USDA Dietary Supplement Ingredient Database Release 2.0

DSID-2

Children's 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, in collaboration with the Office of Dietary Supplements, National Institutes of Health (ODS/NIH) and other federal agencies has developed 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 several pilot studies, please read the Background Information and Pilot Study Research Summary, available at http://dietarysupplementdatabase.usda.nih.gov. The first nationwide study for the DSID was an evaluation of 18 vitamins and minerals in representative adult multivitamin/mineral products (MVMs), originally published in DSID-1 in 2009. For more details, please read the Adult MVM Research Summary, available on the DSID website.

2. Overview of Children's MVM Study

A study of children's MVMs was conducted to estimate the relationship between label values and analytical values for priority vitamins and minerals. Protocols established in the DSID adult MVM studies were applied where appropriate. 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 specified vitamins and minerals using validated methods of analysis 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.

3. Sampling Plan

NDL develops multi-stage probability proportional to size (PPS) sampling plans for foods and beverages in cooperation with statisticians from the USDA National Agricultural Statistics Service (NASS) (Pehrsson et al., 2000). The purpose of each 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. For the children's MVM study, six counties were identified as purchase locations, in the states of AL, CA, MI, MO, NY, and OK.

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.

The purpose of the children's MVM study was to provide nationally representative estimates and measures of variability for specific vitamins and minerals in these products. NDL identified representative top market share (TMS) products using NHANES 2003-04 and 2005-06 dietary supplement data files and information from store surveys. The 21 TMS products identified represented approximately 50% of the market share from the defined NHANES infant/pediatric MVM subset. Children's MVM products representing the lower market share (LMS) were also initially identified using NHANES 2003-2004 and 2005-2006 information. Local store surveys and internet searches were conducted to ensure availability and to record any product name changes. The resulting list of potential LMS products for purchase totaled about 22% of the market share.

For this study, multiple lots of 64 different products were obtained from various market channels including mass merchandisers, health food stores, direct marketers and the internet. Retail products were purchased in 2008 in the six geographic regions mentioned above.

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. Of the 11 minerals analyzed in this study, eight

(calcium, copper, iron, magnesium, manganese, phosphorus, potassium, and zinc) were measured using multi-element inductively-coupled plasma spectrometry (ICP) after wet-ashing. Selenium was analyzed by hydride generation/atomic absorption spectroscopy. Chromium was analyzed using atomic absorption spectroscopy, with a matrix matched standard.

In some cases, more than one method of analysis was used to accurately measure unusual ingredient forms, low ingredient levels or to update methods using newer technologies. For example, iodine levels were determined throughout the study by three different methods. Thiosulfate titration was initially used for supplements with higher levels of iodine and colorimetric measurement for supplements with lower levels of iodine. In the later stages of the study, an inductively-coupled plasma mass spectroscopy (ICP-MS) method was validated in this matrix and produced results that were more consistent than the colorimetric procedure. In fact, the data generated from the ICP-MS method were used to verify or replace the data obtained from the other two methods.

Results for nine vitamins are reported in this study. The major components of vitamin A (retinol and beta-carotene) were measured separately, converted to International Units (IU) and combined as total vitamin A, for comparison to labeled levels. Seven vitamins (thiamin, niacin, riboflavin, vitamin B-6, retinol, beta-carotene and vitamin D) were measured 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. In a few cases, riboflavin was measured using fluorometry and niacin was determined using a microbiological technique. Vitamin C was measured but is not being reported due to high variability within lots for specific matrices and because of methodology issues that were not resolved until after the expiration date for some products.

Quality control (QC) materials were added to each batch of children's MVM products in order to evaluate laboratory precision and accuracy on an on-going basis.
Each batch included a set of product duplicates (two 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 were added to each batch in order to evaluate precision of the 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, mean analytical results were within 2% of the NIST certified or reference level for eight ingredients; mean results were between 2 - 6% of the NIST value for nine ingredients and mean analytical results were between 8 - 11% of the NIST level for three ingredients.

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

Many of the children's MVMs products in this study listed more than one age group or serving size on their labels. The three age groups listed on the children's MVM products were infants (0 to <1 year), 1 to <4 years old and 4 years and older. In some cases the serving size was the same for two age groups and sometimes the serving size was different. In order to evaluate the effect of different serving sizes on the results, two datasets were created and analyzed independently using regression techniques. One dataset contained children's products with serving size information for children that were 4 years and older (n=59 products), while the other dataset was for products with serving size information for children 1 to <4 years of age (n=50 products). The few products labeled for infants also included label information for the 1 to <4 years age group using the same serving size, so the infant products are represented in that dataset.

A regression equation was derived for each supplement ingredient in each dataset using the label value as the independent variable and the percent difference from the label (based on the laboratory analysis) as the dependent variable. Results for each dataset predicted mean analytical levels for a range of labeled levels. To prepare the datasets for analysis, data for each ingredient were identified by supplement, lot, sample and repeated laboratory analysis. Multiple laboratory observations for a sample were averaged and sample means were used for the statistical analysis. Four ingredients (chromium, potassium, manganese and selenium) had data for 15 or fewer supplements and were not analyzed by regression techniques. Descriptive statistics are provided for these nutrients. All data were weighted, using modified NHANES supplement weights to represent market share for children's MVMs.

A jackknife technique was used to calculate CookDistances and the Restricted Likelihood Distance in order to identify overly influential supplement observations. Market shares for individual supplements were considered when applying these statistics. Regression analysis of each dataset was conducted using a SAS mixed model procedure. The two regression equations (for serving sizes associated with the 4 years and older age group and the 1 to<4 years age group) were 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 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 and standard error of an individual observation were calculated at each labeled level. Since the regression equations can be used to predict ingredient values of independent

samples of supplements, standard errors were adjusted to reflect this expected greater prediction variability using sums of squares. For some ingredients, the predicted results for the two datasets were similar and other ingredients had significant differences. Results are reported separately for the two serving sizes.

6. Results and Discussion

In this study, final regression results are reported for the following 16 vitamins and minerals: folic acid, niacin, riboflavin, thiamin, total vitamin A, vitamin B-12, vitamin B-6, vitamin D, vitamin E, calcium, copper, iodine, iron, magnesium, phosphorus, and zinc. In addition, weighted descriptive statistics are provided for chromium, manganese, potassium and selenium. 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.

A. Serving size for ages 4 years and older

Data associated with the age group 4 years and older (n=59 products) were determined to be the primary dataset for applying regression analysis results to products in population studies due to these observations:

- The most common age group for children's MVMs purchased for the study was the 4 years and older category.
- Most products in the study (45/64) contained recommended serving sizes for both the 4 years and older and 1 to <4 years old age groups. The analytical results for all 45 of these products are in both datasets.
- The NHANES files record only one serving size per product. In most cases, the larger serving size is used.

On the DSID-2 web pages, the regression estimates for serving sizes for ages 4 years and older are listed in the section titled, DSID Data Tables and NHANES Applications.

The regression results for ingredients in the children's MVM study (for serving size ages 4 years and older) 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 3 details the weighted descriptive statistics for 4 minerals.

Table 1. Children's MVM Results for Vitamins (Serving size for Ages 4 and older)

Ingredient	Range of Predicted % Differences from Label	Most Common Labeled Level per Serving	Predicted % Difference from Label at Most Common Level
Folic Acid	14 to 22 %	400 mcg	13.8 %
Niacin	5 to 15 %	13.5 mg	5.4 %
Riboflavin	2 to 13 %	1.7 mg	8.6 %
Thiamin	2 to 16 %	1.5 mg	10.6 %
Total Vitamin A	0 to 24 %	2500 IU	22.6 %
Vitamin B-12	8 to 25 %	6 mcg	14.5 %
Vitamin B-6	5 to 19 %	2 mg	6.1 %
Vitamin D	34 to 49 %	400 IU	34.2 %
Vitamin E	14 to 46 %	30 IU	14.0 %

Table 2. Children's MVM Results for Minerals (Serving size for Ages 4 and older)

Ingredient	Range of Predicted % Difference from Label	Most Common Labeled Level per Serving	Predicted % Difference from Label at Most Common Level
Calcium	4 to 31 %	100 mg	19.0 %
Copper	5 to 11 %	2 mg	4.8 %
Iodine	2 to 64 %	150 mcg	24.3 %
Iron	2 to 13 %	18 mg	1.7 %
Magnesium	4 to 6 %	20 mg	4.2 %
Phosphorus	1 to 5 %	100 mg	1.2 %
Zinc	0 to 20 %	12 mg	0.9 %

These results show that two ingredients (magnesium and phosphorus) have predicted percent differences between 0 and 10% above label across the entire regression range. For six ingredients (niacin, riboflavin, vitamin B-6, copper, iron and zinc) predicted percent differences are between 0 and 10% above label at the most common labeled

level and up to 20% above label across the regression range. For four ingredients (calcium, folic acid, thiamin and vitamin B-12), predicted amounts are between 10 and 20% above label at the most common labeled level and up to about 30% above label across the regression range. Vitamin D results are consistently between 30 and 50% above label, with 34% at the most common labeled level. For the remaining ingredients (total vitamin A, vitamin E, and iodine) results were more variable, with the predicted percent differences from label ranging from 0 to 24%, 14 to 46% and 2 to 64%, respectively.

Table 3. Descriptive Statistics for Four Minerals in the Children's MVM Study (Serving size for Ages 4 and older)

Ingredient	Number of Supplements	Mean % Difference from Label	Mean % Difference from Label Standard Error
Chromium	10	43.6 %	4.0 %
Manganese	14	24.0 %	5.9 %
Potassium	5	77.0 %	17 %
Selenium	9	44.1 %	7.3 %

In Table 3, mean percent differences from label were calculated using relative market share information for each product containing these ingredients. These mean percent differences from label include data from a number of labeled levels. These limited results indicate that children's MVMs containing chromium, manganese, potassium or selenium have levels that are, on average, substantially higher than the levels listed on the supplement label.

B. Serving size for Ages 1 to <4 years old

Regression estimates for ingredients in children's MVMs with serving sizes for ages 1 to <4 years old (n=50 products) have been calculated separately and reported in DSID-2 because they may be applicable for some studies. On the DSID-2 website, the data for application to serving sizes for 1 to <4 year olds are listed in Table A1, in the DSID Auxiliary Table section of the Data Files web page.

The regression results for ingredients in the children's MVM study for serving size ages 1 to <4 years are summarized in Tables 4 and 5, below. Table 4 lists the predicted percent difference from label for vitamins and Table 5 lists the predicted percent difference from label for minerals. Table 6 details the weighted descriptive statistics for 4 minerals.

Table 4. Children's MVM Results for Vitamins (Serving size for Ages 1 to <4)

Ingredient	Range of Predicted % Differences from Label	Most Common Labeled Level per Serving	Predicted % Difference from Label at Most Common Level
Folic Acid	12 to 62 %	200 mcg	16.2 %
Niacin	7 to 8 %	7.5 mg	7.5 %
Riboflavin	8 %	0.85 mg	7.8 %
Thiamin	-5 to 23 %	0.75 mg	16.0 %
Total Vitamin A	12 to 23 %	2500 IU	11.5 %
Vitamin B-12	10 to 24 %	3 mcg	15.0 %
Vitamin B-6	-3 to 16 %	1 mg	8.9 %
Vitamin D	37 to 42 %	200 IU	39.5 %

Table 5. Children's MVM Results for Minerals (Serving size for Ages 1 to <4)

Ingredient	Range of Predicted % Difference from Label	Most Common Labeled Level per Serving	Predicted % Difference from Label at Most Common Level
Calcium	13 to 25 %	50 mg	18.6 %
Copper	5 to 7 %	1 mg	4.7 %
Iodine	18 to 41 %	75 mcg	18.1 %
Iron	0 to 12 %	9 mg	2.4 %
Magnesium	3 to 5 %	10 mg	3.9 %
Phosphorus	1 to 12 %	50 mg	1.4 %
Zinc	-1 to 17 %	6 mg	4.2 %

The results for percent differences from label in Tables 3 and 4 are similar to the results in Tables 1 and 2, especially at the most common labeled levels. However, there are cases where there is a significant difference between the regression estimates (due sometimes to linear vs. quadratic relationships) for portions of the regression range. The labeled levels for the age group/serving size 1 to <4 years old tend to be lower than those in the older category, so predicted values related to the lower labeled levels may

be valuable for intake studies. Vitamin E is not reported for the age group/serving size 1 to < 4 years because the results were quite variable.

Results for the mean percent difference from label for the four minerals found occasionally in children's MVMs are similar for the two age groups (see Table 3 and Table 6).

Table 6. Descriptive Statistics for Four Minerals in the Children's MVM Study (Serving size Ages 1 to <4)

Ingredient	Number of Supplements	Mean % Difference from Label	Mean % Difference from Label Standard Error
Chromium	8	44.1 %	4.3 %
Manganese	10	24.5 %	7.0 %
Potassium	3	87.0 %	20 %
Selenium	5	23.9 %	5.6 %

In Table 6, mean percent differences from label were calculated using relative market share information for each product containing these ingredients. These mean percent differences from label include data from a number of labeled levels. These limited results indicate that children's MVMs containing chromium, manganese, potassium or selenium have levels that are, on average, substantially higher than the levels listed on the supplement label.

7. Use of Regression Equations

The regression equations for children's MVMs released in DSID-2 predict the percent differences from label for 16 ingredients found in children's 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 the regression equation identified for the age group/serving size ages 4 years and older have been linked to National Health and Nutrition Examination Survey (NHANES) products at the labeled level 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. Regression equations

identified for ingredients in products with the age group/serving size ages 1 to <4 years old are reported in an auxiliary table, Table A1, available on the Data Files web page on the DSID-2 website.

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 the DSID-2 website. Please refer to that report for further details about how to interpret and use each individual data file.

8. 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

Pehrsson PR, Haytowitz DB, Holden JM, Perry CR, and Beckler DG. 2000. USDA’s National Food and Nutrient Analysis Program: Food Sampling. J Food Comp Anal. 13:379-389.