inclusion of the pantothenic acid antagonist, omega-methyl pantothenic acid, resulted in symptoms including fatigue, insomnia, neurological disorders, decreased eosinopenic response to ACTH, and increased sensitivity to insulin (Refs. 23 and 25). However, much variability was found among individuals studied. A number of symptoms were not reproduced in subsequent trials, and pantothenic acid alone did not completely reverse all of the symptoms found (Refs. 23 and 25). It is possible that the antagonist itself exerted a toxic effect, causing some of the symptoms seen; in one of this series of investigations, depletion of pantothenic acid from the diet, without use of the antagonist, resulted in some of the above symptoms in the two individuals given the pantothenic acid-deficient diet. These symptoms were less severe, and slower to develop, however, than when the antagonist was used (Ref. 24). In another report of the deprivation of pantothenic acid in human subjects, without use of a vitamin antagonist, urine and blood levels of pantothenic acid decreased, but no clinical deficiency signs were seen after 9 weeks of the dietary regimen (Ref. 27). No conclusive response of decreased antibody formation, previously seen in pantothenic acid deficient animals, could be demonstrated in a study of pantothenic acid deficiency in human beings (Ref. 26).

Neurological symptoms of malnutrition, found among rural populations of Asia and among prisoners of war who subsisted on a severely restricted diet for long periods of time, were found to respond to pantothenic acid therapy in some cases (Refs. 5, 28, and 29). The symptom, commonly called "the burning feet syndrome," has shown inconsistent response to treatment with pantothenic acid, however. In addition, it is generally the case that those individuals studied were suffering from multiple vitamin deficiencies so that evaluation of a single causal factor is difficult.

There is evidence to indicate that various groups in the American population consume low to marginal amounts of pantothenic acid in their diets. In most of these studies, adequacy of dietary intake was determined by a comparison between dietary intake of groups with suspected pantothenic acid deficiency and the U.S. RDA's of 3 to 10 mg. Comparison was also made between urinary excretion levels and standard excretion values for normal individuals. It has been found that pregnant and nonpregnant teenage girls (Refs. 2 and 6) and a group of low-income women (Ref. 9) consumed a level of pantothenic acid below recommended amounts in self-selected diets. In addition, the amount of pantothenic acid in the diet has been shown to vary with protein content of the diet (Ref. 7) and the cost of the diet in general (Refs. 8 and 10). In no case, however, was any clinical indication of pantothenic acid deficiency found.

Interrelationships of pantothenic acid with other nutrients have been proposed in a few studies. A sparing action has been attributed to vitamin B-12 in rats fed low pantothenic acid diets (Refs. 30 and 31), while it has been suggested that an increase in copper intake results in greater need for pantothenic acid, in rats also (Ref. 32). Administration of 5 mg thiamine daily for 1 week was found to elevate blood and urine levels of pantothenic acid in a group of human subjects studied for 3 weeks (Ref. 33). The importance of these findings in human nutrition cannot be assessed at this time.

Investigations of pantothenic acid status in human beings suffering from a number of diseases have been conducted. While some studies of cirrhosis due to chronic alcoholism and other liver diseases have shown decreased urine or blood levels of pantothenic acid, other studies show no correlation of urine or blood levels of pantothenic acid with the incidence of the diseases (Refs. 34 through 37). Response of alcoholic neuropathy to pantothenic acid therapy has varied, with most indications that the neurological problems result from multiple nutritional factors (Refs. 34 and 35). The evidence suggests, therefore, that supplementation with pantothenic acid alone would be of virtually no value in the vast majority of cases.

In other studies diabetic patients have been shown to excrete relatively large amounts of pantothenic acid in the urine, but decreased blood concentrations were not found (Ref. 38). The therapeutic use of pantothenic acid has been attempted in some cases of osteoarthrosis and rheumatoid arthritis (Refs. 39 and 40). However, too few patients have been studied to evaluate the results. The amounts of pantothenic acid necessary to alleviate symptoms indicate possibility of a metabolic disorder of the invididual and not a deficiency of pantothenic acid in the usual sense. Pantothenic acid has also been claimed to be of value in the treatment of postoperative ileus (Ref. 5). However, confirmation of the findings is needed. In general, the use of pantothenic acid for any of these abnormal conditions mentioned is not conclusively supported by available experimental evidence. In addition, most of these conditions would require a physician's treatment, and the use of pantothenic acid would be at his direction and not as an OTC product.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing

history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that pantothenic acid deficiency is virtually unknown in the U.S. population and that pantothenic acid, as a single ingredient, is not warranted for OTC drug use. However, the Panel concludes that pantothenic acid may be safely used in daily dosage of 5 to 20 mg in combination products containing other essential nutrients for use in the prevention of multiple vitamin deficincies such as may occur in conjunction with chronic alcoholism, malabsorption syndromes, or severely restricted nutrient intake caused by lack of a nutritionally balanced diet. (See part II. paragraph F.2. above—Safety and part II. paragraph F.7. above—Category I combinations.)

f. *Category I conditions under which pantothenic acid is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publicaton of the final monograph in the FEDERAL REGISTER.

There are no Category I conditions for pantothenic acid as a single ingredient. However, the Panel concludes that calcium pantothenate, dexpanthenol, and panthenol are acceptable sources of pantothenic acid. Daily dosages of 5 to 20 mg based on the *D*-pantothenic acid equivalent ($C_9H_{17}NO_5$, molecular weight 219.2) may be added to certain combinations of other essential nutrients for use in the prevention of multiple vitamin deficiencies such as may occur in conjunction with chronic alcoholism, mal- absorption syndromes, or severely restricted nutrient intake caused by lack of a nutritionally balanced diet. (See part II. paragraph F.2. above—Safety and part II. paragraph F.7. above—Category I combinations.)

g. *Category II conditions under which pantothenic acid is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC pantothenic acid drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that there is no need for an OTC drug preparation of pantothenic acid as a single ingredient since a deficiency of this vitamin occurring as a single vitamin deficiency is virtually unknown in the U.S. population.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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8. *Vitamin B-6.* The Panel's statement on vitamin B-6 includes the following ingredient: pyridoxine hydrochloride.

a. *Reference form.* Dosages recommended in this document for vitamin B-6 are based on the pyridoxine hydrochloride equivalent ($C_8H_{12}ClNO_3$; molecular weight 205.6).

b. *Description.* Vitamin B-6 exists in nature as pyridoxine, pyridoxal, and pyridoxamine. These forms are converted in the body to pyridoxal-5-phosphate, the major coenzyme form of the vitamin, although pyridoxamine exhibits cofactor activity in some circumstances. The only form of vitamin B-6 used in commercial preparations is pyridoxine hydrochloride.

More than 60 enzymatic reactions are known in which pyridoxal phosphate is the cofactor. These reactions are concerned primarily with amino acid and protein metabolism and, to a lesser extent, with nucleic acid synthesis, and carbohydrate and lipid metabolism. Some of the reactions catalyzed by these enzymes include transamination, racemization, decarboxylation, cleavage, synthesis, dehydration, and desulfhydration. The conversion of tryptophan to niacin, the synthesis of regulator amines (norepinephrine, serotonin, and histamine), and the production of porphyrins and hemoglobin are important functions of pyridoxal coenzymes (Refs. 1, 2, and 3).

Deficiency symptoms have been induced in humans by feeding vitamin B-6 deficient diets and/or by administering vitamin B-6 specific antagonists. Clinical observations include inflamation of the mouth and tongue, peripheral neuropathy, increased irritability, mental depression, convulsions, abnormal electroencephalograms, and hypochromic anemia. Biochemical derangements associated with vitamin B-6 deficiency are altered tryptophan metabolism with an increase in the excretion of xanthurenic acid and the inability to convert trytophan to nicotinic acid; low or absent urinary pyridoxine and pyridoxic acid, the major pyridoxine hydrochloride excretory product; impairment in the formation of antibodies; decreased plasma and blood pyridoxal phosphate; and decreased glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) activities in blood and erythrocytes.

Since many of the clinical symptoms are indistinguishable from deficiency symptoms associated with some or all of the other B-vitamins, biochemical findings and response to pyridoxine hydrochloride are relied on to implicate vitamin B-6 as the deficient nutrient. The biochemical assessment of nutritional status has been recently reviewed and evaluated by Sauberlich et al. (Ref. 4). The most reliable tests appear to be as follows: (1) *Direct.* (i) Plasma, erythrocyte, and whole blood vitamin B-6 levels which fall rapidly during vitamin B-6 depletion and rise following supplementation, reflecting intake. Normal plasma or serum levels of vitamin B-6 measured by protozoan assay, are in excess of 50 ng/ml, while levels fall below 25 ng/ml in subjects with biochemical evidence of deficiency. (Ref. 4).

(ii) Progressive decline in urinary pyridoxine and rise following supplementation. Urinary pyridoxine excretions of less than 20 micrograms per gram (μg/g) excreted creatinine are indicative of marginal or inadequate dietary intakes.

(iii) Enzymic determination of pyridoxal-5-phosphate by tyrosine decarboxylation (Ref. 5).

(2) *Indirect.* (i) Increased excretion of tryptophan metabolites (xanthurenic acid, 3-hydroxykynurenine, and kynurenine) after a 2 to 5 g *L*-tryptophan load test.

(ii) Decrease in erythrocyte GOT and GPT activities. The in vitro stimulation of enzyme activity by pyridoxal phosphate is also greater in deficient subjects (E-GOT or E-GPT activation test).

(iii) Urinary excretion of 4-pyridoxic acid.

c. *Safety.* Pyridoxine hydrochloride is readily absorbed and extensively metabolized by man. The major metabolite is 4-pyridoxic acid which accounts for 20 to 40 percent of pyridoxine ingested (Ref. 2).

(1) *Acute toxicity.* No acute toxicity after pyridoxine hydrochloride ingestion has been reported in humans. Oral administration of 4.0 to 5.5 grams/kilogram (g/kg) body weight to rats or mice is lethal to 50 percent of the animals (Ref. 6).

(2) *Chronic toxicity.* (i) "In man, toxic effects were not encountered with daily administation of 50 to 200 mg pyridoxine hydrochloride over periods of months" (Ref. 6). Untoward effects have been observed, however, by some investigators. In one patient with encephalitis, severe aggravation of seizures occurred, and in another deterioration of the encephalographic pattern was observed when pyridoxine hydrochloride was given. Improvement occurred in both individuals after vitamin B-6 therapy was discontinued (Ref. 6).

(ii) Transient induced pyridoxine dependency has been reported (Refs. 7 and 8). Eight normal adult males consumed 200 mg supplementary pyridoxine hydrochloride for 33 days. Eight days following cessation of supplementation, three subjects had abnormal electroencephalographic (EEG) patterns which were normal one week later. All three complained of nervousness, tremulousness, and other ill-defined symptoms of a similar nature. Further experiments using daily supplementation of 300 mg showed similar findings; in addition EEG's became slightly abnormal in three individuals in the final week of supplementation.

(iii) Transient taurinuria and long-lasting general amino-aciduria occurred in a child during pyridoxine hydrochloride treatment for 2 years with 120 mg daily (Ref. 8).

(iv) Diminution in the effectiveness of l-dopa in the treatment of Parkinsonism when pyridoxine hydrochloride, 5 mg or more daily was given (Ref. 9).

(v) Six hundred mg pyridoxine hydrochloride daily has been used to inhibit lactation in postpartum women not wishing to breast feed (Ref. 11). The effect of high levels of pyridoxine on established lactation has not been reported.

Other side effects are less well documented. (*1*) Lethargy was reported for one woman taking 50 mg pyridoxine hydrochloride orally daily (Ref. 12).

(*2*) Excessive energy and insomnia were reported for one woman taking 100 mg pyridoxine hydrochloride orally daily. Symptoms were prevented by the reduction of the dose to 50 mg daily (Ref. 12).

(*3*) Patients treated with large amounts of pyridoxine hydrochloride for homocystinuria may develop folate deficiency (Ref. 13).

(*4*) Somnolence is reported in some individuals treated with as little as 5 mg pyridoxine hydrochloride daily (Ref. 14). Such individuals are considered pyridoxine-sensitive by the author.

(5) An infant with a requirement for extradietary vitamin B-6 was born to a mother who had received large doses of pyridoxine hydrochloride during pregnancy. Since the fetus has the ability to concentrate pyridoxal phosphate, the effect of large doses to the mother, concentrated by the fetus, on fetal metabolism is unknown (Refs. 15 and 16).

d. *Effectiveness.* The requirement for vitamin B-6 by young adults has been based on depletion and repletion studies which show a range of 1.25 to 1.5 mg daily required on a low protein diet and 1.75 to 2.0 mg daily for a high protein diet (Ref. 3). Experience with infant formulas suggest that metabolic requirements are satisfied if vitamin

B-6 is present in amounts of 0.015 mg/g protein (Ref. 3). The requirements of pregnant and lactating women and of the elderly may be higher. Dietary surveys by a number of workers indicate that an appreciable fraction of the United States adult population is not obtaining 1.5 mg vitamin B-6 (Ref. 17). Those segments of the population most vulnerable to low or deficient vitamin B-6 intake are as follows:

(1) *Low income.* Leevy et al. (Ref. 18) found that of the 105 out of 120 randomly selected municipal hospital patients exhibiting hypovitaminemia, 27 percent had low serum levels of vitamin B-6. This finding appeared to correlate with low dietary intakes of the vitamin (based on dietary history) rather than on the nature of the disease. The patients were indigent or of a low-income group.

(2) *Infants.* (i) If the mother has marginal vitamin B-6 intake during pregnancy, or is preeclamptic, the infant may be born with inadequate vitamin B-6 reserves (Ref. 19).

(ii) Clinical signs of vitamin B-6 deficiency were observed in two breast-fed infants receiving maternal milk with a pyridoxine hydrochloride concentration of 0.06 to 0.08 mg/liter. Normal human milk contains about 0.10 mg/liter (Ref. 3).

(iii) Infants fed autoclaved commercial milk formulas low in vitamin B-6 developed symptoms of deficiency responsive to pyrodoxine hydrochloride (Refs. 2 and 3). About 300 cases were reported in the 1950's.

(3) *Pregnant women.* During normal gestation, pyridoxal phosphate is concentrated by the fetus 6.6 times above the plasma concentration of the mother (Ref. 19). Concommitantly, maternal blood or plasma pyridoxal phosphate declines progessively during the course of pregnancy (Refs. 16 and 20) to about one-fourth that of nonpregnant women. Other biochemical changes include increased urinary excretion of xanthurenic acid after an oral tryptophan load (Refs. 21 through 24) which could be normalized by prior pyridoxine hydrochloride administration and low urinary 4-pyridoxic acid excretion after pyridoxine hydrochloride adminstration (Ref. 25).

Forty to 60 percent of 458 normal, pregnant women tested by Heller, Salkeld, and Korner (Ref. 26) were found to be suboptimally supplied with vitamin B-6 in order to saturate erythrocyte GOT (EGOT activation test). Shane and Contractor (Ref. 16) studying 10 pregnant women did not confirm this. The National Research Council recommends a daily intake of 2.5 mg vitamin B-6 daily during pregnancy, a 0.5 mg increase over the normal adult allowance (Ref. 3). Whether this amount of vitamin B-6 is adequate to meet most needs during pregnancy is the subject of current concern (Ref. 27). These changes in metabolism of pregnancy can be shifted toward "biochemical normality" by supplemental pyridoxine hydrochloride of up to 15 or 20 mg daily (Ref. 27). This amount is in excess of the maximum of about 3 mg daily which can be obtained from a well-planned diet (Ref. 17). Heller, Salkeld, and Korner (Ref. 26) after finding biochemical evidence for vitamin B-6 coenzyme depletion in 40 to 60 percent of 458 pregnant women commented: "No evidence was found that this form of vitamin B-6 deficiency had any clinical sequelae for the mother or the fetus during the pregnancy and delivery," but they concluded, "Our results suggest that pyridoxine supplementation is necessary in approximately 50 percent of the pregnant women in order to maintain normal coenzyme saturation" (of EGOT). Shane and Contractor (Ref. 16), who found decreased blood pyridoxal phosphate in pregnant women, cautioned:

> Correction of abnormal metabolism by large doses of pyridoxine may not indicate a vitamin deficiency per se. In pregnancy, for example, it is debatable whether enough pyridoxine hydrochloride should be administered to correct the abnormal metabolism or whether it is even necessary to produce a normal, i.e., nonpregnant, state. As tryptophan metabolism is the most deranged vitamin B-6 status indicator in pregnancy, correction of xanthurenic acid excretion to the levels found in nonpregnants, by administering pyridoxine, would result in high pyridoxal phosphate levels in the fetus. It is possible that this could have an adverse effect on the synthesis of fetal pyridoxal phosphate enzymes and, at worst, lead to high vitamin pyridoxine hydrochloride requirements for the fetus after birth.

Krishnaswamy (Ref. 28) and Iyengar (Ref. 29) reported that many cases of mild to severe stomatitis seen in pregnant women in India responded to treatment with 10 mg for 10 days of pyridoxine hydrochloride.

Thirteen of 14 pregnant women with gestational diabetes were observed to have an increased xanthurenic acid excretion after a tryptophan load test. All were treated orally with pyridoxine hydrochloride 100 mg daily for 14 days. Only two of the fourteen failed to respond with an improved glucose tolerance test. The authors hypothesize that increased xanthurenic acid synthesis during pregnancy may cause gestational diabetes (Ref. 30). They refer to work by Kotake and Murakami (Ref. 31) which shows that xanthurenic acid forms a complex with insulin, acts as an insulin antagonist, and has a diabetogenic effect in animals. Diabetes in pregnancy as at other times requires the skillful management of a physician.

(4) *Women taking oral contraceptives (O.C.).* Many of the biochemical changes in vitamin B-6 metabolism observed during pregnancy are also seen in women taking oral contraceptives. The most notable is a marked disturbance of tryptophan metabolism along the kynurenine-niacin pathway, with abnormally high urinary xanthurenic acid excretion after a loading dose of tryptophan (Refs. 32 through 37). This occurs in 75 to 100 percent of O.C. users (Ref. 38). The abnormality persists as long as the contraceptives are taken and becomes more marked with time (Ref. 36). Abnormal tryptophan metabolism is implicated in the development of depression, which many workers report as a side effect of O.C. use (Refs. 39 and 40), the frequency being as high as 6.6 percent (Ref. 41). Pyridoxine hydrochloride has been used with mixed success by a number of workers to relieve O.C.-related depression (Ref. 12). The most rigorous study was by Adams et al. (Ref. 40). In a double-blind crossover trial of the effect of pyridoxine hydrochloride on depression, 11 of 22 women showing biochemical evidence of vitamine B-6 deficiency responded by significant relief of symptoms to 20 mg pyridoxine hydrochloride, twice daily for 2 months. Placebo administration was without effect.

The increased xanthurenic acid excretion associated with O.C. use may be involved in the development of impaired glucose tolerance tests observed in women taking oral contraceptives (Ref. 42), and improved by pyridoxine hydrochloride administration (Ref. 43).

Other metablic alterations in vitamin B-6 metabolism observed with O.C. use are lowered blood pyridoxal phosphate levels (Refs. 16 and 44), significantly increased in vitro erythrocyte GOT activation in 48 percent of 233 women on oral contraceptives, compared to 18 percent of controls (Ref. 38), elevated E-GPT in vitro stimulation or activation values (Refs. 45 and 46), and 30 percent lower urinary excretion of vitamin B-6 (Ref. 47) than in controls.

A minimum of 20 to 25 mg pyridoxine hydrochloride daily is necessary to normalize tryptophan metabolism in the majority of O.C. users (Refs. 35 and 36), an amount far in excess of that obtainable in the diet. To counteract depression and other possible manifestations of vitamin B-6 deficiency, some workers support the concept of routine pyridoxine hydrochloride supplementation for O.C. users (Refs. 35 and 38).

Leklem et al. (Ref. 48) studied parameters of vitamin B-6 deficiency in 15 O.C. users and 9 controls in a vitamin B-6 depletion and repletion format. Biochemical response to depletion and repletion were parallel in both groups. The only major alter-

ation in metabolism was the response to tryptophan loading. Repletion with 2.0 mg pyridoxine daily for 4 weeks restored all indices in both groups to predepletion or ultra-normal levels. The authors conclude "that if the use of oral contraceptives * * * does alter the requirement for vitamin B-6, the effect is a minor one and of doubtful clinical significance to the majority of women taking these steroid preparations." They suggest that the abnormality in tryptophan metabolism may reflect other metabolic effects of the drug than vitamin B-6 deficiency or antagonism.

(5) *The elderly.* Hamfelt (Ref. 49) and Rose et al. (Ref. 50) measured plasma pyridoxal phosphate and found levels decrease with age. The decrease was associated with alterations in tryptophan metabolism and serum transaminase activity. Pyridoxine hydrochloride supplements (100 mg daily for 14 days) markedly increased the plasma pyridoxal phosphate and corrected other biochemical alterations.

Jacobs, Cavill, and Hughes (Ref. 51) observed a decline in erythrocyte GPT activity with age, by both direct and stimulated measurement. It is uncertain whether or not this reflects pyridoxine deficiency, as no other parameter of pyridoxine metabolism was studied. The diet supplied about 1.5 mg Vitamin B-6 daily. Supplementing the elderly subjects with 10 mg pyridoxine hydrochloride daily for 6 weeks produced a significant increase in transaminase activities. No subjective changes were induced by dietary supplementation.

(6) *Alcoholics.* General vitamin deficiency, which includes vitamin B-6 deficiency, is observed in alcoholics and is thought to be caused by a combination of factors which includes inadequate food intake, possible malabsorption of vitamin B-6 from food (but not of crystalline pyridoxine hydrochloride) (Ref. 52), increased clearance of pyridoxal phosphate, possibly due to increased liver degradation secondary to liver disease (Ref. 53) and possible ethanol-associated release of the vitamin from liver stores and inhibition of new storage (Ref. 54). Individuals with chronic alcohol abuse frequently exhibit lowered plasma levels of pyridoxal-5-phosphate. Acetaldehyde accelerates the degradation of intracellular pyridoxal phosphate (Ref. 55), and a decrease in pyridoxal phosphate enhances the cytotoxicity of acetaldehyde (Ref. 56).

(7) *Conditioned deficiency.* Wohl et al. (Ref. 57) reported deranged tryptophan metabolism in 14 hyperthyroid patients which could be corrected by 50 mg pyridoxine hydrochloride intramuscularly. The normal vitamin B-6 intake of the patients was calculated to be 2.0 to 2.5 mg daily. Although no overt clinical manifestations of deficiency were observed, one of the patients who showed obvious signs of muscular weakness improved after daily treatment with pyridoxine hydrochloride and without other antithyroid therapy. The dose and duration of treatment was not reported.

Depression of plasma pyridoxal phosphate was observed in eight children after accidental burning or scalding. The concentrations remaind low for several weeks with a dietary pyriodoxine hydrochloride supplement of 0.25 mg daily but were restored rapidly to saturation levels, with large doses of 250 mg daily.

An area of potential concern, as yet unstudied in humans, is the effect of pollution on vitamin requirements. Mitchell and Schandl (Ref. 58) refer to animal experiments by Russian workers who found a greatly increased requirement for vitamin B-6 after chronic exposure to an industrially polluted atmosphere or to carbon monoxide, nitrogen peroxide, and ammonia.

Certain other conditions have been reported to be helped by pyridoxine hydrochloride therapy. These include severe atopic dermatitis in children (Ref. 59), infantile convulsions, and childhood bronchial asthma (Ref. 60). Such uncontrolled observations have not demonstrated any consistent relationship of these diseases to vitamin B-6 deficiencies, although a genetic defect responsive to large doses of pyridoxine hydrochloride may be present in some infants with convulsions (Refs. 15, 61, and 62).

(8) *Vitamin B-6 responsive genetic disorders.* Pyridoxine hydrochloride far in excess of that obtainable by diet has been found useful in the treatment of a range of genetic disorders (Ref. 61). These include cystathioninuria treated with 400 mg daily (Refs. 63 and 64), pyridoxine-responsive anemia treated with 5 to 200 mg daily (Ref. 62), pyridoxine-responsive homocystinuria improved with 150 to 15,000 mg daily (Refs. 13 and 65), and xanthurenic aciduria responsive to 80 mg daily (Ref. 66). These conditions are rare, and when diagnosed by sophisticated medical techniques, require the regular and consistent care of a physician for vitamin as well as other forms of therapy.

(9) *Drug-induced deficiency.* The use of drugs in the treatment of a number of diseases induces a vitamin B-6 deficient state if not supplemented with additional large doses of pyridoxine hydrochloride (Ref. 67). These include isoniazid (isonicotinic acid hydrazide), semicarbazide, carbohydrazide, thiosemicarbazide, and cycloserine for the treatment of tuberculosis, penicillamine for Wilson's disease and heavy metal poisoning, hydralazine for hypertension, and hydantoin and succinamide for epilepsy (Ref. 68). Pyridoxine hydrochloride therapy in association with these prescription drugs is most safely administered by prescription also.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that pyridoxine, in the dosage and form identified under Category I conditions below, is safe and effective for use in the prevention and treatment of vitamin B-6 deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which vitamin B-6 is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Pyridoxine hydrochloride is the only acceptable source of vitamin B-6 activity. Dosage is based on the pyridoxine hydrochloride equivalent ($C_8H_{12}ClNO_3$, molecular weight 205.6).

(1) *Dosage*—(i) *For prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 1.5 to 2.5 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(ii) *For treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 7.5 to 25 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.*—The Panel recommends the following Category I labeling:

(i) *Indications.* (*a*) *For prevention of deficiency.* "For use in th prevention of vitamin B-6 deficiency when the need for such therapy has been determined by a physician."

(*b*) *For treatment of deficiency.* "For use in the treatment of vitamin B-6 deficiency when the need for such therapy has been determined by a physician."

(ii) *Warning.* "Caution: Do not take this product if you have Parkinsonism and are currently taking 1-dopa except under the advice and supervision of a physician."

(iii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) should contain the following additional information:

"Increased pyridoxine hydrochloride doses are required in vitamin B-6 dependency syndromes (pyridoxine-responsive anemia, seizures, familial

xanthurenic aciduria, cystationiuria). Supplemental levels of pyridoxine hydrochloride are required when patients take (during receipt of) drugs or chemicals which bind and inactivate pyridoxine hydrochloride (isonicotinic acid hydrazide, cycloserine, hydralazine, penicillamine, semicarbazide)."

g. *Category II conditions under which vitamin B-6 is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC vitamin B-6 drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that the OTC drug use of vitamin B-6 for the following indications is not supported by adequate scientific evidence and that labels purporting such indications are neither truthful nor accurate:

(1) *"For the prevention of kidney stones."* Although vitamin B-6 deficiency in animals (Refs. 69 and 70) can produce increased urinary oxalate and the formation of calcium oxalate renal stones, the role of dietary B-6 deficiency in human stone formation is as yet unclear. Oxaluria may occur in persons ingesting B-6 antagonists such as deoxypyridoxine or isoniazid (Refs. 71 and 72), and occasionally oxalate stone formation is observed. However, the high incidence of urolithiasis found in the Southern United States, and to a greater extent in Asia, has not been associated directly with B-6 deficiency (Refs. 73 and 74) or dependency. The effectiveness of pharmacologic doses of pyridoxine hydrochloride in the treatment of urolithiasis has been studied to a limited extent. Dhanamitta, Valyasevi, and Van Reen (Ref. 75) found no beneficial affect of 3 mg pyridoxine hydrochloride daily for the relief of oxalcrystalluria in 14 Thai infants, whereas supplementation with orthophosphate completely eliminated oxalcrystalluria. Prien and Gershoff (Ref. 74) report in a study of 5 years duration that a regimen of 10 mg pyridoxine hydrochloride daily plus 300 mg magnesium oxide daily is effective in reducing or preventing recurrent urinary calculi in most idiopathic stone formers. Control groups receiving magnesium oxide alone or pyridoxine alone were included. Earlier trials where magnesium oxide alone was used reported similar success in stone prevention (Refs 76, 77, and 78) thus casting doubt on any beneficial role of B-6 in this regimen. Thus, the balance of evidence argues against the use of pyridoxine hydrochloride as effective for therapy or prevention of urolithiasis.

(2) *"For pernicious vomiting of pregnancy."* Reinken and Gant (Ref. 79) found that 24 women with hyperemesis gravidarum had the low serum pyridoxal phosphate levels compared to other pregnant women without vomiting and anorexia in the first trimester. Treatment for 7 days with 100 mg pyridoxine hydrochloride daily produced a normalization of biochemical values and "clinical return to normal." Numbers improved are not recorded and no controls were used. No data are available on the women before vomiting began. Thus, no evidence was presented to support a causal relationship between hyperemesis and vitamin B-6 deficiency.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Vitamin B-6 singly or in combination labeled specifically for use by women taking oral contraceptives.

(1) *Proposed dosage—For prevention of deficiency.* For women taking oral contraceptives, the oral dosage is 20 to 25 mg daily.

(2) *Proposed labeling.* The Panel recommends the following proposed labeling for vitamin B-6 for use with oral contraceptives:

Indication—For prevention of deficiency. "For use in the prevention of vitamin B-6 deficiency in women taking oral contraceptives when the need for such therapy has been determined by a physician."

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9. *Riboflavin.* The Panel's statement on riboflavin includes the following in-

gredients: Riboflavin and riboflavin-5-phosphate sodium.

a. *Reference form.* Dosages recommended in this document for riboflavin are based on the riboflavin equivalent ($C_{17}H_{20}N_4O_6$, molecular weight 376.4).

b. *Description.* Riboflavin is essential for growth and tissue repair in all animals. Riboflavin-5'-phosphate (flavin mononucleotide) and riboflavin-5'-adenosine phosphate (flavin adenine dinucleotide) serve as coenzymes which combine with apoenzymes to form flavoprotein enzymes, a series of oxidation-reduction catalysts including *D*-amino acid oxidase, xanthine oxidase, diaphorase, cytochrome, c reductase, and Warburg's yellow enzyme (Ref. 1). Riboflavin is involved in the conversion of tryptophan to nicotinic acid. Its absence causes a derangement of tryptophan metabolism with increased formation and urinary excretion of anthranilic acid and kynurenine (Ref. 2). Absorption of riboflavin, which occurs primarily in the proximal intestine, is regulated by a saturable transport process. Absorption is decreased by a deficiency of bile acids.

c. *Safety.* No toxicity has been encountered in patients receiving oral riboflavin. Absorbability and bioavailability of riboflavin are not altered by the pressence of other vitamins.

d. *Effectiveness.* Daily requirements for riboflavin in healthy individuals depend on protein intake and energy expenditure. Increased riboflavin of 2.5 to 5.0 mg daily is required in patients with biliary obstruction (Ref. 3) and by individuals with large intakes of alcoholic beverages (Refs. 4 and 5). Women on oral contraceptives have been reported with decreased urinary riboflavin. However, no other evidence of riboflavin deficiency has been reported in such persons.

Clinical episodes of riboflavin deficiency are rare. They include oral, cutaneous, corneal, neurologic, and hematologic lesions. There is atrophy of the epidermis and other changes leading to angular cheilosis, glossitis, scrotal dermatitis, vascularization of the cornea, cataracts, corneal ulcers, and abnormal pigmentation of the iris. Peripheral neuropathy and anemia may be associated with ariboflavinosis (Refs. 6 and 7). Studies with galactoflavin, a riboflavin antagonist, showed that subjects receiving this agent developed anemia which may be due to its directly toxicity or a secondary effect on liver folic acid (Ref. 8). In experimental animals, maternal deficiency of riboflavin may lead to fetal abnormalities including shortening of long bones, micrognathia, cleft palate, hydrocephalus, heart malformations, and eye lesions (Ref. 9). Also, in animal experiments, diminished tissue levels of riboflavin enhance the development of liver tumors in response to the ingestion of carcinogenic azo dyes (Ref. 10).

Depletion of riboflavin produces a decrease in circulating and urinary levels of the vitamin and an increase in glutathione reductase activity following the in vitro addition of flavine adenine dinucleotide to erythrocyte hemolysates (Refs. 4 and 11). A subclinical deficiency occurs in pregnancy (Ref. 12); in the sick and injured (Ref. 13); in normal school children, being present in approximately one-half of 642 New York City school children tested (Ref. 14); and commonly among alcoholics (Ref. 5).

OTC riboflavin-containing products should be evaluated with respect to their ability to increase tissue or body fluid riboflavin levels. Riboflavin absorbability may be documented by measuring urinary excretion of riboflavin, expressing the results in terms relative to creatinine excretion (Ref. 3). The normal male should excrete over 40 percent of a 10 mg dose. Riboflavin may be measured by a fluorometric procedure (Ref. 15), or by microbiological assay (Ref. 16). Riboflavin-deficient patients exhibit a return to normal in erythrocyte glutathione reductase activity after receiving 5 mg riboflavin (Ref. 4).

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that riboflavin, in the dosage and forms identified under Category I conditions below, is safe and effective for use in the prevention and treatment of riboflavin deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which riboflavin is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Acceptable sources of riboflavin activity are riboflavin and riboflavin-5-phosphate sodium. Dosage must be based on the riboflavin equivalent ($C_{17}H_{20}N_4O_6$, molecular weight 376.4).

(1) *Dosage*—(i) *For prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 1 to 2 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(ii) *For treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 5 to 25 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.* The Panel recommends the following Category I labeling:

(i) *Indications*—(*a*) *For prevention of deficiency.* "For use in the prevention of riboflavin deficiency when the need for such therapy has been determined by a physician."

(*b*) *For treatment of deficiency.* "For use in the treatment of riboflavin deficiency when the need for such therapy has been determined by a physician."

(ii) *Warning—For products for the treatment of deficiency.* "Do not exceed the recommended dosage except under the advice and supervision of a physician."

(iii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) should contain the following additional information:

Indications. "Certain persons may require increased levels of riboflavin such as individuals with biliary obstruction, individuals on oral contraceptives, and individuals consuming large quantities of alcohol."

g. *Category II conditions under which riboflavin is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC riboflavin drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

Timed-release preparations of riboflavin have been shown to be erratic in their ability to increase the excretion of riboflavin in urine (Ref. 18). The Panel concludes that adequate and reliable scientific evidence is at present not available to permit the assumption of therapeutic effectiveness for OTC timed-release drug preparations.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of category III conditions to Category I.

None.

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(18) OTC Volume 150098.

10. *Thiamine.* The Panel's statement on thiamine includes the following ingredients: thiamine hydrochloride and thiamine mononitrate.

a. *Reference form.* Dosages recommended in this document for thiamine are based on the thiamine chloride hydrochloride equivalent ($C_{12}H_{17}ClN_4OS.HCl$, molecular weight 337.3).

b. *Description.* Thiamine functions as a coenzyme in the metabolism of alpha-keto acids and 2-keto sugars (Ref. 1). It is responsible for the decarboxylation of pyruvic acid to acetyl coenzyme A (Embden-Meyerhof glycolytic pathway), the decarboxylation of alpha ketoglutarate to succinyl coenzyme A (citric acid cycle), and formation of sedoheptulose phosphate and fructose-6-phosphate (hexose monophosphate shunt). Three-forths of dietary thiamine comes from green vegetables, grains, and meats, and one-fourth from the fortification of flour, cereal, and other commerical food products.

c. *Safety.* Several reports have appeared in the literature of untoward effects resulting from doses of thiamine far exceeding effective therapeutic amounts. A woman taking 10,000 mg thiamine hydrochloride developed headache, irritability, insomnia, and weakness, all of which cleared when the vitamin was stopped, but recurred when only 5 mg thiamine hydrochloride were given for 4.5 weeks (Ref. 2). Since there are many reports in which 50 to 100 mg thiamine were taken daily without adverse effect, it is the view of the Panel that such episodes are individual idiosyncratic reactions.

Because one of the common sources of thiamine is the mononitrate, a question was raised regarding the safety of ingesting the nitrate part of this preparation. A 24.3 mg dose of thiamine mononitrate, which is equivalent to the maximum amount of thiamine hydrochloride (25 mg) that the Panel recognizes as safe and effective for the treatment of thiamine deficiency, would add 4.6 mg nitrate ion (NO_3^-) to the day's intake. An estiamted average daily ingestion of nitrate per capita in the United States is 86 mg. This comes principally from vegetables, but there is a great variation in intake depending upon the type and quantity of the vegetables consumed and the condition of the soil. Until elimination, chiefly via the urine, nitrate is recycled in the body by secretion in the saliva as nitrite. No toxic effects are produced in man by a dose of 1.0 to 1.5 g nitrate ion. The increment of 4.6 mg nitrate ion to the normal average intake from foods would cause the total nitrate intake to be less than one-tenth of the dose known to produce no toxic effects in humans. Since the quantity of nitrate contributed by the maximum recommended treatment dose of thiamine mononitrate would be within the normal variation of the total dietary nitrate contributed by foods alone, it is not reasonable to assign any significant added risk to this incremental source of nitrate. The safety of other thiamine compounds, such as thiamine propyl disulfide and certain phosphoric acid salts of thiamine, has not been evaluated by the Panel.

d. *Effectiveness.* Daily thiamine requirements depend on the number of calories ingested. However, the vitamin is required by those on reducing diets as well as those on complete food deprivation. There is no evidence that the absorption or activity of thiamine is affected when combined with other vitamins.

Pregnancy, lactation, malignancy, high oral carbohydrate intake, parenteral glucose, febrile states, and alcoholism predispose to thiamine deficiency. Administration of pyrithiamine, a thiamine antagonist, produces a deficiency similar to that obtained by withholding thiamine (Ref. 3). Thiaminases occur in tissues of fish (Ref. 4) and various vegetable (Ref. 5). However, they are not usually responsible for thiamine depletion in man. Depletion of thiamine produces biochemical alterations, including an increase in blood pyruvic and lactic acids, reduction in red blood cell transketolase, and clinical abnormalities, including neurologic and/or cardiac lesions, in experimental animals and man (Refs. 6 and 7).

Beriberi, the clinical symptom complex of thiamine depletion, may cause peripheral neuritis (Ref. 8), and may also lead to cardiovascular manifestations (Ref. 9). Symptoms of Wernicke's encephalopathy (Ref. 10) in chronic alcoholics are usually responsive to thiamine given parenterally in doses of 10 mg daily until body repletion of thiamine is obtained (Ref. 11). Occasionally, such symptoms exist in the absence of biochemical evidence of thiamine depletion and in these instances thiamine therapy is without effect (Ref. 11).

Subclinical thiamine deficiency reflected by deficient red blood cell transketolase activity, low blood thiamine, or reduced urinary excretion of thiamine without clinical symptomatology is found in the U.S. population. Subclinical thiamine deficiency occurs among pregnant women (Refs. 12 and 13), alcoholics (Ref. 14), the sick and injured (Ref. 15), school children (Ref. 16) and the aged (Ref 17). In the Ten State Nutrition Survey (Ref. 18), 12 percent of people tested had thiamine deficiency as reflected in urinary thiamine excretion. Biochemical evidence of thiamine deficiency has been reported to be present in 35 percent of pregnant women tested (Ref. 13), 31 percent of routine hospital admissions (Ref. 15), and 68 percent of Blacks as compared with 6 percent of Chinese and 52 percent of Caucasian school children studied in New York City (Ref. 16).

Intestinal absorption of thiamine hydrochloride is an active process (Ref. 19). In healthy subjects, as the dose of thiamine is increased, relatively less is absorbed (Ref. 20). There is a significant reduction of thiamine absorption in the untreated malnourished alcoholic (Ref. 21), in the presence of folate depletion (Ref. 22), and following ingestion of ethanol (Ref. 21). Other forms of thiamine such as the allithiamines (not currently marketed in the United States) exhibit a significantly greater absorbability and produce a higher tissue and body fluid levels of thiamine, with an increase in red blood cell transketolase activity, and there is a report that these compounds correct certain clinical abnormalities refractory to thiamine hydrochloride or thiamine mononitrate (Ref. 23).

The effectiveness of thiamine-containing products is evaluated by the increase in body tissue and fluid thiamine levels following their use. Thiamine-containing products are considered efficacious if they increase tissue or urinary levels of thiamine. Absorba-

bility or bioavailability is documented by mesuring the amount of thiamine in the urine before and after the administration of 5 mg of the drug given orally in a fasting state (Ref. 24). The thiocrome analytical method is employed for this detection.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that thiamine, in the dosage and forms identified under Category I conditions below, is safe and effective for use in the prevention and treatment of thiamine deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which thiamine is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Acceptable sources of thiamine activity are thiamine hydrochloride and thiamine mononitrate. Dosage must be based on the thiamine chloride hydrochloride equivalent ($C_{12}H_{17}ClN_4OS.HCl$, molecular weight 337.3).

(1) *Dosage*—(i) *For prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 1 to 2 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(ii) *For treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 5 to 25 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.* The Panel recommends the following Category I labeling:

Indications—(*a*) *For prevention of deficiency.* "For use in the prevention of thiamine deficiency when the need for such therapy has been determined by a physician."

(*b*) *For treatment of deficiency.* "For use in the treatment of thiamine deficiency when the need for such therapy has been determined by a physician."

g. *Category II conditions under which thiamine is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC thiamine drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that the OTC drug use of thiamine for the following suggested indications appearing in the literature or in the submissions to the Panel is presently not supported by adequate scientific evidence and that labels purporting such indications are neither truthful nor accurate: Dermatoses, multiple sclerosis, infection, drug toxicity, stimulation of mental responsiveness in the absence of thiamine deficiency, cancer, edema of infants, and impotence (Ref. 12).

Thiamine has been used to stimulate appetite, relieve tiredness, correct neurologic diseases, and improve mentation, without a demonstrated deficiency of this vitamin (Ref. 12). The Panel has reviewed data on such use and concludes that there is no evidence that thiamine is of benefit in any symptom complex in the absence of a thiamine deficiency.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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11. *Vitamin A.* The Panel's statement on Vitamin A includes the following ingredients: vitamin A (retinol), Vitamin A acetate, and vitamin A palmitate.

a. *Reference form.* Dosages recommended in this document for vitamin A activity are based on the retinol equivalent expressed in international units (I.U.) ($C_{20}H_{30}O$, molecular weight 286.4 and 0.3 μg retinol is equivalent to 1.0 I.U.).

b. *Description.* Claims have been made for vitamin A sources including retinol (vitamin A alcohol) and its esters formed with edible fatty acids, principally retinyl acetate and retinyl palmitate, derived from synthetic or natural sources such as fish liver oils, particularly that of the cod.

Vitamin A is a generic term for a group of biologically active compounds, including retinol (vitamin A alcohol) and its esters which are of nutritional importance to man and are found in foods commonly consumed by man. Carotenoids have potential vitamin A

activity and after ingestion are converted by the body to a variable degree to the utilizable and physiologically active form. The degree and speed of conversion of the carotenoids, however, are not adequate and sufficiently uniform to recommend their use for therapeutic purposes. For this reason, the term "vitamin A" used subsequently in this document will refer only to retinol and its acetate and palmitate esters. The commercially produced retinyl esters and retinol are predominantly the all-trans isomer with a small and variable percentage of neo-vitamin A (Ref. 1).

Vitamin A is essential for the integrity of the membrane structure and function of all body cells. It also has a specific and vital role in the process of vision. Night blindness (defective dark adaptation) is one of the earliest signs of vitamin A deficiency. Other signs and symptoms include abnormal dryness of the eye and of the skin and other epithelial tissues, softening of the cornea and growth failure.

When vitamin A is absorbed through the intestinal mucosa, it is transported to the liver where it is stored and released into the blood to travel to all the tissues and cells of the body. The blood level of vitamin A is maintained within a normal range as long as the liver stores are capable of supplying the needs of the tissues (Ref. 2). When they are depleted, generally as a result of an insufficient dietary supply of the vitamin or its precursors, the blood level falls and, of course, the tissues are deprived of the amounts needed to maintain their integrity.

c. *Safety.* Acute toxicity in the adult occurs from a dose at or above 2,000,000 to 5,000,000 I.U. (30,000 to 75,000 I.U./kg for a 70 kg man). In the infant 17,000 to 33,000 I.U./kg of body weight can precipitate acute toxic signs. The signs of acute toxicity in adults, which can develop in 6 to 8 hours following ingestion of the dose, are severe headache centered in the forehead and eyes, dizziness, drowsiness, and nausea with vomiting, followed in 12 to 20 hours by redness and swelling of the skin which eventually begins to peel (Ref. 3). In infants, bulging fontanelles (the membrane-covered openings in the still-developing infant skull) caused by abnormal intracranial pressure, loss of appetite, hyperirritability, and vomiting generally occur within 12 hours after dosage and is followed in a few days by a flaking-off of the skin.

The chronic dose inducing toxicity varies with the individuals and doses of 12,000 to 350,000 I.U. daily for infants less than 1 year of age, and from 37,500 to 600,000 I.U. daily for the 1- to 5-year-old age group are reported. The lowest toxic dose of retinol recorded is 12,000 I.U. daily for 7 days. This amount was given to a 2.1 kg infant (probably of premature birth) who had been on parenteral alimentation for 18 weeks. Chronic toxicity developing in a few months is most commonly encountered in infants and children, whereas chronic toxicity in adults may take several months or even years to develop and become evident (Ref. 4). Chronic toxicity results in loss of appetite, headache, blurred vision, muscle soreness after exercise, hair loss, reddish pimples (maculoerythematous eruptions) on the shoulders and back, and general drying and flaking of the skin with pruritis, as well as all the symptoms associated with hypercalcemia (Refs. 3 and 5). Cracking and bleeding of lips, reddened gums, and nosebleed are also reported as signs of toxicity. Enlargement of the liver and spleen may be noted during physical examination, and anemia may also be present. Often painful subcutaneous swelling and swelling in the regions of muscle attachments to long bones due to overgrowth of bone are present. A "pagoda effect" (increased angle of metaphyseal flare) has been described in growing bones of children. Increased cerebrospinal fluid pressure (pseudotumor cerebri with papilledema) seems to be symptomatic of chronic intake in somewhat less than half the cases reported in adults. This syndrome in infants is generally diagnosed on the basis of bulging fontanelles. The most serious implied sequela to toxicity is irreparable damage to the liver, resulting in cell death, fibrosis and cirrhosis, or permanent stunting of bone growth. Two cases have been reported of adult hepatic injury from chronic hypervitaminosis A resulting in portal hypertension and effusion of serous fluid into the abdominal cavity (ascites) (Ref. 6). One patient was a 54-year-old woman who had been taking 100,000 to 1,250,000 I.U. vitamin A daily for 5 years. The other patient, a 62-year-old man, had been consuming 400,000 I.U. daily for 8 years. In the great majority of cases, complete withdrawal of vitamin A results in regression of signs of symptoms in a matter of days, with no apparent changes remaining in a few weeks (Ref. 3).

It is common manufacturing practice to include additional amounts (overages) of vitamins which are subject to deterioration and loss of potency, such as vitamin A, in commercial preparations in order to guarantee the user that he will receive at least the labeled potency before the expiration date set by the manufacturer for that particular preparation. It is not uncommon for vitamin A preparations to contain as much as a 40 percent overage. Overages of at least 25 percent are said to assure maintenance of product potency for 18 to 24 months. It is obvious, then, that much of the published case history data on toxicity may in fact have been observed in patients consuming up to 140 percent (or more) of the labeled amount of vitamin A. This has been taken into consideration in the limitations imposed by the Panel in its recommendation on vitamin A-containing products. Technological improvements in formulation should be developed so that shelf lives of up to 2 years can continue to be met with overages not exceeding 25 percent. Therefore, the Panel concludes that the actual amount of vitamin A present in OTC drug products should not contain overages exceeding 25 percent and that the maximum OTC quantity of vitamin A, including an overage, should not exceed 12,500 I.U. vitamin A based on the retinol equivalent per dosage unit.

d. *Effectiveness.* The Recommended Dietary Allowances (RDA) (Ref. 7) established by the Food and Nutrition Board, NAS/NRC appear to be in excess of the amount of vitamin A needed daily. However, these allowances are based on dietary sources of vitamin A activity of which about 50 percent consist of mixed carotenoids with *B*-carotene predominating. The carotenoids are poorly absorbed and converted by man, particularly when they are consumed in large amounts. Mixed carotenoids generally are assumed to have one-ninth the vitamin A activity, in man, of preformed retinol (Ref. 2).

The U.S. RDA as promulgated in the Dietary Supplement Regulations published in the FEDERAL REGISTER of October 19, 1976 (41 FR 46175) are definitely generous (in excess) when applied to the retinyl esters in pharmaceutical vitamin preparations. In the often cited "Sheffield experiment," it was found that 390 μg (1,300 I.U.) retinol daily was sufficient to restore defective dark adaptation but that it took 750 μg (2,500 I.U.) daily to bring the blood vitamin A level back to what it was before the depletion period (Ref. 8).

One I.U. of vitamin A activity is equivalent to 0.3 μg retinol, 0.344 μg retinyl acetate (Ref. 8) or 0.535 μg retinyl palmitate. Retinol and its esters are readily absorbed from the normal gastrointestinal tract. If the amount ingested is not much greater than the requirement, absorption is complete. Plasma levels reach a maximum about 4 hours after the ingestion of the vitamin and then fall rapidly. Until hepatic saturation takes place, the administration of vitamin A leads mainly to its accumulation in the liver rather than to increased blood levels.

Particular attention should be paid to vitamin A status in patients with diseases in which fat absorption is defective. Serum vitamin A levels are depressed in patients with celiac disease, sprue, obstructive jaundice, and cystic fibrosis. Blood vitamin A levels decrease during chronic disorders accompanied by fever. This is observed in children with rheumatic fever and in patients with infectious hepatitis. Pathology of the liver, as in the latter disease and in cirrhosis, affects vitamin A status. Cirrhosis of the liver usually results in extremely low and sometimes completely absent reserves of vitamin A in the liver. Cancer, tu-

berculosis, and chronic infections, particularly pneumonia, chronic nephrosis, urinary tract infections, and prostate diseases may be associated with increased urinary excretion of vitamin A (Ref. 2) and thus may increase the intake requirement. Chronic renal disease with uremia may result in elevated plasma vitamin A levels (Ref. 9).

The effectiveness of vitamin A preparations in restoring and maintaining blood levels and liver stores depends not only on administration of a suitable dosage regimen but also on the absorption efficiency of the vitamin in the product. It is of no consequence whether the vitamin A is in water solution (water-miscible), emulsion, or oil solution, except that at the highest dosages a water solution results in somewhat larger storage than an oil solution (Ref. 10). This observation may be important to consider in the treatment of persons with defective fat absorption.

As mentioned above, 750 μg (2,500 I.U.) vitamin A orally daily was found to be required to bring the blood levels of vitamin A of depleted adults back to what they were before depletion. This value, then, is the best estimate of a safe minimum effective daily dose for restoring and maintaining normal liver reserves in the healthy adult.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that vitamin A, in the dosage and forms identified under Category I conditions below, is safe and effective for use in the prevention and treatment of vitamin A deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which vitamin A activity is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Acceptable sources of vitamin A activity are vitamin A, vitamin A acetate, and vitamin A palmitate. Dosage must be based on the retinol equivalent expressed in international units (I.U.) ($C_{20}H_{30}O$, molecular weight 286.4 and 0.3 G2T1μg retinol is equivalent to 1.0 I.U.).

(1) *Dosage*—(i) *For prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 1,250 to 2,500 I.U. daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(ii) *For treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 5,000 to 10,000 I.U. daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.* The Panel recommends the following Category I labeling:

(i) *Indications—(a) For prevention of deficiency.* "For use in the prevention of vitamin A deficiency when the need for such therapy has been determined by a physician."

(*b*) *For treatment of deficiency.* "For use in the treatment of vitamin A deficiency when the need for such therapy has been determined by a physician."

(ii) *Warning—For products for the treatment of deficiency.* "Do not exceed the recommended dosage except under the advice and supervision of a physician. Excessive dosages may cause harm."

g. *Category II conditions under which vitamin A is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC vitamin A drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The OTC drug use of vitamin A under the following conditions is unsupported by scientific data and in some instances by sound theoretical reasoning. The Panel concludes that the following suggested indications appearing either in the literature or in the submissions to the Panel for the use of vitamin A are presently not supported by adequate controlled clinical studies and should not be permitted on the market until scientific testing supports their use.

(1) Claims for the value of vitamin A sources for prevention or treatment of the following conditions have not been proven safe or effective for OTC drug use:

(i) "Plantar warts."
(ii) "Acne."
(iii) "Ichthyosis."
(iv) "Hyperkeratosis."
(v) "Stress ulcers."
(vi) "Dry or wrinkled skin."
(vii) "Respiratory infections."
(viii) "Visual defects and diseases of the eye."

(2) Claims for superiority in effectiveness of naturally occurring vitamin A over synthetic vitamin A have not been proven. Evidence is lacking that the claim is valid. The effective form of vitamin A for overcoming vitamin A deficiency (i.e., predominantly all-trans isomers of retinol and its acetate and palmitate esters) is not dependent upon a particular source material or mode of synthesis.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Claims for advantages of water-soluble or water-miscible vitamin A over vitamin A in oil have not yet been substantiated. Evidence is insufficient to prove that the difference in vehicles or molecular dispersion has any effect on the bioavailability for humans and hence the effectiveness of vitamin A for overcoming vitamin A deficiency.

(1) *Evaluation.* Data required includes the demonstration of statistically significant differences between the absorption of vitamin A in oil and that of competing preparations after the administration of 10,000 I.U. of vitamin A per dosage unit, or less, to persons having proven lipid malabsorption from sundry causes. In this discussion we are not concerned about dosages larger than 10,000 I.U. per dosage unit, since such doses would not be OTC.

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12. *Vitamin D.* The Panel's statement on vitamin D includes the fol-

lowing ingredients: cholecalciferol and ergocalciferol.

a. *Reference forms.* Dosages recommended in this document for vitamin D are based on either the cholecalciferol equivalent ($C_{27}H_{44}O$, molecular weight 384.6) or the ergocalciferol equivalent ($C_{28}H_{44}O$, molecular weight 396.6) expressed in international units (I.U.) (0.025 μg vitamin D is equivalent to 1.0 I.U.).

b. *Description.* The importance of vitamin D in human nutrition is well recognized and deficiency states in children (rickets) and adults (osteomalacia) are well-defined.

Vitamin D exists in two forms, vitamin D–2 (ergocalciferol) and vitamin D–3 (cholecalciferol). Vitamin D–3, the naturally occurring form of the vitamin in animal tissues, is formed when ultraviolet irradiation is absorbed by 7-dehydrocholesterol (7-DHC). Areas of the skin in most adults contain 3 to 4 percent of 7-DHC and all of it is beneath the stratum corneum. Due to this unique anatomical relationship, the conversion of 7-DHC to vitamin D–3 is partially regulated by the amount of natural or induced pigment in the corneum. The endogenous production rate of vitamin D–3 is unknown in man, but it must be at least equivalent to the minimal vitamin dietary dose of 200 to 400 I.U. daily essential to cure rickets resulting from lack of vitamin D intake (Ref. 1) since it has been observed that brief ultraviolet skin irradiation is curative (Ref. 2). Vitamin D–2, a synthetic form of the vitamin produced by the ultraviolet irradiation of ergosterol (a plant sterol), is equally as effective in man as vitamin D–3 (Ref. 3).

Following its synthesis within the skin, vitamin D–3 is absorbed via the subepidermal microcirculation and admixes with circulating vitamin D–2 and vitamin D–3 absorbed from dietary sources.

Dietary vitamin D–3 and vitamin D–2 are absorbed primarily from the duodenum and jejunum into lymphatic channels; both bile salts and intraluminal lipids must be present for absorption to occur (Ref. 4). In healthy adults and children, vitamin D is almost completely absorbed by the intestine and the vehicle in which the vitamin is administered (aqueous suspension, oil, milk, or other food) does not affect absorption (Ref. 1). The total content of circulating vitamin D in man is estimated at 25 ng/ml (Ref. 5).

Assimilated vitamin D is then sequestered primarily by the liver for metabolic transformation, or transported to primary storage depots (adipose tissue and muscle) (Refs. 6 and 7), the latter presumably serving as reservoirs to be called upon during deprivation or lack of sunlight exposure. Vitamin D–3 and vitamin D–2 are subsequently metabolized to their respective 25-hydroxylated derivatives, 25-hydroxycholecalciferol (25–OHD_3) and 25-hydroxyergocalciferol (25–OHD_2) by the liver (Ref. 8). Although it has been established that this hepatic 25-hydroxylase system undergoes "feedback" inhibition by the product of the reaction, the feed-back control mechanism is limited and becomes inefficient when large doses of vitamin D are ingested (Refs. 9 and 10).

25–OHD (25–OHD_2 and 25–OHD_3) is the main circulating biologically active form of vitamin D at concentrations ranging between 17 to 23 ng/ml (Ref. 11). A direct correlation has been observed between circulating 25–OHD, calcium concentrations, vitamin D intake, and exposure to sunlight (Ref. 12). It has been demonstrated that 25–OHD is capable of increasing both bone resorption and the intestinal absorption of calcium (Refs. 13 and 14). 25–OHD also increases the renal reabsorption of calcium, sodium, and phosphate (Ref. 15).

The fate of 25–OHD_3 includes sequestration into fat and muscle storage sites and its biological hydroxylation to a number of biologically active metabolites such as 24,25-dihydroxycholecalciferol or 1,24,25-trihydroxycholecalciferol. However, the most important and most biologically active metabolite produced from the 25-hydroxylated vitamin D compounds is 1,25-dihydroxycholecalciferol or 1,25 dihydroxyergocalciferol, subsequently referred to as 1,25-$(OH)_2D$. This conversion occurs enzymatically in the kidney (Ref. 16) and is regulated by a variety of hormonal and ionic factors (Ref. 9), not the least of which is parathyroid hormone (Ref. 17). Reported levels of circulating 1,25-$(OH)_2D$ in adults average 29±2 picograms/ml (pg/ml) with higher levels (49 to 66 pg/ml) reported for the 9 to 18-year-old range (Ref. 18).

Thus, vitamin D is either metabolically transformed into biologically active metabolites by hepatic and renal hydroxylating enzyme systems, or stored in muscle and adipose tissues. However, the bioregulatory feedback system, which controls the metabolic transformation of vitamin D to its biologically active metabolites, appears inadequate to prevent their accumulation. These observations, together with those which demonstrate no urinary excretion of biologically active vitamin D metabolites in a normal population (Ref. 19) and others establishing almost a limitless adipose tissue-muscle reservoir for vitamin D and its biologically active metabolites (Ref. 20), make an evaluation of the minimal dietary requirements of vitamin D for normal skeletal growth and maturation essential.

When estimating total exposure to vitamin D, it is appropriate to consider the length and intensity of exposure to sunlight, the race in question, and the cumulative daily ingestion of the vitamin.

Vitamin D occurs naturally in such animal foods as fatty fish, egg yolk, liver, and butter. Meat (other than liver), human milk, and nonfortified cow's milk are all poor sources.

Much of the milk now available in the U.S. is supplemented with vitamin D to provide a concentration of 400 I.U. per quart (equivalent to 10 μg vitamin D–3 per quart), although a considerable amount of unfortified milk is ingested in certain rural areas of the country. In addition, all brands of evaporated milk and some powdered milk are fortified and a wide variety of other foods, including margarine, milk flavorings, breakfast cereals, bread, and chocolate bars contain vitamin D in varying amounts. Vitamin D is stable in foods. Storage, processing, and ordinary cooking do not affect its activity.

c. *Safety—Vitamin D toxicity.* The symptoms of vitamin D toxicity are due either to the direct effect of the induced hypercalcemia and accompanying electrolyte abnormalities on cognative functions, cardiac rhymicity, renal or gastrointestinal function, or to an indirect effect of diffuse metastic calcification in critical organs such as the kidney, heart, and blood vessels. Symptoms frequently noted first are weakness, fatigue, malaise, dry mouth, vague muscle and bone pains, headache, and metallic or bad taste. Weight loss, diarrhea, anorexia, nausea, and vomiting reflect the gastrointestinal response to hypercalcemia. Thirst, polyuria, nocturia, burning of the eyes, conjunctivitis, generalized pruritis, diminished libido, pancreatitis, renal calculi, diminished hearing acuity, photophobia, rhinorrhea, hyperthermia (in children), and hypertension have also been associated with the hypercalcemic state. Hemiplegia and mental impairment have been reported in children with hypercalcemia, as have a variety of anatomical cardiac defects.

There appears to be a fairly wide range of susceptibility to the toxic actions of vitamin D. Consumption of vitamin D above 2,000 I.U. daily (five times the recommended daily allowance) for prolonged periods has been associated with hypercalcemia in infants and nephrocalcinosis in infants and adults (Ref. 21). It also has been established that approximately 20 percent of normal adults who receive 100,000 I.U. of vitamin D daily will develop hypercalcemia (Ref. 22). Daily intakes of vitamin D ranging from

1,800 to 6,300 I.U. may inhibit linear growth of normal children (Ref. 23). Some children appear to be inordinately sensitive to vitamin D, developing hypercalcemia on vitamin D doses of 1,000 to 2,000 I.U. daily (Ref. 24). Signs and symptoms of vitamin D intoxication have been reported with as little as 25,000 I.U. daily (Ref. 25), although in most cases overt clinical signs of intoxication and hypercalcemia occur when the dose exceeds 50,000 I.U. daily (Ref. 26).

The mean daily dose ingested by patients who are clinically intoxicated with vitamin D has been estimated at 2,080 I.U./kg of body weight or 145,600 I.U. daily in a 70 kg adult (Ref. 27). Consideration of reported vitamin D dose-toxicity relationships must be tempered, however, with the knowledge or renal function and the clinical disorder for which the vitamin is administered. Data obtained from a treated hypoparathyroid population may be misleading since parathyroid hormone plays an essential role in activating vitamin D (Ref. 17). Moreover, although the mean dose of vitamin D essential for control of hypoparathyroid patients is approximately 80,000 I.U. daily (Ref. 18), doses required to correct the hypocalcemia for these patients may vary from 25,000 to 200,000 I.U. daily (Ref. 29). Along similar lines, levels of vitamin D which produce intoxication in patients with renal disease and chronic liver or biliary disease may bear little relationship to the response of normal healthy children or adults to vitamin supplementation since, in disorders characterized by hepatic or renal dysfunction, the response to vitamin D is diminished (Refs. 9, 30, and 31).

One must also bear in mind the hypersensitivity to vitamin D which exists in a variety of clinical states (Ref. 9). Patients with sarcoidosis are especially prone to develop hypercalcemia on very small doses (e.g., 1,000 I.U. daily) of vitamin D (Ref. 32). Recent data are also consistent with the observation that self-medication with multivitamin preparations containing vitamin D may lead to renal calculi in adults (Ref. 33). Direct correlations between the ingestion of vitamin D supplements and recurrent renal calculi have been made in individuals ingesting no more than 1,100 to 1,650 I.U. daily (Ref. 33). Finally, it should be emphasized that excessive calcium intakes (greater than 1.0 g daily) as may often exist in growing children predisposed to vitamin D intoxication (Ref. 34), and that clinical evidence of toxicity may appear as early as 12 days (Ref. 35) or not until years after vitamin D treatment is initiated (Ref. 36).

d. *Effectiveness.*—(1) *General comments on vitamin D requirements.* The amount of vitamin D essential to achieve optimal circulating levels of its biologically active metabolites in any given individual is dependent upon age, rate of growth, efficiency of intestinal absorption (especially of fat), the integrity of hepatic and renal function, length and intensity of exposure to sunlight, the nature of ingested drugs, and skin color. Heavily pigmented skins can prevent up to 95 percent of ultraviolet radiation from reaching the deeper layers of skin where vitamin D is synthesized (Ref. 37). In fact, children born of Black mothers may have relatively lower levels of circulating 25-OHD_3 because of these maternal deficits (Ref. 38). The effects of medications, such as phenobarbital and diphenylhydantoin, on circulating levels of calcium and 25-OHD exemplify the need to explore drug intake as well as dietary histories when assessing vitamin D status. In a clinical study of adult outpatient epileptics on both anticonvulsants, significantly lower levels of serum calcium (19 percent) and 25-OHD (33 percent) were observed (Ref. 39).

Similar but less marked changes were observed in individuals on single drug therapy. A subsequent study of 56 pediatric epileptic outpatients on anticonvulsant medication yielded similar results with the lowest levels of serum calcium, serum 25-OHD, and bone density observed in children on multiple anticonvulsant drug regimens (Ref. 40). These observations are consistent with the reported increased incidence of clinical rickets and osteomalacia in children and adults subjected to anticonvulsant medication (Refs. 41, 42, and 43). Cholestyramine, because of its ability to chelate vitamin D within the gastrointestinal tract, also results in lower plasma 25-OHD (Ref. 11).

Rickets and osteomalacia resulting from dietary vitamin D insufficiency are relatively rare in young or middle-aged adults in the United States, since the mature skeleton with its relatively slow turnover rate is able to withstand short periods of vitamin D deficiency without deleterious effects, and vitamin D depots in fat and muscle are often more than sufficient to maintain skeletal integrity. It has been documented, however, that nutritional or conditional deficiencies of vitamin D develop in British subjects of any age when the diet contains less than 70 I.U. vitamin D daily (Ref. 44). The usual dietary history obtained from vitamin D-depleted individuals is of avoidance of fatty foods or of being a strict vegetarian. Migratory immigrants, (Refs. 45 and 46), premature infants (Ref. 47), elderly females (Refs. 48 and 49), and individuals routinely ingesting food with excessive phytic acid content (Ref. 45), also appear to be most susceptible to the nutritional form of osteomalacia that characteristically responds to small doses of vitamin D.

Limited exposure to sunlight may contribute significantly to the osteomalacia of elderly females since they, as a group, particularly when living alone, tend to have physical disabilities which limit mobility, and then become apathetic and reluctant to go outdoors.

Since natural dietary sources and sunlight exposure may often prove insufficient to supply the vitamin D required to prevent rickets and osteomalacia especially in rapidly growing young infants and elderly individuals, the practice of fortification of foods with vitamin D has enjoyed considerable international success. Methods of supplementation have been haphazard, with practices and regulations not only differing from country to country but also changing from time to time (Ref. 1). Moreover, analyses of foods demonstrated that the actual content of vitamin D is often higher than stated on the label because of an excess or an overage of the vitamin added by the manufacturer to allow for possible deterioration over a 2-year shelf life (Ref. 1). The error intrinsic to the vitamin D bioassay, which often differs from the actual value by plus or minus 20 percent, plus factors in packaging and processing, all contribute to the overage needed by the manufacturer. Estimated overages for vitamin D in multivitamin drops approach 50 percent in order to offset an estimated 30-percent degradation. Vitamin D overage in chewable tablets may also approximate 30 to 40 percent, especially if the tablets also contain minerals. In fact, this overage may equal as much as 100 percent or more of the label claims in the United States. The Panel concludes that no more than 25 percent vitamin D may be included in any OTC drug product as an overage.

Concerns about overage, excess food fortification, and potential long-term toxic effects of cumulative doses of vitamin D led a select Committee on Nutrition of the American Academy of Pediatrics (Ref. 1) to recommend that "efforts be taken to ensure a total vitamin D intake of 400 I.U. daily by all infants and children. At the same time, an attempt should be made to restrict the intake from all sources to an amount not greatly in excess of this figure."

The Committee on Nutrition considered also the practice of fortifying foods other than milk or infant formula products with Vitamin D to be unjustified and recommended its discontinuation (Refs. 1 and 50).

(2) *Vitamin D prophylaxis in full-term and premature infants.* The minimal requirement of vitamin D has never been established for infants. Estimates of the essential dose range are from approximately 100 I.U. (Refs. 51 and 52) to approximately 400 I.U. daily (Refs. 53 and 54); although 2.5 μg (100 I.U.) vitamin D daily prevents rickets and ensures adequate intestinal absorption of calcium, it would appear that intakes of 300 to 600 I.U. daily promote better linear growth and are at least as effective as greater intakes (Refs. 52 and 54).

Studies in pregnant women during the last trimester (Ref. 55) and in formula-fed premature infants (Ref. 47) emphasize the need for initiation of vitamin D prophylaxis within the first 2 weeks of life and reveal that rickets is preventable and rates of linear growth are as rapid with vitamin D intakes of 100 to 200 I.U. daily as with intakes of 400 to 1,200 I.U. daily (Refs. 56, 57, and 58). Reports of rickets in premature infants treated with vitamin D doses as large as 5,000 I.U. daily (Ref. 59) may be due entirely to an inadequate dietary supply of calcium. A daily dose of 400 I.U. vitamin D in full-term infants or in premature infants when initiated within the first 2 weeks of life appears more than adequate. This dose is probably in excess of the actual need.

(3) *Vitamin D prophylaxis in children and adolescents.* With the exception of heavily pigmented populations and those of poor socioeconomic status, definitive evidence of rickets beyond infancy in the United States is rare. Maximal calcium absorption and skeletal growth can be achieved with total vitamin D intake of 400 I.U. daily (Ref. 60). There are also observations that 200 I.U. vitamin D daily in normal healthy children between 2 and 5 years of age promote maximal calcium absorption from the intestine (Ref. 61).

(4) *Vitamin D prophylaxis in adults.* The amount of vitamin D essential for normal skeletal turnover in the Caucasian adult is for all practical purposes satisfied by eating an average diet and casual exposure to sunlight. Osteomalacia may occur when vitamin D intakes are less than 70 I.U. daily, accompanied by a lack of sunlight exposure as might be expected in cloistered or relatively immobilized elderly individuals (Ref. 62). Reports of osteomalacia in pregnant (Ref. 63) and lactating female populations ingesting diets relatively deficient in vitamin D and calcium stress the need for adequate vitamin D intakes and sunlight exposure during the pregnancy to ensure the integrity of both the maternal and fetal skeleton (Ref. 55). A total daily intake of vitamin D of 400 to 500 I.U. should be quite sufficient for pregnant females with average sunlight exposure to maintain normal maternal and fetal 20-OHD levels.

(5) *Estimated intakes of vitamin D.* To date there are scanty data regarding vitamin D intake in the U.S. Recently, Hahn et al. (Ref. 12) were able to show that vitamin D intakes of adult individuals on random diets living in the metropolitan St. Louis area averaged 1,710 I.U. weekly. These estimates appear quite reasonable since the correlation between estimated intake and circulating 25-OHD proved to be quite good (Ref. 12). Surveys of vitamin D intakes of infants and children reveal wide variations in the amount ingested. Children whose intake approximates the recommended allowance are in the minority, the majority ingesting amounts which prove to be either considerably smaller or greater than the recommended allowance (Ref. 40). In 1964, a Canadian survey conducted in areas where dairies added varying amounts of vitamin D to fresh milk indicated that 6 percent of the children were getting less than 400 I.U. daily, 93 percent ingested between 400 and 2,000 I.U. daily, and 1 percent over 2,000 I.U. daily (Ref. 64). A second Canadian survey of 1,000 children was conducted in 1966 prior to governmental regulations restricting fortification of foods with vitamin D. The survey included children from birth to age 5.5 years and was made in areas where vitamin D was not added to fresh milk (Ref. 65). In 38 children, vitamin D was not ingested either as supplements or fortified milk; 259 children had estimated vitamin D intakes which were less than 400 I.U.; 389 children had intakes between 401 and 1,000 I.U.; 314 had intakes over 1,000 I.U., and in 22 the daily intake exceeded 1,800 I.U. Thus, in this study, over 70 percent of the children had daily vitamin D intakes greater than 400 I.U.; 33 percent were ingesting over 1,000 I.U. daily. No specific estimate was made of sunlight exposure.

A survey made in Britain in 1951 indicated that some children were ingesting at least 35,000 I.U. vitamin D daily from a variety of proprietary preparations. Three years following governmental regulations which led to a sharp reduction in vitamin D content of fortified foods and vitamin preparations in that country, a survey of 307 infants under the age of 1 year revealed that the average daily intake of vitamin D was 300 I.U. for the lowest quarter of the group and 1,100 I.U. for the highest quarter, whereas the average intake of the remaining infants was approximately 600 I.U. (Ref. 66). It appears that a detailed U.S. population survey of total vitamin D intake (diet plus supplemental vitamins) and total sunlight exposure is indicated. Additional measurements of average circulating 25-OHD levels of individuals of various ages and race should be included.

e. *Conclusion.* The Panel has reveiwed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that vitamin D, in the dosage and forms identified under Category I conditions below, is safe and effective for use in the prevention of vitamin D deficiency when the need for such therapy has been determined by a physician.

The minimal effective dose of vitamin D is defined as either the amount of any vitamin D source(s) which would prevent the development of symptomatic or radiographic evidence of rickets in children or osteomalacia in the adult, or the amount of any vitamin D source(s) which, when combined with sunlight exposure, would maintain the circulating level of 25-OHD within the normal limits of 17 to 23 ng/ml.

In either case, 400 I.U. vitamin D daily would appear more than adequate in the growing child and 100 I.U. daily sufficient for the adult with a mature skeleton. The maximum effective dose in adults is 200 I.U. since greater concentrations do not appear to increase the intestinal absorption of calcium in mature people. The maximum safe dose has not yet been determined. However, for an adult it appears that dosages greater than 1,000 to 1,200 I.U. daily may ultimately prove toxic and contribute to the formation of renal calculi and myocardial infarction.

The Panel concludes that a total dose of 400 I.U. vitamin D to healthy infants, growing children, and pregnant women who are subjected to normal sunlight exposure is appropriate. The Panel also recognizes that there may be additional populations at risk such as elderly or cloistered individuals, food faddists, highly pigmented individuals, and persons of poor socioeconomic status, for whom routing daily ingestion of natural vitamin D-containing foodstuffs is difficult, and for whom an extradietary intake of vitamin D up to 400 I.U. daily may be indicated.

Concerns about overdosage with vitamin D in the form of fortified foods and OTC drugs, based on the known multisystemic effects of vitamin D-induced hypercalcemia, are well founded. However, data on potential long-term, deleterious effects of cumulative vitamin D intakes consumed by the average citizen in the form of OTC drugs and fortified foods, and the relationships of the cumulative vitamin D intake to working habits, age, sunlight exposure, race, and socioeconomic

status are essentially nonexistent. Recent studies are consistent with the hypothesis that long-term consumption of vitamin D may be a precipitating cause of myocardial infarction in man (Refs. 67, 68, and 69), and that a daily intake of 1,200 I.U. may be the critical level. Reports of renal calculi in patients self-medicated with multivitamin preparations containing vitamin D also warrant attention (Ref. 33). These data bear consideration, since the relationship between the increasing incidence of atherosclerotic vascular disease in man and the chronic ingestion of nonhypercalcemic doses of vitamin D is still unknown.

f. *Category I conditions under which vitamin D activity is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Acceptable sources of vitamin D activity are cholecalciferol and ergocalciferol. Dosage must be based on either the cholecalciferol equivalent ($C_{27}H_{44}O$, molecular weight 384.6) expressed in international units (I.U.) or the ergocalciferol equivalent ($C_{28}H_{44}O$, molecular weight 396.6) expressed in international units (I.U.) (0.025 ug vitamin D is equivalent to 1.0 I.U.).

(1) *Dosage—For prevention of deficiency.* For children under 18 years of age, the oral dosage is 400 I.U. daily. For adults 18 years of age and older, the oral dosage is 200 I.U. daily.

(2) *Labeling.* The Panel recommends the following Category I labeling:

(i) *Indication—For prevention of deficiency.* "For use in the prevention of vitamin D deficiency when the need for such therapy has been determined by a physician."

(ii) *Warning.* "Do not take this product if you have a history of kidney stones except under the advice and supervision of a physician."

g. *Category II conditions under which vitamin D activity is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC vitamin D drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The OTC drug use of vitamin D under the following conditions is unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that the following labeling claims and forms of vitamin D should not be permitted on the OTC market until scientific testing supports their use: (1) Claims that vitamin D is effective in lowering serum cholesterol, preventing or curing senile osteoporosis.

(2) Claims which suggest that multivitamin preparations containing minerals and vitamin D are superior to forms containing vitamin D alone.

(3) The use of 25-, 1,25-, or 24,25-hydroxylated forms of vitamin D, or of synthetic derivatives such as 1-alpha-vitamin D and 5,6-trans-vitamin D, cannot be sanctioned at any dosage.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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13. *Vitamin E.* The Panel's statement on vitamin E includes the following ingredients: Tocophersolan (*d*-alpha-tocopheryl polyethylene glycol 1,000 succinate), alpha-tocopheryl acetate, alpha-tocopheryl acid succinate, and vitamin E.

a. *Reference form.* Dosages recommended in this document for vitamin E, for use in combination products only and not as a single ingredient, are based on the *dl*-alpha-tocopheryl acetate equivalent expressed in international units (I.U.) ($C_{31}H_{52}O_3$, molecular weight 472.7, 1 mg *dl*-alpha-tocopheryl acetate is equivalent to 1 I.U.).

b. *Description.* Vitamin E is a form of alpha-tocopherol expressed in international units (I.U.) of vitamin E based on the following equivalents (Ref. 1):

1 mg *dl*-alpha-tocopheryl acetate=1 I.U.
1 mg *dl*-alpha-tocopheryl acid succinate=0.89 I.U.
1 mg *dl*-alpha-tocopherol=1.1 I.U.
1 mg *d*-alpha-tocopheryl acetate=1.36 I.U.
1 mg *d*-alpha-tocopherol=1.49 I.U.
1 mg *d*-alpha-tocopheryl acid succinate=1.21 I.U.

Preparations of *d*- or *dl*-alpha-tocopherol contain not less than 33 percent total tocopherols, of which not less than 50 percent consists of *d*- or *dl*-alpha-tocopherol (Ref. 1).

Preparations of *d*- or *dl*-alpha-tocopheryl acetate contain not less than 25 percent of *d*- or *dl*-alpha-tocopheryl acetate of which not less than 95 percent consists of *d*- or *dl*-alpha-tocopheryl acetate (Ref. 1).

The *d*- and *dl*- forms of alpha-tocopherol or its esters shall not be present in the same preparation except as a consequence of the dilution of a *dl*-form with suitable vehicles which may contain some *d*- form (Ref. 1).

Assay procedures are set forth in an official compendium (Ref. 1).

Marketed preparations of vitamin E include liquids (drops and elixir), soft or hard gel capsules, tablets, and injectables. Water-miscible or -soluble forms, made by emulsification with polyethylene glycol 1,000 or polysorbate 80, also are available.

c. *Safety.* An unpublished review of trials on over 9,000 cases by Salkeld (Ref. 2) showed that doses of vitamin E of 3,000 I.U. for up to 11 years and 55,000 I.U. for a few months in a few subjects had no detrimental effect on a variety of clinical and biochemical parameters. These high doses were well tolerated. Only 8 percent of approximately 1,000 patients complained, mostly about gastrointestinal disturbance. However, on the basis of animal studies, the Food and Nutrition Board, NAS/NRC (Ref. 3) and Bieri (Ref. 4) urged caution whenever consumption of large doses of vitamin E for long periods of time is encountered or contemplated. According to Bieri (Ref. 4), "conceivably, the ingestion of large doses of vitamin C or vitamin E could appreciably reduce an individual's vitamin A status."

In a letter to the editor, Briggs (Ref. 5) referred to six clinical cases of gastrointestinal irritation from the consumption of wheat germ oil, two cases of severe weakness with creatinuria after the daily ingestion of 800 I.U. vitamin E daily for 3 weeks, and a striking creatinuria in a physician who took 2 to 4 g vitamin E daily for several months.

d. *Effectiveness*—(1) *Requirement.* The requirement for vitamin E in body tissues is related to the polyunsaturated fatty acid (PUFA) content of cellular structures (Ref. 3). Since the composition of fatty acids in tissues can be affected by the type of dietary fat, it is not possible to establish a firm recommended allowance. Individuals ingesting diets low in PUFA will have lower intakes of vitamin E, and also lower requirements, than individuals consuming diets higher in PUFA (Ref. 3).

"The minimum adult requirement for vitamin E when the diet contains the minimum of essential fatty acids is not known, but is probably not more than 3 to 6 I.U. per day." The Food and Nutrition Board, NAS/NRC recommends a range of from 4 I.U. daily for infants to 15 I.U. daily for adult males and pregnant and lactating women (Ref. 3). Also recommended is a vitamin E:PUFA ratio of 0.4 mg Vitamin E to 1 g PUFA. Thompson et al. (Ref. 6) consider the use of the vitamin E:PUFA ratio to be impractical and, from analysis of the Canadian diet and the fact that there is no evidence of extrinsic vitamin E deficiency in adults in Canada, conclude that the adult requirement for vitamin E is less than 15 I.U. daily.

(2) *Deficiency.* Vitamin E deficiency has been experimentally produced in man with great difficulty (Ref. 7). After 30 months depletion, the experimental subjects were apparently unaffected in all respects except for slight reductions in erythrocyte survival time and, of course, lower tissue vitamin E levels. Leonard and Losowsky (Ref. 8) have reported beneficial effects on red cell survival time from the administration of alpha-tocopherols to persons with low (0.15 to 0.4 mg/100 ml) plasma levels of vitamin E. Their subjects consisted of six individuals with malabsorption disorders and two chronic alcoholics, one of whom failed to respond to therpay adequately as indicated by the plasma vitamin E level. Of the remaining seven, five showed an increased red cell survival time.

Low serum levels of vitamin E, and of lipoproteins, are found normally in newborn infants and they are lower still in premature infants. In the U.S., edema and anemia attributed to vitamin E deficiency have been reported in low birth weight infants fed commercial formulas that have a low content of the vitamin (Ref. 3). Other studies with low birth weight infants consuming similar formulas, however, have not revealed any deficiency signs or symptoms (Ref. 3). Leonard, Doyle, and Harrington (Ref. 9) found that infants born to mothers with plasma vitamin E levels below 0.7 mg/100 ml have extremely low plasma E levels and they recommend that all mothers with plasma vitamin E levels below 0.7 mg/100 ml in the last trimester of pregnancy be supplemented with vitamin E. Tancredi et al. (Ref. 10) have reported on six premature infants with anemia which failed to respond to vitamin E therapy.

The Committee on Nutrition of the American Academy of Pediatrics (Ref. 11) "concluded that supplementary administration of vitamin E is not required for premature or full-term infants receiving human milk or formulas of cow milk, except, possibly, when dietary intake of fat is markedly reduced. Dietary supplements of vitamin E seem desirable for patients with prolonged steatorrhea from any cause; relatively large doses may be needed to maintain normal plasma concentrations."

Persons afflicted with conditions that interfere with normal digestion or absorption of fats and fat-soluble vitamins may develop vitamin E deficiency (Ref. 12). Powell (Ref. 13) found that five of eight individuals with long-standing obstructive jaundice had low plasma vitamin E levels and increased in vitro hydrogen peroxide hemolysis. They also had reduced red cell survival times which did not always return to normal with vitamin E therapy. Three persons with normal plasma vitamin E levels also had reduced red cell survival times. A reduced survival time in hepatolenticular disease was not altered by vitamin E.

Deficiency is also found in patients with cirrhosis of the liver and, since vitamin E is normally transported in the blood in association with the beta-lipoprotein fraction, very low plasma levels of vitamin E are found in a-beta-lipoproteinemia.

The above statements are in essential agreement with a 1973 statement of the Food and Nutrition Board, NAS/NRC (Ref. 14), which says that "The wide distribution of vitamin E in vegetable oils, cereal grains, and animal fats makes a deficiency in humans very unlikely. Premature infants or individuals with impaired absorption of fats may require supplemental vitamin E, but they should, in any event, be under the care of a physician." Horwitt (Ref. 15), in his introduction to an international symposium on vitamin E, pointed out that "the application of knowledge from animal studies to human needs for vitamin E has proved to be extraordinarily difficult. Whereas deficiencies of vitamin E in animals cause a bewildering variety of pathological symptoms, correlations with human disorders have for the most part escaped us. The difference may not be due to the fact that animals have different requirements than man, but rather that man is rarely, if ever, so deficient in vitamin E as are animals fed diets that have no significant amounts of tocopherols."

Severe vitamin E deficiency in man may be associated with widespread tissue deposition of oxidized lipids, creatinuria, erythrocyte-membrane lipid intolerance to oxidants, and ceroid deposits in the intestines (Ref. 12).

(3) *Therapeutic claims.* Large (generally 400 I.U. or more) daily doses (Refs. 16, 17, and 18) of vitamin E have been claimed to benefit human fertility (Ref. 19), cardiovascular disease (Ref. 20), peripheral vascular diseases (Refs. 16 and 21), Dupuytren's contracture and Peyronie's disease (Refs. 22 and 23), and thromboembolic states. Beneficial results have also been claimed for the use of vitamin E in the treatment of leg cramps (Ref. 24), porphyria (Ref. 25), the anemia of protein-calorie malnutrition (Ref. 26) and the anemia and associated edema of low birth-weight infants (Refs. 27 and 28). All of these claims, and others, have been denied (Refs. 14, 17, and 29 through 33) with perhaps some room left open for further study of the effectiveness of vitamin E in the treatment of hemolytic anemia in low birth-weight infants, intermittent claudication, dupuytren's contracture, and Peyronie's disease.

There is some evidence that Caucasian women on combined-type oral contraceptives may experience a decrease in plasma tocopherol levels (Ref. 34). Also, Mustafa (Ref. 35) has reported that animals (rats) receiving 66 parts per million (ppm) vitamin E were insensitive to 0.1 ppm ozone, and exhibited fewer pulmonary biochemical complications from 0.2 ppm ozone as compared with animals receiving 11 ppm vitamin E. He suggests that "the findings may be of relevance to human population exposed to photochemical smog."

(4) *Absorption of commercial vitamin E preparations.* The tocopherols are readily subject to destruction in the digestive tract. Therefore, the acetate or succinate esters, which are quite stable, are generally used in commercial preparations. The esters are readily split in the intestinal wall and the alcohol is absorbed as such, mainly into the lymph stream attached to chylomicrons. After transport to the liver, they enter the blood stream attached to beta-lipoproteins. Normally,

the plasma vitamin E level varies directly with that of the plasma cholesterol.

The following information about the absorption of tritiated alpha-tocopherol is available (Ref. 36). Control subjects absorb between 55 to 78 percent of an orally administered dose of between 12 to 25 micro Curie (uCi) in 1 mg of unlabeled vitamin. Radioactivity appears in the plasma between 1 and 3 hours, peaks between 5 and 9 hours, and falls exponentially with a mean half-life of 53 hours. Chemically, almost all of this radioactivity is associated with free alpha-tocopherol. In patients with malabsorption due to impaired intraluminal digestion with obstructive jaundice, the absorption of a test dose varied from 6 to 16 percent. All these patients had steatorrhea, but there was no correlation between the degree of steatorrhea and the malabsorption of the vitamin. After surgical relief of obstructive jaundice in one of these patients, vitamin E absorption returned to normal. In three patients with chronic pancreatic insufficiency, without malabsorption, net absorption of vitamin E ranged from 32 to 39 percent; the abnormally low absorption was corrected in one patient by the addition of pancreatic supplements. In five patients with untreated adult celiac disease, absorption ranged from 23 to 58 percent. In this group of patients, there was a significant statistical correlation between failure to absorb the vitamin and the degree of steatorrhea. Two patients with intestinal lymphangiectasis absorbed only 29 percent of the orally administered dose, despite a coefficient of fat absorption of over 85 percent.

Beckman (Ref. 37) found a dose of 100 mg of alpha-tocopherol to bring about a peak serum tocopherol level in 4 hours. When the tocopherol was given as drops, a rise in the serum level of 25±14 percent was observed; with tablets there was a rise of 34±14 percent. Goldbloom (Ref. 38) also found that a single dose of either 2 mg or 10 mg tocopherol caused a peak rise in the tocopherol serum level to occur 4 hours after the administration to healthy full-term newborn infants. He found no difference in the absorption of *d*-alpha-tocopheryl acetate, *dl*-alpha-tocopheryl acetate, and *d*-alpha-tocopheryl polyethylene glycol 1,000 succinate. Hashim and Schuttringer (Ref. 39) reported a serum peak 7.5 hours after an oral dose of 600 mg *d*-alpha-tocopherol to a healthy adult male. An adult male with malabsorption associated with chronic pancreatitis had a flat curve. Gounelle and Rouquette (Ref. 40) reported a blood level two to three times normal from the 6th to the 9th hours after the administration of a 200 mg dose of tocopherol. Kelleher and Losowsky (Ref. 41) found that, of a dose of 200 mg of labeled vitamin E acetate, 20 controls absorbed 75 percent on the average. Nineteen steatorrhea cases averaged 61 percent absorption. Absorption was dose-related. They also reported (Ref. 42) that radioactivity in the plasma was maximal 6 to 12 hours after dosing. In some patients with severe deficiency and severe steatorrhea, they found no detectable plasma response even with absorption of up to 40 percent of an orally administered "physiological" dose. Schmandke, Sima, and Maune (Ref. 43) reported 96.9±13 percent of a 10 mg dose of alpha-tocopherol to be absorbed. The percentage absorbed decreased as the dose was increased, e.g., 87.3±13.5 percent of a 30 mg dose was absorbed as compared to 81.5±6 percent of a 100 mg dose and 55.2±28.8 percent of a 2,000 mg dose.

As indicated in the report by Kelleher and Losowsky (Ref. 42), plasma levels of alpha-tocopherol may be misleading in some types of lipid abnormalities. Bieri and Poukka (Ref. 44), in several cases of a-beta-lipoproteinemia, found normal red blood cell tocopherol content and normal resistance to hemolysis after vitamin E therapy, although plasma tocopherol levels remained very low. The red blood cell alpha-tocopherol content may be more informative than the plasma level.

There is not much information available by which to judge the relative efficacy of water-miscible or -soluble forms of vitamin E. Melhorn and Gross (Ref. 45) found *d*-alpha-tocopheryl polyethylene glycol 1,000 succinate to be much better utilized by premature infants than alpha-tocopheryl acetate. The addition of bile salts or emulsification in Tween 80 had no effect on the absorption of oily preparations of vitamins A and E in a patient with xanthomatous biliary cirrhosis (Ref. 46). In children with biliary obstruction, there was a severe defect in the absorption of both fat-soluble and water-soluble vitamin E preparations (Refs. 47 and 48). And, as mentioned above, no advantage of *d*-alpha-tocopheryl polyethylene glycol 1,000 succinate over the fat-soluble esters was found in healthy full-term newborn infants (Ref. 38).

In children and adults with cystic fibrosis, Melhorn (Ref. 49) obtained the best intestinal absorption with alpha-tocopheryl polyethylene glycol 1,000 succinate (TPEGS) in combination with a pancreatic enzyme preparation (cotazyme). Next best was alpha-tocopheryl acetate plus pancreatic enzyme. Last and quite poor was alpha-tocopheryl acetate alone. Unfortunately TPEGS without pancreatic enzyme was not used in comparison, nor were any other tocopherol preparations. With TPEGS plus pancreatic enzyme, the serum vitamin E level peaked in 8 hours at more than seven times the pretreatment level. Melhorn (Ref. 50) does state that, in his opinion, "the ideal approach to the therapy and prophylaxis of the vitamin E deficiency of prematurity would be a water-soluble form of the vitamin."

(5) *Nutrient interrelationships.* The dietary requirement for vitamin E increases when the intake of polyunsaturated fatty acids (PUFA) increases (Refs. 2 and 51). Vitamin E appears to enhance the absorption, lymphatic transport, and storage of vitamin A (Ref. 52). It may also have a stabilizing effect on the vitamin A of the cell membranes (Ref. 53). Large doses of vitamin E may counteract the toxic effects of excessive amounts of vitamin A (Ref. 54). However, as emphasized by Bieri (Ref. 4), whereas small amounts of alpha-tocopherol enhance carotene utilization (in the rat), large doses markedly reduce the amount of vitamin A formed from carotene and stored in the liver.

According to Melhorn and Gross (Ref. 55), red blood cell hydrogen peroxide fragility was markedly increased in children with vitamin E sufficiency but with iron deficiency anemia of moderate to severe degree, and the sensitivity to hydrogen peroxide was raised significantly during the administration of iron dextran. The rise in peroxide fragility could be prevented by priming patients with vitamin E during the administration of iron. Patients who received vitamin E therapy in addition to iron dextran showed a delay in reticulocyte response and also a rise in hemoglobin.

Asfour and Firzli (Ref. 56), in a study of undernourished and anemic Lebanese children, found no evidence that low serum vitamin E was causally related to either iron deficiency anemia or increased red blood cell hemolysis.

Selenium and vitamin E appear to have a sparing effect upon each other (Refs. 57 and 58). This appears to be of no practical importance in human nutrition. Although Money (Ref. 59) suggests a possible etiological role of vitamin E and selenium deficiencies in the sudden death syndrome of infants, this has not been confirmed.

Corrigan and Marcus (Ref. 51) have reported one case of a 55-year-old man with arteriosclerotic heart disease and type IV hyperlipoproteinemia who developed a prolonged prothrombin time and ecchymoses while on warfarin therapy and self-prescribed vitamin E (up to 1,200 I.U. daily for two months). A subsequent trial showed that the effect of warfarin on coagulation time was demonstrably enhanced after 4 weeks of daily vitamin E ingestion (800 I.U. daily). Vitamin K-dependent coagulation factors II, VII, IX, and X de-

clined, reaching their lowest point by the 42d day. On that day, multiple ecchymoses appeared. Vitamin E therapy was immediately stopped but warfarin was continued. In seven days, the levels of vitamin K-dependent coagulation factors returned to pre-vitamin E values, and concomitantly all clinical evidence of bleeding disappeared.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that vitamin E is safe, but that there is no proven therapeutic indication for its use as an OTC vitamin and mineral drug product as a single ingredient as discussed below under Category II conditions. The Panel does recognize the use of vitamin E, but only when in combination, as discussed below in Category I conditions. (See also Part II. paragraph F. above—Combination Policy.)

The minimum effective oral dose might be defined as the daily amount of any vitamin E scource which would raise a low plasma tocopherol level to within the normal range and maintain it there, and/or would reduce an elevated in vitro peroxide erythrocyte hemolysis to normal. A dose of 3 to 6 I.U. daily might be more than adequate for healthy adults on diets containing a minimum of PUFA and for infants. Similar persons on diets high in PUFA may require as much as 30 I.U. daily (Ref. 60). Individuals with intestinal malabsorption, cirrhosis of the liver, or a-beta-lipoproteinemia may require daily doses of vitamin E varying from within the normal range to 400 I.U. or more daily. In such cases, the effective doses would have to be individually determined by a physician. Therefore, the Panel concludes that, although Vitamin E is safe, it is not appropriate for OTC use as a single ingredient. Allowable combinations containing vitamin E are discussed elsewhere in this document. (See Part II. Paragraph F.7. above—Category I combinations.)

The maximum safe dose has not been determined. For an adult, it certainly is higher than 400 I.U. daily.

f. *Category I conditions under which vitamin E is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

There are no Category I conditions for vitamin E as a single ingredient. However, the Panel concludes that tocophersolan, alpha-tocopheryl acetate, alpha-tocopheryl acid succinate, and vitamin E are acceptable sources of vitamin E activity. Daily dosages of 30 I.U. based on the *dl*-alpha-tocopheryl acetate equivalent ($C_{31}H_{52}O_3$, molecular weight 472.7 and 1 mg *dl*-alpha-tocopheryl acetate is equivalent to 1 I.U.) vitamin E may be added to certain combinations of other essential nutrients in the prevention of multiple vitamin deficiencies such as may occur in conjuction with chronic alcoholism malabsorption syndromes, or severely restricted nutrient intake caused by lack of a nutritionally balanced diet when the need for such therapy has been determined by a physician. (See part II. paragraph F.2. above—Safety and part II. paragraph F.7. above—Category I combinations.)

g. *Category II conditions under which vitamin E is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC vitamin E drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that vitamin E is safe but there are no proven therapeutic indications for OTC drug use in man. Certain infants may require vitamin E but only under the direct care of a physician. Accordingly, no therapeutic claims of any kind are permitted for any OTC vitamin E drug preparation where vitamin E is the single active ingredient. Allowable combinations containing vitamin E and other vitamins are discussed elsewhere in this document. (See part II. paragraph F. above—Combination Policy.)

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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14. *Vitamin K.* The Panel's statement on vitamin K includes the following ingredient: phytonadione (phylloquinoe (vitamin K-1) and the menaquinones).

a. *Description.* At present, vitamin K-1 is the only form of vitamin K found in oral pharmaceutical preparations. Vitamin K-1 (2-methyl-3-phytyl-1,4-naphthoquinone) is also known as phylloquinone, 3-phytyl-menadione, phytomenadione, and phytonadione. It is the major form of vitamin K synthesized by plants and, therefore, it is the major dietary form of vitamin K for man. The formula for vitamin K-1 (phytonadione) is $C_{31}H_{46}O_2$ and the molecular weight is 450.7. Vitamin K-2 (menaquinone-7), originally found in fish meal, is a product of bacterial synthesis, as are all of the menaquinones with vitamin K activity, from menaquinone-6 through menaquinone-13. Menaquinone-4 is synthesized in animals and birds from menadione (2-methyl-1,4-naphthoquinone, vitamin K-3). Judging from the nature of vitamin K homologues stored in the liver, 40 to 50 percent of the human's requirement for vitamin K is met by plant sources and the remainder from microbiological biosynthesis (Ref. 1).

b. *Safety.* Synthetic water-soluble vitamin K analogues, e.g., menadiol tetrasodium diphosphate, are not available OTC. They are ineffective as antidotes to anticoagulant therapy (Ref. 2). In large amounts (5 to 30 mg daily) they have been claimed to have been responsible for hemolytic anemia, hyperbilirubinemia, kernicterus, and death in newborns, particularly prematures (Refs. 3 and 4). Menadione powder is irritating to the respiratory tract and to the skin, and a solution of it in alcohol is a vesicant.

c. *Effectiveness.* Clinically significant vitamin K deficiency because of dietary inadequacy rarely, if ever, occurs in the United States, except in newborn infants whose gastrointestinal tracts are sterile for the first few days after birth. The various pathological situations in which bleeding due to vitamin K deficiency may occur all require medical attention for diagnosis and management; therefore, labeling for OTC self-medication is inappropriate. Furthermore, vitamin K may represent a hazard for many patients on anticoagulant therapy.

The human requirement for vitamin K is not accurately known since so much of it is met through biosynthesis by intestinal micro-organisms, but a good estimate is around 1 μg/kg of body weight daily. Olson (Ref. 1) has calculated that "a normal mixed" diet for an adult in the U.S. will contain from 300 to 500 μg vitamin K daily.

The most commonly used technique for measuring the vitamin K content of foods is the chick bioassay, in which the prothrombin level of the blood of deficient chicks fed test diets is compared with a standard curve resulting from the feeding of known amounts of phylloquinone (Ref. 1). In man, in the absence of liver disease, the plasma prothrombin concentration is a measure of vitamin K adequacy.

Any disorder or therapeutic measure (e.g., chloestyramine (Ref. 5)) that hinders the delivery of bile to the small bowel reduces the absorption of vitamin K and can produce a reduction in plasma prothrombin concentration which can be prevented or corrected by parenteral vitamin K or by oral vitamin K with bile salts. Since the efficiency of absorption of vitamin K homologues from the intestine is

poor and variable, ranging from 10 to 70 percent (Ref. 1), vitamin K is generally administered parenterally for better control over plasma levels. Oral preparations are, however, on the market but available only on prescription by a physician. Malabsorption syndromes associated with sprue, pellagra, bowel shunts, regional ileitis, and ulcerative colitis may also cause a secondary vitamin K deficiency, as may prolonged therapy with intestinal antibiotics (e.g., neomycin) when used in combination with diets low in vitamin K.

Vitamin K deficiency is manifested by a prolonged clotting time caused by a lack of one or more of four coagulation factors normally produced in the liver, i.e. prothrombin (factor II), proconvertin (factor VII), Christmas factor (factor IX), and Stuart factor (factor X). Anti-coagulant therapy, when used in the treatment of a condition such as myocardial infarction, interferes with the action of one or more clotting factors. Synthetic water-soluble vitamin K analogues, e.g., menadiol tetrasodium diphosphate, are not effective as antidotes for anticoagulant therapy (Ref. 2) but are useful in the treatment of vitamin K deficiency.

Although low plasma prothrombin levels due to vitamin K deficiency cannot be said to be rare among newborn infants, individuals with fat malabsorption and individuals on long-term antibiotic therapy with plasma prothrombin levels sufficiently low to be responsible for bleeding are found much less commonly. In the management of all situations in which clinically significant vitamin K deficiency may develop, medical supervision is necessary.

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that vitamin K, owing to the potentiality for harmful effect, is not generally recognized as safe for use for the prevention or treatment of vitamin K-1 deficiency except under the supervision of a physician. (See Part III, paragraph A.14.f. below—Category II conditions.) Products containing vitamin K should be available only on prescription.

e. *Category I conditions under which vitamin K is generally recognized as safe and effective and not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which vitamin K is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC vitamin K drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that phytonadione should not be permitted on the OTC drug market until scientific testing supports its safety for OTC use.

Evaluation. Clinically significant vitamin K deficiency rarely, if ever, occurs in the U.S. because of dietary inadequacy, except in newborn infants. The various pathological situations in which bleeding due to vitamin K deficiency may occur require close medical supervision for diagnosis and treatment. The ready availability of OTC vitamin preparations containing vitamin K would present a hazard for many patients on anticoagulant therapy. Products containing vitamin K should be available only on prescription and not permitted on the OTC market.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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IV. MINERALS

Minerals are commonly defined as those chemical elements or their salts which are noncombustible and inorganic, the substances remaining in the ash after combustion of natural materials at a high temperature. Certain individual elements at issue in this document are essential dietary ingredients (commonly known as essential minerals) in that they are required in the diet of animals and man. By convention, though not scientifically correct, certain essential nonmineral elements are included along with the essential minerals; these include chlorine, fluorine, and iodine. Although these are not actually minerals in themselves, but are often found combined in nature as part of mineral salts, they are included in nutrition among the "minerals." Nutritionists often divide the essential minerals into two groups. Macrominerals are those needed in relatively larger amounts in the diet (generally over 0.1 percent of the diet) such as calcium, phosphorous, magnesium, potassium, sodium, and chlorine. Microminerals are needed in trace quantities and are commonly known as trace minerals; these include iron, zinc, manganese, copper, iodine, and fluorine. However, the mineral elements discussed in this document are considered in alphabetical order.

The dosages recommended in this document for minerals have been derived from the available scientific data. The Panel is also aware of the RDA (Ref. 1) and the dietary supplement regulations published in the FEDERAL REGISTER of October 19, 1976 (41 FR 45156). However, the Panel emphasizes that only drug considerations are applicable to the "OTC drug use" recommendations contained in this document.

It should also be noted that sulphur and cobalt are minerals which are required in the diet of all animals, but in monogastric animals only when combined as part of one or more organic compounds. Sulphur is a part of certain amino acids and vitamins, and cobalt is a part of the vitamin B-12 molecule. By tradition then, these are not counted among the essential minerals, since the inorganic form is generally inactive as a source of the amino acids or vitamins.

There are certain other mineral elements which have been shown to be required by certain experimental animals. These are silicon, tin, selenium, chromium, nickel, vanadium, molybdenum, and possibly others, but their need by humans either is not established or is considered to be so small that there is no need for their presence in OTC preparations.

It should also be noted that there are a number of additional minerals, such as aluminum, beryllium, barium, lithium, cadmium, lead, arsenic, and strontium, which do not appear to be dietary essentials and most of which can be toxic. They should not be present in biologically significant amounts in OTC minerals since there is no known use of them for this purpose.

REFERENCE

(1) "Recommended Dietary Allowances," 8th Ed., National Academy of Sciences, Washington, DC, 1974.

The Panel has classified the following mineral active ingredients as Category I for OTC drug use for the prevention and/or treatment of deficiency:

Calcium
- Calcium caseinate
- Calcium citrate
- Calcium glubionate
- Calcium gluconate
- Calcium lactate
- Calcium phosphate dibasic
- Calcium sulfate
- Precipitated calcium carbonate

Iron
- Ferrous sulfate, dried
- Ferrous succinate
- Ferrous lactate
- Ferrous fumarate
- Ferroglycine sulfate
- Ferrous glutamate
- Ferrous gluconate

Zinc
- Zinc Sulfate

The Panel has classified the following mineral active ingredients as Category II for OTC drug use for the prevention and/or treatment of deficiency:

Copper
- Cupric gluconate
- Cupric oxide
- Cupric sulfate

Fluoride
- Calcium fluoride
- Sodium fluoride

Iodine
- Calcium iodate
- Potassium iodide

Iron
- Ferric versenate
- Ferric citrate
- Ferrocholinate
- Ferric sulfate
- Ferric ammonium citrate

Magnesium
- Magnesium carbonate
- Magnesium chloride
- Magnesium gluconate
- Magnesium hydroxide
- Magnesium oxide
- Magnesium silicate
- Magnesium sulfate
- Magnesium trisilicate

Manganese
- Manganese chloride
- Manganese gluconate
- Manganous oxide

Phosphorus
- Calcium phosphate dibasic

Potassium
- Potassium chloride
- Potassium gluconate
- Potassium sulfate

Zinc
- Zinc hydroxide
- Zinc oxalate
- Zinc phytate
- Zinc sulfide

The Panel has classified the following mineral active ingredients as Category III for OTC drug use for the prevention of deficiency:

Iron
- Ferrous citrate
- Ferric ammonium phosphate
- Ferric phosphate
- Ferric pyrophosphate
- Ferrous tartrate
- Ferrous carbonate

Zinc
- Zinc carbonate
- Zinc chloride
- Zinc gluconate
- Zinc lactate
- Zinc oxide

1. *Calcium.* The Panel's statement on calcium includes the following ingredients: calcium caseinate, calcium citrate, calcium glubionate, calcium gluconate, calcium lactate, calcium phosphate dibasic, calcium sulfate, and precipitated calcium carbonate.

a. *Reference form.* Dosages recommended in this document for calcium are based on elemental calcium (Ca, molecular weight 40.1).

b. *Description.* Calcium, the most abundant cation and fifth most common element of the human body, not only serves as the principal component of skeletal tissue, imparting to it the structural integrity essential to support the increasing body size of the individual during growth, but also plays a vital role in a variety of physiological and biochemical processes. The calcium ion influences blood coagulation, neuromuscular excitability, cellular adhesiveness, nerve impulse transmission, maintenance and function of cell membranes, activation of enzyme reactions, and hormone secretion.

The average adult human contains 1,000 to 1,200 g calcium or 21 to 25 g/kg of fat-free body tissue. Over 99 percent of body calcium resides in the skeleton in the solid mineral phase of bone as a variant of poorly crystalline hydroxyapatite. The skeleton functions as a reservoir of insoluble complexed forms of calcium and is in dynamic equilibrium with physiochemically soluble forms of circulating calcium which is maintained at a remarkably constant level of 9.5 to 10.3 milligrams/deciliter (mg/dl) (or slightly higher when using atomic absorption spectroscopic analytical methods) with a diurnal plasma variation of ± 3 percent. Approximately 55 percent of circulating calcium is bound to proteins (primarily albumin). The majority (over 95 percent) of the nonprotein-bound calcium in blood is composed of the ionized calcium moiety, a physiologically important factor regulating membrane transport enzyme activity and hormonal secretion. Although the circulating calcium level in man is controlled primarily by parathyroid hormone, a variety of other harmones (i.e., thyroid, androgens, estrogens, cortisol), vitamins (i.e., vitamin D) and minerals (i.e., magnesium and inorganic phosphate) prevent the fluctuation of calcium over a wide range despite the insoluble skeletal reservoir and wide variations in calcium intake and output.

c. *Safety.* Calcium intakes ranging from 1,000 to 2,500 mg daily do not result in hypercalcemia in normal individuals. Ingestion of larger amounts, as may be necessary in ulcer patients consuming large amounts of milk and antacid products, chiefly calcium carbonate-containing products, may result in hypercalcemia and in repaid deterioration of renal function (Refs. 1, 2, and 3). An acquired or inherited vitamin D-sensitive hyperabsorption of calcium occurs in patients with sarcoidosis (Ref. 4) or in certain hypercalciuric individuals with renal calculi. In these subjects, hypercalcemia and/or hypercalciuria results from a vitamin D supplementation of diets which rarely affects normal individuals (Ref. 5). The symptoms of hypercalcemia are due to either a direct effect of elevated circulating calcium levels on cognative functions, cardiac rhythmicity, renal or gastrointestinal function, or indirect effect of diffuse metastatic calcification on critical organs such as kidney, heart, and blood vessels. Although individuals with slight degrees of hypercalcemia may, in fact, be asymptomatic, symptoms frequently noted initially are weakness, fatigue, malaise, dry mouth, vague muscle and skeletal aches, headache, and a metallic or bad taste. Weight loss, diarrhea, anorexia, nausea, and vomiting reflect the gastrointestinal response to hypercalcemia. Thirst, polyuria, nocturia, burning of eyes, conjunctivitis, generalized pruritis, diminished libido, pancreatitis, renal calculi, diminished heavy activity, photophobia, rhinorrhea, and hyperthermia in children have also been noted in the hypercalcemic state. Hemiplegia and mental impairment have been reported in children with hypercalcemia as have a variety of anatomical cardiac defects.

d. *Effectiveness.* A number of dietary surveys reveal that among western populations the mean calcium intake ranges from 500 to 1,200 mg calcium daily (Refs. 6 through 10). At all ages after 12 years, men consume more calcium than women and, at all ages, there are individual men and women who ingest two to four times the recommended allowances of calcium (Ref. 7). Many adult women ingest less than the recommended allowance of calcium. The absorptive efficiency of the intestine, however, is dependent on the amount of exposure to ultraviolet light (Ref. 11) and vitamin D intake, the sex and age of the individual, the food source, and the total calcium content of the source. Whereas, during periods of active skeletal growth, children may absorb up to 75 percent of ingested calcium, normal adults with daily intakes of 400 to 1,000 mg absorb 30 to 60 percent (Ref. 12). Dietary factors which increase calcium absorption include certain amino acids such as lysine and arginine, vitamin D, and lactose. Cocoa, soy beans, kale, spinach (or other high oxalate-containing foods), and foods with high phosphate content such as unpolished rice, hexaphosphoinositol in bran or wheatmeal

(Refs. 10, 13, and 14), decrease the intestinal absorptive efficiency for calcium. Other factors which decrease calcium absorption include the ingestion of alkali, decreased gastrointestinal transit time, stress, immobilization, thyroid hormone, and cortisol or any of its synthetic analogues. Antibiotics such as penicillin, neomycin, and chloramphenicol may actually enhance the absorption of calcium (Refs. 15 and 16).

The effect of inorganic phosphorus on calcium absorption is controversial. Earlier reports of an inhibition of calcium absorption induced by supplemental phosphate feeding (Ref. 17) conflict with later studies demonstrating no effect of dietary phosphorus increments on calcium absorption (Ref. 18). Calcium absorption is more efficient in males than in females. This may be explained by reports of stimulated calcium absorption when androgens are administered to females (Ref. 19). Absorption decreases as individuals age (Refs. 20 and 21). The adaptive efficiency of the intestine to fluctuations in calcium intake is one whereby, with decreasing calcium intake, the percent absorbed increases (Refs. 21 and 22). This intestinal adaptive efficiency appears to be blunted by the aging process (Ref. 21). Despite the recognized inverse relationship between calcium absorption and calcium intake, prolonged fasting paradoxically results in decreased absorption (Ref. 23), and absorption may actually increase as calcium intake rises with absorptive capacities of more than 1 g daily documented at intakes of 7.5 g (Ref. 24). Although it has been reported that calcium is significantly better absorbed when given as the lactate than as the gluconate salt (Ref. 25), it has also been observed that, in normal volunteers, no difference exists in the utilization of calcium from milk, or from gluconate, lactate, carbonate, or sulfate salts (refs. 26 through 28).

The full-term infant contains about 25 g calcium, about half of which is deposited during the last lunar month of pregnancy at a rate of approximately 300 mg daily. It has been demonstrated that the reproductive process in not impaired when the diet of pregnant women ranges between 700 to 1,100 mg daily (Refs. 29 and 30). More recent estimates place the calcium requirement of pregnant women at 2,000 mg daily (Ref. 31), although this has been contested (Ref. 32).

A newborn baby receives about 200 mg calcium daily while ingesting 650 ml of breast milk. By 8 months of age, the infant's daily calcium intake has increased to 350 mg (Ref. 33). Assuming a maintenance calcium requirement of 3 mg/kg of body weight and an efficiency of utilization of 30 percent, it has been estimated that a lactating mother will require from 1,000 to 2,000 mg calcium daily in order to insure an adequate calcium supply for the nursing infant and insure her skeletal balance of calcium (Ref. 34). The needs for the third trimester of pregnancy and normal lactation as recommended by the Joint FAO/WHO Expect Group on Calcium Requirements has been set at 1,200 mg daily (Ref. 8) although it was recognized that many women lactated adequately at lower intakes.

A premature infant needs about 90 to 120 mg/kg calcium and 60 to 90 mg/kg phosphorus daily, amounts which are easily provided by 100 g whole cow's milk (Ref. 35). An average 1-month-old infant weighing 4 kg will obtain 235 mg calcium daily from breast milk and at 3 months approximately 300 mg calcium daily, amounts sufficient to meet his or her skeletal demands (Ref. 36). Formula-fed children up to 1 year of age require no more than 600 mg calcium daily for adequate skeletal development and growth (Ref. 10). For children from 1 to 10 years on adequate viatmin D intakes, 800 mg calcium daily appears sufficient to insure normal skeletal growth (Ref. 10). Preadolescent growing children, however, may need two to four times as much calcium as does an adult (Ref. 10). Higher intakes of calcium in the order of 1,000 to 1,500 mg daily are recommended during preadolescence and puberty because of the demands of rapid skeletal growth. Intakes greater than this need not be advocated since maximal calcium retention occurs in children and young adults at this level of intake.

Although the majority of young and middle-aged adults are capable of maintaining a positive calcium balance on an average daily intake of 600 to 1,000 mg, higher intakes may be essential to maintain mineral and skeletal homeostasis in elderly individuals (Refs. 7 and 36).

The age-related needs for additional dietary calcium may result in part from the observations that absorption as well as the adaptive efficiency of the intestine to fluctuations in calcium intake decreases with age. Negative calcium balances observed in osteoporotic patients on low, but seemingly, adequate, calcium intakes have been variably ascribed to slow and noncompensatory adaptation to low calcium intakes, defective renal adaptation and relative hypercalciuria, and lactose intolerance resulting from intestinal lactase deficiency.

Evidence that calcium deprivation leads to osteoporosis in man stems primarily from controversial retrospective and epidemiological studies. Some reports reveal no significant difference in the incidence of "osteoporosis" between patients who patients who historically ingested less than 500 mg calcium daily and those with intakes greater than 1,500 mg daily (Refs. 37, 38, and 39). Others demonstrate a lower calcium intake in symptomatic "osteoporotic" indivduals than in age-matched normal control subjects (Refs. 41 through 47). Epidemiological and dietary survey studies may ultimately prove misleading, regardless of the conclusions derived, unless more specific emphasis is placed on evaluating dietary habits, the degree of mobilization, the daily intake of minerals other than calcium, the dietary intake of protein and vitamin D and the extent of sunlight exposure.

Modern diets which are characteristically rich in animal proteins and phosphorus, with low calcium/phosphorus ratios, may prove deleterious to bone since they may promote hypercalciuria and stimulate the release of parathyroid hormone with a resultant progressive decrease in bone mass (Refs. 48 through 51). Immobilization or the relative inactivity which often attends the infirmities of age promotes skeletal demineralization. Peculiar dietary habits may also lead to increased urinary calcium loss and a negative calcium balance despite an adequate intake. Although calcium intakes may in fact be adequate in geriatric populations, an associated vitamin D deficiency may prevent maximal absorption of the ingested calcium. It has been determined that long-term calcium supplements (2 to 3 years of 700 to 800 mg daily) lead to detectable increments in skeletal mass in elderly females with long histories of subnormal calcium intake (Ref. 52).

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that calcium, in the dosage and forms identified under Category I conditions below, is safe and effective for the prevention of calcium deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which calcium is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Acceptable sources of calcium are calcium caseinate, calcium citrate, calcium glubionate, calcium gluconate, calcium lactate, calciumphosphate dibasic, calcium sulfate, and precipitated calcium carbonate. Dosage must be based on elemental calcium (Ca, molecular weight 40.1).

(1) *Dosage—For prevention of deficiency.* For adults, children 1 to under

10 years of age, and children 12 years of age and older, the oral dosage is 400 to 800 mg daily. For preadolescent and pubescent children 10 to under 12 years of age and for pregnant and lactating women, the oral dosage is 600 to 1,200 mg daily. For elderly adults over 51 years of age, the oral dosage is 500 to 1,000 mg daily. For infants 6 months to under 1 year of age, the oral dosage is 300 to 600 mg daily. For infants under 6 months of age, the oral dosage is 200 to 400 mg daily.

(2) *Labeling.* The Panel recommends the following Category I labeling:

Indication—For prevention of deficiency. "For use in the prevention of calcium deficiency when the need for such therapy has been determined by a physician."

g. *Category II conditions under which calcium is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC calcium drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

h. *Category III conditions for which the available data are insuffcient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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2. *Copper.* The Panel's statement on copper includes the following ingredients: cupric gluconate, cupric oxide, and cupric sulfate.

a. *Description.* Copper is an essential trace element for humans. The adult body contains about 75 to 150 mg copper (Ref. 1). Plasma copper levels are about 100 μg/100 ml. Over 90 percent of plasma copper is in the form of ceruloplasmin, an alpha$_2$-globulin essential for the utilization of iron in hemoglobin synthesis. The rest is loosely bound to albumin or amino acids (Refs. 2 and 3). Copper is a constitutent of many enzymes, including cytochrome oxidase, monoamine oxidase, tyrosinase, and superoxide dismutase and is important for a variety of metabolic functions, including energy metabolism and the normal development of bone, connective tissue, and the central nervous system (Refs. 3 and 4).

Copper is currently sold OTC as part of vitamin-mineral preparations or by itself. It is primarily in the form of copper sulfate or copper gluconate (sometimes "chelated" with amino acids), and amounts are generally 2 mg or less per dose.

b. *Safety.* Excessive accumulation of copper in the liver and other tissues in Wilson's disease, a rare genetic disease also known as hepatolenticular degeneration, results from a defect in the handling of copper by the body and is not related to excessive copper consumption (Refs. 3, 4, and 5). Elevated plasma copper and ceruloplasmin levels are found in pregnant women, in users of oral contraceptives and other estrogen-containing preparations, and in individuals with various diseases, such as portal and biliary cirrhosis, thyrotoxicosis, leukemia, and certain malignancies and infections, but in these cases the changes occur regardless of the copper level in the diet (Refs. 1, 3, 4, and 5).

Monogastric mammals, such as rats and pigs, can tolerate fairly large chronic intakes of copper (200 times the normal intake), and generally show symptoms of copper poisoning only after the acute ingestion of very large amounts (Ref. 6). However, the maximum dose of copper, consumed chronically or acutely, which is safe for humans is not accurately known. The Joint FAO/WHO Expert Committee of Food Additives has estimated that 0.5 mg/kg daily is a safe level of copper intake (Ref. 7).

Signs of acute toxicity have been reported after the ingestion of a single dose of as little as 5 to 32 mg copper (Ref. 8). Wyllie (Ref. 8) described a poisoning at a cocktail party in which these amounts of copper were found in the cocktails, but it is possible that substances other than copper may have been responsible for the toxicity. This report alone provides insufficient evidence to conclude that this low level of copper is toxic.

After the rapid ingestion of copper in mg amounts (in most cases, the exact amount can only be roughly estimated), symptoms of copper intoxication, such as nausea, vomiting, diarrhea, headache, and dizziness, may occur (Refs. 8 through 11). In severe cases, after the ingestion of gram quantities of copper (usually copper salts), there may be tachycardia, hypotension, coma, methemoglobinemia, hemolytic anemia, jaundice, uremia, and even death (Refs. 12 and 13). Acute symptoms of copper intoxication have also been reported after the topical application of copper sulfate to the wounds of a seriously burned patient (Ref. 13).

Verified cases of chronic copper poisoning in humans have rarely been reported in the literature (Refs. 14 and 15). However, there has been one case reported of suspected chronic copper poisoning in a 15-month-old child whose family's hot water system contained 79 ug copper/100 ml, a concentration much higher than that found in other households in the area (Ref. 16).

c. *Effectiveness*—(1) *Absorption and excretion.* With usual diets, about 30 percent of the copper in foods is absorbed (Refs. 4 and 5). Absorption takes place by active transport primarily in the stomach and upper small intestine (Ref. 3). Copper in foods may become linked to amino acids, proteins, phytates, other trace elements, or other substances, leading to variable effects on copper absorption (Refs. 3 and 5). Small, stable complexes may actually be absorbed more readily than the free copper ion of copper salts such as cupric sulfate (Refs. 4 and 5). Several elements, including calcium, cadmium, mercury, silver, zinc, and molybdenum, may compete with copper for absorption or otherwise antagonize copper metabolism (Refs. 3 and 4). Ascorbic acid has been shown in animal studies to interfere with copper absorption (Ref. 3). Studies in rats have shown that intrapyloric administration of very large quantities of copper results in the passive absorption of about 10 percent of the dose (Ref. 17).

Bile is the major route of copper excretion, although a small amount of copper is excreted in the urine (Refs. 2 and 3). Sweat and menstrual losses are usually negligible, but individuals living in a hot climate may lose significant amounts of copper in sweat (Refs. 5 and 18).

(2) *Dietary intake and requirement.* Copper is found widespread in foods. Especially good dietary sources of copper are nuts, liver, some shellfish, kidney, raisins, and dried legumes. Cow's milk is a particulary poor source of copper (Refs. 1 and 19). Typical U.S. diets contain about 2 to 5 mg copper daily (Ref. 20), although an individual consuming foods high in copper (Ref. 19) could easily obtain more. Variable amounts of copper in water supplies may also contribute to the copper intake (Ref. 21).

Recommended daily copper intakes have been suggested in several studies. Requirements for infants and children have been estimated at 0.05 to 0.1 mg/kg of body weight daily (Ref. 1). In a study of boys aged 3 to 6 years, it was concluded that 0.053 to 0.085 mg copper/kg body weight was required daily (Ref. 22). In another study, preadolescent girls had a requirement of at least 1.3 mg copper daily in order to maintain a copper balance (Ref. 23). In most metabolic studies of adults, 2 mg copper daily was adequate to maintain a copper balance (Refs. 5 and 20).

However, Butler and Daniel (Ref. 18), who performed metabolic balance studies on young women, have suggested that the estimated requirement of 2 mg may be inadequate to cover the needs of some persons, particularly those with large sweat losses. Also, Klevay (Ref. 24) has hypothesized that our diets may be deficient in copper relative to zinc and that this imbalance may contribute to hypercholesterolemia and coronary heart disease.

(3) *Copper deficiency in humans.* Copper deficiency is rare in humans but there have been a number of case reports observed in unusual situations (Ref. 25), e.g., premature infants fed low-copper milk formulas (Refs. 26 and 27), severely malnourished infants rehabilitated on milk diets (Ref. 28), an infant with chronic malabsorption (Ref. 29), and infants (Refs. 25 and 27) and adults (Refs. 30 and 31) on long-term total parenteral nutrition following bowel surgery. Deficiency symptoms include a hypochromic anemia, neutropenia (low levels of neutrophils, a type of white blood cell), and skeletal abnormalities in infants. Copper deficiency was alleviated in these cases

with oral or parenteral copper supplementation at levels comparable to the U.S. RDA.

Menkes's steely-hair syndrome (formerly called "kinky-hair syndrome") is an inborn error of metabolism occurring in one out of about 35,000 live births (Ref. 32). The disease becomes clinically evident in the first few months of life and is characterized by growth retardation, neutrological damage, convulstions, bone changes, problems with temperature regulation, peculiar hair (like steel wool) and an early death (usually by 3 years of age) (Refs. 32 and 33). Low levels of copper in the blood and tissues of infants with steely-hair syndrome appear to result from impaired intestinal absorption of copper (Refs. 32 and 33). Copper may be absorbed in sufficient amounts when oral doses of copper (as cupric sulfate) are administered at about ten times the normal infant requirement (0.52 mg/kg daily, compared with 0.05 mg/kg daily) (Ref. 33). However, parenteral administration of copper given intramuscularly, intravenously, and even subcutaneously, is more effective and is certainly the preferred route of administration (Refs. 34, 35, and 36). Proper diagnosis and treatment of this disease require a physician.

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based on the available data, the Panel concludes that copper is not appropriate for the OTC drug market for the prevention or treatment of copper deficiency since copper deficiency in man is rare and because of the potential for copper toxicity at relatively low levels of intake.

e. *Category I conditions under which copper is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which copper is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC copper drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that there is no demonstrated need or justification for cupric gluconate, cupric oxide, and cupric sulfate in OTC drug preparations for the prevention of treatment of deficiency because of the potential for copper toxicity at relatively low levels of intake and the absence of any demonstrated need for OTC copper preparations to prevent or treat a deficiency. Therefore, no OTC drug use of copper is recommended since conditions which indicate the need for therapeutic use of copper require the close supervision of a physician.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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3. *Fluoride.* The Panel's statement on fluoride includes the following in-

gredients: calicum fluoride and sodium fluoride.

a. *Description.* Although considerable information exists regarding fluoride metabolism in a variety of animal species, there are limited data on the fate of ingested fluoride in man. In certain endemic areas the fluoride content of drinking water approximates 4.0 to 5.8 ppm (Ref. 1).Ordinary drinking water, which often contains up to 1 ppm, contributes approximately 1.0 to 1.5 to the daily fluoride intake. The average daily U.S. diet also contains 0.25 to 0.30 mg fluorine (Ref. 2), although specific foods such as tea, baking powders, wines, fresh mackeral, dries salmon, or unwashed apples sprayed with fluoride-containing insecticides may contain up to 6.3 mg/liter (wines) or 2.7 mg/100 g (fresh mackeral) (Ref. 2). Fluoride is widely distributed in nature, and food contents usually reflect both soil and atmospheric concentrations of fluoride. Specific in this regard is the use of different forms of fertilizer, with fluoride contents ranging from 0.01 to 9.88 percent (Ref. 3).

The gastrointestinal tract is the major site of fluoride absorption in man, although fluorine is absorbed via the lungs following inhalation of industrial atmospheric contaminants as may occur in cryolite workers, steel and metal workers where fluorospan is used as a flux, chemical workers using hydrofluoric acids, workers in brick factories using fluorine-rich clay and those employed in the manufacture of phosphate compounds. Hydrogen fluoride is minimally absorbed by the skin although the resulting burn is of much greater consequence than the minute amount of fluoride absorbed. The degree of absorption of fluoride correlates with its solubility. Relatively soluble compounds such as sodium fluoride are well absorbed by the gastrointestinal tract, whereas relatively insoluble forms such as cryolite (Na_3AlF_6) and the fluoride found in bone meal (fluoroapatite) are poorly absorbed (Refs. 4 and 5).

Radioactive fluoride absorption studies in human subjects reveal that the isotope enters the blood extremely rapidly when given by mouth (Refs. 6 and 7). The greatest urinary fluoride concentration after the oral ingestion of a single dose of sodium fluoride occurs within 2 hours (Refs. 8 and 9). The absorption of fluoride from vitamin-containing fluoride preparations containing 0.1 mg fluoride is also quite rapid with increments of blood-fluoride concentrations from 0.15 ppm to 0.26 ppm noted 1 hour after the ingestion of a tablet containing a vitamin-fluoride combination (Ref. 10). The fluoride content of plasma of humans ingesting communal water with fluoride contents of 0.15 to 2.5 ppm is relatively constant at 0.12 to 0.15 ppm (Ref. 11). Once absorbed, renal excretion and skeletal mineral sequestration are the principal mechanisms which regulate circulating fluoride levels.

The percentage of ingested fluoride that appears in the urine amounts to 50 to 65 percent of the daily intake (Refs. 12, 13, and 14). It appears that when humans ingest small amounts of fluoride (i.e., 1 ppm) for a prolonged period, the daily urinary excretion is a greater fraction of the intake. Labile skeletal fluoride reserves are excreted more rapidly by adults than children; also, the more rapid metabolic activity of developing bone in children liberates more of the sequestered fluoride and, as such, maintains elevated blood and urine fluoride concentrations over a much longer time interval (Ref. 15).

b. *Safety.* A lethal dose of fluoride (2.5 to 5 g) produces signs of violent gastrointestinal irritation, shock, and death within 2 to 4 hours. The safety factor assuming the ingestion of a quart of water daily at 1 ppm fluoride concentration (i.e., 1 mg fluoride) is at least 2,500-fold (Ref. 16). Crippling fluorosis occurs when humans ingest or inhale 20 to 80 mg fluoride or more for 10 to 20 years, and enamel hyperplasia noted in children within the first 8 years of life with graded severity when the drinking water contains 2 to 5 ppm fluoride or more. There are reports of retinopathy and others describing optic neuritis and macular edema after daily doses of 30 mg fluoride for 6 weeks. Atopic dermatitis, urticaria, pruitis, and edema have also been reported to occur in patients using fluoride-containing vitamins and toothpastes (Ref. 16, 17, and 18).

c. *Effectiveness.* Skeletal deposition of fluoride is a continuing process in which 25 to 50 percent of the ingested fluoride is deposited daily. The concentration of fluoride in bones and teeth depends on the total daily intake and length of exposure, with skeletal levels reportedly increasing with age (Ref. 19). Studies in humans 26 to 90 years of age who have drunk water containing 0.1 to 4.0 ppm fluoride for at least 10 years reveal no significant histological changes in soft tissue and bones (Refs. 20 and 21). The concentration of fluoride in the skeleton increases in an essentially linear fashion with an increase in fluoride content of drinking water up to 4 ppm (Refs. 20 and 21). Fluoride is desposited in bone by simply ionic exchange with the hydroxyl groups of hydroxyapatite (Ref. 22). The skeletal deposition of fluoride is reversible. Skeletal mobilization is slow but predictable with a biological halftime (i.e., the period required to mobilize and remove from the body half of the skeletal fluoride) of 1 to 2 years (Ref. 12). Although ingestion of large doses of fluoride (i.e., up to 16.2 ppm) induces a variety of pathological changes in man such as mottled enamel and crippling bone disease (Ref. 23), the ingestion of water containing fluoride up to 8 ppm reportedly produces no deleterious bone changes other than dental mottling (Ref. 24) and may in fact retard the rate of bone loss which normally attends senescence (Refs. 1, 14, and 24) and dental caries (Ref. 25).

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that there is no justification for an OTC drug preparation containing fluoride for the prevention or treatment of deficiency.

e. *Category I conditions under which fluoride is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which fluoride is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC fluoride drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that calcium fluoride and sodium fluoride for the prevention or treatment of fluoride deficiency are not justified as an OTC vitamin or mineral drug preparation since the small amounts needed for fluoride balance are easily provided in the diet.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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4. *Iodine.* The Panel's statement on iodine includes the following ingredients: calcium iodate and potassium iodide.

a. *Description.* Elemental iodine as contained in the above ingredients will be referred to as iodine in this document. Although iodine is a scarce element, it is widely distributed and concentrated in a variety of food sources. Iodine in the plasma is concentrated in the thyroid, salivary, mammary, and gastric glands and in the kidney. It is essential for the proper synthesis of thyroid hormone and a deficiency or excess of this element may alter thyroid function.

b. *Safety*—(1) *Chronic toxicity.* The long-term ingestion of large doses of iodine (40 mg to several grams daily over a period of months to years) may alter thyroid function and produce symptoms of iodism in some individuals (Refs. 1 and 2).

When exogenous iodine intake is increased, the thyroid takes up the excess but does not metabolize it. This protective mechanism is operative until the amount ingested exceeds 2 mg. Thereafter, the thyroidal iodine uptake is diminished. This protective effect prevents the accumulation of so much iodine that thyroid hormone sythnesis is inhibited. It is for these reasons that iodine-induced goiter, hypothyroidism, and hyperthyroidism (Jod-Basedow disease) occur rarely and almost always in individuals with underlying thyroid abnormalities (Refs. 1 and 2). Pregnant women ingesting several grams of iodine daily may bear infants with a goiter that can cause respiratory distress (Ref. 1).

The chronic ingestion of large amounts of iodine, as discussed above, can produce iodism in some individuals. This syndrome has a variable presentation but may include a metallic taste, rhinorrhea, headache, an acne-form skin lesion, parotitis, and pulmonary edema (Refs. 2, 3, and 4). Minor side effects occurred in 11 percent of 2,404 patients with chronic obstructive pulmonary disease who received oral potassium iodide chronically (Ref. 1).

(2) *Acute toxicity.* The acute toxicity of iodine in humans is poorly documented. Relatively large daily doses (200 mg to 4 g iodide as potassium iodide) administered over 4 months produced no symptoms of hyperthyroidism or toxicity (Ref. 1). The acute toxicity of iodine in animals has been reviewed elsewhere (Ref. 1). Rarely, angioedema, serum sickness, and hemorrhagic skin lesions occur in sensitive individuals (Refs. 1 and 3).

c. *Effectiveness.* Iodine is an essential nutrient which is required for the synthesis of thyroid hormone.

Iodine requirements, as determined by epidemiological data and metabolic balance studies, are probably between 100 to 200 μg daily (Refs. 4 through 7). The requirements vary widely among indivuduals and are influenced by factors such as age, differences in urinary clearance, sex, and the ingestion of foods such as cabbage, peaches, and almonds containing goitrogenic substances. Goiter is generally prevented by the injestion of 50 to 75 μg (1 μg/kg) daily in adults (Refs. 5 and 6). Children and pregnant and lactating females require larger amounts (Refs. 4 and 5).

Dietary sources of iodine include water, vegetables, meat, eggs, and dairy products, although the amount present in these substances ultimately depends on the iodine content of the soil as well as that of animal feeds. Iodized salt (76 μg/g), seafoods (fish and seaweed) and some breads are particularly rich sources of iodine (Ref. 8). The American dietary intake of iodine is highly variable, but is estimated to range from 240 to 740 μg daily (Ref. 9). The average American consumes something more than 300μg daily, well in excess of those amounts recognized as necessary for adequate nutrition (Ref. 1).

Dietary iodine as the iodide is rapidly absorbed by normal persons in the fasting state. Free and bound iodide and iodates are converted largely to iodide in the gastrointestinal tract before they are absorbed. Some iodide is absorbed from the stomach, but most is absorbed from the small intestine. Absorption of iodide in the nonfasting individual is virtually complete in 3 hours (Ref. 4). Soybean products interfere with the reabsorption of thyroxine so that chronic ingestion of such products can induce depletion and goiter (Ref. 10). No substances are known to alter the absorption of inorganic iodide (Ref. 10).

Since there are no renal mechanisms for the conservation of iodine, when dietary intake is inadequate, deficiency will ultimately result.

A diet deficient in iodine is the most common cause of simple goiter, an enlargement of the thyroid gland involving an increase in the size and number of epithelial cells. Endemic goiter occurs in populations living in mountainous and inland areas where soils have been leached of iodine and the dietary intake of seafoods is minimal. Those states in the Great Lakes region and in the Pacific northwest are the major endemic areas in the United States.

Although the incidence of goiter in the United States has decreased markedly since the introduction of iodized

salt (Ref. 6), several recent surveys indicate that approximately 5 percent of the population in Michigan and Texas have goiters (Refs. 11, 12, and 13), with a higher frequency among females of the childbearing age. It is important to emphasize that these cases of goiter are not necessarily related to iodine deficiency, since their occurrence is not correlated with indices of iodine under-nutrition as indicated, for example, by the daily urinary excretion of iodine (Ref. 14). There are reasons to believe that factors other than iodine deficiency may be important in the induction of simple goiter. Iodine deficiency does not produce goiter in 100 percent of patients. Iodine replacement does not eradicate goiter completely. Also, within a given endemic area, the incidence of goiter does not correlate with iodine intake. Postulated goitrogenic factors include genetically determined deficiencies in enzymes responsible for the synthesis of thyroid hormones, the ingestion of dietary goitrogens, and infectious agents.

Data from the Ten State Nutrition Survey for 1968-1970 published in 1972 by the U.S. DHEW showed that only a small number of individuals in the population showed evidence of iodine deficiency (Ref. 14). There was no correlation between this deficiency and the prevalance of goiter.

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that there is no rationale for the inclusion of iodine in OTC drug products for the prevention or treatment of iodine deficiency.

e. *Category I conditions under which iodine is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which iodine is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC iodine drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that there is not rationale for the inclusion of calcium iodate or potassium iodide as a source of elemental iodine in OTC drug products for the prevention or treatment of iodine deficiency. Recent evidence for the increased consumption of iodine taken together with the decreased incidence of goiter in endemic areas indicate that adequate amounts are available to the general population. Additionally, the excessive ingestion of iodine is not without risk, and treatment with iodine when required should be closely supervised by a physician.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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5. *Iron.* The Panel's statement on iron includes the following ingredients: Ferric ammonium citrate; ferric ammonium phosphate; ferric citrate; ferric phosphate; ferric pyrophosphate; ferric sulfate; ferric versenate; ferrocholinate; ferroglycine sulfate; ferrous carbonate; ferrous citrate, ferrous fumarate; ferrous glutamate; ferrous gluconate; ferrous lactate; ferrous succinate; ferrous sulfate, dried; and ferrous tartrate.

a. *Reference form.* Dosages recommended in this document for iron are based on elemental iron (Fe, molecular weight 55.8).

b. *Description.* The term iron used in this document refers to elemental iron. Iron is a component of the heme molecule and, as such, plays a vital role in biologic processes involving oxygen and electron transport. The total body iron of a normal adult male is approximately 4 g. Most of the iron (2.5 g) is incorporated into the hemoglobin of red blood cells and a significant protion (1.0 g) is stored in the reticuloendothelial system (bone marow, spleen, liver). The remainder is found in myoglobin and respiratory enzymes (Ref. 1).

Iron stores are maintained through a balance of absorption and elimination. Iron absorbed from food goes to storage sites and the iron released from aging red cells is recycled. In the adult male and postmenopausal female, daily obligatory losses of iron are balanced by iron absorption from food. Each day, iron in the amount of 0.5 to 1.0 mg is lost from the body through exfoliation of gastrointestinal and dermal cells, biliary secretions, sweat, gastrointestinal blood loss, and urinary excretion (Refs. 2, 3, and 4). Women of childbearing age lose additional iron through menstrual bleeding.

Because the amount lost each day is so limited, absorption plays a major role in regulating iron balance (Ref. 5).

The average American diet contains 6 mg iron per 1,000 kilocalories (kcal) providing 10 to 20 mg daily (Refs. 6 through 9). Even though the availability of iron from foods is highly variable and accurate absorption data are difficult to obtain, it has been estimated that iron-replete individuals absorb 5 to 10 percent or the equivalent of 0.5 to 2.0 mg iron from food each day (Ref. 6). Iron-depleted individuals absorb two to three times more (Refs. 8 and 10).

Iron is principally absorbed in the duodenum and upper jejunum through a complex, poorly understood process. The amount of iron which is absorbed increases with the dose, but the fraction of the dose which is absorbed decreases. Innumerable factors affect the absorption of iron, including the food source and the status of the iron stores. In general, iron from vegetables is more poorly absorbed than that from animals (heme iron) and individuals with low stores absorb a greater amount of iron than those who are iron replete. Accelerated erythropoiesis also enhances iron absorption, even in the absence of depleted iron stores (Ref. 11).

Ascorbic acid increases the absorption of food iron by reducing ferric iron to the more soluble ferrous state and through formation of a soluble iron-ascorbate chelate. Doses greater than 200 mg may increase the absorption of iron salts by 25 to 50 percent (Ref. 12). However, in view of the fact that recommended Category I iron doses without vitamin C will adequately prevent iron deficiency, there is no rationale for adding large amounts of vitamin C to approved iron preparations. Small doses of vitamin C do not significantly increase iron absorption.

There are various degrees of iron undernutrition. Initially, tissue iron stores are partially or totally depleted. Thereafter, serum iron is diminished and red cell production is impaired. Eventually, severe iron deficiency results in an anemia characterized by small red blood cells deficient in hemoglobin.

The prevalence of iron deficiency is difficult to extrapolate from the medical literature because most of the data is based only on the presence of overt animia. Also, because iron deficiency without anemia is more dificult to establish, it is frequently overlooked in epidemiologic studies. Therefore, the propensity of any given population for iron deficiency is best assessed on the basis of what is known about iron balance.

(1) *Menstruating females.* In this group, menstrual losses must be added to the basal iron losses. Several investigators have established that the average menstrual blood loss is approximately 40 ml or the equivalent of 0.7 mg iron daily (Refs. 10 and 13). The 90th percentile for menstrual iron loss has been estimated to be 1.35 mg daily and the 95th percentile, has been estimated to be 1.75 mg daily (Ref. 9). If basal iron losses (0.5 to 1.0 mg) are added to these figures, this population would have to absorb a total of 1.2 to 2.75 mg iron daily to maintain adequate body iron stores. A dietary intake of 2,500 calories would provide a sufficient amount of iron for most women (10 percent absorption of 15 mg dietary iron, providing 1.5 mg absorbed iron). Beaton et al. (Ref. 7) have demonstrated that a daily dietary iron intake of 11 to 12 mg or more prevented iron deficiency, as judged by serum iron, total iron binding capacity, and iron saturation. However, it is apparent that iron balance in these individuals is at best precarious, as demonstrated by the studies of Scott and Pritchard (Ref. 14) which showed the absence of iron stores in the bone marrow in 24 percent of college women. Another 42 percent had greatly diminished iron stores. The incidence of iron deficiency anemia may be as high as 10 percent in this population (Refs. 8, 10, and 15). In view of the high prevalence of iron deficiency in this population, the variable absorption of iron from food, the borderline caloric intake in this group, and the possibility of excessive iron loss secondary to unrecognized menorrhagia, it seems reasonable to provide 10 to 30 mg of exogenous (extradietary) iron daily (1 to 3 mg absorbed) for women of child-bearing age to supplement the dietary intake and preserve iron stores. This is a liberal figure because it does not take into account any increased iron absorption which may result from negative iron balance.

(2) *Lactating females.* An additional 0.5 to 1.0 mg iron is lost daily through lactation, an amount approximately equivalent to daily menstrual losses (Refs. 9 and 16). Because lactating women are usually amenorrheic, iron requirements for this group are approximately the same as those for menstruating females. Therefore, 10 to 30 mg of exogenous (extradietary) iron should be available to this population as well.

(3) *Pregnant females.* In pregnancy, iron requirements are greatly increased because iron is transferred to the growing fetus and placenta during the latter half of pregnancy. Also, blood loss at delivery and the expansion of blood volume that occurs during pregnancy contribute to increased iron requirements. When the iron savings from 9 or more months of amenorrhea are taken into consideration, the net increase in iron requirement will average 500 mg for the entire time period (Ref. 8). The resulting deficit is highly variable and may range from 0 to 750 mg iron (Ref. 8). The estimated daily requirements for absorbed iron range from 2 to 5 mg (mean 3.5 mg) (Refs. 6, 7, and 17). Even through iron absorption is increased in pregnancy (30 percent during the second trimester; 40 percent during the third trimester), it is unlikely that dietary sources of iron will be sufficient for this population. This inadequacy is further supported by the apparent decreased caloric and iron intake of pregant women as compared to their nonpregnant counterparts (Refs. 9, 18, and 19). The incidence of iron deficiency anemia in this population varies from 10 to 20 percent, in communities with adequate levels of nutrition, to 50 percent in areas of poor diets (Refs. 6 and 17). Iron depletion without anemia may be much more common (Ref. 8). Chanarin and Rothman (Ref. 20) demonstrated that a daily dose of 30 mg iron was sufficient to maintain hemoglobin levels throughout pregnancy, as did Iyengar and Apte (Ref. 21). In contrast, DeLeeuw, Lowenstein, and Hsieh (Ref. 22) found that 39 mg iron was insufficient to achieve an optimal hemoglobin mass and to maintain iron stores in 50 percent of their subjects. A daily dose of 78 mg was effective. On the basis of the high prevalence of iron deficiency in this group of individuals, iron balance studies, and therapeutic trials, the Panel recommends a daily dose of 30 to 60 mg iron be made available to this population to maintain iron stores and prevent iron deficiency.

(4) *Infants and children (6 months to 5 years of age).* Iron nutriture in infancy is at best marginal, and iron deficiency is the most prevalent nutritional deficiency in infants. This is a consequence of the increased iron requirements arising from growth, a tripling of the blood volume during this period, and the low iron content of the diet. Human milk and cow's milk contain very little iron. Iron in egg yolk and iron from iron pyrophosphate in fortified cereals are inadequately available (Refs. 23 and 24).

The prevalence of iron deficiency anemia in the 6 months to 5 year age group is high in all areas of the U.S. and varies with the socioeconomic status and age of the population studied (Refs. 24 through 28). Preliminary results of the Hanes survey show an overall prevalence of anemia (hemoglobin less than 11 g percent) to be 6.4 percent (range of 5.07 to 17.62 percent) in the 1- to 5-year age group (Ref. 29). Anemia was more prevalent in Blacks and in children from families earning incomes below the poverty level. The high prevalence (13 to 22 percent) of an iron saturation index below 15 percent and the finding that dietary intakes were below the standard in 95 percent of this population suggest that the anemia may arise from iron deficiency. When the data are broken down by age, it is apparent that iron deficiency is much more prevalent in the first years of life. Owen, Lubin, and Garry (Ref. 25) surveyed a cross-sectional sample of children 1 to 6 years of age and found the overall incidence of anemia (hemoglobin less than 10 g percent) to be 5 percent. However, 39 and 45 percent of a group of children, 12 to 23 months of

age, from upper middle and lower middle class families, respectively, had transferrin saturations of less than 15 percent. Several studies of economically deprived children indicate that the incidence of anemia is very high (59 to 68 percent) (Ref. 26). Although the prevalence of anemia is lower in children 3 to 5 years of age, it is also a significant problem. Incidences ranging from 2.8 percent to 12 percent have been reported (Refs. 24 and 29).

Iron requirements for infants have been estimated by two methods. The first is based upon calculations of the net total body iron which must be realized during the first year of life. The second method is based on the daily intake of iron which produces the highest hemoglobin levels. The Committee on Nutrition of the American Academy of Pediatrics based its recommended iron intake of 1 mg/kg daily, to a maximum of 15 mg daily per infant, on the results of the second method (Ref. 23).

In view of the occurrence of iron deficiency in this population and the sporadic use of iron-fortified foods, the Panel recommends that an iron preparation containing a daily dose of 10 to 15 mg be made available for use in children 6 months to 5 years of age.

c. *Safety.* Because iron absorption is limited by a protective mucosal block, chronic intoxication from amounts found in food or medicines is not likely to occur in normal individuals. A primary consideration in making medicinal iron available in an OTC preparation is whether prolonged or excessive iron intake will result in iron overload. Disorders of iron load appear to be rare (Ref. 30) and are characterized by an accumulation of iron in the reticuloendothelial system or in the parenchymal cells of various organs. Although there is some debate with regard to terminology, most authorities used the term "hemosiderosis" to describe the presence of iron accumulation without tissue damage and "hemochromtosis" to describe fibrosis and organ damage resulting from excessive iron deposition (Refs. 30, 31, and 32).

Primary or idiopathic hemochromatosis is thought by most authorities to be a disease characterized by an excessive absorption of dietary iron caused by an inherited inborn error of metabolism. When definite causative factors for iron overlaod can be identified, the term "secondary hemosiderosis" or "hemochromatosis" is used. The latter can be caused by the prolonged ingestion of excessive iron or by conditions which increase the absorption of iron. Alcoholics with cirrhosis may have a secondary hemosiderosis. The high iron content of some alcoholic beverages and the increased iron absorption associated with alcoholic liver disease contribute to the iron overload observed in these individuals (Ref. 31 and 32). Iron overload is also associated with porta-caval shunts, chronic pancreatitis, and a variety of hematological disorders characterized by an increased and/or ineffective erythropoiesis (Refs. 31 and 32). Repeated transfusions and, very rarely, the prolonged or excessive intake of medicinal iron may be associated with hemosiderosis or hemochromatosis (Refs. 31 and 33 through 37).

Acute iron intoxication resulting from the accidental ingestion of large amounts of iron by children between the ages of 2 to 4 years appears to be a greater health problem than does chronic iron intoxication. In the U.S., iron and vitamins are the fourth most frequently ingested toxic substances in children under the age of five (Ref. 38). It has been estimated that one child dies each month from an overdose of elemental iron (Ref. 39). A 32-month survey or iron intoxication reports received by the National Clearing House for Poison Control Centers revealed that 74 percent of all iron intoxications occurred in the 1- to 2-year-old age group. Only 8 percent occurred in the population greater than 5 years of age (Ref. 40).

The ingestion of large doses overwhelms the mucosal block which normally exists for iron. Initially, symptoms can be related to the direct corrosive action of large doses of iron on the gastrointestinal tract (vomiting, diarrhea, melena, dehydration). The severe shock, which may or may not follow, may be due to elevated serum levels of ferritin or free iron. Metabolic acidosis and central nervous system depression are frequently observed in severe cases (Ref. 41 and 42).

All iron products are potentially toxic. Reduced (elemental) iron is said to have a safety margin 100-fold greater than iron salts (Ref. 41). However, in micronized form, it is absorbed as well as the ferrous salts and should be considered potentially toxic.

The ingestion of more than 150 mg/kg is considered serious by some (Ref. 41). The estimated "average" lethal dose for children is 200 to 250 mg/kg iron. This amount would approximate 2 to 4 g elemental iron in the 6 months to 5-year-old age group (Ref. 43).

Oral iron in a total daily dose of 200 mg may cause nausea, abdominal cramping, constipation, and diarrhea in 5 to 15 percent of patients. Several controlled trials reviewed by Fairbanks, Fahey, and Beutler (Ref. 44) have demonstrated that there is no significant difference in the incidence of gastrointestinal intolerance caused by various iron salts when administered in bioequivalent doses. Such side effects are uncommon if the total daily dose is 100 mg or less.

d. *Effectiveness.* Any iron preparation which is absorbed 80 percent as well as a ferrous sulfate solution by the method of Brise and Hallberg (Ref. 45) is considered effective.

Solutions of some ferrous salts are well-absorbed, as demonstrated by the studies of Brise and Hallberg (Ref. 46). It will be assumed that nonenteric coated tablets of the same salts will also be well absorbed if they pass the dissolution test described below. Dissolution tests may not correlate well with bioavailability. However, the practical limitations of all methods currently available to study iron absorption in a rigorous, meaningful way do not warrant that such tests be required for preparations for which there is reasonable evidence of effectiveness.

Absorption studies will be required for enteric-coated and sustained-release preparations of Category I iron salts, as well as for any product containing iron salts or combinations not listed in Category I or II (See Part IV, paragraph A.5.h. below—Category III conditions.) A dissolution test will be sufficient if it can be demonstrated that results correlate with absorbability as measured by the method of Brise and Hallberg (Ref. 45) or any comparable test.

A rise in hemoglobin in response to iron therapy in individuals with well-defined iron deficiency anemia has been used to document the effectiveness of a variety of iron products. However, because the doses recommended for OTC use are inadequate to treat iron deficiency anemia, this method would be inappropriate to document effectiveness in this group of products.

Dissolution Test. Since iron is most efficiently absorbed in the duodenum and jejunum, in vitro studies of the dissolution rate of all products should show a release of a significant percentage (80 percent) of their elemental iron content after 120 minutes in actual or simulated digestive fluids (60 minutes in gastric fluid and 60 minutes in intestinal fluid). The method described by Middleton, Nagy, and Morrison, or a comparable method, should be used (Refs. 44 and 47).

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that iron, in the dosages and forms identified under Category I conditions below, is safe and effective for the prevention of iron deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which iron is generally recognized as safe and effective and is not misbranded.*

The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Acceptable sources of iron are ferroglycine sulfate; ferrous lactate; ferrous fumarate; ferrous glutamate; ferrous gluconate; ferrous succinate; and ferrous sulfate, dried. Dosage must be based on elemental iron (Fe, molecular weight 55.8). The iron content of a product must be labeled in terms of elemental iron.

(1) *Dosage—For prevention of deficiency.* For menstruating and lactating women, the oral dosage is 10 to 30 mg daily. For pregnant women, the oral dosage is 30 to 60 mg daily. For children 6 months to under 5 years of age, the oral dosage is 10 to 15 mg daily. For infants under 6 months of age, the Panel recommends the advice and supervision of a physician. For combination products other than for use in pregnancy, the oral dosage for adults and children 5 years of age and older is 10 to 20 mg daily.

(2) *Labeling.* The Panel recommends the following Category I labeling:

(i) *Indication—For prevention of deficiency.* "For use in the prevention of iron deficiency when the need for such therapy has been determined by a physician."

(ii) *Warning.* "*Caution:* The treatment of any anemic condition should be under the advice and supervision of a physician."

g. *Category II conditions under which certain iron compounds are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC iron drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The OTC drug use of certain iron salts, complexes, and combinations or use in certain target groups listed below is unsupported by scientific data, and in some instances, by sound theoretical reasoning.

(1) The following iron salts or complexes are poorly soluble and absorbed when compared to the well-absorbed standard, ferrous sulfate (Ref. 46):

(i) Ferric versenate.
(ii) Ferric citrate.
(iii) Ferrocholinate.
(iv) Ferric sulfate.
(v) Ferric ammonium citrate.

(2) Iron in combination with any of the following: Magnesium trisilicate, cobalt, copper, cyanocobalamin, intrinsic factor, liver stomach concentrate, molybdenum.

A number of substances have been combined with iron salts for the purposes of increasing absorption, minimizing gastrointestinal intolerance, potentiating erythropoietic activity, or preventing oxidation. Some of these are discussed briefly as follows:

(i) *Magnesium trisilicate* retards iron absorption, presumably by absorption of iron to the insoluble particles in the antacid preparation (Ref. 48). (ii) *Cobalt.* (Ref. 49) Large doses (60 to 150 mg) of cobaltous chloride have a nonspecific erythropoietic effect in various types of anemia unresponsive to other hematinics. There is no evidence that cobalt iron combinations produce a more rapid hematologic response than iron alone in iron-deficient patients. Further, the administration of these doses for prolonged periods of time is associated with anorexia, nausea, vomiting, and, less frequently, with more severe problems such as rash, flushing, tinnitus, deafness, and thyroid hyperplasia. Smaller doses have negligible erythropoietic effects (Refs. 44 and 49).

(iii) *Miscellaneous hematinics (copper, cyanocobalamin, intrinsic factor, liver stomach concentrate, and molybdenum).* Although all of these substances may play a role in erythropoiesis under certain circumstances, it has not been demonstrated that any of them will increase the hematologic response to iron (Ref. 44).

(iv) *Surface active agents.* Polysorbate 20 (400 mg), dioctyl sodium sulfosuccinate (150 mg), sodium laurel sulfate (200 mg), cholic acid (146 mg), and dehydrocholic acid (37 mg) do not significantly increase the absorption of iron (Ref. 50).

(3) *Adult males and postmenopausal females.* In this population, sufficient body stores of iron are theoretically maintained because daily obligatory losses of iron are balanced by iron absorption from food. Thus, unless there are unusual sources of iron loss (e.g., excessive gastrointestinal blood loss), dietary iron is generally sufficient to maintain iron nutrition in this population.

Recent nutritional surveys have raised the possibility of iron deficiency in the adult male population. Although the mean dietary intake for all adult males, aged 18 to 44, was above 10 mg, 41 percent of Blacks and 15 percent of Whites in the low-income group had intakes below the standard (10 mg). Twenty-five percent of Blacks and 15 percent of Whites with incomes above poverty level also had intakes below the standard (Ref. 51). Although 6.15 percent of males in the low-income group and 3.5 percent of males with incomes above poverty level had hemoglobin levels below 14 g/100 ml (Ref. 52), less than 2 percent had evidence of iron deficiency as measured by the iron saturation index (less than 15 percent) (Ref. 53). The Ten State Nutrition Survey did not measure dietary intakes in the population studied, but noted an unexpectedly high incidence of "low" (less than 14 g/100 ml) serum hemoglobins in this population. In the low-income-ratio States, about 20 percent of Whites, 40 percent of Blacks, and 15 percent of Spanish American adult males between 17 and 59 years of age had low serum hemoglobins. In the high-income-ratio States, about 11 percent of Whites, 30 percent of Blacks, and 20 percent of Spanish Americans had low hemoglobin levels (Ref. 54). When FAO/WHO criteria for low serum hemoglobin (less than 13 g/100 ml) are applied to these data, the incidence is reduced by approximately one-half. There was no correlation between the serum hemoglobin and serum iron or transferrin saturation in this group of males (Ref. 55). Although a high incidence of "deficient" transferrin saturaton was noted, the standard used (less than 20 percent) was much higher than the value generally accepted as indicative of iron deficiency (less than 15 of 16 percent) (Refs. 16 and 56). In view of insufficient evidence for iron deficiency in this population, there is no recommendation for an OTC iron preparation for this group.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as specifically noted below for certain target populations.

(1) The following are questionable sources of elemental iron for OTC vitamin and mineral drug products because of insufficient data demonstrating effectiveness. If it can be shown by the method of Brise and Hallberg (Ref. 45) that these sources are absorbed at least 80 percent as well as the reference standard ferrous sulfate, dried, any of these iron preparations would then be acceptable as a source of elemental iron.

(i) Ferrous citrate.
(ii) Ferric ammonium phosphate.
(iii) Ferric phosphate.
(iv) Ferric pyrophosphate.
(v) Ferrous tartrate.
(vi) Ferrous carbonate.

(2) Category I salts of iron in combination with therapeutic laxative doses of dioctyl sodium sulfosuccinate. Dioctyl sodium sulfosuccinate in combination with iron must be tested in placebo-controlled, double-blind studies to show that it improves the tolerance of the vitamin/mineral preparation without impairing its effectiveness.

(3) All category I products for men and women over 60 years of age in oral doses of 10 to 20 mg daily. The evidence for iron deficiency in a substantial portion of the geriatric population is equivocal.

Several U.S. nutritional surveys indicate that dietary iron intake may be lower than 10 mg in a significant portion of the population over the age of 59 (Refs. 18, 19, and 57). This is presumably due to the reduced caloric intake in this group (Refs. 9 and 58). In the Ten State Survey, approximately 60 to 70 percent of females over 60 years of age and 37 to 45 percent of males over 60 years of age had iron intakes of less than 10 mg (Ref. 59). These findings were generally consistent with other nutritional surveys (Refs. 18 and 57).

In the same population, approximately 20 percent of males and 6 percent of females had "low" serum hemoglobin levels (less than 14 g/100 ml for males and less than 12 g/100 ml for females) (Ref. 60). The transferrin saturation indices for persons with "low" hemoglobin levels cannot be determined from the Ten State Nutrition data. However, 50 percent of those individuals with "deficient" hemoglobin levels (less than 10 g/100 ml for females and less than 12 g/100 ml for males) had deficient transferrin saturations (less than 15 percent for females and less than 20 percent for males). The prevalance of "deficient" hemoglobin levels was generally much lower (0 to 5 percent) in this population (Ref. 60). There was also evidence for iron deficiency, i.e., deficient transferrin saturations, in approximately 5 percent of women and 15 percent of men who had "adequate" serum hemoglobin concentrations (Ref. 61). The findings of the Ten State Survey suggest that the unsatisfactory hemoglobin levels are related to inadequate dietary iron intake, but they are not conclusive.

The presence of iron deficiency in the geriatric population is also supported by a British study of 475 people over the age of 65 living at home, which found the prevalence of iron deficiency with and without anemia to be 19 percent for women and 15 percent for men. In the population studied, there was a significant association between iron deficiency and the presence of gastrointestinal lesions capable of causing blood loss or a history of chronic salicylate ingestion (Ref. 62).

The results of the Ten State Nutritional Survey were not confirmed by the preliminary Hanes report which found the overall prevalance of "low" serum hemoglobins in this population to be 8.82 percent. The overall prevalence of low transferrin saturation was 2.76 percent. Furthermore, although Blacks aged 60 years and over had the highest prevalance of low hemoglobins for any age group regardless of income level (23 to 30 percent), only 0.8 percent had low values for percent transferrin saturation. Thus, there was no indication that the low hemoglobin levels observed were primarily related to iron deficiency (Ref. 63).

On the basis of suggestive evidence for iron in this population, a preparation containing 10 to 20 mg iron may be marketed. A prevalence of 10 percent iron deficiency, defined as a percent transferrin saturation of less than 15 percent, must be demonstrated in this population within 5 years.

(4) No claims for improved gastrointestinal tolerance will be permitted until substantiated, using a double-blind, crossover study which compares bioequivalent doses of the iron preparation in question with a Category I iron preparation. The doses studied must be comparable to those recommended in this document for Category I iron preparation.

(5) All Category I products in doses of 10 to 20 mg for adolescent males (aged 12 to 17 years). The estimated iron requirements for adolescent males is 1 to 2 mg based upon a basal loss of 0.8 mg daily and a 0.6 mg daily requirement for growth and expansion of blood volume. Until recently, there have been few studies of iron nutrition in this group. The Ten State Nutrition Survey found that 16.8 percent of Whites, 30.6 percent of Blacks, and 14.3 percent of Spanish American Boys between the ages of 13 and 16 surveyed in the low-income-ratio States had serum hemoglobins of less than 12 gram percent (Ref. 64). The corresponding figures for boys surveyed in the high-income-ratio States were 9.5 percent, 25.2 percent, and 21.9 percent (Ref. 65). There was a positive correlation between serum hemoglobin and transferrin saturation in this population. However, the standard for deficient transferrin saturation was higher than that generally accepted as indicative of iron deficiency. Preliminary results of the Hanes survey show that the mean dietary iron intake for this population is 70 percent below the standard (18 mg daily) (Ref. 66). The prevalence of anemia for boys (7.9 percent) was much higher than for girls of the same age (1.9) percent, an unexpected finding which agrees with those of the Ten State Nutrition Survey (Ref. 67). Also, the percentage of low hemoglobin values were four to six times higher in Blacks than in Whites regardless of income (Ref. 68). Using the same standards as the Ten State Nutrition Survey, 7.66 percent had a "low" transferrin saturation, i.e., less than 20 percent. Although more studies are needed, preliminary data suggest that iron balance in adolescent males may be precarious. On this basis, an OTC iron preparation containing 10 to 20 mg to prevent iron deficiency is placed in Category III for 5 years. Iron nutrition studies which show that a high prevalence of anemia correlates with an iron saturation of less than 15 percent or studies which demonstrate a 10 percent prevalence of iron deficiency with or without anemia in accordance with FAO/WHO standards will be sufficient to move this preparation to Category I.

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6. *Magnesium.* The Panel's statement on magnesium includes the following ingredients: Magnesium carbonate, magnesium chloride, magnesium gluconate, magnesium hydroxide, magnesium oxide, magnesium silicate,

magnesium sulfate, and magnesium trisilicate.

a. *Description.* Elemental magnesium as found in the above magnesium preparations will be referred to as magnesium in this document. Magnesium is the fourth most plentiful cation in the body. The body contains 20 to 28 g or approximately 2,000 meq magnesium, 55 percent of which is present in bone combined with calcium and phosphorus and 27 percent in muscle. The remainder (18 percent) is distributed elsewhere in nonmuscular soft tissues and body fluids. In plasma, 55 percent exists as free magnesium. The remainder is complexed (13 percent) and protein bound (32 percent) (Refs. 1 and 2).

b. *Safety.* Since the kidney is capable of excreting 40 to 60 meq magnesium daily, hypermagnesemia rarely occurs except in persons with renal failure (Ref. 2). Central nervous system depression, anesthesia, and flaccid paralysis may occur when serum levels exceeds 8 meq/liter (96 mg/liter). In addition, profound depression of the central nervous system respiration, and of the heart may follow the parenteral administration of magnesium sulfate for the treatment of eclampsia.

c. *Effectiveness.* Magnesium is an important activator or cofactor for many enzyme systems, particularly those responsible for the energy transformation of phosphate bonds. It also plays a role in protein synthesis and in maintaining electrical potentials in the neuromuscular system.

On the basis of metabolic balance studies, magnesium requirements may be met by 0.30 to 0.35 meq/kg daily (250 to 300 mg daily for a 70 kg man) (Ref. 1). Dietary sources include cereals, nuts, seafoods, peas, beans, corn, and soybeans. Seelig (Ref. 3) reviewed the literature and concluded that occidental diets provide an average intake of 250 to 300 mg daily (10 meq or 120 mg/1,000 kcal). The range is between 150 to 480 mg magnesium daily.

Magnesium is probably absorbed in the small bowel, although absorption of magnesium from rectal enemas indicates that absorption can also occur in the colon (Ref. 1). Approximately 44 percent of magnesium is absorbed when the dietary intake is in the normal range of 250 to 300 mg (21 to 25 meq) daily. However, the extent of absorption is profoundly influenced by the nature of the diet, the dose of magnesium, and the intestinal transit time. Phosphate and calcium may hinder magnesium absorption. The latter apparently competes for a ccmmon absorptive pathway (Ref. 4). In a study of 13 subjects given magnesium orally, those receiving 22.8 mg (1.9 meq) daily absorbed 75.8 percent, while those receiving 240 mg (20 meq) daily absorbed 43.3 percent. Subjects receiving 564 mg (47 meq) daily absorbed only 23.7 percent (Ref. 1). Thus, the fraction absorbed decreases as the dose increases, although the absolute amount absorbed increases.

The kidney is the major organ of elimination. Intravenous studies have demonstrated that little endogenous magnesium is lost through the fecal route under normal circumstances (Ref. 1). The striking ability of the body to conserve magnesium has been demonstrated by deprivation experiments. Urinary excretion of magnesium falls to less than 12 mg (1 meq) daily within 4 to 6 days of magnesium restriction (Refs. 1 and 5).

Because magnesium is present in many foods, is absorbed efficiently, and is conserved by the kidneys, deficiency of this element in the normal population is essentially nonexistent.

Symptomatic deficiency in man is usually associated with a serum magnesium level that is 10 to 30 percent of normal (normal range is 1.5 to 2.5 meq/liter or 18 to 30 mg/liter). It is rarely caused by dietary deficiency alone but may occur as a complication of certain conditions as in alcoholism with malnutrition or the prolonged administration of parenteral fluids, which are usually low in magnesium. With the exception of a rare, inherited renal magnesium-wasting syndrome (Ref. 5), deficiency almost always occurs in association with factors that decrease magnesium absorption (malabsorption syndromes, steatorrhea, the concurrent administration of calcium) or increase magnesium elimination (diuretics, alcohol, diarrhea, nasogastric suction, parathyroid disorders, malignant osteolytic disease, kidney disease, hyperaldosteronism, diabetic ketoacidosis, excess vitamin D, thyrotoxicosis, and perhaps kwashiorkor) (Refs. 1, 5, and 6).

Clinically, magnesium deficiency is characterized by neuromuscular, behavioral, and cardiac disturbances, such as tetany, convulsions, ataxia, tremors, depression, irritability, and psychosis. Treatment is almost always by intramuscular or intravenous injection (Ref. 2) because oral doses above 2 g (140 meq) regularly produce an osmotic diarrhea. Also, as noted earlier, the fraction absorbed decreases following large oral doses of magnesium. Only a few cases of hypomagnesemia responding to oral magnesium supplements have been cited in the literature (Refs. 5, 7, 8, and 9).

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based on the available data, the Panel concludes that magnesium is not justified for the prevention or treatment of magnesium deficiency as an OTC mineral drug.

e. *Category I conditions under which magnesium is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which magnesium is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the category II conditions be eliminated from OTC magnesium drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that there is no rationale for the inclusion of elemental magnesium in the form of magnesium carbonate, magnesium chloride, magnesium gluconate, magnesium hydroxide, magnesium oxide, magnesium silicate, magnesium sulfate, and magnesium trisilicate in OTC drug products for the prevention or treatment of magnesium deficiency. Such a deficiency due solely to inadequate dietary intake is essentially nonexistent. When magnesium depletion occurs in association with disease, treatment by replacement is usually required by the parenteral route.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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7. *Manganese.* The Panel's statement on manganese includes the following ingredients: Manganese chloride, manganese gluconate, and manganous oxide.

a. *Description.* Manganese occurs in nature chiefly in the form of its oxides. Hydrated manganous salts are pink in color, anhydrous manganous salts are usually white, manganates are green, and permanganates form solutions which are characteristically deep purple violet. Manganese is frequently present in mineral supplements and in hematopoietic preparations, but its value in such products has yet to be demonstrated (Ref. 1).

b. *Safety.* The homeostatic mechanism for regulating the concentration of manganese in the body is very precise. Manganese is absorbed from the small intestine and is then transported via the blood in the trivalent form bound to a beta$_1$-globulin, transmanganin. Whole blood contains 1.5 to 3 μg/100 ml manganese equally divided between plasma and the red blood cells. Manganese is excreted in the bile; this constitutes the principal mechanism for regulating the amounts of manganese in the tissues. With a high manganese intake, the element is also excreted in the pancreatic juice. The amount excreted in the urine is very small. About 12 to 20 mg manganese are present in the body of a 70 kg man, but not all of this amount exists in the dynamic pool of available manganese. High levels of manganese occur in bone, liver, kidney, pancreas, and the pituitary, whereas the concentration in the skeletal muscle is very low. The manganese in bone cannot be mobilized to meet a need. The stores of managanese, in the order of their importance, are found in the liver, skin, and skeletal muscle. There is not a special store in the newborn (Ref. 2).

Chronic manganism in man has been a major industrial hygiene problem in the manganese-ore processing industry. The disease is characterized by a nonspecific, dust-related, lung disease and a progressive central nervous system affliction similar to the symptoms of Parkinson's disease (Refs. 3 and 4). Although manganese entered the body by inhalation, a considerable amount of this manganese eventually passed through the gastrointestinal tract and was absorbed (Ref. 5). Kawamura et al. (Ref. 6) reported severe manganese poisoning in 16 of 25 individuals exposed to drinking water containing 3 to 10 ppm manganese. Two deaths were reported, but the period of exposure was not specified.

c. *Effectiveness.* Manganese is an essential element for higher animals and man. Manganese deficiency in animals results in the impairment of growth, reproduction, glucose tolerance, blood clotting, proper skeletal formation, and function of the central nervous system (Ref. 4). Manganese is known to be an integral part of several enzymes, notably pyruvate carboxylase, which play important roles in mammalian metabolism. These roles involve mucopolysaccharide synthesis, sugar metabolism, and protecting the cell from the effects of destructive oxygen radicals (Ref. 2). Overt and unequivocal deficiency of manganese in man is not known, suggesting that the average dietary intake of 2.5 to 7 mg daily meets the requirement (Ref. 7). Most human foods contain measurable amounts of manganese. Cereal products, leafy fresh vegetables, nuts, and dried fruits are the richest sources (Ref. 8).

A role for manganese has been postulated in disease conditions, such as atherosclerosis (Ref. 8), severe liver disorders (Ref. 9), lupus erythematosus (L. E.) (Ref. 8), "the hydralazine (poisoning) syndrome" (Ref. 8), extrapyramidal disease (Ref. 10), and alcaptonuria (Ref. 11), but no satisfactory explanation which would be a basis for manganese therapy exists.

Hartman, Matrone, and Wise (Ref. 12) hypothesized that manganese interfered with iron absorption. Thomson and Valberg (Ref. 13) reported that both iron and manganese were absorbed to a greater extent when the other was not present in a solution used to perfuse the duodenum of rats. Pollack et al. (Ref. 14) observed incresed manganese absorption in iron deficiency. The latter observations suggested that iron and manganese have a metabolic pathway in common. Diez-Ewald, Weintraub, and Crosby (Ref. 15) also reported increased manganese absorption concomitantly with increased iron absorption in iron deficiency. However, feeding high levels of manganese (14,000 ppm) caused blood loss from the gastrointestinal tract. Moreover, the work by Borg and Cotzias (Ref. 16) suggests that manganese may also interfere with iron metabolism by replacing iron in hemoglobin. Mena et al. (Ref. 5) suggested that iron deficiency anemia played a role in an individual's susceptibility to manganese toxicity.

Although the antagonism of iron metabolism by manganese was often only achieved at high manganese concentration, the source of iron that was used in these studies was often a highly biologically available form of iron, not representative of all forms of iron usually in one's diet, and often was present in the diet at levels in excess of the requirement. There is no doubt that manganese imbalance, albeit at high levels, can resut in an alteration in iron metabolism. Whether levels of manganese two to ten times the median adult intake (10 to 50 mg daily) taken by man over a long period would contribute to the iron undernutrition due to low dietary iron intake is not known.

Chronic manganese poisoning, with severe central nervous system effects, appears long after exposure to manganese and is not necesarily associated with high tissue levels of manganese. A diagnosis of manganism is very difficult, if not impossible, in the absence of known exposure to high levels of manganese. No information is at hand regarding the risk to man of relatively high dietary intakes of manganese over a lifetime.

d. *Conclusion.* the Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that because of the potential for manganese toxicity, and in the absence of any demonstrated need for OTC drug preparations of manganese to prevent a deficiency, manganese is not generally recognized as safe or effective therapy for any disease condition.

e. *Category I conditions under which manganese is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final moniograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which manganese is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC manganese drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that, because of the potential for manganese toxicity and the absence of any demonstrated need for OTC drug preparations of manganese chloride, manganese gluconate, and manganous oxide for the prevention or treatment of deficiency, manganese is not generally recognized as safe or effective OTC therapy for any disease condition.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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8. *Phosphorus.* the Panel's statement on phosphorus includes the following ingredient: calcium phosphate dibasic.

a. *Description.* The average daily phosphorus intake of adults in the U.S. is estimated at 0.8 to 1.5 g daily (Refs. 1, 2, and 3). The primary source of calcium in the American diet is milk. Other major sources of phosphorus include poultry, fish, and meat. Nonnutritious soft drinks containing excess phosphorus in the form of phosphoric acid also serve as sources for children and adults alike. The relatively greater availability of phosphate-containing foodstuffs has resulted in a calcium/phosphate dietary ratio much lower than that recommended to maintain the integrity of skeletal tissue (Ref. 4). This matter is ot some concern since diets with low calcium/phosphorous ration have led to progressive bone loss in rats (Ref. 5), dogs (Ref. 6), and horses (Ref. 7).

The efficiency of phosphate absorption is a function of both the dietary intake and the food source (Ref. 1). Sixty to 70 percent is absorbed on a normal intake and maximal absorption (up to 90 percent) achieved on very low intakes (Ref. 8). Most, if not all, phosphorus is absorbed as free phosphates and various inorganic esters are hydrolyzed by specific intestinal phosphatases prior to absorption. The phosphate in organic phosphate esters such as phytic acid of cereals and seeds are not available to man since the human intestine lacks the enzyme, phytase, essential for hydrolysis of the organic esters. Organic phosphate ester compounds may also interfere with calcium absorption since they form insoluble calcium salts within the intestinal lumen (Ref. 9). In animals, certain substances, i.e., unsaturated fatty acids, iron, and aluminum, intefere with intestinal phosphate absorption (Refs. 10, 11, and 12). Vitamin D increases intestinal phosphate absorptionin certain animal species (Ref. 13). A direct effect of vitamin D or its biologically active metabolites on phosphate absorption in man is still to be adequately defined. There is no known effective physiological mechanism regulating the intestinal absorption of phosphorus in man; the control of phosphate economy is achieved primarily by variations in dietary intake and renal excretion (Ref. 14). Fecal phosphorus represents both unabsorbed phosphorus and that secreted into the gastrointestinal tract. In man, with phosphorus intakes of approximately 1 to 1.5 g daily, the endogenous secretion of phosphate into the intestinal lumen is 3 mg/kg daily (Ref. 8). Dietary phosphorus is absorbed to a greater extent than calcium and consequently the renal excretion of phosphorus is much greater than that of calcium (Ref. 14).

With normal renal function, urinary phosphorus usually amounts of variation in phosphate clearance occurs with the usual pattern, that of a matutinal increase in urinary phosphorus-creatinine ratios. this circadian rhythm is related to physical activity with the nadir appearing a few hours after the end of sleep. The loss of diurnal variation in adrenal insufficiency states and the documented inverse correlation between phosphate excretion and plasma cortisol levels suggest that this rhythm is also controlled by the adrenal glands (Refs. 15, 16, and 17).

In man, the tubular reabsorption of phosphate cleared by the glomeruli is normally 85 to 95 percent (Ref. 14). This process is rate-limited with an upper limit of maximum tubular reabsorptive capacity of 4 to 8 milligrams/minute (mg/min). The tubular resorption of phosphate is increased by cortisol (physiological levels) and growth hormone, and decreased by digoxin, estrogen, parathyroid hormone, and pharmacological levels of cortisol or structurally related synthetic analogues (Refs. 14 through 18). The renal tubular reabsorption of filtered phosphorus is also decreased by elevations in serum calcium (Ref. 19).

b. *Safety.* Since the kidney is capable of excreting 600 to 900 mg phosphorus daily, hyperphosphatemia is rare in the absence of chronic renal disease and then only when the glomerular filtration rate falls below 20 milliliters/minute (Ref. 14). Hyperphosphatemia is also characteristic of disorders of parathyroid secretion and metabolism such as hypoparathyroidism and pseudohypoparathyroidism (Ref. 20) and can be accentuated by phosphate feeding. There are no specific signs or symptoms of hyperphosphatemia per se, although the hypocalcemia often associated with the hyperphosphatemia can result in enhanced neuroexcitability, tetany, and convulsions (Ref. 20). Chronic phosphate feeding induces secondary hyperparathyroidism and soft tissue calcification in dogs (Ref. 21), and may stimulate secondary hyperparathyroidism in man (Ref. 22).

c. *Effectiveness.* Of the 11 to 14 g phosphate per kg fat-free tissue in the normal adult, 85 percent is in the skeleton. The remainder is distributed between tissue and membrane components of skeletal muscle, skin, nervous tissue, and other organs. Whereas most of the phosphorus in soft tissue and cell membranes is in the form of organic esters, almost all of the phosphorus in bone is contained in the mineral phase as inorganic orthophosphate and small amounts of inorganic pyrophosphate. The regulation of plasma phosphate is not as readily explained as that of plasma calcium, since not only is the circulating phosphate in equilibrium with skeletal and cellular inorganic phosphate, but also with a large number of organic compounds which result from cellular metabolism. The phosphate ion is essential for the metabolism of carbohydrate, lipids, and protein via the intermediation of a multitude of enzyme systems and the metabolic potential of so-called "high energy phosphate" compounds. Phosphate also functions to modify acid-base equilibrium in plasma and within cells, and also plays

a fundamental role in modifying the development and maturation of bone, in the renal excretion of hydrogen ions, and in modifying the effect of the B-vitamins. In the human adult, serum inorganic phosphate ranges between 2.5 to 4.4 mg/dl, with a mean of 3.5 mg/dl. Dietary phosphate, stage of growth and age, time of day, hormonal interplay, and renal function all contribute to the variability of the fasting serum phosphate concentration.

Eighty-eight percent of the plasma phosphate is unfilterable, some of which is complexed with mono or divalent cations such as sodium^{+}, calcium^{++}, and magnesium^{++}. At normal Blood pH, 85 percent of the ultrafilterable phosphate is in the form of HPO_4^{-2}, the remainder existing mainly as $H_2PO_4^{-}$.

The concentratin of plasma phosphate varies with age. In prepubertal children, the main values for circulating phosphate approximates 5 to 6 mg/dl. Normal adult human values are gradually approached by the third decade after which plasma phosphate decreases progressively between ages 20 and 40 years and begins to rise in females in the postmenopausal period.

With the exception of young infants, the recommended allowance of phosphorus daily is the same as that of calcium, although the calcium/phosphorus ratio of diets ingested through the world today is reportedly less than 0.75 (Refs. 4, 23, and 24). The calcium/phosphorus ratio of cow's milk is 1.3/1 as compared with a calcium/phosphorus ratio of 2/1 in breast milk (Ref. 23). A high phosphate/calcium ratio may contribute to the syndrome of idiopathic hypocalcemia and tetany of infants on formula feeding.

Phosphorus depletion in man, a syndrome characterized by weakness, anorexia, malaise, and skeletal aches can occur during prolonged and excessive intake of nonabsorbable antacids. Specific abnormalities such as hemolytic anemia, granulocyte dysfunction, and erythrocyte glycolysis also result from phosphate depletion (Refs. 25, 26, and 27). The syndrome has been experimentally produced in man and is readily reversed when the medication is discontinued and sufficient amounts of dietary phosphorus are consumed (Refs. 28 and 29). Its frequency in the very large population of individuals ingesting antacids is unknown, but is probably rare based on the infrequency of published reports of this complication. Recognition and appropriate therapy require medical supervision, particularly when adjustments in drug therapy for peptic ulcer are involved.

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that phosphorus for the prevention or treatment of phosphorus deficiency is not justified as an OTC mineral drug preparation.

e. *Category I conditions under which phosphorus is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which phosphorus is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC phosphorus drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that there is no rationale for the inclusion of calcium phosphate dibasic in OTC drug preparations for the prevention or treatment of deficiency since phosphate deficiency is virtually nonexistent.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Cateory I.

None.

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9. *Potassium.* The Panel's statement on potassium includes the following ingredients: potassium chloride, potassium gluconate, and potassium sulfate.

a. *Description.* Potassium is the principal intracellular cation. The average 70 kg adult body contains approximately 3,500 meq (140 g) potassium. Of this total, 65 meq (2.6 g) occurs in the extracellular fluid. The remainder occurs primarily in the muscle (3,000 meq or 120 g), liver (200 meq or 8 g), and red cell mass (235 meq or 10 g) (Refs. 1 and 2). In healthy individuals, better than 90 percent of the daily input of potassium is excreted in the urine. The residue appears in the sweat and feces. Elimination through sweat is significant only in the tropics where potassium levels approach those of sodium. Although potassium loss in the feces can be significant, amounting to 5 to 10 meq daily (200 to 400 mg daily) in healthy individuals, the kidney serves as the main organ for potassium elimination. Filtered potassium is virtually completely reabsorbed in the proximal convoluted tubule. The majority of urinary potassium is accounted for by active secretion in the distal tubule in exchange for sodium under the influence of aldosterone.

b. *Safety.* Hyperkalemia (plasma levels in excess of 4 meq/liter) may be caused by acute or chronic renal failure, shock, massive tissue injury, severe metabolic or respiratory acidosis, adrenal insufficiency, accelerated catabolic state, and gastrointestinal hemorrhage. Although it is capable of causing severe muscle weakness and pain, hyperkalemia's chief danger is cardiac arrest. Typical electrocardiographic changes include prolongation of the PR interval, peaking of the T waves, and prolongation of the QRS complex.

Under normal circumstances, hyperkalemia is an uncommon event because the kidney is able to excrete large potassium loads. Daily amounts of potassium in excess of 5 meq/kg (500 meq) have been ingested chronically in divided doses without evidence of intoxication. On the other hand, even the normal kidney has a limited capacity for handling large single doses of potassium. Doses of 1.0 meq/kg or 40 mg/kg may increase the serum potassium by as much as 1 meq/liter and doses of 2 to 2.5 meq or 80 to 100 mg/kg may produce serum potassium levels of 6 to 8 meq/liter (Ref. 3).

Since the kidney is the principal organ of elimination, patients with renal failure are predisposed to hyperkalemia. Although patients with chronic severe uremia (blood urea nitrogen greater than 100 mg percent) are frequently able to eliminate the usual daily intake of potassium as evidenced by normal or slightly elevated serum potassium, their ability to excrete an acute load of this ion is clearly abnormal. Three hours following a dose of 1 meq/kg, 4 to 39 percent of the potassium appears in the urine in contrast to 49 to 100 percent in normal subjects. Also, the serum concentration may increase by 1.5 to 3.5 meq/liter resulting in cardiac toxicity (Ref. 3).

The consumption of potassium in the form of concentrated salts has been shown to cause irritation and even destruction of tissues in the gastrointestinal tract.

Enteric coated tablets of potassium chloride containing approximately 8 meq have been associated with a number of cases of intestinal ulceration and obstruction (Ref. 4).

c. *Effectiveness.* Potassium is absorbed efficiently in the jejunum and ileum when the concentration exceeds 5 to 6 meq/ml (200 to 300 mg). In humans, absorption is not influenced by the presence of sodium or the direction of movement of water (Ref. 5).

The normal diet provides 50 to 150 meq potassium daily (Refs. 1 and 6). Food tables show that animal and vegetable foods contain significant quantities of potassium making it difficult to design a calorically adequate diet which is low in potassium (Ref. 1).

The serum potassium concentation is frequently a poor indicator of total body stores. Hypokalemia (plasma levels less than 3.5 meq/liter) is generaly consistent with total body potassium depletion. However, the latter may frequently be accompanied by a normal or even high serum potassium concentration, e.g., in end-stage uremia and in diabetic ketoacidosis. The presence or absence of signs and symptoms of hypokalemia, however, is related to serum potassium concentration (Ref. 7). These include lethargy, irritability, decreased deep tendon reflexes, tetany, paresthesias, muscle weakness, paralytic ileus, and electrocardiographic changes which include depression of the ST segment, prolongation of the QRS complex, and U waves. Hypokalemia also increases the sensitivity of the myocardium to the toxic effects of digitalis.

A renal conservation mechanism for potassium has been demonstrated in deprivation states which is relatively inefficient and certainly not absolute (Refs. 1 and 3). Renal absorption during potassium deprivation is sluggish. On diets of 15 to 20 meq (600 to 800 mg) potassium daily the 24-hour urine potassium of normal subjects decreases to 20 to 25 meq (800 to 1,000 mg) after 1 week and to 10 to 15 meq daily (400 to 600 mg) in 2 weeks. A total body potassium deficit of 8 to 10 percent (250 to 300 meq or 10 to 12 g) occurs prior to the attainment of equilibrium. Following prolonged, severe potassium deprivation, the 24-hour urine potassium may reach levels as low as 3 to 5 meq/liter (120 to 200 mg/liter). A low sodium diet enhances the ability of the kidney to conserve potassium (Ref. 3) and high sodium intake stimulates potassium excretion.

Hypokalemia is generaly associated with conditions in which there are substantial extrarenal or excessive renal losses of potassium. It is rarely caused by decreased intake alone. Several review articles on hypokalemia (Refs. 1, 2, 8, 9, and 10) discuss its association with one or more of the following conditions: (1) Decreased intake together with obligatory potassium losses in anorexic and comatose patients, and in alcoholics (low serum potassium observed in 10 of 30 alcoholics in one study) (Ref. 11);

(2) Excessive gastrointestinal losses due to emesis, laxative abuse, diarrhea, prolonged nasogastric suction, and fistulas. Diarrhea is the major cause of hypokalemia in children (Ref. 12);

(3) Excessive renal losses as a result of diuretics, renal tubular acidosis, metabolic alkalosis, excessive adrenal corticosteroids, surgery, consumption of significant quantities of licorice (greater than 100 g daily); and

(4) Redistribution of serum potassium due to alkalosis or the administration of insulin with or without glucose.

Potassium depletion is rarely associated with dietary insufficiency except, perhaps, in the alcoholic. Indeed, even with the provocation of diuretic therapy, dietary sources of potassium are generally sufficient to cover the increased loss (Refs. 9 and 10) so that potassium supplementation is not routinely indicated. When potassium supplementation is indicated, a dose of 40 to 100 meq (1.6 to 4.0 g) potassium daily readily corrects the hypokalemia in adults (Ref. 10). Since laboratory tests are required to establish the diagnosis of hypokalemia and to assess the effectiveness of therapy, OTC drug use of potassium is unwarranted.

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that potassium for the prevention or treatment of potassium deficiency is not justified as an OTC mineral drug preparation.

e. *Category I conditions under which potassium is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30

days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which potassium is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC potassium drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that, in general, dietary sources provide more than adequate amounts of potassium. Although potassium depletion may be a frequent complication of diuretic use and alcoholism, the need for supplementation in these situations should be assessed by a physician. Routine supplementation with small amounts of potassium is not indicated. For these reasons there is no justification for the inclusion of potassium chloride, potassium gluconate, or potassium sulfate in any OTC drug preparation for the prevention or treatment of potassium deficiency.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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10. *Zinc.* The Panel's statement on zinc includes the following ingredients: zinc carbonate, zinc chloride, zinc gluconate, zinc hydroxide, zinc lactate, zinc oxalate, zinc oxide, zinc phytate, zinc sulfate, and zinc sulfide.

a. *Reference form.* Dosages recommended in this document for zinc are based on elemental zinc (Zn, molecular weight 65.4).

b. *Description.* Zinc is a part of at least 18 enzymes and enzyme cofactors, including alkaline phosphatase and alcohol dehydrogenase (Ref. 1). It is involved in protein synthesis and nucleic acid synthesis (Ref. 2). The mobilization of vitamin A from the liver into the plasma requires zinc (Ref. 3).

Zinc is distributed in bone (20 percent), muscle (63 percent), blood (2 percent), and other organs (Ref. 4), totaling about 2.2 g in the body (Refs. 4 and 5). Zinc is excreted from the body via the feces, urine, and skin (Refs. 6, 7, and 8). The pancreatic contribution to fecal excretion is estimated to be about 1.5 mg daily in adults (Ref. 7). Urinary losses of zinc average 0.5 mg daily. As much as 1 mg zinc/liter sweat may be lost (Ref. 8). In hot and arid climates, this rate of loss could be a significant drain on the body economy. Dermal losses under normal conditions may average 2.8 mg daily (Ref. 9). Total menstrual loss of zinc is only 0.3 to 0.6 mg per menses (Ref. 10). A daily turnover of 6 mg zinc can be calculated from radioisotope studies (Refs. 11 and 12).

c. *Safety.* In humans, daily therapeutic doses of zinc have been used ranging from 33 to 44 mg elemental zinc, i.e., from 3.3 to 4.4 times the RDA for children (Ref. 13), to 150 mg elemental zinc or 10 times the RDA for adults (Refs. 14 through 21). The only side effects reported for time periods of up to 6 months were occasional mild nausea and mild diarrhea. The most careful studies of possible subtle side effects were by Greaves and Skillen (Ref. 16) and Czerwinski (Ref. 18), who reported no evidence for hematological, hepatic, or renal toxicity as assessed by a number of biochemical parameters in patients treated with zinc sulfate (10 times the RDA) for 4 to 6 months.

(1) *Acute zinc toxicity.* Zinc sulfate is sometimes used as an emetic, as vomiting occurs after the ingestion of 1 to 2 g zinc sulfate, i.e., 225 to 450 mg elemental zinc (Ref. 22). Other symptoms of zinc toxicity are fever, nausea, stomach cramps, and diarrhea in 3 to 12 hours following ingestion (Ref. 23).

Death has been reported after consumption of 6 g zinc as zinc sulfate in an adult woman. Complications included hemorrhagic pancreatitis and severe renal damage (Ref. 24). Intervention of hemodialysis (Ref. 25) or chelation therapy (Ref. 26) probably prevented death in two other cases. In the former, an unknown quantity of metallic zinc was dissolved in hydrocholoric acid and swallowed by an adult male alcoholic. This resulted in diarrhea, weakness, vomiting, severe epigastric pain, jaundice, and severe renal failure of greater than 4 days duration, then partial renal failure for an additional 15 days. In the second case, 4 g metallic zinc on day 1 and 8 g on day 2 were consumed by a 16-year-old boy. Mental and muscular incoordination were reported. Many cases of acute toxicity occur after food or drink is prepared or stored in galvanized vessels (Ref. 23).

The severely toxic zinc levels in the above cases appear to be about 400 times the Recommended Dietary allowances of 15 mg zinc established by the Food and Nutrition Board, NAS/NRC (Ref. 27).

(2) *Chronic zinc toxicity.* A review of studies by Van Reen (Ref. 23), Bremner (Ref. 28), and Calhoun, Smith, and Becker (Ref. 29) indicates that in rats, zinc is toxic when present in the diet at 0.5 to 1.0 percent levels over many weeks. This represents 100 to 200 times normal requirements.

Many of the toxic effects of zinc result from its interaction with other essential elements, primarily copper, iron, and calcium (Refs. 23, 28, and 29). The mineral imbalance caused by excessive levels of zinc results in both direct and indirect disturbances in the absorption and metabolism of these minerals.

Whether long-term superoptimal levels of zinc consumption are hazardous or not has been the subject of recent reports (Refs. 30 and 31). Based on epidemiological evidence supported by preliminary animal experiments, Klevay (Ref. 31) proposes the hypothesis that a high ratio of zinc to copper intake predisposes to coronary heart disease, perhaps by a metabolic effect on cholesterol metabolism.

d. *Effectiveness.* The relative availability of various zinc salts has been studied by the chick growth assay technique. Zinc oxide, carbonate, chloride, and zinc metal were as available as zinc sulfate, even though their solubilities in water are quite different (Refs. 32 and 33). Zinc sulfide was not nutritionally available. No such studies have been reported in humans. Food generally decreases the availability of zinc salts. The ultimate absorption of zinc is determined by the inter-

action of many factors. It is known that phytate (inositol hexaphosphate) is abundant in grains, nuts, and legumes. High phytate consumption by animals or humans results in an increased zinc requirement to maintain balance (Refs. 34, 35, and 36). Calcium in the presence of phytate lowers the availability of zinc (Ref. 37). Other dietary components can complex zinc to form insoluble or unabsorbable ligands. Reinhold, Ismail-Beigi, and Faradji (Ref. 38) have recently shown fiber to be as important as phytate in this respect. Whole grain foods are rich in both. Phosphate salts given at the same time as zinc sulfate can reduce its absorption, and phosphate in the form of milk does so to a greater extent (Ref. 39). Pecoud, Donzel, and Schelling (Ref. 39) measured serum zinc levels as an indication of relative absorption. A 25-mg zinc dose gave about one-half the response of a 50-mg dose, providing the subject was fasting. Taking zinc sulfate with milk, cheese, brown bread, or coffee reduced serum zinc response by at least 43 percent. Meat had no effect.

Research on human requirements for zinc from Western diets recently has been reviewed (Refs. 40 and 41). Although experimental design and assay techniques vary widely, in no instance is negative balance observed in adults when greater than 18 mg dietary zinc is consumed daily (Ref. 41). Negative balance occurs at an intake of 5 to 6 mg daily (Ref. 41). It appears that zinc sufficiency is achieved at an intake of 8 to 10 mg daily (Ref. 41). There are no balance studies of adolescents, lactating women, or the elderly. In pregnancy, positive zinc balance may require 26 to 29 mg daily (Ref. 9). It is yet unexplained why infants consuming breast milk have a negative zinc balance, losing more than 1 percent total body zinc daily (Ref. 42). The loss may be even greater if the mother's milk is low in zinc. Animal studies show that maternal dietary zinc deficiency resulted in zinc deficiency of the offspring due to lowered zinc content of the milk (Ref. 43). Zinc availability in the postweaning diet may be critical in reversing this trend. Unfortunately no data are available.

A recent study of the zinc content of typical meals served in a hospital showed a range of 7 to 16 mg zinc daily. The average was 11.3 mg zinc daily (Ref. 44). Higher zinc content was associated with the higher protein diet, reflecting the fact that foods highest in zinc are meat, eggs, milk products, and shellfish. The more vegetarian diet found in North China supplies an estimated 9.5 mg zinc daily (Ref. 45). Assuming that 20 to 30 percent of dietary zinc is absorbed, Sandstead reviewed data which indicate that many groups of people in the United States are consuming diets marginal to deficient in zinc (Ref. 40).

Discussion of zinc deficiency in the U.S. necessitates review of techniques for assessing zinc deficiency. Currently metabolic balance studies, isotope turnover studies, plasma zinc levels, urinary zinc excretion, hair zinc content, and taste acuity are being used. No technique has been demonstrated to provide direct evidence of zinc deficiency. The critical test remains a definitive response to oral supplementation with zinc under controlled conditions (Ref. 41).

Evidence that marginal zinc deficiency does occur is presented in the work of Henkin and Bradley, (Ref. 46), Henkin et al. (Ref. 47) and Schechter et al. (Ref. 48), who find that a decrease in taste/smell acuity may be corrected by zinc administration. Hambidge et al. (Ref. 49) reported that of 10 children living in the Denver area and having low hair zinc concentration, 7 had poor appetites, 8 had heights below the tenth percentile (Harvard growth charts), and 5 of 6 showed lowered taste acuity. After 1 to 3 months of daily dietary zinc supplementation (1 to 2 mg/kg zinc sulfate), taste acuity returned to normal and hair zinc increased in 5 of the 10 children. The children were drawn from a group of 338 upper- and middle-class Caucasians.

Hallbook and Lanner (Ref. 19) treated leg ulcer patients with zinc. One group had initial serum zinc levels of less than 110 μg percent and the other had initial levels greater than 110 μg percent. Those with low serum zinc had slower healing, and this defect was corrected by 600 mg zinc sulfate daily. Pories et al. (Ref. 15) also found shortened healing time in surgical patients when zinc sulfate was given orally. It appears that zinc supplements do not accelerate wound healing unless there has been previous depletion of this element.

Abnormally high urinary zinc levels are observed in alcoholics (Ref. 50), and such patients are a higher risk population for zinc deficiency. Fasting obese patients have up to 10-fold increases in urinary zinc but no change in plasma levels and a cumulative loss of 10 to 15 percent of total body zinc. High urine zinc levels are seen in renal disease, diabetes, liver disease, porphyria, proteinuria, trauma, and kwashiorkor (Refs. 51 and 52).

Zinc depletion has been associated with the use of various drugs, including histidine (Ref. 53), penicillamine (Ref. 54), phenytoin (Ref. 55), thiamazole (Ref. 56), and thiazides (Ref. 57).

Human dietary zinc deficiency has been documented in the Middle East (Refs. 57 through 64). Dwarfs with extreme iron deficiency anemia and retarded sexual development responded to treatment with zinc sulphate by growth and sexualfunctioning. Studies by Ronaghy et al. (Refs. 65 and 66) suggest that less severe zinc deficiency might contribute to short stature with delayed puberty. Clinical deficiency states are associated with low levels of zinc in hair as well as plasma zinc (Ref. 67).

Zinc deficiency may occur in association with other diseases. Caggiano et al. (Ref. 68) reported a case of zinc deficiency occurring secondary to intestinal malabsorption, recurrent infection, and hypogammaglobulinemia. Again, retarded growth and hypogonadism were seen, both responsive to zinc supplementation.

Zinc deficiency might be expected in many other types of generalized malabsorption. The low plasma zinc levels and reduced taste acuity observed in celiac sprue and regional enteritis (Refs. 69 and 70) imply possible deficiency in these diseases. One severe case of deficiency in regional enteritis, responsive to zinc therapy, was reported by Sandstead (Ref. 40).

Clinical and biochemical indications of zinc deficiency are found to accompany sickle cell disease. In controlled studies of patients with sickle cell anemia complicated by leg ulcers, those treated with zinc sulfate had a healing rate that was three times faster than the placebo group (Ref. 14). Prasad et al. (Ref. 20) observed hypogonadism and growth retardation in a group of 36 patients with sickle cell anemia. Those treated with oral zinc sulfate responded by weight gain and in some cases by growth and sexual development. Plasma zinc in sickle cell disease is below normal (Refs. 20 and 71) as is erythrocyte and hair zinc. Urinary zinc excretion is elevated, probably associated with increased hemolysis in this disease.

Moynahan (Ref. 13) reported in 1974 that in infants suffering from acrodermatitis enteropathica, treatment with zinc led to complete clearance of skin lesions and restored normal bowel function. Malabsorption is thought to be one of the defects in zinc metabolism leading to zinc deficiency in this disease (Ref. 72). The effectiveness of zinc treatment has been confirmed by others (Refs. 73 through 77).

In patients with acrodermatitis enteropathica who became pregnant, there were, out of the seven pregnancies reported, one abortion and two major congenital malformations (Ref. 78). The malformations were similar to those seen in the offspring of zinc-deficient rats. Zinc deficiency in animals need only be transient to have teratogenic effects on the fetus. Burch, Hahn, and Sullivan review a wealth of additional circumstantial evidence which strongly suggests that zinc deficiency in pregnant humans

may result in congenital anomalies (Ref. 7).

Cohen, Schechter, and Henkin reported that in 19 patients with second and third degree burns, 84 percent showed decreased taste acuity (Ref. 79). Of these, the serum zinc was decreased and urinary zinc was elevated compared to 150 controls. Carr and Wilkinson (Ref. 80) also found persistent, highly elevated urinary zinc in severely burned children. A substantial decrease in tissue zinc following thermal injury has been reported (Ref. 31).

Recently, in a controlled study, 220 mg zinc sulfate given three times daily improved joint pain and stiffness in a group of patients with rheumatoid arthritis (Ref. 21). This promising observation requires confirmation with further attention to the zinc status of patients and the long-term effects of therapy.

Use of zinc in the management of conditions such as acrodermatitis enteropathica, sickle cell disease, and rheumatoid arthritis requires the direct supervision of a physician. Zinc is therefore not appropriate for OTC use.

e. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based on the available data, the Panel concludes that zinc sulfate, in the dosage identified under Category I conditions below, is the only acceptable source of elemental zinc which is safe and effective for the prevention of zinc deficiency when the need for such therapy has been determined by a physician.

f. *Category I conditions under which zinc is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

Zinc sulfate is the only zinc source which may be used as a Category I source of zinc. Dosage must be based on elemental zinc (Zn, molecular weight 65.4).

(1) *Dosage—For prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 10 to 25 mg daily. For pregnant and lactating women, the oral dosage is 25 mg daily. For children under 1 year of age, the Panel recommends the advice and supervision of a physician.

(2) *Labeling.* The Panel recommends the following Category I labeling:

Indication—For prevention of deficiency. "For use in the prevention of zinc deficiency when the need for such therapy has been determined by a physician."

g. *Category II conditions under which zinc is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC zinc drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that the effectiveness of zinc hydroxide, zinc oxalate, zinc phytate, and zinc sulfide is not supported by the scientific evidence because absorption of these salts is not substantiated. Zinc depletion associated with sickle cell anemia, acrodermatitis enteropathica, celiac disease, and other gastrointestinal disorders should be diagnosed and managed directly under a physician's continuing care, and OTC zinc preparations for those purposes are not safe and appropriate. Similarly, self-medication with zinc for leg ulcers or rheumatoid arthritis should not be attempted, despite preliminary reports suggesting that zinc may be useful in treating those conditions. Leg ulcers and rheumatoid arthritis require diagnosis and management by a physician, not OTC management.

h. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

There are insufficient data to establish the safety or effectiveness of zinc carbonate, zinc chloride, zinc gluconate, zinc lactate, and zinc oxide.

Data to demonstrate bioavailability or isotope absorption tests are required to show serum zinc elevation greater than 80 percent of that of zinc sulfate as a single ingredient and when combined with vitamins and minerals.

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The Food and Drug Administratin has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 345, to read as follows:

PART 345—VITAMIN AND MINERAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—[Reserved]

Subpart D—Labeling

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 345.1 Scope.

An over-the-counter vitamin and mineral drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 345 in addition to each of the general conditions established in § 330.1 of this chapter.

§ 345.3 Definitions.

(a) *Vitamin drug.* An agent which is essential in small amounts for the maintenance of normal metabolic functions but is not synthesized within the body and, therefore, must be furnished from exogenous sources and that is labeled for use in the prevention or treatment of a deficiency when the need for such therapy has been determined by a physican.

(b) *Mineral Drug.* An agent, or its salts, which is noncombustible and inorganic and remains in the "ash" after combustion of natural materials at a high temperature and that is labeled for use in the prevention or treatment of a deficiency when the need for such therapy has been determined by a physican.

Subpart B—Active Ingredients

§ 345.10 Vitamin active ingredients.

The active ingredients of the product consist on one or more of the following when used within the dosage for each ingredient identified in § 345.50(d):

(a) *Vitamin C.* Acceptable sources of vitamin C activity are ascorbic acid, ascorbyl palmitate, calcium ascorbate, niacinamide ascorbate (for use only in combinations requiring both niacin and vitamin C), and sodium ascorbate: *Provided,* That the dosage identified in § 345.50(d)(1) or (2) is based on the *L*-ascorbic acid equivalent ($C_6H_8O_6$, molecular weight 176.2).

(b) *Vitamin B–12.* Cyanocobalamin is only acceptable source of vitamin B-12 activity: *Provided,* That the dosage identified in § 345.50(d)(3) is based on the cyanocobalamin equivalent ($C_{63}H_{88}CoN_{14}O_{14}P$, molecular weight 1355.4).

(c) *Folacin.* Folic acid is the only acceptable source of folacin activity: *Provided,* That the dosage identified in § 345.50(d)(4) is based on the pteroyl mono-*L*-glutamic acid equivalent ($C_{19}H_{19}N_7O_6$, molecular weight 441.4).

(d) *Niacin.* Accpetable sources of niacin activity are niacinamide and niacinamide ascorbate: *Provided,* That the dosage identified in § 345.50(d)(5) or (6) is based on the niacinamide equivalent ($C_6H_6N_2O$, molecular weight 122.1).

(e) *Pantothenic acid.* Accpetable sources of pantothenic acid activity are calcium pantothenate, dexpanthenol, and panthenol: *Provided,* That the dosage identified in § 345.50(d)(7) is based on the *D*-pantothenic acid equivalent ($C_9H_{17}NO_5$, molecular weight 219.2): *And provided,* That pantothenic acid is not used as a single active ingredient drug product but may be used only in combinations identified in § 345.20(a)(1), (2), (3), (4), (5), (6), (7), (b)(1), (2), and (3).

(f) *Vitamin B–6.* Pyridoxine hydrochloride is the only acceptable source of vitamin B–6 activity: *Provided,* That the dosage identified in § 345.50(d)(8) or (9) is based on the pyridoxine hyrochloride equivalent ($C_8H_{12}ClNO_3$, molecular 205.6).

(g) *Riboflavin.* Acceptable sources of riboflavin activity are riboflavin and riboflavin-5-phosphate sodium: *Provided,* That the dosage identified in § 345.50(d)(10) or (11) is based on the riboflavin equivalent ($C_{17}H_{20}N_4O_6$, molecular weight 376.4).

(h) *Thiamine.* Acceptable sources of thiamine activity are thiamine hydrochloride and thiamine mononitrate: *Provided,* That the dosage identified in § 345.50(d)(12) or (13) is based on the thiamine chloride hydrochloride equivalent ($C_{12}H_{17}ClN_4OS.HCl$, molecular weight 337.3).

(i) *Vitamin A.* Acceptable sources of vitamin A activity are vitamin A, vitamin A acetate, and vitamin A palmitate: *Provided,* That the dosage identified in §345.50(d)(14) or (15) is based on the retinol equivalent expressed in international units ($C_{20}H_{30}O$, molecular weight 286.4 and 0.3 microgram retinol is equivalent to 1.0 international unit).

(j) *Vitamin D.* Acceptable sources of vitamin D activity are cholecalciferol and ergocalciferol: *Provided,* That the dosage identified in § 345.50(d)(16) is based on either the cholecalciferol equivalent ($C_{27}H_{44}O$, molecular weight 384.6) expressed in international units or the ergocalciferol equivalent ($C_{28}H_{44}O$, molecular weight 396.6) expressed in international units (0.025 microgram vitamin D is equivalent to 1.0 international unit).

(k) *Vitamin E.* Acceptable sources of vitamin E activity are tocophersolan, alpha-tocopheryl acetate, alpha-tocopheryl acid succinate, and vitamin E: *Provided,* That the dosage identified in § 345.50(d)(17) is based on the *dl*-alpha-tocopheryl acetate equivalent expressed in international units ($C_{31}H_{52}O_3$, molecular weight 472.7 and 1 milligram *dl*-alpha-tocopheryl acetate is equivalent to 1.0 international unit): *And provided,* That vitamin E is not used as a single active ingredient drug product but may be used only in combinations identified in § 345.20(a)(1), (5), (6), (7), and (b)(1).

§ 345.12 Minerals.

The active ingredients of the product consist of one or more of the following when used within the dosage for each ingredient identified in § 345.70(d):

(a) *Calcium.* Acceptable sources of calcium are calcium caseinate, calcium citrate, calcium glubionate, calcium gluconate, calcium lactate, calcium phospahte dipasic, calcium sulfate, and precipitated calcium carbonate: *Provided* That the dosage identified in § 345.70(d)(1) is based on elemental calcium (Ca, molecular weight 40.1).

(b) *Iron.* Acceptable sources of iron are ferroglycine sulfate; ferrous fumarate; ferrous glutamate; ferrous gluconate; ferrous succinate; and ferrous lactate; and ferrous sulfate, dried: *Provided,* That the dosage identified in § 345.70(d)(2) is based on elemental iron (Fe molecular weight 55.8). The iron content of a product must be labeled in terms of elemental iron.

(c) *Zinc.* Zinc sulfate is the only acceptable source of zinc: *Provided,* That the dosage identified in § 345.70(d)(3) is based on elemental zinc (Zn, molecular weight 65.4).

§ 345.20 Permitted combinations of active ingredients.

The combination product may consist of any of the following:

(a) *Combinations for prevention of deficiency.* (1) All Category I vitamin ingredients identified in § 345.10 may be combined within the recommended dosage ranges for the prevention of deficiency identified in § 345.50(d). This combination may additionally contain pantothenic acid identified in § 345.10(e) within the dosage range identified in § 345.50(d)(7) and/or vitamin E identified in § 345.10(k) within the dosage identified in § 345.50(d)(17).

(2) All Category I B-vitamin ingredients identified in § 345.10 (b), (c), (d), (f), (g), and (h) may be combined within the recommended dosage ranges for the prevention of deficiency identified in § 345.50(d). This combination may additionally contain pantothenic acid identified in § 345.10(e) within the dosage range identified in § 345.50(d)(7).

(3) All Category I B-vitamin ingredients identified in § 345.10 (b), (c), (d), (f), (g), and (h) may be combined with vitamin C identified in § 345.10(a) all within the recommended dosage ranges for the prevention of deficiency identified in § 345.50(d). This combination may additionally contain pantothenic acid identified in § 345.10(e) within the dosage range identified in § 345.50(d)(7).

(4) Any combination identified in subparagraphs (1), (2), or (3) of this paragraph may be combined with iron identified in § 345.12(b) within the dosage range for prevention of deficiency identified in § 345.70(d)(2): *Provided,* That the combination is labeled for the prevention of vitamin and iron deficiencies.

(5) Any combination identified in subparagraph (1) of this paragraph may be combined with zinc identified in § 345.12(c) within the dosage range identified in § 345.70(d)(3). This combination may additionally contain iron identified in § 345.12(b) within the dosage range identified in § 345.70(d)(2) and/or calcium identified in § 345.12(a) within the dosage range identified in § 345.70(d)(1): *Provided,* That the combination is labeled for the prevention of vitamin and zinc (iron and/or calcium) deficiencies.

(6) Any combination identified in subparagraph (1) of this paragraph may be combined with calcium identified in § 345.12(a) within the dosage range identified in § 345.70(d)(1). This combination may additionally contain iron identified in § 345.12(b) within the dossage level identified in § 345.70(d)(2) and/or zinc identified in § 345.12(c) within the dosage range identified in § 345.70(d)(3): *Provided,* That the combination is labeled for the prevention of vitamin and calcium (iron and/or zinc) deficiencies.

(7) All Category I vitamin ingredients identified in § 345.10 may be combined with zinc identified in § 345.12(c) for prevention of deficiency in persons who use alcohol to excess, provided all ingredients are present at dosage levels for treatment of deficiency identified in § 345.50(d) or at the maximum dosage level for prevention of deficiency identified in § 345.50(d) or § 345.70(d) when dosage levels for treatment of deficiency have not been specified. This combination may additionally contain pantothenic acid identified in § 345.10(e) within the dosage range identified in § 345.50(d)(7) and/or vitamin E identified in § 345.10(k) within the dosage identified in § 345.50(d)(17).

(8) Any combination for prevention of deficiency in pregnant women is permitted: *Provided,* That all Category I vitamin ingredients identified in § 345.10 are combined with iron identified in § 345.12(b): *And provided,* that all ingredients are present within the dosage range for prevention of deficiency in pregnant women identified in § 345.50(d), or within the prevention dosage range if no pregnancy dosage range has been specified. This combination may additionally contain zinc identified in § 345.12(c) and/or calcium identified in § 345.12(a) within the dosage range for prevention of deficiency in pregnant women identified in § 345.70(d), or within the prevention dosage range if no pregnancy dosage range has been specified.

(b) *Combinations for the treatment of deficiency.* (1) All Category I vitamin ingredients identified in § 345.10 (a), (d), (f), (g), (h), and (i) within the dosage ranges identified in § 345.50(d) for the treatment of deficiency may be combined with all Category I vitamin ingredients identified in § 345.10 (b), (c) and (j) which have no established dosage range for the treatment of deficiency: *Provided,* That these ingredients are present at the maximum dosage level identified in § 345.50(d) for the prevention of deficiency. This combination may additionally contain pantothenic acid identified in § 345.10(e) within the dosage range identified in § 345.50(d)(7) and/or vitamin E identified in § 345.10(k) within the dosage range identified in § 345.50(d)(17) and provided that the combination is labeled for the treatment of deficiency.

(2) All Category I B-vitamin ingredients identified in § 345.10 (d), (f), (g), and (h) within the dosage ranges identified in § 345.50(d) for the treatment of deficiency may be combined with all Category I B-vitamin ingredients identified in § 345.10 (b) and (c) which have no established dosage range for the treatment of deficiency: *Provided,* That these ingredients are present at the maximum dosage level identified in § 345.50(d) for the prevention of deficiency. This combination may additionally contain pantothenic acid identified in § 345.10(e) within the dosage range identified in § 345.50(d)(7): *Provided,* That the combination is labeled for the treatment of deficiency.

(3) All Category I B-vitamin ingredients identified in § 345.10 (d), (f), (g), and (h) within the recommended dosage ranges identified in § 345.50(d) for the treatment of deficiency may be combined with vitamin C identified in § 345.10(a) within the dosage range identified in § 345.50(d)(2) and with all Category I B-vitamin ingredients identified in § 345.10 (b) and (c) which have no established dosage range for the treatment of deficiency: *Provided,* That these ingredients are present at the maximum dosage level identified in § 345.50(d) for the prevention of the deficiency. This combination may additionally contain pantothenic acid identified in § 345.10(e) within the dosage range identified in § 345.50(d)(7): *Provided,* That the combination is labeled for the treatment of deficiency.

Subpart C—[Reserved]

Subpart D—Labeling

§ 345.50 Labeling of vitamin drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "vitamin."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases:

(1) *For products containing vitamin C identified in § 345.50(d)(1) for prevention of deficiency.* "For use in the prevention of vitamin C deficiency when the need for such therapy has been determined by a physician."

(2) *For products containing vitamin C identified in § 345.50(d)(2) for treatment of deficiency.* "For use in the treatment of vitamin C deficiency when the need for such therapy has been determined by a physician."

(3) *For products containing vitamin B-12 identified in § 345.50(d)(3) for prevention of dietary deficiency.* "For use in the prevention of vitamin B-12 dietary deficiency when the need for such therapy has been determined by a physician."

(4) *For products containing folacin identified in § 345.50(d)(4) for prevention of deficiency.* "For use in the prevention of folic acid deficiency when the need for such therapy has been determined by a physician."

(5) *For products containing niacin identified in § 345.50(d)(5) for prevention of deficiency.* "For use in the prevention of niacin deficiency when the need for such therapy has been determined by a physician."

(6) *For products containing niacin identified in § 345.50(d)(6) for treatment of deficiency.* "For use in the treatment of niacin deficiency when the need for such therapy has been determined by a physician."

(7) *For products containing vitamin B-6 identified in § 345.50(d)(8) for prevention of deficiency.* "For use in the prevention of vitamin B-6 deficiency when the need for such therapy has been determined by a physician."

(8) *For products containing vitamin B-6 identified in § 345.50(d)(9) for treatment of deficiency.* "For use in the treatment of vitamin B-6 deficiency when the need for such therapy has been determined by a physician."

(9) *For products containing riboflavin identified in § 345.50(d)(10) for prevention of deficiency.* "For use in the prevention of riboflavin deficiency when the need for such therapy has been determined by a physician."

(10) *For products containing riboflavin identified in § 345.50(d)(11) for treatment of deficiency.* "For use in the treatment of riboflavin deficiency when the need for such therapy has been determined by a physician."

(11) *For products containing thiamine in § 345.50(d)(12) for prevention of deficiency.* "For use in the prevention of thiamine deficiency when the need for such therapy has been determined by a physician."

(12) *For products containing thiamine identified in § 345.50(d)(13) for treatment of deficiency.* "For use in the treatment of thiamine deficiency when the need for such therapy has been determined by a physician."

(13) *For products containing vitamin A identified in § 345.50(d)(14) for prevention of deficiency.* "For use in the prevention of vitamin A deficiency when the need for such therapy has been determined by a physician."

(14) *For products containing vitamin A identified in § 345.50(d)(15) for treatment of deficiency.* "For use in the treatment of vitamin A deficiency when the need for such therapy has been determined by a physician."

(15) *For products containing vitamin D identified in § 345.50(d)(16) for prevention of deficiency.* "For use in the prevention of vitamin D deficiency when the need for such therapy has been determined by a physician."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing vitamin C identified in § 345.50(d)(1) and (2)—*(i) *For products containing 0.2 meq (5 mg) or higher of sodium per unit of dose.* The sodium content must be stated per dosage unit (e.g., tablet, teaspoonful) when some or all of the source of vitamin C is sodium ascorbate if the sodium content is 0.2 meq (5 mg) or higher.

(ii) *For products containing more than 5 meq (125 mg) sodium per unit of dose.* "Do not take this product if you are on a sodium-restricted diet except under the advice and supervision of a physician."

(iii) *For products containing vitamin C identified in § 345.50(d)(2) for the treatment of deficiency.* (*a*) "Patients with gout and/or a tendency to form kidney stones may be at increased risk when taking more than the recommended dose.'

(*d*) "Diabetics taking more than 500 milligrams vitamin C daily may obtain false readings in their urinary glucose test."

(2) *For products containing vitamin B-12 identified in § 345.50(d)(3) as the only active ingredient. "Caution:* This preparation is for the prevention of vitamin B-12 dietary deficiency and cannot be safely used for the treatment of vitamin B-12 dietary deficiency."

(3) *For combination products for the prevention or treatment of multiple deficiencies which contain a prevention dose of vitamin B-12 identified in § 345.50(d)(3).* "This product cannot be safely used for the treatment of vitamin B-12 deficiency."

(4) *For products containing 1 milligram folacin per unit of dose identified in § 345.50(d)(4)*—(i) *"Caution:* The use of folic acid for treatment of anemia without the direction of a physician may be dangerous."

(ii) "Do not exceed the recommended daily dosage."

(5) *For combination products for the prevention or treatment of multiple deficiencies which contain a prevention dose of 1 milligram folacin per unit of dose identified in § 345.50(d)(4).* "This product cannot be safely used for the treatment of folic acid deficiency."

(6) *For products containing vitamin B-6 identified in § 345.50(d)(8) and (9). "Caution:* Do not take this product if you have Parkinsonism and are currently taking l-dopa except under the advice and supervision of a physician."

(7) *For products containing riboflavin identified in § 345.50(d)(11).* "Do not exceed the recommended dosage except under the advice and supervision of a physician."

(8) *For products containing vitamin A identified in § 345.50(d)(15). "Do not exceed the recommended dosage except under the advice and supervision of a physician. Excessive dosages may cause harm."*

(9) *For products containing vitamin D identified in § 345.50(d)(16).* "Do not take this product if you have a history of kidney stones except under the advice and supervision of a physician."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions" followed by "or as directed by a physician":

(1) *For products containing vitamin C identified in § 345.10(a) for prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 50 to 100 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(2) *For products containing vitamin C identified in § 345.10(a) for treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 300 to 500 milligram daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(3) *For products containing vitamin B-12 identified in § 345.10(b) for prevention of dietary deficiency.* For adults and children 1 year of age and older, the oral dosage is 3 to 10 micrograms daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *For products containing folacin identified in § 345.10(c) for prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 0.1 to 0.4 milligram daily. For pregnant and lactating women, the oral dosage is 1.0 milligram daily. For those persons who use alcohol to excess, the oral dosage is 1.0 milligram daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(5) *For products containing niacin identified in § 345.10(d) for prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 10 to 20 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(6) *For products containing niacin identified in § 345.10(d) for treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 25 to 50 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(7) *For products containing pantothenic acid identified in § 345.10(e) provided that pantothenic acid is not used as a single ingredient product but may be used in combinations identified in § 345.20(a)(1), (2), (3), (4), (5), (6), (7), (b)(1), (2), and (3):* For adults and children 1 year of age and older, the oral dosage is 5 to 20 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(8) *For products containing vitamin B-6 identified in § 345.10(f) for the prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 1.5 to 2.5 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(9) *For products containing vitamin B-6 identified in § 345.10(f) for the*

treatment of deficiency. For adults and children 1 year of age and older, the oral dosage is 7.5 to 25 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(10) *For products containing riboflavin identified in § 345.10(g) for the prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 1 to 2 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(11) *For products containing riboflavin identified in § 345.10(g) for the treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 5 to 25 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(12) *For products containing thiamine identified in § 345.10(h) for the prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 1 to 2 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(13) *For products containing thiamine identified in § 345.10(h) for the treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 5 to 25 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(14) *For products containing vitamin A identified in § 345.10(i) for the prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 1,250 to 2,500 international units daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(15) *For products containing vitamin A identified in § 345.10(i) for the treatment of deficiency.* For adults and children 1 year of age and older, the oral dosage is 5,000 to 10,000 international units daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

(16) *For products containing vitamin D identified in § 345.10(j) for the prevention of deficiency.* For children under 18 years of age, the oral dosage is 400 international units daily. For adults 18 years of age and older, the oral dosage is 200 international units daily.

(17) *For products containing vitamin E identified in § 345.10(k), provided that vitamin E is not used as a single ingredient but may be used in combinations identified in § 345.20(a) (1), (5), (6), (7), and (b)(1).* For adults and children 1 year of age and older, the oral dosage is 30 international units daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

§ 345.70 Labeling of mineral drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "mineral."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases:

(1) *For products containing calcium identified in § 345.12(a).* "For use in the prevention of calcium deficiency when the need for such therapy has been determined by a physician."

(2) *For products containing iron identified in § 345.12(b).* "For use in the prevention of iron deficiency when the need for such therapy has been determined by a physician."

(3) *For products containing zinc identified in § 345.12(c).* "For use in the prevention of zinc deficiency when the need for such therapy has been determined by a physician."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

For products containing iron identified in § 345.12(b). "*Caution:* The treatment of any anemic condition should be under the advice and supervision of a physician."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions" followed by "or as directed by a physician":

(1) *For products containing calcium identified in § 345.12(a) for prevention of deficiency.* For adults, children 1 to under 10 years of age, and children 12 years of age and older, the oral dosage is 400 to 800 milligrams daily. For preadolescent and pubescent children 10 to under 12 years of age and for pregnant and lactating women, the oral dosage is 600 to 1,200 milligrams daily. For elderly adults over 51 years of age, the oral dosage is 500 to 1,000 milligrams daily. For infnats 6 months to under 1 year of age, the oral dosage is 300 to 600 milligrams daily. For infants under 6 months of age, the oral dosage is 200 to 400 milligrams daily.

(2) *For products containing iron identified in § 345.12(b) for prevention of deficiency.* For menstruating and lactating women, the oral dosage is 10 to 30 milligrams daily. For pregnant women, the oral dosage is 30 to 60 milligrams daily. For children 6 months to under 5 years of age, the oral dosage is 10 to 15 milligrams daily. For infants under 6 months of age, there is no recommended dosage except under the advice and supervision of a physician. For combination products other than for use in pregnancy, the oral dosage for adults and children 5 years of age and older, is 10 to 20 milligrams daily.

(3) *For products containing zinc identified in § 345.12(c) for prevention of deficiency.* For adults and children 1 year of age and older, the oral dosage is 10 to 25 milligrams daily. For pregnant and lactating women, the oral dosage is 25 milligrams daily. For children under 1 year of age, there is no recommended dosage except under the advice and supervision of a physician.

§ 345.78 Labeling of permitted combinations of active ingredients.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any and identifies the product as either a "multiple vitamin" or a "multiple vitamin with minerals."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases:

(1) *For combinations containing only vitamins identified in § 345.20(a)(1), (2), and (3) for prevention of deficiency.* "For the prevention of deficiencies of vitamins named on the label when the need for such therapy has been determined by a physician."

(2) *For combinations containing vitamins and minerals identified in § 345.20(a)(4), (5), and (6) for prevention of deficiency.* "For the prevention of deficiencies of vitamins and minerals named on the label when the need for such therapy has been determined by a physican."

(3) *For combinations identified in § 345.20(a)(7) for prevention of deficiency.* "Useful as an aid in the prevention of deficiency of vitamins named on the label and zinc in persons using alcohol to excess when the need for such therapy has been determined by a physican."

(4) *For combinations identified in § 345.20(a)(8) for prevention of deficiency.* "For the prevention of deficiencies of vitamins named on the label and iron in pregnant women when the need for such therapy has been determined by a physican."

(5) *For combinations containing only vitamins identified in § 345.20(b)(1), (2), and (3) for treatment of deficiency.* "For the treatment of deficiencies of vitamins named on the label when the need for such therapy has been determined by a physican."

§ 345.80 Professional labeling.

The lebeling of the product provided to health professionals contains the following information:

(a) *For products containing vitamin C identified in § 345.10(a).* (1) "When diabetics ingest large quantities (greater than 500 milligrams daily) of vitamin C, the following false results may occur when testing for glycosuria: (i) false-negatives for glucose oxidase enzyme strip-tests and (ii) false-positives for tests based on copper reduction."

(2) "The ingestion of daily doses of 1,000 milligrams or more vitamin C may result in harmful effects due to hyperoxaluria and to increased urinary acidity and uric acid excretion; oxalate and uric acid crystalization may occur in the kidney or bladder, especially in patients prone to renal stone formation. Additional risk factors include consumption of foods containing high levels or exalate, and small intestinal disease states, e.g., resectioning, evidencing increased urinary oxalate. Persons consuming these excessive amounts of vitamin C should be under a physican's supervision."

(3) "No exogenous vitamin C should be ingested for 48 to 72 hours prior to conducting amine-dependent stool occult blood tests, to prevent a false-negative test resulting from a high fecal excretion of ascorbic acid."

(b) *For products containing vitamin B-6 identified in § 345.10(f).* "Increased pytidoxine hyrochloride doses are required in vitamin B-6 dependency syndromes (pytidoxine-responsive-anemia, seizures, familial xanthurenic aciduria, cystationiuria). Supplemental levels of pyridoxine hydrochlordie are required when patients take (during receipt of) drugs or chemicals which bind and inactivate pyridoxine hydrochloride (isonicotinic acid hydrazide, cycloserine, hydralazine, penicillamine, and semicarbazide)."

(c) *For products containing riboflavin identified in § 345.10(g).* "Certain individuals may require increased levels of reboflavin, such as individuals with biliary obstruction, individuals or oral contraceptives, and individuals consuming large quanities of alcohol."

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before June 14, 1979. Such comments should be addressed to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before July 16, 1979. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it had been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: March 1, 1979.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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