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Report

Progress in developing analytical and label-based dietary supplement databases at the NIH Office of Dietary Supplements

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Abstract

Although an estimated 50% of adults in the United States consume dietary supplements, analytically substantiated data on their bioactive constituents are sparse. Several programs funded by the Office of Dietary Supplements (ODS) at the National Institutes of Health enhance dietary supplement database development and help to better describe the quantitative and qualitative contributions of dietary supplements to total dietary intakes. ODS, in collaboration with the United States Department of Agriculture, is developing a Dietary Supplement Ingredient Database (DSID) verified by chemical analysis. The products chosen initially for analytical verification are adult multivitamin-mineral supplements (MVMs). These products are widely used, analytical methods are available for determining key constituents, and a certified reference material is in development. Also MVMs have no standard scientific, regulatory, or marketplace definitions and have widely varying compositions, characteristics, and bioavailability. Furthermore, the extent to which actual amounts of vitamins and minerals in a product deviate from label values is not known. Ultimately, DSID will prove useful to professionals in permitting more accurate estimation of the contribution of dietary supplements to total dietary intakes of nutrients and better evaluation of the role of dietary supplements in promoting health and well-being. ODS is also collaborating with the National Center for Health Statistics to enhance the National Health and Nutrition Examination Survey dietary supplement label database. The newest ODS effort explores the feasibility and practicality of developing a database of all dietary supplement labels marketed in the US. This article describes these and supporting projects.
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1. Introduction

Dietary supplement use in the United States (US) is high. At least 50% of the population claims that they have used

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dietary supplements (Millen et al., 2004; Radimer et al., 2004). Sales of dietary supplements in 2005 were over $20 billion (Anonymous, 2006). Yet questions still remain about the quality, efficacy, and safety of some dietary supplements. To evaluate the public health impact of these products, it is necessary to document and quantify dietary supplement intakes, and to do this, the composition of dietary supplements must be known (Dwyer et al., 2003).

The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined dietary supplements and established a framework for regulating them as foods, including rules for the contents of dietary supplement labels and requiring Good Manufacturing Practices for supplements. The Act did not include mandatory registration or certification of dietary supplement ingredient contents as is required for prescription drug products in the US. The complete definition of dietary supplements may be found at the Food and Drug Administration (FDA) home page (FDA, 2007). The determination of what should be included in a dietary supplement database depends not only on legal definitions but on consumer definitions; consumers may confuse the term "dietary supplements" with similar products such as meal replacements used for reducing diets or other purposes, and also with oral nutritional supplements such as Ensure®, Suplena®, and others which are sold for medicinal purposes.

DSHEA also established the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH). The goal of ODS is to foster an enhanced quality of life and health for the US population by strengthening knowledge and understanding of dietary supplements through evaluation of scientific information, support of research, dissemination of research results, and education of the public. Three key components of its mission are evaluating the quality, safety, and efficacy of dietary supplements, as documented in its strategic plan (ODS, 2004).

This paper focuses on the current status of the development of national label and analytical databases for the composition of dietary supplements in the US, updating previous reports on the work of the ODS and its federal agency partners (Dwyer et al., 2006). This work is important for research on dietary supplement-health relationships. It is also vital for public health purposes, such as documenting population intakes of nutrients and other bioactive constituents from all sources, including dietary supplements, and ensuring that intakes are neither excessive nor deficient. The ultimate goal is to obtain quantitative estimates for the bioactive components in dietary supplements, to assess the variability and/or possible bias in stated values for them and to release and maintain one or more on-line databases for dietary supplements.

2. Progress in development of a chemically validated Dietary Supplement Ingredient Database (DSID)

ODS is sponsoring the development of a DSID for ingredients of public health importance in dietary supplements. It will initially include representative estimates supported by selected analytical testing for the vitamin and mineral content of commonly used supplements.

2.1. Cross-agency and cross-department collaboration

A cooperative agreement was signed in 2005 between the National Cancer Institute (NCI) and the US Department of Agriculture (USDA) Agricultural Research Service (ARS) to continue updating nutrient values for its food composition databases, to assemble information on constituents for special food and dietary supplement composition databases, and to develop analytical methods for other constituents of interest in foods. This effort was an extension of the National Food and Nutrient Analysis Program (NFNAP) (Pehrsson et al., 2000, 2003; Phillips et al., 2006; Haytowitz et al., 2002). ODS provided supplementary funding to the NCI/ARS NFNAP project to develop and populate a dietary supplement database.

2.2. Priority components and products for analysis

For certain ingredients in dietary supplements, including folic acid, calcium, and vitamin D, better evidence on very high and low intakes is needed, particularly because of public health concerns about inadequate or excessive intakes of these nutrients (Bischoff-Ferrari et al., 2005; Jackson et al., 2006; Hartman et al., 2005; Balk et al., 2007). For botanicals (plant and animal materials or extracts), the needed analytical accuracy from the public health standpoint depends on whether the substance is expected to have potent beneficial or adverse effects, its toxicity, and other characteristics.

Although an analytical database of all ingredients in dietary supplements will take years to develop, it is important to begin obtaining these values, particularly for ingredients with high relevance to public health. Other bioactive compounds are also of interest, but analytical methods are often lacking.

The most critical components to include in the DSID have been identified using a priority ranking system based on the nutrients and other components of greatest public health interest (Dwyer et al., 2006). Ingredients of highest priority to be addressed first are folic acid/folate, β-carotene, calcium, vitamin E, zinc, vitamin A, vitamin C, iron, magnesium, selenium, vitamin B6, vitamin D, vitamin B12, omega-3 fatty acids (decosahexanoic acid, alpha-linolenic acid), potassium, sodium, and iodine. Other high-priority ingredients to be addressed as resources permit are thiamin, riboflavin, niacin, vitamin K, pantothenic acid, copper, lycopene, biotin, chromium, lutein, phosphorus, manganese, *Ginkgo biloba* (ginkgo flavonol glycosides and ginkgoterpenes, bilobalide and ginkgolides A and B), caffeine, soy isoflavones, and molybdenum. Caffeine content has been evaluated in dietary supplements that were representative of those used for weight loss and

for sports performance in the US marketplace (Andrews et al., in press).

Current priority product categories for the DSID include multivitamin-mineral supplements (MVMs), antacids (which often contain calcium and magnesium), vitamins E and C, B vitamins, calcium, other single mineral supplements, and multi-mineral supplements. MVMs were identified using the definition employed by Radimer (Radimer et al., 2004). Children's and prenatal MVMs are somewhat less popular with fewer sales than adult MVMs, but are also of interest. MVMs are among the most commonly consumed dietary supplements by Americans; 35% of US adults who participated in NHANES 2001–2002 reported taking them (Radimer et al., 2004), and Americans spent an estimated $3.5 billion for MVMs in 2005 (Anonymous, 2006). Therefore, these are the first dietary supplements that have been selected for analyses.

2.3. Categorizing products to be included in the database

Principles for the categorization of dietary supplements for research purposes include: (1) identification and standardization of a useful classification scheme, (2) an explicit rationale and logic for the categorization criteria, (3) mutually exclusive categories, and (4) homogeneity. The prevalence of dietary supplement use was based on data from the National Health and Nutrition Examination Surveys (NHANES), which are conducted by the National Center for Health Statistics; therefore, the NHANES classification scheme, which was based on the intended use, mutually exclusive categories, and constituents in the products, was used for categorization.

Supplements are composed of single components (vitamins and minerals) as well as complex materials (e.g., black cohosh and ephedra). Thus a database of values for composition of supplements may not correspond directly to traditional food composition databases, and standard reference materials may differ in the analytical methods used to evaluate their composition. The appropriate analytical method to identify and quantify complex materials may rely on a single component that is characteristic of that material, such as carotene, which may be characteristic of carrots or spinach, and vitamin C, which is characteristic of citrus fruit or raw potatoes. Validation methods for constituents of botanicals vary, and often include several compounds. Typical components used to identify complex supplement materials are unique terpenes and flavonols for *Gingko biloba* or unique combinations of these and other components that are characteristic of the complex supplement being quantified.

2.4. Quantifying dietary supplement components

For most dietary supplements, only label declarations and few chemically determined values were publicly available. To produce analytical data to populate a DSID based upon chemical analysis, appropriate reference standards and validated analytical methodologies were vital. To have access to these resources, ODS drew extensively on a complementary effort at ODS, the Dietary Supplements Methods and Reference Materials Program (Salhanha et al., 2004). To ensure data quality, the Dietary Supplements Methods and Reference Materials Program funded the development of both reference materials for products of interest to the DSID and analytical methodology for constituents when they were available.

2.4.1. Analytical methods development and validation

Because dietary supplements have matrices, excipients (constituents included with them to make them more shelf stable or easier to administer), and other factors that are different from foods, the appropriateness of chemical methods developed for foods cannot automatically be assumed. ODS and FDA have partnered with the Association of Official Analytical Chemists International (AOACI) to improve methods for dietary supplement analyses. Botanical quality initiatives have been launched and are described elsewhere (Betz, 2006). Numerous analytical methods for vitamins and minerals in foods were available from AOACI (Sullivan and Carpenter, 1993), and specific methods for some vitamins (including MVMs) were available from the US Pharmacopeia (USP) (USP, 2002). Through the AOACI Official Methods program (AOACI, 2003), analytical methods were validated, or are currently being validated for ephedra, aristolochic acid, s-adenosylmethionine, β-carotene, chondroitin sulfate, glucosamine (potassium and sodium sulfate salts), St. John's Wort constituents, *Ginkgo biloba* flavonols and terpenes (bilobalide and ginkgolides A and B), saw palmetto phytosterols and fatty acids, and bitter orange (*Citrus aurantium*) synephrine. AOACI identified the following as being on their planned work list to develop validation methods: red clover (isoflavone glycosides biochanin A, formononetin, genistein and daidzein), L-carnitine, B vitamins, black cohosh (actein and 23-epi-26-deoxyactein), omega-3-fatty acids, soy isoflavones green tea catechins, lutein, turmeric (curcumin), ginger (gingerols), milk thistle (silymarin, silybin and constituents thereof), *Pygeum* (African plum) (fatty acids and phytosterols), and flaxseed (the lignans seconisolaricesinol and maiteresinol and fatty acids). Other components/materials of interest were hawthorn (dimeric procyanidin B-2, hyperoside, vitexin), biotin, feverfew (parthenolide), proanthocyanidins, colostrom, creatine, podophyllotoxins, valerian (valerenic acids), Baical skullcap (baicalin cardiac glycosides), goldenseal (berberine, hydrastine), chaste-tree or *Vitex-agnus-castus* L (agnuside, aucubin, casticin), choline, and pine bark extract (proanthocyanidins).

Using criteria for qualitative, quantitative, and economically reasonable analyses similar to those used for foods (Holden et al., 2001), the USDA ARS Food Composition Laboratory (FCL) and Nutrient Data Laboratory (NDL) and other DSID collaborators reviewed the current status of analytical methods for nutrients in dietary supplements

and categorized them into three groups "adequate and robust" (those meeting all three criteria), "adequate but limited" (meeting two of the criteria), and "inadequate" for those failing to meet two or more of the criteria. Analytical methods from the AOACI and USP were reviewed by the DSID working group, and when standardized methods were already available and adequate, they were used by FCL and NDL to analyze DSID priority ingredients.

2.4.2. Standard Reference Materials® (SRMs)

SRMs help to confirm that an individual laboratory's analytical method provides accurate results (Sharpless et al., 2004). A MVM SRM (SRM 3280®) was developed in a partnership between ODS and the National Institute of Standards and Technology (NIST); values will be assigned for more than 30 vitamins, minerals, and carotenoids in this material using several methods, some of which include the use of stable isotopes as internal standards. A calcium carbonate SRM already exists. NIST also developed SRMs for ephedra and omega-3 fatty acids in cod liver oil and is developing SRMs for *Ginkgo biloba*, saw palmetto, St. John's wort, bitter orange, green tea, beta-carotene, alpha-tocopherol, berries of various *Vaccinium* species, soy, and black cohosh. For the botanical materials, the SRMs are available in several forms, typically as the whole plant, extract from the plant, and/or the finished consumer product, and each form represents different analytical challenges. Values for concentrations of active and marker compounds are assigned in these SRMs, along with nutrients and toxic elements where appropriate. These SRMs can also be used during method development to determine whether a method provides good results.

2.5. NDL pilot studies on the unique problems of dietary supplement analysis

The NDL led a series of pilot studies on the unique problems of dietary supplement handling and analyses which are discussed in detail elsewhere (Roseland et al., 2008; Dwyer et al., 2007). For MVMs such factors included the sample handling requirements caused by the various forms in which products are sold (capsules, pills, and gel caps) and matrix effects caused by excipients that may affect procedures necessary to ensure accuracy and precision. The NDL developed sampling plans for purchasing products based on current NHANES dietary supplement label information, weighted frequency, and sales channel (e.g., retail stores, Internet, mail order) information and conducted a study to assess the variability for analytical nutrient values among products labeled at the same level.

2.6. Identifying qualified laboratories

Most food-based commercial and many non-profit laboratories are more familiar with analyzing foods than dietary supplements. Existing laboratories may lack the capacity, capabilities, or interest to develop the requisite expertise for analyzing dietary supplements. In 2004, NDL announced its interest in identifying laboratories for the analysis of dietary supplements by issuing a "sources sought" solicitation to find interested and experienced laboratories. In 2005, it issued a request for proposals, reviewed the proposals, and awarded contracts. NDL recognized the need for a study of sample handling and analytical methods for vitamins and minerals of interest. To that end, NDL sent test samples to the qualified laboratories and requested analyses for 23 nutrients. The NDL and collaborators (FCL and NIST) identified qualified laboratories and analytical methods, developed protocols for purchasing, storing and shipping of products, and evaluated handling and analysis of samples. NDL also instituted quality control procedures to be followed for the analyses of dietary supplement products.

The laboratories were also asked to share their protocols and recommendations for sample handling and homogenization and to address encapsulation and other problems posed by the matrices. ODS, NDL, and FCL convened a group of federal experts and consultants on laboratory methods to review proposed analytical protocols for dietary supplements. From these deliberations (Roseland et al., 2008), NDL identified the best laboratories and methods for analysis of each nutrient for future work.

Laboratories whose analyses of the majority of the nutrients had $<10\%$ coefficient of variation met the criterion of an acceptable precision level. Six of the 23 nutrients (beta-carotene, retinol, alpha-tocopherol, chromium, vitamin B12, and vitamin D) showed higher variability and needed further study to obtain more consistent analytical results.

2.7. Developing an analytical survey of MVMs based on percent Daily Values (%DVs)

There is no generally agreed-upon definition for MVMs; definitions currently in the literature vary widely. Even in national surveys, a single definition has not been employed (Yetley, 2007). For the purposes of the study described below, MVMs were defined as containing three or more vitamins and/or minerals in a pill, capsule, or gel cap form (Radimer et al., 2004).

The ultimate goal for the DSID is to report the results of a systematic survey of dietary supplement composition, including the individual ingredients in supplements and indicators of data quality, just as is being done for foods (NDL, 2006). To determine the feasibility and approach to this long-term goal, the DSID cross-department working group organized a pilot study. Seven high priority nutrients were initially chosen because their analyses involved many different analytical challenges. Subsequently, 16 additional nutrients were added to the study. For most minerals in the NDL pilot study, analytical methods were robust or adequate. For example, analytical coefficients of variation

(CVs) (representing between-day variability) for the minerals in acceptable laboratories were at or below 10% and sometimes below 5%. In contrast, the status of methods for vitamins was mixed, especially for some of the B vitamins because of the lack of consensus on generally accepted methods. For the water-soluble vitamins, variability in acceptable laboratories was below 10% for most, except for vitamin B12, which is determined by microbiological assay and had variability as high as 30%. For the fat-soluble vitamins and provitamins, CVs for alpha-tocopherol and vitamin K in acceptable laboratories were approximately 10%, but variability was higher for beta-carotene, retinol and vitamin D, with CVs between 15% and 20%.

In planning the %DV study, the 541 adult MVMs reported to be consumed in NHANES 2001–2002 were searched, and summaries of the %DV levels for each of the 23 vitamins or minerals were obtained. Two, three, or four major %DV levels for each nutrient were chosen for study based on the weighted frequency of use and extended range of %DV levels.

For each of the 23 nutrients of interest in the %DV pilot study, six representative MVMs were chosen for analysis randomly from each of the most commonly occurring %DV levels. Samples were sent to qualified laboratories. Means, medians, ranges, and within- and between-lot variability were calculated.

Analytically determined values were compared to labeled values to determine the extent to which labels reflect the actual contents of the products. In this small study, the relationship between label declaration values and actual analytical data was complex, varying from small differences with some nutrients to very large differences with others (Dwyer et al., 2007). These and other pilot studies have laid the groundwork for a future comprehensive analytical survey of specific product types. In addition, the %DV level approach will be evaluated as an aid in planning the scope and number of samples to be analyzed for other studies of adult MVMs. Other questions that may affect future sampling plans include how dietary supplement composition changes over time and which nutrients and constituents change the most.

A comprehensive adult MVM study began in late 2006 to obtain representative analytic values for key nutrients in these products. It involved the analysis of 35 products that were purchased at six geographic locations and sent to contracted and cooperating laboratories for analyses of mean nutrient levels for each product.

2.8. Developing representative sampling plans

The sampling plan for products in the comprehensive adult MVM study was developed in collaboration with the USDA's National Agricultural Statistical Service to collect product samples that were statistically representative of those typically consumed in that category from all the marketing sectors through which the products were sold. These include not only mass-market retail sales in supermarkets, drugstores, natural and health food stores, and other stores, but also multilevel marketing and direct sales over the Internet and by mail order. It is necessary to sample all the channels because the products in these various markets may be quite different (Anonymous, 2006). For example, certain products are developed by different manufacturers who may use different specifications with significantly different ingredients. Current market channel data (e.g., Internet, supermarkets, health food stores, health practitioners, and door-to-door sales) and usage data were obtained from information collected by the Natural Marketing Institute (Harleysvllle, PA). Using these data, representative products in specific market channels were purchased using a sampling plan, and the product samples were then shipped to the laboratories for analysis. Statistical analysis of the analytical results will establish estimates for nutrient levels in adult MVMs reported in the NHANES survey.

2.9. Additional progress: caffeine-containing dietary supplements

Working with its federal partners, the NDL has evaluated 54 dietary supplements marketed for energy, sports performance, or weight loss that seemed likely to contain caffeine. One reason for the study was that consumers may not realize that some dietary supplements contain caffeine. Ingredients such as guarana, yerba mate, cocoa, kola, and tea are signals that caffeine may be present. Those who need to avoid caffeine need to know about natural sources of caffeine in supplements (Andrews et al., in press). NDL found that if taken at the maximum recommended label amounts, about 50% of the products studied would provide >200 mg caffeine/day, which is more caffeine than in two cups of brewed coffee (NDL, 2006). For products having a label amount for comparison ($n = 28$), 89% ($n = 25$) of the products had analytically based caffeine levels between -16% and $+16\%$ of the labeled levels.

2.10. Next steps

Subsequent studies are planned for the analyses of specialty adult MVMs (such as prenatal MVMs), child MVMs, and calcium products (including antacids). Products to be analyzed in further studies include other single and double-component supplement products, especially vitamin D products, glucosamine and chondroitin products, and fish oil supplements. Botanical ingredients will also be studied as validated analytical methods and reference materials for them become available.

The ultimate structure of the DSID also needs further consideration. It will include estimates both from the dietary supplements in NHANES and for other dietary supplements based on market share information (Roseland et al., 2008). Issues to be addressed include the

following: (1) if the DSID should consist solely of analytic data or be a mix of analytical data by brand name, as well as generic products and default products; (2) if suitably documented analytical data from manufacturers should be included; (3) if the definitions and categories used in the databases should be the same as those used in NHANES; and (4) if food and dietary supplement composition databases should be included in a single source (Au and Murphy, 2006).

The composition of MVMs for brands sold in mass-market retail stores is fairly consistent for many, but not all, nutrients and constituents. However, some brands used in multilevel marketing and health food stores have widely varying levels of the same nutrients in amounts greater than the recommended DV (Roseland et al., 2008). Brands with three or more constituents, but not the entire range of vitamins and minerals, are often specialty brands, like stress formulas, products for bone health, antioxidants, etc. This leads to the fifth issue which is whether these products should be included as MVMs or in another category.

Finally, the most appropriate user-friendly ways to harmonize the DSID with food composition databases need consideration. These issues will be addressed as the studies proceed.

3. Progress with the NHANES Dietary Supplement Label Database (NHANES-DSLD)

Currently dietary supplement use in the US is documented by collecting dietary supplement information in NHANES, the nation's population-based survey to assess the health and nutritional status of adults and children in the US (NCHS, 2007a). NHANES is a nationally representative sample of non-institutionalized civilians in the US. About 5000 people are surveyed each year in 15 communities nationwide, and public data releases are provided every 2 years. Information on dietary supplement use is vital for achieving the goals of NHANES. However, the NHANES-DSLD, by design, can only include those dietary supplements reported as taken by the participants. Thus, while the participants are a representative sample of the US population, the dietary supplements reported do not include all supplements available in the marketplace. Local and regional surveys by other investigators are also important to provide additional information on particular geographical or ethnic groups.

3.1. Collection of information on dietary supplement use from NHANES respondents

NHANES collects information on dietary supplements such as vitamins, minerals, other dietary supplements (both prescription, such as Tri-Vi-Flor™, and those available without prescription), and antacids (which are commonly used as calcium supplements) taken in the last month. Respondents in the household interview who report that they have taken dietary supplements are asked to provide the containers, and about 88% of the respondents do so. Supplement containers are viewed and the interviewer records the product name, amounts of ingredients for vitamins and minerals, and other information. Details on supplement use, such as how long the product has been used, how often it was taken over the last month, and how much was taken the previous day are also collected. The NHANES-DSLD can then be used to define supplement composition in the absence of analytical data on the composition of marketed products to quantify nutrient intakes.

3.2. Updating of the NHANES-DSLD

A dietary supplement label database relies on label declarations of ingredients for its information. The Supplement Facts panel on supplement labels must contain serving size, a list of ingredients, amount per serving size, and %DV for vitamins and minerals, if a DV has been established. If the dietary ingredient is of botanical origin, the scientific name of the plant or the common or usual name as standardized in Herbs of Commerce, 2nd Edition (McGuffin et al., 2000) is required. The name of the plant part used, whether the dietary ingredient is a proprietary blend (i.e., a blend exclusive to the manufacturer), the total weight of the blend, and the components of the blend in order of predominance by weight are listed.

Federal regulations describing mandatory and optional label information, including details on the terminology for label information are available in Title 21 of the Code of Federal Regulations (CFR, 2004). Dietary supplement specific requirements are found in 21CFR§ 101.3 (identity labeling), 101.4 (designation of ingredients), 101.36 (nutrition labeling), 101.17 (warning statements) and 101.93 (claims).

The NHANES-DSLD contains data from two sources-nutrient information taken from dietary supplement labels collected from respondents in NHANES and additional label data obtained by NHANES nutritionists through letters to manufacturers and distributors, company websites, other internet sources, and the Physician's Desk Reference (PDR, 2004).

3.3. Publicly available label NHANES-DSLD

The NHANES-DSLD is in a SAS format and is publicly available to researchers, the public, and others (NCHS, 2000, 2002, 2007b). It can be used to obtain ingredients reported on the dietary supplement label and as a source of information about default data for generic dietary supplements. The data are posted on the same website in spreadsheet format to allow easy access to the data, sorting, and importing the information into other databases. It consists of three separate Excel worksheets—a supplement information sheet, an ingredient information sheet, and a blend information sheet. The database

contains information for the same products as those collected in the NHANES-DSLD in 1999–2000 (approximately 1900 products) and 2001–2002 (2200 products), and the 2006 release reflects approximately 2000 products from 2003 to 2004.

3.4. Uses of the NHANES-DSLD

The uses include estimating total dietary intakes of nutrients from foods and dietary supplements; exploring the relationships between dietary supplement intake, diet, nutritional status, and health over time; monitoring trends in dietary supplement use, health risk behaviors, and environmental exposures over time; and exploring other emerging public health issues, such as the impact of fortification of foods with folic acid and consumption of folic acid-containing dietary supplements on folate nutritional status. The supplement-specific nutrient information contained in the database can be tracked to individuals who report having taken a specific or generic supplement (Radimer et al., 2004). The nutrients can then be combined with dietary nutrient intake data to calculate total nutrient intakes.

In July 2006, the National Center for Health Statistics sponsored a hands-on data user's session for those interested in using the NHANES-DSLD. The next data user's conference will be in Washington, DC in 2008.

3.5. Other NHANES developments

The NHANES Online Analyst for Dietary Supplements (NOADS) is a web-based tool for analysis of total nutrient intakes and their relationship to biomarkers of nutritional status. NOADS uses dietary supplement, food consumption, and related biomarker data derived from NHANES surveys of 1999–2000 and 2001–2002. A prototype with values for folate and vitamin B12 is now available for teaching purposes, and it may be expanded in the future. NHANES is currently piloting 24-h dietary supplement and antacid product intake as part of the 24-h food recall. If the pilot is satisfactory this will permit better estimates of usage patterns of dietary supplements.

4. Development of a label database of all dietary supplements marketed in the US (DSLD-USA)

Although the NHANES-DSLD provides a valuable way to document intakes of dietary supplements, the data only cover dietary supplements taken by respondents participating in the NHANES, and the data releases are in 2-year cycles, approximately 2 years after collection. As a result, the only dietary supplements included are a portion of the total number of dietary supplements in the marketplace. In addition, no information is available on newer products. Therefore, the NHANES-DSLD, while a useful source of data, is not sufficient by itself.

The ODS is now investigating the feasibility of the design, development, implementation, maintenance, and enhancement of a new, web-based application for cataloging all known dietary supplement labels. A single, publicly available, and easily accessible electronic database with complete and comprehensive label information for dietary supplements, including a list of the ingredients, amounts of ingredients, manufacturer information, etc., would serve multiple research and educational needs. For example, it is frequently necessary in research studies to estimate total intakes of essential nutrients as well as other nutrients and bioactive constituents; this requires quantitative data on the vitamin, mineral, other nutrient, botanical, and other bioactive content of both foods and supplements. Without such information, the design of studies to evaluate the effectiveness and safety of dietary supplement ingredients can be hampered. A resource documenting information about dietary supplement ingredients and products consumed by the US population and subgroups might provide useful information for the public health community in developing effective consumer educational materials and programs.

Dietary supplements marketed in the US are regulated as foods. Thus, unlike drugs, there is no central source of supplements (and therefore labels) that could be used by researchers to map product use with nutrient or other dietary supplement ingredient intake by participants in research studies. ODS held two workshops in collaboration with federal and non-federal partners to explore research needs for assessing dietary supplement intake. As early as 2001, when ODS held one such workshop, there was considerable agreement among government, industry, and academic stakeholders that a national dietary supplement database, such as DSLD-USA would support and enhance research activities. Such interest has continued. See web links to the summaries of two workshops ODS held in collaboration with federal and non-federal partners to explore research needs for assessing dietary supplement intake (ODS, 2006).

4.1. Challenges in developing the DSLD-USA

4.1.1. Acquiring data and sampling framework

Ultimately it will be necessary to develop a sampling framework to capture the range and breadth of all products in the marketplace. Although it is desirable for DSLD-USA to contain all labels, the constantly changing dietary supplement marketplace and the array of channels through which they are marketed makes it necessary to develop a framework for sampling from the universe of products in the marketplace. The task is complicated because label information is needed not only for products in the usual retail stream, but also for those available through other channels (e.g., health/fitness clubs, ethnic markets, door-to-door, Internet, television, healthcare facilities, and practitioners) because the ultimate goal of

the project is to obtain label data on the universe of dietary supplements used in the US.

4.1.2. Assuring accuracy and quality of information in the DSLD-USA

Chemical analysis of product composition to ensure accuracy with label information is a long-term goal. Database quality control procedures to ensure that label information is accurately captured in the database include an automated process to verify that the label information is in a suitable format and complete relative to the database components; that the codes and data ranges are reasonable; and that it is possible to distinguish between true zeros, trace amounts, and missing data. Each version of the label must be frozen and given a unique identifying number. The database must be in a user-friendly format. Additional desirable features are described below.

Currently NHANES-DSLD does not capture a digital image of the product because of limitations of costs and resources. However, existing and emerging computer technology makes it possible to obtain clearly readable digital images of container labels.

Methods for verifying the accuracy of label information collection include reliability checks for data entry, a coding system to reflect the source of the data (e.g., a code to identify if the information is based on label report alone, obtained from analytical data from the manufacturer, or provided from a third party), and the quality of the data. Some label information must be converted into uniform units of measure because no consistent approach has been used for listing composition of products on dietary supplement labels.

The National Nutrient Database for Standard Reference is the repository of information for more than 140 nutrients in over 7000 foods (NDL, 2006). Methods to identify the food products in this database with unique product identification codes (nutrient database numbers) are already available. A similar system for dietary supplements would facilitate product identification across different applications and establish during what year or range of years the product was sold in the marketplace. Methods being considered include structured product labeling (SPL). For example, FDA now requires drug manufacturers to submit prescription drug label information to FDA in electronic SPL format, that allows healthcare providers and the general public to more easily access the product information found in the FDA-approved package inserts (“labels”) for all approved medicines in the US (CDER, 2006).

All dietary supplement databases would benefit from a structured vocabulary and dictionary, and a DSLD-USA would provide an opportunity to build such a function into the software. Structured vocabulary refers to a set of terms, headings, or concept codes, and their interrelationships that may be used to support information retrieval. In the context of information retrieval from labels, the vocabulary should be accompanied by rules for how to apply the terms. It is important to develop description facets for product name, part of plant, product form (such as capsule or tablet), product type, usage instructions, manufacturer, etc. The composition data themselves become entries in the database rather than descriptive factors. Thus, in addition to database entries reflecting label information, the user of such a database would be able to search and collate all entries that are related to the same characteristics or ingredients.

A complete DSLD-USA also needs to include multiple synonyms that may be used to describe the same ingredients on labels. A dictionary of synonyms is a listing of words with each word having two or more corresponding terms whose meanings are considered to be the same in a wide range of contexts. Abbreviations and their full forms may be treated as synonyms. For example, “vitamin B2” and “riboflavin” are synonyms. There are various initiatives trying to develop a synonyms resource for variations in spelling and use of alternative names to refer to the same ingredient, e.g., ephedra, ephaedra, ephedrine alkaloids, and Ma Huang. This is a major issue in a dietary supplement database because manufacturers may put a familiar name or spelling on the label, even a local or regional name, rather than a standard name. The inclusion of synonyms would help to assure that entries in the database can be searched and identified so that product ingredients and characteristics for which multiple names/terms may be used among different products can be collated for analysis and evaluation. The addition of a system for incorporating a search engine, a dictionary of synonyms, and/or structured vocabulary would permit users of the database to find the same constituents from the Supplement Facts panel on the label and other label information when multiple terms are used among marketed products.

4.1.3. Updating and archiving

If the DSLD-USA becomes a reality, it will be necessary to develop the resources to respond to, monitor, and collect new label data and changes to label data in a timely fashion to keep the database up-to-date. The factors that trigger updates of information in the database, processes for updating, methods for tracking formulation, label changes within a product line, adding new products, and dropping discontinued products from the current version of the database must all be specified. Earlier versions of the database must be retained and archived because they may be needed for research purposes, especially with time series data.

4.1.4. Next steps in creating DSLD of all dietary supplements marketed in the US

The ultimate goal is to collect data on all dietary supplements marketed and sold in the US. This includes, but may not be limited to, vitamins, minerals, botanicals, and other constituents of dietary supplements that are listed in sources such as the US Pharmacopoeia (USP, 2002, 2004) and other authoritative references or that have a Chemical Abstracts Service registry number and common name (PubChem, 2007; McGuffin et al., 2000). The initial

priority is information on vitamin-mineral containing products and other ingredients in dietary supplements that are of public health significance or other criteria.

5. Other related activities

5.1. State of the science conference on MVMs and chronic disease risk in adults

In May 2006, ODS joined with the NIH Office of Medical Applications of Research, other NIH Institutes and Centers, and other federal partners to sponsor this State-of-the-Science conference, and an accompanying evidence-based review that dealt with issues of MVM safety and efficiency. The evidence report commissioned by the Agency for Healthcare Research on Quality to inform the discussion at the Conference is available (AHRQ, 2006b), and the proceedings of the conference appear as a supplement to the American Journal of Clinical Nutrition (Coates et al., 2007). The final report of an outside expert panel convened for this Conference is also available (AHRQ, 2006a). The panel concluded that MVM use has grown rapidly over the past several decades, and dietary supplements are now used by more than half of the adult population in the US. They tend to be used by those who practice healthier lifestyles, thus making observational studies of the overall relationship between MVM use and general health outcomes difficult to interpret. Information about the actual amount of total nutrients that Americans consume from diet and supplements was judged insufficient, and the panel called for improved methodology for obtaining accurate and current data on the public's total intake. Specifically, it called for new MVM databases that detail the exact composition of dietary supplements and for the databases to be updated on a continuous basis and to be made available to the research community. As to efficacy, the panel found that there were few rigorous studies upon which to base clear conclusions and recommendations. It recommended that rigorous randomized controlled trials of individual supplements be conducted using well-validated measures to test both efficacy and safety of individual supplements in the prevention of chronic disease. The panel concluded that the present evidence was insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease, and that the resolution of this important issue would require advances not only in research, but improved communication and collaboration among scientists, health care providers, patients, industry, consumers, and the public.

5.2. Cooperative agreements

ODS is supporting work on a dietary supplement software module to accompany the University of Minnesota food and supplement composition and dietary assessment software, Nutrition Data System for Research. A dietary supplement assessment module that allows for the automated collection and coding of dietary supplement use has been developed and incorporated into this software. The module is designed for use in conjunction with the software's 24-h dietary recall features, thus facilitating the assessment of both food and supplemental sources of nutrients (Harnack et al., 2008). ODS is also supporting work on the validity and reliability of reports of dietary supplement intakes being carried out by the University of Hawaii Cancer Research Center (Murphy et al., 2006).

5.3. Motivations for dietary supplement use

ODS has carried out secondary analyses of national survey data to obtain better information on the motivations for dietary supplement use among Americans. Items on motivations for their use will be included in the 2007 National Health Interview Survey supplement on complementary and alternative medicine, jointly sponsored by the NIH National Center for Complementary and Alternative Medicine and ODS.

6. Conclusions

An analytical database of all ingredients in dietary supplements will take many years to develop. Yet interest in the health benefits of dietary supplements continues to be high. Concerns about both excessive and deficient intakes of nutrients and exposures to other bioactive constituents in supplements also continue. The widespread use of dietary supplements and fortified foods makes better data on dietary supplement composition important both for planning purposes and to investigate dietary supplement-health relationships. The DSID is being populated with analytically verified values for MVMs, and the work is gradually being extended to other categories of dietary supplements. At the same time, the NHANES-DSLD is being updated, and a DSLD-USA of all dietary supplements marketed in the US is in the feasibility stage. Federal officials and their collaborators are now discussing how to best integrate the various databases so that they will complement each other and stay up-to-date in the constantly changing, non-regulated field of dietary supplements. The assistance of federal partners is making the ultimate goal, an analytically supported dietary supplement database that can be used in NHANES and other national surveys and by researchers and others in the scientific community, a reality.

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