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Dietary supplement ingredient database (DSID): Preliminary USDA studies on the composition of adult multivitamin/mineral supplements☆

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Abstract

The Nutrient Data Laboratory of the United States Department of Agriculture (USDA) is collaborating with the Office of Dietary Supplements (ODS), the National Center for Health Statistics (NCHS), and other government agencies to design and populate a dietary supplement ingredient database (DSID). This analytically based, publicly available database will provide reliable estimates of vitamin and mineral content of dietary supplement (DS) products. The DSID will initially be populated with multivitamin/mineral (MVM) products because they are the most commonly consumed supplements. Challenges associated with the analysis of MVMs were identified and investigated. A pilot study addressing the identification of appropriate analytical methods, sample preparation protocols, and experienced laboratories for the analysis of 12 vitamins and 11 minerals in adult MVM supplement products was completed. Preliminary studies support the development of additional analytical studies with results that can be applied to the DSID. Total intakes from foods and supplements are needed to evaluate the associations between dietary components and health. The DSID will provide better estimates of actual nutrient intake from supplements than databases that rely on label values alone.

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Disclaimer

Certain commercial products are identified to adequately the experimental procedure. Such identification does not imply endorsement or recommendation by the NIST or the USDA, nor does it imply that the materials identified are necessarily the best available for the purpose.

Keywords

Dietary supplements; Analytical database; DSID; Multivitamin; Pilot study; Nutrients

1. Introduction: why a dietary supplement ingredient database (DSID)?

According to the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2000, over 50% of American adults reported using a dietary supplement (DS) within the past 30 days (Radimer et al., 2004). American consumers take supplements of vitamins, minerals, amino acids, fatty acids, botanicals and other types of products for their alleged health effects that range from “increased vitality” to “prevention of chronic diseases.” In 2005, sales in the DS industry exceeded $20 billion (Anonymous, 2006). The intake of DSs containing vitamins and minerals contributes to the total intake of these nutrients. For some individuals, supplements contribute a larger proportion of micronutrient intake than do intakes from foods alone (Dwyer et al., 2003a).

The prevalent use of DSs has made it important to monitor the actual composition of these products to obtain more accurate dietary intake information for research purposes than can be obtained from existing databases that rely primarily on label information for product composition (Dwyer et al., 2003a). Information on the contribution of nutrient-containing supplements to total dietary intake is essential for dietary assessment and planning and the study of diet-health relationships (Dwyer et al., 2003a,b). Current studies underway include the effects of multivitamin/mineral (MVM) supplements on total nutrient intakes and relationships to disease risks (Murphy et al., 2007). Currently available DS databases tend to be designed for specific purposes and usually contain only composition data that have been derived from product labels, with no independent analytical confirmation. The Nutrient Data Laboratory (NDL) at the Agricultural Research Center (ARS), US Department of Agriculture (USDA), in collaboration with the Office of Dietary Supplements (ODS) of the National Institutes of Health, is responding to the need from the research community for a DS database that is supported, in part, by analytical data in a manner analogous to food composition databases.

The goals for the dietary supplement ingredient database (DSID) project are to: (a) develop reliable estimates of nutrients and other bioactive components in DS products; (b) support improved dietary intake assessments in research by providing analytical measures of the nutrient content of marketed DSs; (c) report on analyzed levels of nutrients relative to labeled values; and (d) release and maintain a publicly available on-line composition database for a variety of DSs including MVMs, single nutrient products, fish oil products containing omega-3-fatty acids, and botanicallybased supplements. Furthermore, this publicly available database will give healthcare professionals and consumers access to information on analyzed levels of DSs.

In the early stages of this project, a pilot study was conducted to answer underlying research questions that arose in the development of appropriate protocols for vitamin and mineral analysis in supplement products. This study also identified challenges involved in generating analytical data for representative DS products for the DSID. The DSID project will focus first on MVMs because MVMs are the most commonly consumed type of DS in the US. In fact, approximately 35% of US adults in the 1999–2000 NHANES reported taking a MVM within the past month (Radimer et al., 2004).

1.1. Investigation of key challenges in creating the DSID

Key challenges identified by NDL as fundamental to establishment of the DSID included:

a. identifying analytical priorities among the numerous DS products with various nutrient amounts available in the US;

b. identifying suitable analytical reference materials for analysis of unique matrices which are typical of DS;

c. assessing the effectiveness of sample preparation procedures and analytical methods for DS ingredients because few published reports give details of recommended methods;

d. identifying qualified laboratories with expertise in using complex nutrient analysis methods;

e. designing strategies to sample products that are representative of diverse market channels; and

f. developing a systematic approach for description and categorization of supplement products so that appropriate comparisons can be made when evaluating results.

Investigations of each challenge are described below, along with specific findings. A laboratory-based pilot study conducted for the purpose of addressing the key challenges of identifying qualified laboratories and methods of analysis is also discussed.

1.2. Overview of DS and MVM definitions

The Dietary Supplement Health and Education Act (DSHEA) of 1994 defines DSs to include forms such as gel caps, pills, capsules, and tablets, and in terms of ingredients and intended uses. DSHEA includes definitions of many terms relating to DS and specifies the rules for the contents of a DSs label (Food and Drug Administration (FDA), 1994). The supplement facts panel for each product must list nutrient content and percent contribution to the US Daily Value (%DV). The US %DV were developed by the FDA as label reference values for use by consumers in making point-of-purchase comparisons among foods relative to their nutrient content (IFIC, 2004). Specific forms of ingredients such as d- or dl-alpha tocopherol may be named in the supplement facts section or the ingredient section of the label (FDA, 2005).

The literature reveals that there is wide variation in the definitions of MVMs in current use. Even national surveys do not use a consistent definition (Yetley, 2007). The original working definition for MVMs for future DSID pilot study work was based upon a paper published by the National Center for Health Statistics (NCHS) in which several categories for supplement products were identified. In the NCHS paper, MVM products are defined as containing “three or more vitamins with or without minerals” (Radimer et al., 2004). This is the definition currently being used for MVM products in the DSID project.

2. Materials and methods for pilot study to evaluate methods and laboratories

2.1. Key challenge: (a) identification of analytical priorities among the numerous DS products with various nutrient amounts available in the US

Priorities were established to determine which nutrients and types of products to investigate first because examining the universe of DSs to obtain the analytical content of every product would be inordinately expensive. The initial step in prioritizing which product types to study was to obtain information on ingredient contents and reported consumption patterns of DS from the NHANES 1999–2000 DS data file (NCHS, 2004; Radimer et al., 2004). NHANES provides information obtained from nearly 5000 individuals annually, including food intake records assessed with two 24-hour dietary recalls plus reported DS intake over the previous

month. Products from this data set were grouped into general categories. Specific products reported three or more times were assigned to a general category based upon product name. These products within each category were summed and the categories were ranked by frequency of use. MVMs were the category of products reported most frequently, as noted earlier, and thus were identified to be studied first. Other highly ranked supplement product categories initially identified for analysis due to frequency of use were antacids, calcium supplements, B-complex, vitamin E and vitamin C products (Radimer et al., 2004).

To determine nutrient priorities for analysis, DS ingredients were ranked using a weighting system that included four factors: population exposure based upon frequency of reported use, research interest, availability of valid analytical methods and measurement capabilities, and public health importance (Dwyer et al., 2006). Each factor was assigned a weight given the relative importance and each item was scored for that factor. The weighted scores were then rank ordered to yield a priority list. The seven highest priority DS ingredients designated as “Tier 1” nutrients were folic acid, vitamin C, retinol, beta-carotene, vitamin E (alpha-tocopherol), calcium, and iron. Second priority “Tier 2” nutrients identified for subsequent study following completion of Tier 1 analysis were riboflavin, thiamin, niacin, vitamin B-6, vitamin B-12, vitamin D, vitamin K, phosphorus, potassium, copper, selenium, chromium, manganese, magnesium, zinc, and iodine. Ingredients of lower priority will be considered for study in later phases of DSID research (Dwyer et al., 2007).

2.2. Key challenge: (b) identification of suitable reference materials for analysis of matrices typical of DSs

Appropriate reference materials for analysis of nutrients in DS are essential for validation of the methods used to analyze these products and for on-going quality control. Certified reference materials (CRMs) are used as reference samples for assessment of inter-laboratory variability, for providing traceability of values of an in-house control material, determining whether a method is controlled during routine use, and for testing accuracy of the assay system during development of an analytical method (Phillips et al., 2007). CRMs available for vitamins and minerals at the time of the study were only food-based matrices. Nutrient levels are significantly lower in the foodbased reference materials than in the MVM samples. For this study, a MVM standard reference material (SRM) under development in a partnership between the National Institute of Standards and Technology (NIST) and ODS, SRM 3280, was donated by NIST (Sharpless et al., 2004). Certified values for many of the nutrients of interest will be available from NIST in 2007. Specific reference materials used in this study are listed in the discussion of laboratory methods.

2.3. Key challenges: (c) assessment of sample preparation procedures and laboratory methods of analysis and (d) identification of qualified laboratories

A limited number of analytical laboratories have the necessary capability and requisite experience to analyze DSs. The matrix effects of capsules, pills, and gel caps should be considered when determining the adequacy of proper laboratory sample preparation procedures and nutrient analysis techniques. The applicability of established food and pharmaceutical methods to the analysis of multi-ingredient supplements must be assessed.

Manufacturing processes specific to DSs that may affect analytical results must also be considered. Manufacturers and other industry representatives have indicated that amounts of some nutrients are added in excess to allow for possible degradation throughout the shelf-life so that the labeled amounts are still contained in the product when it reaches its expiration date. Certain ingredients such as vitamin B-12 and beta-carotene are encapsulated for longterm protection. The coating may be composed of protein, starch, or alginate material. Encapsulation presents analytical challenges because the beadlets (agglomerates of

granules containing vitamins or other ingredients within the tablet) may be unevenly distributed within the MVM tablet rather than be homogenously blended, and the coating thickness of the beadlets may be inconsistent (Szpylka and Devries, 2005).

An analytical pilot study was conducted to address key challenges of DS nutrient analysis, specifically for MVM products. The purpose was to assess sample preparation and method protocols to obtain consistent and accurate results. This work was done to identify laboratories to be used for subsequent studies as well as to establish preferred protocols for sample handling.

For this study, MVM-1, a commercial product, was purchased in bulk (6000 pills of a single lot). Product MVM-2 was NIST SRM 3280, under development, provided by NIST. MVM-1 and MVM-2 were sent to multiple laboratories for the analysis of the Tier 1 nutrients identified above. The products were sent three times over a period of several months. Six commercial and research laboratories experienced with the analysis of DSs and the analysis of vitamin and minerals participated in this study. From among the six participating laboratories, four laboratories were selected to analyze samples for each nutrient. All six laboratories analyzed at least two nutrients. Decisions regarding which nutrients would be analyzed at each laboratory were based upon laboratory experience, capabilities, and to a lesser extent, laboratory cost.

Each laboratory was sent blinded samples of the two MVM products, plus one reference material. MVM-1 was sent in duplicate for selected nutrients. Each batch sent for analysis included the MVM-1 product, the MVM-2 product, and one or more of the following food-based SRMs or CRMs:

1. NIST SRM 1846, Infant Formula, for vitamin C, folic acid, calcium, and iron.
2. CRM 421(vitamin-enriched milk powder made by BCR, a producer of reference materials located in Belgium) for alpha-tocopherol.
3. Bureau Communautaire de Références (BCR) 485 (lyophilized mixed vegetables) for beta-carotene; or
4. VMA 399 (fortified ready-to-eat cereal from American Association of Cereal Chemists) for retinol.

The laboratories were instructed to weigh and homogenize 20 tablets of each MVM sample. A 20-tablet composite was used for sub-sampling to minimize errors that may occur due to variability in ingredient composition for individual tablets. This is recommended practice by the US Pharmacopeia for such products (USP, 2002). Laboratories were given general information about each sample matrix and approximate ranges expected for each nutrient. The laboratories were instructed to use their customary methods of analysis for each nutrient and to report these protocols and methods with the results. Instructions were given to assay all samples on the same day that they were homogenized and to analyze all samples in a batch in the same run.

3. Results of pilot study to evaluate methods and laboratories

3.1. Sample preparation results

Homogenization equipment used in the six participating laboratories varied, and included mortar and pestle, coffee mill, and other high-speed mills. Five of the laboratories homogenized 20 pills for analysis, and one laboratory homogenized 12 pills. Most laboratories in this study used saponification in the analysis of the fat-soluble vitamins to release vitamins from any potential encapsulation. However, one laboratory failed to

mention any sample handling methods specific to encapsulation. Five of the six laboratories provided detailed reports of their standard operating procedures.

3.2. Laboratory and method evaluation for seven Tier 1 nutrients

Results obtained from four laboratories for each nutrient were evaluated. To assess within—laboratory precision (n = 3 replications), the relative standard deviation (RSD) for each nutrient was calculated (standard deviation/analytical mean times 100). The RSD range for folic acid for all labs (n = 4 labs) was 3.0–31.5%; for alphatocopherol, 1.7–10.3%; for iron, 0.5–16.6%; for vitamin C, 2.1–29.5%; for calcium, 0.8–9.2%; for beta-carotene, 2.9–30.9%; and for retinol, 2.4–24.1%.

Four of the six laboratories showed acceptable method precision and sample handling procedures for at least one of the seven Tier 1 nutrients. These laboratories were chosen to participate in the analysis of the Tier 2 nutrients (seven vitamins and nine minerals) for a total of 23 nutrients in the MVM samples (n = 5); two laboratories were not sent additional samples. One to three of the four laboratories were assigned analysis of each Tier 2 nutrient. The research protocols used for Tier 1 nutrients were used for Tier 2 nutrients, except that food-matrix SRMs were not sent, in anticipation of using the NIST SRM 3280 preliminary values. Any specific questions or issues that arose during this initial phase were discussed with the laboratories.

3.3. Laboratory and method evaluation for 23 nutrients

For each nutrient, one to three labs analyzed the two MVM products five times over a period of several months. (Tier 1 nutrients were analyzed two additional times.) RSDs were calculated and evaluated as a measure of precision for each nutrient. Table 1 lists method summary, method reference, and RSD information obtained for each nutrient by each laboratory.

For quantification of water-soluble vitamins (ascorbic acid [vitamin C], vitamin B-6, niacin, riboflavin, and thiamin) high performance liquid chromatography (HPLC) methods were used. Folic acid was analyzed by laboratories using both HPLC and microbiological techniques. Vitamin B-12 was determined using a microbiological assay. For the water-soluble vitamins, analytical RSDs indicating betweenday variability in acceptable laboratories were below 10%, or between 10% and 15%, except for vitamin B-12 where variability as high as 30% was noted.

The fat-soluble vitamins were analyzed using HPLC. Analytical RSDs were approximately 10% for alpha-tocopherol (vitamin E) and vitamin K. Variability was higher for beta-carotene, retinol, and vitamin D, with analytical RSDs between 15% and 20%.

For most minerals evaluated in the study, analysis by inductively-coupled plasma (ICP) optical emission spectro-metry was used. Iodine, chromium, and selenium were exceptions. Iodine was analyzed using thiosulfate titration, chromium analysis was by graphite furnace atomic absorption spectrometry, and selenium analysis was by atomic absorption. Analytical RSDs for the minerals analyzed by ICP at acceptable laboratories were at or below 10%, and sometimes below 5%. The analytical RSD for iodine was less than 20%, while selenium and chromium were less than 15%.

A panel of federal experts and scientific consultants on analytical methods convened to review this pilot study data and to identify laboratories, methods of analysis and acceptable RSD ranges to be used for subsequent studies. The panel included individuals from ODS, FDA, NIST, NDL, and the Food Composition Laboratory of ARS, USDA. In addition to within-laboratory precision for each nutrient, analytical means were compared to

preliminary data from several government laboratories for the two MVM products to evaluate accuracy. Acceptable laboratories were determined to be those having both acceptable methods and acceptable precision which was defined as RSD <10% for most nutrients. However, experts agreed that the acceptable methods for chromium, iodine, and vitamins were such that acceptable precision was from <15% to <20% (Dwyer et al., 2007).

Tables 2 and 3 summarize the methods and RSD levels for each nutrient having acceptable precision data and acceptable preliminary accuracy assessments. For most nutrients, one or two laboratories were identified as acceptable to carry out future work. For iodine and vitamin B-12, only one laboratory was identified to perform subsequent analyses. It should be noted that this information on laboratory methods and precision is a work in progress. The applicability of this information is limited because it represents only results from laboratories and specific methods used in this study.

3.4. Identification of laboratories for future work

A competitive government contract process was conducted to request proposals and award contracts. Several laboratories were identified for future work using criteria of technical merit, quality control procedures, organizational qualifications, past performance, and demonstration of acceptable performance on analytical check samples (Dwyer et al., 2007).

4. Discussion of sampling and categorization strategies for DSID

4.1. Key challenge: (e) development of strategies to sample products that are representative of diverse market channels

Once laboratories were identified, planning began for analysis of samples of representative MVM products. Sampling plans must consider factors such as product characteristics, frequency of use, and consumer market channels. NDL has developed a sampling plan for foods and beverages, established in cooperation with statisticians from the USDA National Agricultural Statistics Service (NASS). The plan permits the selection of sample units from multiple geographic areas of the US to obtain reliable and representative estimates of means with known variability for nutrient content (Pehrsson et al., 2006). The research design used for this type of sampling is a stratified random sampling survey, in which a group of sampled units (supplement products) are drawn from an underlying population and a set of measurements (component assays) are made on these units (Cochran, 1977; Holden and Davis, 1995). The probability that a supplement product is sampled is linked to the likelihood that the product was produced and consumed, so that the analytical data yields unbiased estimates of the mean and variance of component content. NDL has consulted with statisticians to set up a sampling frame and product-specific plans for the collection of DS product samples, to assure that samples being analyzed represent a defined population. In addition to the experience acquired in the NDL sampling program for foods, other resources used to develop current DSID sampling plans include NHANES DS data files which are populationweighted to indicate reported usage trends, current market data showing product-specific channels, and extensive consultations with NASS and other cooperating statisticians.

Consumers purchase DSs from a variety of channels, not only “brick and mortar” retail outlets such as supermarkets and drug stores. Market data can provide details regarding commonly used supplement product brands, types, and market channels (Roseland, 2007). These data are useful in developing sampling plans for purchasing representative products proportional to estimated use in geographic regions across distribution channels, including mass market retail, natural food and health stores, Internet, multi-level marketing, and direct sales.

For evaluating individual nutrient variability within a specific supplement type such as MVMs, nutrient levels in representative products can be analyzed according to a sampling plan that selects products statistically representative of those typically consumed.

4.2. Key challenge: (f) development of approach for description and categorization of products

Because of the many dimensions of DS product characteristics and intended uses, a multi-faceted approach for categorization by function, type, or number of specific nutrients is needed for the development of the DSID. Identifying these characteristics and other factors such as intended specific user groups and intended health benefits may be helpful for database and research purposes. Four criteria to apply when developing supplement product categories are discussed by Dwyer et al. (2007). Without a system with which to group similar products, appropriate comparisons of analytical levels cannot be made when evaluating results. In addition, categorization of DSs is essential for identifying appropriate products for chemical analysis. The DS data files from NHANES 1999–2000 were the starting point for identifying logical groupings of these products.

First, the NHANES file was sorted to obtain a list consisting only of products containing one or more of the dietary reference intake (DRI) nutrients for which recommended intake requirements were provided. DRI nutrients are vitamins and minerals with reference values that are quantitative estimates of recommended nutrient intake for use in planning and assessing diets for healthy people in a variety of settings, including labeling purposes (IOM, 2000). The resulting data set consisted of 1319 supplements with labeled nutrient amounts. Labeled nutrient amounts for each supplement were converted to standard units where necessary and then to percent DV (% DV) so that data could be compared from one product to another. For example, where 400 International Units (IU) of vitamin D was listed in the NHANES file, the equivalents of 10 micrograms and 100% DV were calculated for the DSID data file.

This data set was then evaluated using cluster analysis, configuration analysis, and individual nutrient analysis. For the cluster analysis, the % DV file was sorted for products containing vitamins and minerals up to 1000% DV, resulting in a data set of 1080 supplements. This data set was analyzed applying both the SAS Version 8.1 (SAS, 1999) Fastclus procedure and hierarchical cluster procedure, but clusters of nutrient content patterns could not be clearly defined for products containing vitamins. A subset of supplement products ($n = 273$) containing no vitamins and at least one of the DRI minerals resulted in eight clusters of mineral content patterns. Data sets with at least one vitamin had even more numerous patterns, making them more complicated and requiring further statistical analysis.

For the configuration analysis, the NHANES 1999–2000 data were sorted based only upon the criteria of presence or absence of the DRI ingredients. The list of 1319 DSs showed a total of 484 configuration patterns, indicating that ingredient patterns are not consistent, even when ingredient levels are removed from consideration.

Because no obvious product groupings were apparent using the previously mentioned strategies, each nutrient was individually evaluated in MVM products. When the NHANES data ($n > 2$ vitamins) were sorted by nutrient and each nutrient sorted and then summed by %DV level, it became obvious that there were some ingredient levels more commonly found than others. For vitamins and minerals in different MVM products, numerous levels of specific nutrients were present but three or four levels were most commonly found. This individual nutrient grouping system was used as the basis for sampling representative MVM products for the next study.

5. Future plans

Following the analytical pilot study, an individual nutrient study was planned and conducted, comparing labeled versus analytical nutrient values. Up to 4 of the most common %DV levels for each of the 23 nutrients were identified, and 6 products from each level were analyzed for each nutrient. This %DV specify study will evaluate the variability for products labeled at the most common nutrient levels and will aid in planning the scope and number of samples to be analyzed in future studies.

In addition, a study is being planned to analyze multiple lots of adult MVM products that are commonly reported in the US. The objectives of the study are to estimate actual content for priority nutrients in these products using samples obtained nationwide and assess variability among lots based upon the geographic sampling plan (US Department of Agriculture, 2007). Results from these analytical studies will be used to make initial observations on actual content per nutrient and variability within and among products.

6. Conclusions

Preliminary work has addressed key challenges of DS research by prioritizing nutrients and products, using appropriate reference materials, establishing sample preparation procedures, determining valid protocols for products with unique matrices, defining representative sampling plans, and considering categorization criteria for supplements.

Statistical applications such as modeling will be used to consider valid ways to apply the analytical results to make reasonable estimates of nutrient content for DS product and nutrient categories. During this process, NDL scientists will consult with statisticians to consider options for regression analysis examining nutrient levels in DS products.

A comprehensive relational database will be developed for the final release of the DSID (DSID-1), applying the statistical findings from analytical results. This database will incorporate the needs of major stakeholders and customers. The DSID will include estimates of actual nutrient intake from supplements including indications of reliability of data, enabling researchers to make better estimates of nutrient intake than by using databases that rely on label values alone. Data will be provided in a publicly accessible format. The DSID will be made available to the public on the NDL website (www.ars.us-da.gov/dsid).

When completed, the DSID will contain analytically verified data for assessing the total US intake of nutrients and other components from foods and supplements.

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Table 1

Methods and precision for individual laboratories analyzing two multivitamin/mineral products

Nutrient	General methology[a]	RSD[b] for MVM-1	RSD[b] for MVM-2	Primary method source[c]
Ascorbic acid	Fluorometric	4.32	4.13	AOAC 967.22[d]
	HPLC UV/VIS detection	14.67	15.47	In-house method[e]
	Reverse phase HPLC electrochemical detection	12.67	13.11	In-house method[e]
Folic acid	Microbiological method	4.43	4.41	AOAC 944.12[d]
	Microbiological trienzyme method	14.93	15.14	AOAC 2004.05[d]
	Reverse phase HPLC-UV/VIS detection	2.44	4.61	USP 26[f] Assay ⟨411⟩ method 1
Niacin	HPLC with UV detection at 270nm	1.76	6.04	USP 28[h] Assay ⟨441⟩
	HPLC with UV detection at 280nm	8.39	6.89	USP 23[h] Assay ⟨441⟩
Riboflavin	HPLC with UV detection at 270nm	5.86	6.03	USP 28[g] Assay ⟨481⟩
	HPLC with UV detection at 280nm	5.99	3.65	USP 23[h] Assay ⟨481⟩
Thiamin	HPLC with UV detection at 270nm	5.22	8.63	USP 28[h] Assay ⟨481⟩
	HPLC with UV detection at 280nm	6.92	6.36	USP 23[h] Assay ⟨531⟩
Vitamin B-6	HPLC with UV detection at 270nm	8.89	8.58	USP 28[g] p. 2166
	HPLC with UV detection at 280nm	11.67	7.48	USP 23[h] p. 2153
Vitamin B-12	Microbiological	26.44	8.55	AOAC 952.20, 960.46 Assay ⟨441⟩
Alpha-tocopherol	HPLC fluorescence detection (Ex λ = 290, Em λ = 330)	3.07	5.01	In-house method[e]
	HPLC fluorescence detection (Ex λ = 290, Em λ = 330)	15.10	16.31	In-house method[e]
	Reverse phase HPLC fluorescence detection	9.60	4.80	In-house method[e]
Beta-carotene	Reverse phase HPLC with UV light detection	23.87	21.63	In-house method[e]
	Reverse phase HPLC with UV/VIS detection at 450 nm	15.26	14.55	In-house method[e]
Retinol	HPLC with UV detection at 325nm	11.37	17.58	AOAC 992.04[d]
	HPLC with UV detection at 325nm	9.17	8.68	In-house method[e]
	Multi-phase extraction with HPLC-UV/VIS detection at 325 nm	4.38	5.60	USP 23[h] Assay ⟨571⟩
Vitamin D	HPLC with UV 254nm	26.02	5.03	AOAC 982.29[d]
	HPLC at UV 265nm	10.07	16.13	USP 23[h] Assay ⟨581⟩
Vitamin K	HPLC fluorescence detection	8.63	12.45	AOAC 999.15[d]
	HPLC fluorescence detection	5.98	3.98	In-house method[e]
Calcium	AAS and ICP	7.01	5.94	AOAC 985.01[d]
	Multi-element ICP-AES	3.49	5.80	EPA 200.7[i]
Copper	Multi-element ICP-AES	1.17	4.26	AOAC 985.01[d]
	Multi-element ICP-AES	5.79	8.14	EPA 200.7[i]
Iron	AAS at 248.3 and ICP	4.73	3.39	AOAC 985.01[d]

Nutrient	General methology[a]	RSD[b] for MVM-1	RSD[b] for MVM-2	Primary method source[c]
	Acid digestion with multi-element ICP-AES detection at 259.94 nm	10.19	8.94	EPA 200.7[i]
Magnesium	Multi-element ICP-AES	1.35	2.11	AOAC 985.01[d]
	Multi-element ICP-AES	3.71	8.67	EPA 200.7[i]
Manganese	Multi-element ICP-AES	1.90	1.16	AOAC 985.01[d]
	Multi-element ICP-AES	13.52	14.29	EPA 200.7[i]
Phosphorus	Multi-element ICP-AES	1.80	1.30	AOAC 985.01[d]
	Multi-element ICP-AES	12.69	9.32	EPA 200.7[i]
Potassium	Multi-element ICP-AES	5.00	2.33	AOAC 985.01[d]
	Multi-element ICP-AES	9.62	4.99	EPA 200.7[i]
Zinc	Multi-element ICP-AES	2.55	2.02	AOAC 985.01[d]
	Multi-element ICP-AES	7.61	6.01	EPA 200.7[i]
Chromium	AAS	2.02	7.56	EPA 218.1[i]
	Multi-element ICP-AES	19.98	23.99	EPA 200.7[i]
Iodine	Thiosulfate titration	10.80	10.66	AOAC 935.14, 932.21[d] and USP 23[h]
Selenium	AAS	5.12	8.60	AOAC 986.15[d]
	Multi-element ICP-AES	6.16	4.46	EPA 200.7[i]

[a] HPLC = high performance liquid chromatography, UV/VIS = ultraviolet-visible spectrophotometry, AAS = atomic absorption spectrometry, ICP = inductively-coupled plasma optical emission spectrometry, AES = atomic emission spectrometry.

[b] RSD = relative standard deviation (n = 5).

[c] Method used may be a modified method.

[d] AOAC = AOAC, 25.

[e] Laboratory combined procedures from several sources or used an unpublished method.

[f] USP 26 = USP, 2002.

[g] USP 28 = USP, 2004.

[h] USP 23 = USP, 1995.

[i] EPA = EPA, 1994.

Table 2

Acceptable methods and relative standard deviations for minerals in DSID preliminary studies

Nutrient	Acceptable method of analysis[a]	Acceptable relative standard Deviation	Number of acceptable laboratories
Calcium	ICP	<10	2
Copper	ICP	<10	2
Iron	ICP	<10	2
Magnesium	ICP	<10	2
Manganese	ICP	<10	2
Phosphorus	ICP	<10	2
Potassium	ICP	<10	2
Zinc	ICP	<10	2
Chromium	Graphite furnace AAS	<15	1
Iodine	Thiosulfate titration	<20	1
Selenium	AA	<15	1

[a] ICP = inductively-coupled plasma optical emission spectrometry, AAS = atomic absorption spectrometry, AA = atomic absorption.

Table 3

Acceptable methods and relative standard deviations for vitamins in DSID preliminary studies

Nutrient	Acceptable method of analysis[a]	Acceptable relative standard deviation	Number of acceptable laboratories
Folic Acid	Microbiological	<10	3
Niacin	HPLC with UV/VIS detection	<10	2
Riboflavin	HPLC with UV/VIS detection	<10	1
Thiamin	HPLC with UV/VIS detection	<10	2
Vitamin B-12	Microbiological	<30	1
Vitamin B-6	HPLC with UV/VIS detection	<10	2
Ascorbic acid	HPLC-fluorescence	<10	1
Alpha-tocopherol	HPLC with fluorometric detection	<10	1
Beta-carotene	HPLC with UV/VIS detection	<20	2
Retinol	HPLC	<15	2
Vitamin D	HPLC	<20	2
Vitamin K	HPLC	<10	Additional method validation necessary

[a] HPLC = high performance liquid chromatography, UV/VIS = ultraviolet-visible spectrophotometry.