USDA Dietary Supplement Ingredient Database Release 4.0 (DSID-4)

Adult Multivitamin/mineral (AMVM-2017) Dietary Supplement Study

Research Summary

Prepared by

Dietary Supplement Ingredient Database Team

Karen W Andrews, Pavel A Gusev, PhuongTan Dang, Sushma Savarala, Laura Oh, Renata Atkinson and Malikah McNeal

August 2017

US Department of Agriculture
Agricultural Research Service
Beltsville Human Nutrition Research Center
Nutrient Data Laboratory
10300 Baltimore Avenue
Building 005, Room 107, BARC-West
Beltsville, Maryland 20705
Voice: 301-504-0630, Fax: 301-504-0632
Email: ndlinfo@ba.ars.usda.gov

1. Introduction

Nearly half of US adults report taking dietary supplements (DS) (1). A single serving of a DS may contain amounts of nutrients or other bioactive compounds that exceed their concentration in foods. During the manufacturing of DS, ingredients may be added in amounts exceeding the label claims in order to compensate for losses during shelf life. However, these amounts are not standardized for specific ingredients or among the different manufacturers. DSID pilot studies have also identified a number of ingredients in a variety of product categories with mean content below label claims. Thus, actual ingredient amounts are unknown to consumers and researchers. Epidemiological studies of nutrient intake and health currently use the manufacturer's label as the source of information on ingredient content in dietary supplements.

In order to provide a tool to more accurately estimate intakes from dietary supplements, an analytically validated database for high priority ingredients in dietary supplement products has been developed. The Dietary Supplement Ingredient Database (DSID; https://dsid.usda.nih.gov) is a collaboration of the Agricultural Research Service (ARS)/ Nutrient Data Laboratory (NDL), and the National Institutes of Health (NIH)/Office of Dietary Supplements (ODS) with other federal partners (National Center for Health Statistics of the Centers for Disease Control and Prevention, Food and Drug Administration, National Cancer Institute of the National Institutes of Health and National Institute of Standards and Technology [NIST] of the Department of Commerce). ODS is the primary funder of the DSID, which builds on the well-recognized strengths of the NDL in developing databases that support assessments of intakes of nutrients from foods. For national DSID studies, representative supplement products are purchased and tested by experienced laboratories for their ingredient content.

In previous releases of the DSID, analytical estimates from the first adult MVM (AMVM-2009) study (2), were reported. The relationships between the analytical and labeled content in these nationally representative adult MVM samples were evaluated by weighted regression analysis. The DSID estimates were based on adult MVMs purchased in 2006-07 as part of a sampling plan incorporating information from a variety of sources. Results were first reported in 2009. The DSID application tables for the adult MVM-2009 study data are linked to NHANES 2003-2008 files (the 2 year cycles preceding, coinciding with and following the products' year of purchase).

The second adult MVM (AMVM-2017) study was initiated to answer questions about how the adult MVM label information and ingredient levels change over time. The goal of this study was to assess to what degree DSID adjustments are time-specific or applicable to additional cycles of NHANES. In addition, new ingredients were added to the DSID for this product category. Vitamins A and D, and chromium are a particular focus in this study due to public health interest and improvements in analytical methodology for these ingredients.

2. Overview of the Adult MVM-2017 Study

A study of adult MVMs (dietary supplements containing three or more vitamins with or without minerals or other bioactive components) was conducted to estimate the relationship between label values and analytical values for 21 vitamins and minerals.

Products identified as representative of the US market were purchased from nationwide retail outlets and through direct-to-consumer sales channels. Samples of multiple lots of these products were sent to qualified laboratories for the analysis of ingredients using validated methods and appropriate quality assurance measures. The final analytical dataset was statistically analyzed using regression techniques to estimate relationships between label claims and analytically measured ingredient content at a range of label levels.

3. Sampling Plan

A national sampling plan for adult MVMs was developed to identify and purchase dietary supplement product samples that represent the US market. A national sampling of adult MVMs was conducted for two purposes:

- To provide representative estimates for ingredients in products commonly reported by the US population (top market share [TMS] products).
- To obtain additional data on lower-market share (LMS) products identified as representative and purchased in different regions of the country.

Representative adult MVM products were identified using weighted frequency data from the NHANES 2007-08, a 2010 DS use survey by an independent marketing firm, and 2010 market share information from the Nutrition Business Journal (3). To attain geographically diverse sample sources across different market channels and to combine precise estimates of mean content with reliable assessments of product and lot variability, a statistical plan was developed for DS purchase. In 2011, 124 products were purchased. Retail products were purchased in 6 representative U.S. counties in 6 states, with 64 (three lots each) from the mass market channel (e.g., Safeway, Target, Sam's Club), and 30 (three lots each) from the natural health channel (e.g., Whole Foods, GNC, organic markets). Thirty (30; two lots each) were purchased from direct channels (products sold exclusively on-line or from multi-level marketers like Amway).

4. Laboratory Analysis and Quality Control

The purchased products were sent to NDL for processing. Relevant information on each product purchased (e.g., ingredient names and levels, lot number, purchase location and date, and expiration date) was recorded in NDL's in-house database. Samples were repackaged and sent for laboratory analysis in defined batches. Each product sample sent to labs contained at least 30 units (tablets, capsules or liquid serving amounts) of the MVM product. Labs were instructed to homogenize at least 30 sample

units before sub-sampling for analysis (per the United States Pharmacopeia (USP) recommendations for the analysis of dietary supplements).

Qualified analytical contract laboratories analyzed the sample sets using validated sample-handling protocols and appropriate methods to obtain analytical information about ingredient levels (Table 1). The major components of vitamin A (retinol and beta-carotene) were measured separately, converted to international units (IU) and combined to calculate total vitamin A for comparison to label levels.

Table 1. Analytical Methods

Nutrients	Analytical Method Used
Calcium Copper Iron Magnesium Manganese Phosphorus Potassium Zinc	Multi-element inductively coupled plasma spectrometry (ICP) with wet ashing methodology
Selenium	Hydride generation/atomic absorption spectroscopy
Iodine	ICP- mass spectroscopy (MS) with wet ashing
Chromium	ICP- mass spectroscopy (MS) with wet or dry ashing
Beta-carotene Retinol	High-performance liquid chromatography (HPLC) with ultraviolet detection at 542 nm
Niacin Riboflavin Thiamin Vitamin B6	HPLC with ultraviolet detection at 210 nm
Vitamin C	HPLC with ultraviolet detection at 254 nm
Folic acid	Microbiological method using the bacteria, *Enterococcus hirae*
Vitamin B-12	Microbiological method using the bacteria, *Lactobacillus delbrueckii*
Vitamin E	HPLC with fluorescence detection
Vitamin D	HPLC-MS-MS

Quality control (QC) materials were analyzed with samples of adult MVM products to evaluate laboratory precision and accuracy. NIST Standard Reference Material (SRM) 3280, an MVM matrix with certified values for vitamins and minerals, was sent in each

batch to monitor laboratory measurement accuracy. In addition, each batch included a set of product duplicates (two sets of 30 tablets/capsules of the same MVM product with different test sample identification numbers) that were analyzed for all ingredients in the study, and at least two in-house control materials. For each in-house control material, a case of a single lot of an adult MVM product was purchased and samples were sent with each batch to evaluate the precision of laboratory methods over time in a matrix similar to the study products.

Analytical retests for ingredients in specific products were conducted to check unusually high or low results, high variability among product lots, and questionable data in batches where QC results showed a bias. For each sample analyzed, laboratory results reported in mg/g or µg/g were compared to label levels and a percent difference from the label levels was calculated.

5. Statistical Analysis

Ingredient data from laboratory analyses were prepared for weighted regression analysis by applying market share estimates as product weights. Market share estimates were based on data from NHANES and from an independent marketing firm, as previously discussed in Section 3. To identify overly influential supplement observations, a jackknife technique was used to calculate Cook's distances and restricted likelihood distances.

Relationships between the label and percent difference from label were estimated by regression with SAS® mixed model procedures. For each supplement ingredient, the label value was the independent variable and the percent difference from the label level (based on the laboratory analysis) was the dependent variable. Percent differences from label were calculated: ((analytical value – label value)/label value) × 100%. Three models (mean, linear and quadratic) were used to fit the data for all ingredients, and the most complex and statistically significant model was selected. Lab, supplement within label level and lot within supplement were modeled as random sources of variation. The accuracy of the models' predictions was assessed with validation techniques.

The selected regression equations were used to predict mean analytical levels for each ingredient in adult MVMs: label value × (1 + predicted percent difference/100). In the DSID-4 files, these mean predictions are shown in data tables as predicted percent differences from the label levels or as predicted mean values in international units (IU), mg, or µg per serving or per day.

In addition, the standard error of the mean (SEM), 95% confidence intervals (CI) for the mean, and the standard error (SE) of an individual observation were calculated at each label level. Because the regression equation could be used to predict ingredient values of independent supplement samples, SE were adjusted to reflect this expected greater prediction variability.

6. Results and Discussion

Detailed results for this study, including regression equation parameters and predicted values, are listed in the data files released in DSID-4. Regression results are reported for 21 vitamins and minerals: folic acid, niacin, riboflavin, thiamin, vitamin A, vitamin B-12, vitamin B-6, vitamin C, vitamin D, vitamin E, calcium, chromium, copper, iodine, iron, magnesium, manganese, phosphorus, potassium, selenium, and zinc. Regression results for mean predicted percent differences from the label amount and the associated SE and CI varied by ingredient and, in some cases, by ingredient level.

The regression results and SEM for the most common labeled level for each ingredient in the adult MVM-2 study are summarized in Tables 2 and 3 below. Table 2 lists the predicted mean percent differences from labeled levels for vitamins, and Table 3 does the same for minerals. If a linear or quadratic regression model was selected, a range of label levels was predicted. If a means model was selected, the predicted mean percent difference was not dependent on the label level.

Table 2. Predicted Mean Values for Vitamins in Adult MVMs-2

Ingredient	Range of Predicted Mean Percent Differences from Label Levels	Most Common Label Level per Serving	Predicted Mean Percent Difference at Most Common Label Level	Predicted SEM at Most Common Label Level
Folic acid	-15.4% to 24.0%	400 µg	23.6%	1.9%
Niacin	4.48%	20 mg	4.48%	0.96%
Riboflavin	1.95% to 18.7%	1.7 mg	17.4%	2.4%
Thiamin	-3.52%	1.5 mg	-3.52%	1.1%
Vitamin A	-8.52 to 49.3%	3500 IU	25.6%	2.6%
Vitamin B-12	21.8%	6 µg	21.8%	2.2%
Vitamin B-6	9.08%	2 mg	9.08%	1.6%
Vitamin C	5.08%	60 mg	5.08%	1.4%
Vitamin D	19.8% to 45.5%	400 IU	40.5%	1.4%
Vitamin E	9.36%	30 IU	9.36%	1.9%

Table 3. Predicted Mean Values for Minerals in Adult MVMs-2

Ingredient	Range of Predicted Percent Differences from Label Levels	Most Common Label Level per Serving	Predicted Percent Difference at Most Common Label Level	Predicted SEM at Most Common Label Level
Calcium	8.09%	200 mg	8.09%	2.0%
Chromium	9.67% to 29.4%	120 µg	20.4%	2.0%
Copper	-1.55% to 15.4%	2 mg	6.42%	2.3%
Iodine	20.2%	150 µg	20.2%	2.8%
Iron	0.84%*	18 mg	0.84%*	1.6%
Magnesium	-0.23%*	50 mg	-0.23%*	1.4%
Manganese	4.42% to 13.0%	2 mg	7.43%	0.79%
Phosphorus	-3.90% to 15.2% to	20 mg	15.2%	2.3%
Potassium	-1.70% to 5.29%	80 mg	2.50%	0.55%
Selenium	10% to 26.4%	55 µg	23.9%	1.7%
Zinc	3.92% to 13.9%	15 mg	4.55%	0.70%

*Not significantly different from label

For two minerals, iron and magnesium, the mean predicted amounts were not significantly different from label claims. For all vitamins, the mean predictions were significantly different from label. Five ingredients (niacin, vitamin B-6, vitamin C, vitamin E, calcium) had predicted mean percent differences from label between 0% and 10% above label at the most common label level and across the entire regression range (mean models). Seven ingredients (chromium, iodine, selenium, folic acid, vitamin A, vitamin B-12 and vitamin D) had predicted mean percent differences from label >20% above label level at the most common label level. Folic acid, vitamin A and vitamin D had the largest ranges of percent differences from label (up to 69% for retinol) followed by selenium, chromium, copper, and phosphorus (up to 19% for chromium). One ingredient, thiamin, had predicted means slightly below label level for the entire regression range.

In both adult MVM-2009 and adult MVM-2017 studies, overages in mean ingredient content, at the product level, were found for most vitamins (with thiamin a consistent exception) and minerals (all but magnesium in adult MVM-2017). An evaluation of changes in the percent differences from label, variability and in regression models are pending. The information obtained from this monitoring study will be used to plan the frequency and scope of updates to the DSID in order to provide up-to-date tools for nutrient intake assessment from MVM and other DS.

We now provide estimates for chromium and vitamins A and D in adult MVMs, which were found to have mean percent differences from label ranging from 20-40% above label. More detailed results for the adult MVM-2017 study are available on the “Data

Files" page of the DSID website. DSID application tables and linking codes are also provided for the 2009-2014 NHANES DS files.

7. Use of DSID Data

The regression equations for the adult MVM-2017 study released in DSID-4 (Table 1) predict the mean percent differences from label levels for 21 ingredients in dietary supplements consumed in the United States. The predicted amounts are linked to label levels for each ingredient (Table 2 and adult MVM-2017 calculator) and are not specific to any brand or supplement. These predictions (predicted mean values) are intended for research purposes and are not meant to provide analytical estimates for ingredients in individual products.

Measures of variability are reported with predicted means, as discussed previously. The SE for an individual observation is much larger than the SEM because it represents the error of prediction for an individual sample vs. the error of prediction of a mean value for many products.

Results predicted by regression for mean percent differences from label level and SE have been assigned linking codes that may be applied to NHANES DS data files or used for other studies of DS intake. The predicted analytical content from the DSID can be used to replace label ingredient information to more accurately assess ingredient intakes from dietary supplements in *large* population surveys.

Documentation about the DSID-4 data files and instructions for appropriate use of the files are described in the report, *DSID-4 Data File Documentation,* available on the "Data Files" page of the website. Please refer to that report for additional information on how best to interpret and use each data file.

An online, interactive, Adult MVM-2017 Calculator has been released with DSID-4. This calculator allows the user to enter ingredient information from MVM labels and generate the appropriate predicted mean values, SE and CI for those labeled levels.

The adult MVM-2017 calculator is based on the chemical analysis of products purchased in 2011, and so provides more current data than the calculator with results from the original adult MVM (adult MVM-2009) study (products purchased in 2006-07). The calculator that is based on the adult MVM-2009 study is also available on the DSID website and can be used for historical data or trends analysis.

8. Future Research

DSID pilot studies are underway to evaluate ingredient quantities in prescription prenatal MVMs and green tea dietary supplements. In addition, a study evaluating the phytochemical content of botanical dietary supplements containing turmeric/curcumin is planned.

9. References

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