USDA Dietary Supplement Ingredient Database Release 2.0

DSID-2

Adult MVM Research Summary

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1. Introduction

The Nutrient Data Laboratory (NDL), Beltsville Human Nutrition Research Center (BHNRC), Agricultural Research Service (ARS), USDA, has been working with the Office of Dietary Supplements, National Institutes of Health (ODS/NIH) and other federal agencies to develop a Dietary Supplement Ingredient Database (DSID) to evaluate levels of ingredients in dietary supplement products. The DSID is funded, in large part, by the Office of Dietary Supplements. It builds on the well-recognized strengths of the USDA/ARS in developing databases that support the assessment of intake of nutrients from foods. ODS provides leadership, jointly with its federal partners, in making this a reality. The consortium of federal agencies includes ODS and partners at USDA/ARS, the National Center for Health Statistics of the Centers for Disease Control and Prevention (NCHS/CDC), the Food and Drug Administration (FDA) , the National Cancer Institute (NCI), NIH, and the National Institute of Standards and Technology (NIST) of the Department of Commerce.

For more detailed information on the background for this project and for information about the DSID pilot studies, please read the Background Information and Pilot Study Research Summary, available on the DSID-2 website.

2. Overview of the Adult MVM study and Data Releases

A study of adult MVMs (dietary supplements containing 3 or more vitamins) was conducted to estimate the relationship between label values and analytical values for 18 vitamins and minerals. Products identified as representative of the U.S. market were purchased from nationwide retail outlets and through direct 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 analysis techniques to estimate ingredient means and variability at a range of labeled levels. These statistical results and their NHANES application tables have been released in DSID-2 (http://dsid.usda.nih.gov).

NOTE: Adult MVM results were originally released in DSID-1 in April 2009. DSID-1 adult MVM results have been replaced with updated data for selected ingredients and statistical updates for additional ingredients. For more information, see section 6A, Adjustments to Data for DSID-2.

3. Sampling Plan

NDL develops multi-stage probability proportional to size (PPS) sampling plans for food and beverages in cooperation with statisticians from the USDA National Agricultural Statistics Service (NASS) (Pehrsson et al., 2000). The purpose of the sampling plan is to select sample units from multiple geographic areas of the U.S. that, when analyzed, can provide reliable and representative estimates of means and variability for nutrient content. Similarly, NDL has consulted with statisticians to set up a sampling frame and

product-specific plans for the collection of dietary supplement product samples, to assure that samples being analyzed are representative of the market place. The sampling frame was developed by first ordering the counties of the US by census region, district, generalized Consolidated Metropolitan Statistical Areas (gCMSAs), and county size. Then the locations for product sampling were selected proportional to the population, using Chromy's PPS, probability minimum replacement (PMR) procedure.

In addition to the experience acquired in the NDL sampling program for foods, other resources used to develop the dietary supplement sampling plans include National Health and Examination Survey (NHANES) dietary supplement data files which are population-weighted to indicate reported usage trends, market share information from the supplement industry, survey results from dietary supplement researchers, and consultations with cooperating statisticians.

NDL has conducted a national sampling of adult MVMs for two purposes:

- To provide nationally representative estimates for nutrients in products commonly reported by the U.S. population (Top Market Share (TMS) products).
- To obtain additional data for lower-market share (LMS) products for the purpose of conducting statistical regression analysis across a range of labeled nutrient levels.

To identify TMS adult MVMs, NDL commissioned an independent marketing firm to obtain current market data (2006) including the names of commonly reported adult MVMs by brand name and type. Data for the most frequently reported products were cross-referenced to product prevalence and frequency of intake information from two surveys: the National Health and Nutrition Examination Survey (NHANES) 2001-02 and the Multiethnic Cohort (MEC) study of supplements reported by adults in Hawaii and California (Murphy, 2006). The information was combined so that products currently on the market would be included along with products commonly reported in national surveys.

Based on the current national market-share data, the products identified as TMS represented over 55% of adult MVMs reported. Products were purchased in six U.S. states: MD, MN, TX, CA, GA, and VA. Samples (n=210) for 35 different products were obtained from retail market channels proportional to estimated use including mass merchandisers and health food stores. In addition, products were purchased from direct marketers, multilevel marketers, the internet, and medical practitioners.

Lower market share (LMS) adult MVM products were identified using NHANES 2003-04 dietary supplement data. LMS adult MVM products were defined as products with market share below the TMS products and reported in NHANES 2003-04 by >1 respondent or with >0.01% weighted frequency. Samples of approximately 80 representative LMS products were obtained from various market channels including mass merchandisers, health food stores, direct marketers, internet, and medical practitioners. Retail products were purchased in the same 6 geographic locations as the TMS products. All of the products analyzed for this study were purchased in 2006-

07. The levels of vitamins and minerals for up to six lots of each TMS product and up to three lots of each LMS product were measured in 2007-08.

4. Laboratory Analysis and Quality Control

Products were purchased in the channels and regions noted above and sent to NDL for processing. Relevant information from each product purchased (ingredient names and levels, lot number, purchase location and date, expiration date, etc.) was recorded in NDL's in-house database. Samples were repackaged and sent for laboratory analysis in defined batches.

Qualified analytical contract and collaborative laboratories analyzed the sample sets using validated sample-handling protocols and appropriate methods, to obtain analytical information about ingredient levels. Eight minerals (calcium, copper, iron, magnesium, manganese, phosphorus, potassium, and zinc) were analyzed by inductively-coupled plasma spectrometry (ICP) after wet-ashing. Selenium was analyzed by hydride generation/atomic absorption spectroscopy and iodine levels were determined by thiosulfate titration. Five vitamins (vitamins C and B-6, thiamin, riboflavin and niacin) were analyzed using high performance liquid chromatography (HPLC) with UV detection. Two vitamins (folic acid and vitamin B-12) were determined using microbiological methods and vitamin E was analyzed using HPLC with fluorescence detection.

For the adult MVMs, some data were received for vitamin A (beta-carotene and retinol), vitamin D and chromium, but concerns about methodological issues prevent the reporting of final data for these ingredients. Laboratory methods for these ingredients have improved and national estimates for these ingredients are reported in the children's MVM results published in DSID-2. NDL's follow-up study of adult MVMs, begun in 2012, is expected to provide data for these ingredients in a future DSID release.

Quality control (QC) materials were added to each batch of adult MVM products in order to evaluate laboratory precision and accuracy on an on-going basis. Each batch included a set of product duplicates (2 sets of 20 tablets of the same MVM product with different test sample IDs) 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 a MVM product with a similar matrix to the study samples was purchased. These control materials were added to each batch in order to evaluate precision of laboratory methods over time in a similar product matrix.

National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 3280, a MVM matrix with certified values for vitamins and minerals, was also sent in each batch. In this study, for nine of the 18 ingredients, mean analytical results were within 2% of the NIST certified or reference level. For seven ingredients, mean

results were within 2 to 6% of the NIST value and for two ingredients, mean analytical results were within 10-11% of the NIST levels.

Analytical retests for ingredients in specific products were identified 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 or µg/g were compared to labeled levels and a percent difference from label was calculated.

5. Statistical Analysis

Ingredient data from laboratory analysis were prepared for statistical analysis by averaging duplicate observations and obtaining market share product weights for weighted regression analysis. Market share weights were based on data from NHANES and from an independent marketing firm, as previously discussed in section 3. A jackknife technique was used to calculate CookDistances and the Restricted Likelihood Distance in order to identify overly influential supplement observations.

Using a SAS mixed model procedure, regression analysis was used to compare the label to analytical values across the full range of labeled levels. A regression equation was derived for each supplement ingredient using the label value as the independent variable and the percent difference from the label (based on the laboratory analysis) as the dependent variable.

The resulting equations predict mean analytical levels in the product category (expressed as a predicted percent difference from the label or as a predicted value in IU, mg or mcg/serving) for a range of labeled levels. In addition, the standard error of the mean (SEM) and the standard error of an individual observation were calculated at each labeled level. Since the regression equation can be used to predict ingredient values of independent samples of supplements, standard errors were adjusted using sums of squares to reflect this expected greater prediction variability.

6. Results and Discussion

In this study, final data are reported for the following 18 vitamins and minerals: folic acid, niacin, riboflavin, thiamin, vitamin B-12, vitamin B-6, vitamin C, vitamin E, calcium, copper, iodine, iron, magnesium, manganese, phosphorus, potassium, selenium and zinc. Regression results for mean predicted percent differences from label and the associated standard errors varied by ingredient and ingredient level, in most cases. Detailed results for this study, including all regression equations and applications to NHANES dietary supplement data files, are listed in the data files released in DSID-2.

The regression results for the most common labeled level for each ingredient in the Adult MVM study are summarized in Tables 1 and 2, below. Table 1 lists the predicted percent difference from label for vitamins and Table 2 lists the predicted percent difference from label for minerals.

Table 1. Adult MVM Results for Vitamins

Ingredient	Range of Predicted % Differences from Label	Most Common Labeled Level per Serving	Predicted % Difference from Label at Most Common Level
Folic Acid	8 to18 %	400 mcg	13.2 %
Niacin	0 to 6 %	20 mg	0.9 %
Riboflavin	4 to 14 %	1.7 mg	13.9 %
Thiamin	-7 to 9 %	1.5 mg	-6.4 %
Vitamin B-12	9 %	6 mcg	8.6 %
Vitamin B-6	-5 to 6 %	2 mg	5.4 %
Vitamin C	8 to 9 %	60 mg	8.3 %
Vitamin E	5 to 6 %	27 IU	6.0 %

Table 2. Adult MVM Results for Minerals

Ingredient	Range of Predicted % Differences from Label	Most Common Labeled Level per Serving	Predicted % Difference from Label at Most Common Level
Calcium	7 to 29 %	162 mg	14.1 %
Copper	1 to 16 %	2 mg	7.4 %
Iodine	26 %	150 mcg	26.2 %
Iron	-1 to 16 %	18 mg	0.9 %
Magnesium	2 to 9 %	100 mg	2.3 %
Manganese	4 to 7 %	2 mg	6.5 %
Phosphorus	8 %	109 mg	8.4 %
Potassium	7 to 12 %	80 mg	8.2 %
Selenium	22 to 26 %	20 mcg	25.5 %
Zinc	-1 to 10 %	15 mg	4.3 %

For seven ingredients (niacin, vitamin B-12, vitamin C, vitamin E, magnesium, manganese and phosphorus), predicted percent differences from label are between 0 and 10% above label at the most commonly labeled level and across the entire regression range. For four ingredients (thiamin, vitamin B-6, iron and zinc), predicted percent differences from label range from slightly below label (-1 to -7%) up to 16% above label across the regression range. All 11 of these ingredients have a predicted percent difference from label between 0 and 10% above label for the most commonly labeled level except for thiamin, where the mean is predicted to be 6.4% below label at 1.5 mg/serving.

For four ingredients (copper, potassium, folic acid and riboflavin), predicted percent differences are between 0 and 20% above label across the regression range. For calcium, the predicted percent differences from label range from 0 to 30% above labeled levels and for two ingredients (iodine and selenium), the predicted percent difference from label was between 20 and 30% above label for the entire regression range.

A. Adjustments to Data for DSID-2

Adult MVM results were originally released in DSID-1 in April 2009. Since that release, NDL has made adjustments to analytical data received from our laboratories for thiamin and vitamin B-6, and has collaborated with our statistician to optimize and update the statistical evaluation of the adult MVM data. For the March 2012 DSID-2 release, the changes to the final regression estimates and release files for adult MVMs include the following:

1. Optimized statistical calculations to separate lot and sample variance so that, for example, a product lot analyzed three times had the same influence as a lot analyzed once. The change in predicted % difference from label between DSID-1 and DSID-2 estimates was $\leq$ 2% for most ingredient levels. Differences were greater than 2% for folic acid (2.5 - 5%), potassium (0 - 3.6%) and selenium (0.5 - 7.2%). See information for thiamin and vitamin B-6, below.

2. Lower thiamin and vitamin B-6 levels in regression predictions, due to laboratory data adjustments for conversion of hydrochloride to the free form of the vitamins. These data adjustments were necessary because analytical data had been reported in most batches as the hydrochloride form and in some batches as the free form. Conversions were applied as appropriate and new finalized data were statistically evaluated.

3. An added application table which links labeled levels and predictions to NHANES 2007-08 data (not available in 2009), and updated tables for NHANES 2003-04 and 2005-06 applications.

4. The adult MVM calculator modified to apply updated DSID-2 regression equations.

5. Modifications to the format for the DSID Linking Codes in Tables 2-5.

Users of these data should update their data files using the DSID-2 files, because the DSID-2 results replace the information that was released in DSID-1.

B. Use of Regression Equations

The regression equations for adult MVMs released in DSID-2 predict the percent differences from label for 18 ingredients found in adult supplements sold in the U.S. The predictions are linked to labeled levels for each ingredient and are not brand or supplement specific. These predictions estimate the mean ingredient levels per serving and are applicable to MVMs reported in large population surveys of supplement use. The predicted SEM is the standard error (SE) for this mean prediction. The regression equations also estimate the SE for an individual product at specific labeled levels. This SE is much larger than the SEM because it represents the error of prediction for an individual product vs. the error of prediction of a mean value for many products.

Results predicted by regression for the mean percent difference from label and the standard errors have been linked to NHANES products at the labeled levels reported for those ingredients. The predicted results from the DSID can be used to replace information from labels to more accurately assess ingredient intakes from dietary supplements.

The details of the DSID-2 data files and instructions for appropriate use of the files are described in a separate report, “DSID-2 Data Files and Description” available on our website. Please refer to that report for further details about how to interpret and use each individual data file.

An on-line interactive adult MVM calculator has been released with DSID-2. This calculator allows the user to enter ingredient information from dietary supplement labels and generate the appropriate predicted mean values and standard errors at those labeled levels.

7. Future Plans

Additional DSID studies are underway to evaluate ingredient quantities in over-the-counter prenatal MVMs and to analyze the omega-3 fatty acid content of fish and plant oil products. Future data releases are planned to include results from these two studies and to report estimates for vitamin D, vitamin A and chromium in adult MVMs.

References

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