# Multivitamin and multimineral dietary supplements: definitions, characterization, bioavailability, and drug interactions[1–3]

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**ABSTRACT**

Although *multivitamins*, *multiminerals*, and similar terms (eg, *multis* or *multiples*) are commonly used, they have no standard scientific, regulatory, or marketplace definitions. Thus, *multivitamins-multiminerals* refers to products with widely varied compositions and characteristics. Multivitamin-multimineral composition databases use label values as surrogates for analyzed values. However, actual vitamin and mineral amounts often deviate from label values. Vitamin and mineral bioavailability for dietary supplements also lacks a standard scientific and regulatory definition and validated in vitro and animal models that accurately reflect human bioavailabilities. Systematic information on the bioavailability and bioequivalence of vitamins and minerals in marketed products and on potential drug interactions is scarce. Because of limited information on product characteristics, our ability to directly compare results across studies, estimate changes in usage patterns or intakes over time, and generalize from published results to marketed products is problematic. *Am J Clin Nutr* 2007;85(suppl):269S–76S.

**KEY WORDS** Vitamin and mineral supplements, bioavailability, bioequivalence, drug interactions, supplement composition, supplement definitions

## INTRODUCTION

Product definitions and other product characteristics (eg, composition, bioavailability, and bioequivalence and potential for drug interactions) are important for assessing the scientific quality of published research, making comparisons among study results, evaluating time trends in consumer use patterns and intakes, and generalizing results from studied to marketed products. However, these important product-related methodologic details are often inadequately considered or described or inconsistently dealt with in research and population monitoring settings and publications. This manuscript focuses on these product-related issues.

## MULTIVITAMIN-MULTIMINERAL DEFINITIONS

Although *multivitamin-multimineral* (MVM) and similar terms (eg, *multis* or *multiples*) are commonly used, they have no standard or defined meaning and can refer to products with widely varied compositions and characteristics.

### Monitoring and research definitions

Since the 1980s, several nationally representative surveys have collected dietary supplement information (**Table 1**). Questionnaire differences within a survey series and across surveys, however—such as the types of supplement products for which information was sought; whether vitamin- and mineral-containing drugs, nonnutrient supplements, or supplements in forms other than pills and tablets were included; the duration of supplement usage; and the availability of product composition information—make it difficult to track changes in supplement use and intakes over time or across surveys (1–12). Even when a survey series asks the same question over time (eg, National Health Interview Survey, 1987–2000), the results are confounded because of the constantly evolving composition and intended use of marketed products.

Product categorization differences also occurred among surveys and associated publications. The heterogeneity in the MVM category definitions that have been developed by users of national surveys is described in **Table 2** (1–12). When respondents rather than data users are asked to identify their use of MVMs, errors can occur. For example, some respondents answered questions about MVM use by describing non-MVMs (eg, botanicals, sports drinks, and amino acids), which suggests that respondents' perception of MVMs may not match that of scientists (5, 13, 14). In some cases, nonnutritionist interviewers incorrectly recorded MVM products (13, 15). In one survey, the interview questionnaire asked respondents whether they ever used vitamins for health and treatment, and then respondents were shown a card that listed not only MVMs but non-vitamin-mineral supplements (eg, DHEA, coenzyme Q10) as possible responses, making interpretation of results difficult (8).

Reports from published studies also exhibited either a lack of standardization of MVM supplement definitions and categorizations or a lack of sufficient information to ascertain how the study defined or categorized MVMs (16). Categorizations varied from systems that focused on the product's intended use (eg, body building, weight loss), ingredients (eg, vitamin and mineral

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**TABLE 1**
Dietary supplement information in national surveys[1]

| Survey | Question | Time period | Composition data |
|---|---|---|---|
| NHANES I (1971–1974) | Any vitamins or minerals? (response choices: multiple vitamins, multiple vitamins and minerals, iron only, multiple vitamins and iron, other) | Regularly (daily); irregularly (≥ 1/wk) | No |
| NHANES II (1976–1980) | Any vitamins or minerals? (response choices: 29 categories plus other) | Regularly (daily); irregularly (≥ 1/wk) | No |
| NHANES III (1988–1994) | Any vitamins or minerals? (included use of some prescription medicines and laxatives reported elsewhere in the interview) | Last month | Yes |
| NHANES (1999–2000) | Any vitamins, minerals, or other types of dietary supplements? (included prescription supplements) | Past month | Yes |
| NHANES (2001–2002) | Any vitamins, minerals, or other? (included prescription and nonprescription supplements) | Past 30 d | Yes |
| NHANES (2003–2004) | Any vitamins, minerals, or other dietary supplements? (included prescription and nonprescription supplements) | Past 30 d | Yes |
| NHIS 1986 (FDA supplement) | Any vitamin, mineral, or fluoride products? (Is it prescription?) | Past 2 wk | Yes |
| NHIS 1987 (cancer supplement) | Any vitamin or mineral supplement? Have you used multiple vitamins; vitamins A, C, and E; calcium? | Past 12 mo | Yes |
| NHIS 1992 (cancer supplement) | Any vitamin or mineral supplement? Have you used multiple vitamins; vitamins A, C, and E; calcium? | Past 12 mo | No |
| NHIS 2000 (cancer supplement) | Any vitamin or mineral supplement (multiple vitamins; vitamins A, C, and E; calcium); also use of single herbal or botanical supplements | Past 12 mo | No |
| NHIS 2002 (CAM supplement) | Vitamins for health and treatment<br>Any of the following vitamins in high doses? | Ever use | No |
| CSFII (1994–1996) | Any vitamin or mineral supplement? (in pill or liquid form, fish oil, fiber supplement) | Every day? Almost every day? Every so often? Not at all? | No |

[1] From references 1–12. CAM, complementary and alternative medicine; CSFII, Continuing Survey of Food Intakes by Individuals; FDA, Food and Drug Administration; NHIS, National Health Interview Survey; NHANES, National Health and Nutrition Examination Survey.

content), sources of ingredients (eg, antacids as a source of calcium) (16), disease perspectives (eg, antioxidants and cancer) (4), or consumer behaviors (eg, herbal versus MVM users) (17).

### Regulatory definitions

No regulatory definitions exist for MVMs. In the United States, dietary supplements may contain multiple ingredients, including vitamins, minerals, herbs or other botanicals, and amino acids; dietary substances for use by humans to supplement the diet by increasing the total dietary intake; concentrates, metabolites, constituents, and extracts; or combinations of one or more of these ingredients (18). The European Commission proposed to define food supplements as concentrated sources of nutrients (primarily vitamin and mineral salts) marketed in dose form (eg, capsules, tablets, sachets, etc) to supplement the nutrient intake in a normal diet (19). The United Nation's *Codex Alimentarius* completed similar international standards for food supplements (20).

### Marketplace definitions

A search of MVM products marketed on the Internet reveals a variety of products described as *multivitamin*, *multimineral*, *multis*, *multiple nutrients*, and *multivitamin/mineral*. These include "one-a-days" and specialized products (eg, MVMs for men, senior women, menopause, persons with diabetes, daytime or nighttime, performance, energy, menopause, hair). Many products do not include MVM terms in their names but contain similar types and amounts of vitamins and minerals as MVM-labeled products.

MVMs vary in the types, numbers, and amounts of vitamins and minerals they contain and whether they contain other nonvitamin and nonmineral ingredients (eg, dietary fiber, botanicals, glucosamine, lycopene). The same brand name with modifiers (eg, Brand X calcium plus) is used for products that differ in composition. Some products bearing the same brand name come in different forms (eg, pill or liquid) but differ in composition.

## CHARACTERIZATION

Manufacturers determine both the types and levels of vitamins and minerals in MVMs (18). Information is scarce on the actual amounts of vitamins and minerals in these products; therefore, label declarations of vitamin-mineral content are often used as surrogates for actual levels. US regulations require that the amount of a vitamin or mineral is always equal to or greater than the label declaration after batch-to-batch variations and expected shelf life losses are taken into account.

Relatively few data are available that compare analyzed with declared label values in marketed products. Trade associations from the United States and the United Kingdom identified overages consistent with good manufacturing practices of 30–100% of declared value for vitamin A; 50% for vitamin B-12; 30–50% for ergocalciferol; 30% for cholecalciferol, folic acid, thiamine, biotin, β-carotene, vitamin K, riboflavin, niacin, vitamin B-6,

**TABLE 2**
Examples of multivitamin-multimineral categorization in national surveys[1]

| Category | Definition | Survey |
|---|---|---|
| Mulivitamin-multiminerals | | |
| Multiple vitamins and minerals; multivitamin-multimineral | Undefined | NHANES I, II; NHIS 1987, 1992, 2000, 2002; CSFII |
| | ≥ 3 vitamins with or without minerals and names (do not refer to a specific vitamin or mineral) | NHANES 1999–2000 |
| | Must contain at least thiamine; riboflavin; niacin; vitamins A, B-12, B-6, C, and D; calcium; and iron, but not fluoride | NHANES III |
| | Contains vitamins A, D, E, C, B-6, and B-12; thiamine; riboflavin; niacin; folic acid; calcium; phosphorus; iodine; iron; and magnesium | NHIS 1986 |
| Combinations of vitamins and minerals with other products | Undefined | NHANES 1999–2000, NHANES 2001–2002 |
| | At least one vitamin and one mineral plus other ingredients | NHIS 1986 |
| Multivitamins | | |
| Multivitamins; multiple vitamins | Undefined | NHANES I, II, III; NHIS 1987, 1992, 2000; CSFII. |
| | ≥ 2 vitamins | NHANES 1999–2000 |
| | No minerals and vitamins A, D, E, C, B-6, and B-12; thiamine; riboflavin; folic acid; and niacin | NHIS 1986 |
| | Example: one-a-day and not high-dose or megavitamin | NHIS 2002 |
| Other vitamin combinations | Contains no minerals, not a multivitamin as defined above, and contains ≥ 2 vitamins | NHIS 1986 |
| Multiple vitamins with iron | Undefined | NHANES I, II |
| | With iron or other minerals | CSFII |
| | Must contain thiamine; riboflavin; niacin; vitamins A, B-12, B-6, C, and D; and iron | NHANES III |
| | Is a multivitamin and contains iron | NHIS 1986 |
| Multivitamins with vitamin C | Must contain vitamin C and thiamine, riboflavin, niacin, and vitamins A and D | NHANES III |
| Multivitamins with fluoride | Must contain at least thiamine; riboflavin; niacin; vitamins A, B-12, B-6, C, and D; fluoride ± iron and no other minerals | NHANES III |
| Multiple vitamins with additional supplements | Undefined | NHANES II |
| Multiminerals | | |
| Multiminerals | Undefined | NHANES III, NHANES 2001–2002 |
| | ≥ 2 minerals and no vitamins | NHANES 1999–2000 |
| | Contains no vitamins and the following minerals: calcium, phosphorus, iodine, iron, and magnesium | NHIS 1986 |
| Other mineral combination | Contains no vitamins, is not a multimineral as defined above, and contains ≥ 2 minerals | NHIS 1986 |

[1] From references 1–12. CSFII, Continuing Survey of Food Intakes by Individuals; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey.

and vitamin C; and 5% for vitamin E (21). However, underages have also been reported in US and Canadian products (22, 23). Comparisons of analyzed with label values showed selenium deviations from −19% to 23% (23) and up to 2.5 times label value (24) for products marketed in Canada and the United States, respectively. For Canadian products, vitamin E analyzed values deviated from label declarations by −41% to 57%, and vitamin D was within 15% of the stated dose (23).

Compositional databases are often developed by recording label values from respondent supplement containers because analytic data are not available or by using defaults based on simplified questionnaires or composition of commonly used products because of interview time or budget constraints. Comparisons of intake estimates derived from a simplified inventory (25) or default product categories (26) showed that the accuracy of results based on defaults or simplified questionnaires varied by nutrient.

## BIOAVAILABILITY

### Definitions: bioavailability and bioequivalence

The concept of vitamin and mineral bioavailability for dietary supplements lacks standard scientific and regulatory definitions. Commonly used definitions include concepts of absorption (27) and some also include utilization (eg, availability for use or storage) (28–30). For some nutrients, beneficial functions of unabsorbed nutrients (eg, binding of bile salts by calcium in the gut) would be missed by absorption-based definitions (27).

**TABLE 3**
Examples of considerations of bioavailability and bioequivalency of the Dietary Reference Intakes (DRIs)

| Nutrient | Bioavailability and bioequivalency |
|---|---|
| Vitamin A | DRI expressed as μg retinol activity equivalents (RAE): 1 μg RAE = 1 μg *all-trans*-retinol = 2 μg supplemental *all-trans*-β-carotene = 12 μg dietary *all-trans*-β-carotene = 24 μg other dietary provitamin A carotenoids |
| Iron | Algorithm for estimating dietary iron bioavailability: 18% bioavailability from a total diet based on differences in absorption from heme- and nonheme-iron sources in a mixed US diet |
| Niacin | No adjustment is made for bioavailability, but the requirement is expressed in niacin equivalents (NEs), which allows for some conversion of the amino acid tryptophan to niacin |
| Vitamin B-6 | Bioavailability of 75% is assumed from a mixed diet |
| Folate | DRI expressed as dietary folate equivalents (DFEs): 1 μg DFE = 0.6 μg folic acid from fortified food or as a supplement taken with meals = 1 μg food folate = 0.5 μg supplement taken on an empty stomach |
| Vitamin B-12 | An assumed absorption from foods of 50% is included in the DRI, advise adults aged ≥51 y that foods fortified with vitamin B-12 or supplements containing vitamin B-12 be used to meet the DRI because of reduced absorption of food forms |

Similar to the situation for drugs, definitions of nutrient bioavailability may benefit from a provision for functionality at sites of action not dependent on systemic blood circulation for delivery of the active moiety (31).

Bioequivalence is closely related to the concept of bioavailability (31, 32). For some nutrients, equal absorption does not mean equal biological effects because the nutrient sources are chemically different, resulting in differences in nutrient activity (27). Bioavailability and bioequivalence factors are the basis for adjustments for some nutrient reference values (**Table 3**) (33–35). For example, differences in the activity of different chemical sources of vitamin A and folate are converted to vitamin equivalents when setting Recommended Dietary Allowances (RDAs). The effect on intake estimates for folate equivalents versus micrograms is illustrated in **Figure 1** (36). For other nutrients (eg, iron, niacin, vitamin B-6, and vitamin B-12), RDA or Adequate Intake (AI) values are adjusted on the basis of different bioavailabilities and bioequivalencies from mixed diets, making their use for dietary supplements problematic.

## Factors affecting bioavailability

Vitamin and mineral bioavailability in MVMs is affected not only by product but also by host factors. Host factors include homeostatic mechanisms that regulate absorption or excretion depending on the nutrient status of the host (eg, the iron status of the host affects iron absorption) (27, 29). These factors vary by age, sex, and physiologic state (eg, pregnancy) (29, 30, 37). Homeostatic mechanisms may regulate circulating concentrations of nutrients within a tight range and are therefore insensitive to changes in ingested amounts or to utilization at the site of action (27). The size of the ingested load may affect bioavailability [eg, the absorption load of calcium varies inversely as the logarithm of the load size (27), and single high doses of folic acid exceed the metabolic capacity for reduction and methylation (38)]. These complex host factors are the basis for questions as to the validity of including utilization in definitions of nutrient bioavailability (27). They also give rise to concerns that higher bioavailability is not necessarily better (27, 29).

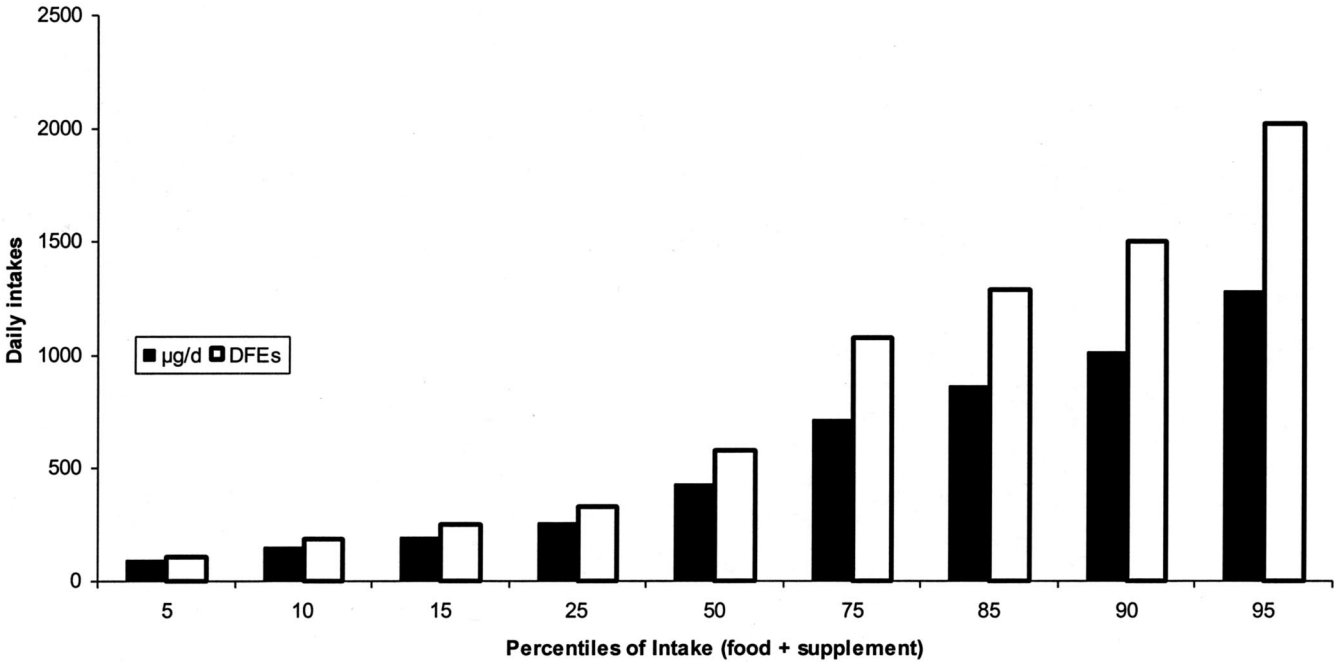



**FIGURE 1.** Percentiles of total folate intakes (foods + supplements) of women aged 31–50 y from the National Health and Nutrition Examination Survey 2001–2002 expressed as amount (μg/d) or as dietary folate equivalents (DFEs)/d. Intake distributions are adjusted for intraindividual variations in intakes to represent usual intakes (36).

**TABLE 4**
Reported interactions of vitamins and minerals with drugs[1]

| Vitamin or mineral | Drug | Type of interaction |
|---|---|---|
| Vitamin A | Abciximab, acenocoumarol, ancrod, anisindione, antithrombin III human, argatroban, bivalirudin, clopidogrel, danaparoid, defibrotide, dermatan sulfate, desirudin, dicumarol, eptifibatide, fondaparinux, heparin, lamifiban, pentosan polysulfate sodium, phenindione, phenprocoumon, sibrafiban, tirofiban, warfarin, xemilofiban | Increased risk of bleeding |
| | Acitretin, carob, etretinate, isotretinoin, tretinoin | Increased risk of vitamin A toxicity |
| | Bexarotene | Increased risk of retinoid toxicity |
| | Colestipol | Decreased vitamin A effectiveness |
| | Minocycline | Increased risk of pseudotumor cerebri (benign intracranial hypertension) |
| Niacin | Atorvastatin, cerivastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin | Increased risk of myopathy or rhabdomyolysis |
| | Cholestyramine, colestipol | Decreased niacin absorption |
| | Nicotine | Flushing and dizziness |
| Folic acid | Colestipol | Decreased bioavailability of vitamin and mineral preparations possible |
| | Fosphenytoin, phenytoin | Increased seizure frequency and decreased phenytoin concentrations |
| | Pancreatin, sulfasalazine | Decreased absorption of folate |
| | Pyrimethamine | Pharmacodynamic antagonism of the antiparasitic effect |
| | Triamterene | Decreased utilization of dietary folate |
| Vitamin B-6 | Altretamine | Adversely affects the response duration of altretamine |
| | Amiodarone | Enhances amiodarone-induced photosensitivity reactions |
| | Contraceptives (combination), hydralazine, isoniazid, penicillamine | May increase vitamin B-6 requirements |
| | Fosphenytoin, phenytoin | Reduced phenytoin concentrations |
| | Levodopa | Decreased drug effectiveness |
| Vitamin B-12 | Aminosalicylic acid, cimetidine, omeprazole, ranitidine | Reduced cyanocobalamin absorption |
| | Ascorbic acid | Reduced amounts of cyanocobalamin available for serum and body stores |
| | Chloramphenicol | Decreased hematologic response to cyanocobalamin |
| | Colestipol | May decrease the bioavailability ofvitamin and mineral preparations |
| | Contraceptives (combination) | Decrease in serum vitamin B-12 concentrations |
| Ascorbic acid | Aluminum carbonate (basic), aluminum hydroxide, aluminum phosphate, dihydroxyaluminum aminoacetate, dihydroxyaluminum sodium carbonate, magaldrate | Aluminum toxicity (personality changes, seizures, coma) |
| | Amygdalin | Increased metabolism of amygdalin, leading to increased cyanide concentrations |
| | Cyanocobalamin | Reduced amounts of cyanocobalamin available for serum and body stores |
| | Indinavir | Decreased plasma indinavir concentrations |
| Vitamin E | Anisindione, phenprocoumon | Enhanced response to anticoagulants |
| | Cholestyramine | Malabsorption of fat-soluble vitamins, decrease in fat-soluble vitamin absorption |
| | Colestipol, orlistat | Decreased vitamin E effectiveness |
| | Dicumarol, warfarin | Increased risk of bleeding |
| Vitamin K | Pau d'arco | Reduced vitamin K effectiveness |
| | Warfarin | Decreased anticoagulant effectiveness |
| Calcium | Alendronate, etidronate, levothyroxine, risedronate, tiludronate | Reduced drug absorption |
| | Amprenavir, aspirin, atenolol, bisacodyl, bismuth subcitrate, cefpodoxime, proxetil, chlortetracycline, ciprofloxacin, demeclocycline, doxycycline, enoxacin, gemifloxacin, grepafloxacin, hyoscyamine, ibandronate, iron, itraconazole, ketoconazole, levofloxacin, lomefloxacin, methacycline, minocycline, norfloxacin, ofloxacin, oxytetracycline, pefloxacin, rolitetracycline, sparfloxacin, sucralfate, temafloxacin, tetracycline, ticlopidine, trovafloxacin mesylate, zalcitabine | Reduced drug efficacy |
| | Atazanavir | Reduced plasma concentration of drug |
| | Bemetizide, bendroflumethiazide, benzthiazide, buthiazide, chlorothiazide, chlorthalidone, clopamide, cyclopenthiazide, cyclothiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polystyrene sulfonate, polythiazide, quinethazone, trichlormethiazide, xipamide | Milk-alkali syndrome (hypercalcemia, metabolic alkalosis, renal failure) |
| | Digitoxin, digoxin | Cardiotoxicity: arrhythmia and cardiovascular collapse |
| | Guar gum | Delayed calcium absorption |
| | Potassium phosphate, potassium phosphate (dibasic), potassium phosphate (monobasic), sodium phosphate, sodium phosphate (dibasic), sodium phosphate (monobasic) | Decreased phosphate absorption |
| | Verapamil | Reversal of hypotensive effects |

(*Continued*)

**TABLE 4** (*Continued*)

| Vitamin or mineral | Drug | Type of interaction |
|---|---|---|
| Magnesium | Allopurinol, amprenavir, aspirin, atazanavir, azithromycin, bisacodyl, bismuth, subcitrate, captopril, cefdinir, cefditoren pivoxil, cefpodoxime proxetil, chloroquine, chlorpromazine, chlortetracycline, cimetidine, cinoxacin, ciprofloxacin, demeclocycline, doxycycline, enoxacin, fexofenadine, gabapentin, gatifloxacin, gemifloxacin, grepafloxacin, hyoscyamine, ibandronate, iron, itraconazole, levofloxacin, levothyroxine, lomefloxacin, minocycline, misoprostol, moxifloxacin, mycophenolate mofetil, nalidixic acid, norfloxacin, ofloxacin, oxytetracycline, pefloxacin, penicillamine, rolitetracycline, rosuvastatin, rufloxacin, sotalol, sparfloxacin, sucralfate, temafloxacin, tetracycline, ticlopidine, tipranavir, trovafloxacin mesylate, zalcitabine | Decreased drug effectiveness |
| | Alendronate, atevirdine, etidronate, mycophenolate sodium, mycophenolic acid, potassium phosphate, risedronate, sodium phosphate, tiludronate | Decreased drug absorption |
| | Delavirdine, lansoprazole | Decreased drug bioavailability |
| | Calcitriol, doxercalciferol | Hypermagnesemia |
| | Atazanavir, clofazimine, digoxin | Decreased plasma drug concentration |
| | Amikacin, dibekacin, gentamicin, kanamycin, netilmicin, streptomycin, tobramycin | Neuromuscular weakness |
| | Cisatracurium, rapacuronium, succinylcholine, vecuronium | Enhanced neuromuscular blockade |
| | Dicumarol | Increased risk of bleeding |
| | Didanosine, mefenamic acid, quinidine, rocuronium | Increased risk of adverse drug effects |
| | Felodipine, isradipine | Hypotension |
| | Glipizide, glyburide, nicardipine, nifedipine | Hypoglycemia |
| | Labetalol | Bradycardia and decreased cardiac output |
| | Polystyrene sulfonate | Increased risk of metabolic alkalosis |
| | Levomethadyl | Increased risk of QT prolongation |
| | Tacrolimus | Increased drug exposure |
| Iron | Acetohydroxamic acid, cefdinir, cinoxacin, ciprofloxacin, demeclocycline, doxycycline, gatifloxacin, gemifloxacin, grepafloxacin, ibandronate, levodopa, levofloxacin, lomefloxacin, methacycline, methyldopa, minocycline, moxifloxacin, mycophenolate mofetil, norfloxacin, ofloxacin, oxytetracycline, penicillamine, rolitetracycline, temafloxacin, tetracycline, trovafloxacin mesylate | Decreased drug effectiveness |
| | Acetohydroxamic acid, aluminum carbonate basic, aluminum hydroxide, aluminum phosphate, calcium, chloramphenicol, cholestyramine, demeclocycline, dihydroxyaluminum aminoacetate, dihydroxyaluminum sodium carbonate, doxycycline, enoxacin, magaldrate, magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, methacycline, minocycline, oxytetracycline, rolitetracycline, sodium bicarbonate, tetracycline | Decreased iron effectiveness |
| | Etidronate, sparfloxacin, trientine, zinc | Reduced drug absorption |
| | Gossypol, soy protein, trientine, vanadium, zinc | Reduced iron absorption |
| | Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole | Reduced iron bioavailability |
| | Levothyroxine | Hypothyroidism |
| Zinc | Cinoxacin, ciprofloxacin, enoxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, tetracycline | Decreased drug effectiveness |
| | Gemifloxacin, sparfloxacin | Decreased drug absorption |
| | Penicillamine | Decreased zinc absorption |
| | Copper | Decreased zinc or copper absorption |
| | Iron | Decreased zinc or iron absorption |

[1] From reference 57.

Hoag and Hussain (32) identified 2 categories of product formulation factors that affect bioavailability and bioequivalence: factors that affect product dissolution or release from the dosage form and factors related to excipients or inactive ingredients that may affect drug stability, drug absorption, and metabolic processes. Product dissolution or release is the basis of pharmacopoeial dissolution test methods (28). Different chemical forms of nutrients and nutrient-nutrient interactions may affect bioavailability, eg, different forms of inorganic iron or zinc vary in bioavailability (39, 40), vitamin C interacting with inorganic iron may enhance bioavailability of the iron (39), and decreasing the levels of magnesium and calcium increases the bioavailability of iron (41). The formulations, fillers, coatings, excipients, and surfactants of products affect the completeness or rate of release of calcium (27, 42), vitamin E (43, 44), pyridoxal phosphate (45), iron (46), folic acid (47), and vitamin B-12 (48).

## Testing of bioavailability

Currently, in vitro and animal models do not accurately reflect human bioavailabilities and, therefore, human testing is the gold standard (27). Similar to their quality assurance standards for drugs, the United States Pharmacopeia (USP) has published disintegration and dissolution standards for evaluating MVMs (28). These standards assume that in vitro acid solubility is a surrogate for in vivo absorption. However, the usefulness of these standards for nutrients not dependent on acid solubility for absorption (eg, calcium) has been questioned (27). The failure of US marketed products to meet USP dissolution standards was reported

for a prenatal MVM (22), folic acid in prenatal MVMs (49, 50), and renal MVMs (51). Similar failures of dissolution and disintegration were reported for MVMs marketed in Canada as compared with USP standards (52), for folic acid–containing products marketed in the United Kingdom as compared with British Pharamcopoieal standards (53), and for iron-containing products in Sweden (54). In the United States, the use of USP standards by manufacturers is voluntary and not required by regulation.

## DRUG INTERACTIONS

Drug-nutrient interactions are the result of both host and nutrient-drug factors. These interactions can make a drug less effective, increase the action of a drug, or cause unexpected side effects. There are also reports of certain drugs decreasing the effectiveness of vitamins and minerals. Little research-based information is available on potential or actual drug-vitamin or drug-mineral interactions. Reported interactions include vitamin E and aspirin with the potential for an additive antithrombotic effect and between vitamin E and warfarin related to an increased risk of bleeding (55). An antioxidant supplement containing vitamins C and E, $\beta$-carotene, and selenium used in the treatment arm of a randomized controlled clinical trial blocked the beneficial response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL (56). The vitamin-drug and mineral-drug interactions that have been reported in the Thomson *Micromedex Healthcare Series* are listed in **Table 4** (57).

Dietary supplement manufacturers have not been required to evaluate the potential for drug interactions, but legislation to mandate the reporting of serious adverse effects is currently under consideration. Reports of suspected or documented adverse events may be voluntarily submitted to the Food and Drug Administration's MedWatch program (58) or other organizations, such as poison control centers. If drug-MVM supplement interactions are documented, information identifying this would more likely be required for drug labeling than for supplement labeling. However, manufacturers and retailers may voluntarily place warning statements on MVMs. These statements do not require review or approval by the Food and Drug Administration.

## CONCLUSION

The definitions and categorization of MVM products are not standardized. These differences can affect estimates of both prevalence and intakes and make it difficult to compare trends over time, make direct comparisons from one study or survey to another, or generalize from published results to marketed products. The variable composition of marketed MVMs and the inaccuracy of label declarations underscore the need for more systematic analysis of vitamin and mineral content of MVMs. Deviations of even 25–50% from label values, given the relatively high quantities of vitamins and minerals in marketed MVMs, can result in significant errors in estimates of dietary intakes from MVMs. It is unclear whether a single definition of bioavailability can apply to all vitamins and minerals because factors affecting nutrient absorption and the relation of circulating nutrient concentrations to functional effects at sites of action vary among nutrients. Although drug definitions of bioavailability are often applied to nutrients, inherent differences between drugs and nutrients require that drug definitions be modified if they are to be usefully applied to vitamins and minerals. Drug interactions with MVM ingredients are rarely systematically studied but may interfere with or augment the effects of some drugs in unexpected ways.

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