MINUTES OF THE NUTRITION COORDINATING COMMITTEE (NCC) MEETING, NATIONAL INSTITUTES OF HEALTH (NIH)
Rockledge 2, Conference Room 9100-9104, Bethesda, MD
June 4, 2009 2:00- 4:00 PM

WELCOME

Dr. Pam Starke-Reed, Deputy Director, NIH Division of Nutrition Research Coordination (DNRC), convened the meeting at 2:06 PM and welcomed participants. Participating via phone were; Dr. Krishan Arora, NIH NCRR; Dr. Sanja Basaric, NIH NHGRI; CAPT Shirley Blakely, FDA; Dr. Lynn Bosco, NIH OBSSR; Dr. Paul Cotton, NIH NINR; Ms. Karen Donato, NIH NHLBI; Dr. Shirley Gerrior, USDA CSREES; RADM Van Hubbard, NIH DNRC; Ms. Marguerite Klein, NIH ODS; Ms. Michele Lawler, HRSA; Ms. Holly McPeak, OS ODPHP; Dr. Dan Raiten, NIH NICHD; Dr. Charles Reynolds, CMS; Dr. William Riley, NIH NIMH; Ms. Theresa Smith, NIH NIAMS; Dr. Derrick Tabor, NIH NCMHD; and Dr. Susan Yanovski, NIDDK. The agenda for the meeting is provided as Appendix A, and the list of attendees is provided as Appendix B.

APPROVAL OF MINUTES FROM THE MARCH 5, 2009 NCC MEETING

Minutes from the March 5, 2009 NCC meeting had previously been sent to NCC members via email. Dr. Starke-Reed asked if there were any other corrections to the minutes. There were none. Dr. John Milner, National Cancer Institute (NCI), made a motion to approve the minutes, and Dr. Paul Coates, Office of Dietary Supplements (ODS), seconded the motion. The minutes were thus approved and will be posted on the DNRC website, http://www.dnrc.nih.gov, along with the minutes from previous NCC Meetings.

VITAMIN K: AN UPDATE

Dr. Sarah Booth, Senior Scientist at the Vitamin K Laboratory at the Jean Mayer USDA Human Nutrition Research Center at Tufts University provided an update on vitamin K. The goal of research conducted at the Vitamin K Laboratory is to improve the understanding of how diet impacts bone and vascular health in older men and women. To meet this goal, the forms, amounts, and biological activity of vitamin K in the food supply are being studied. Information is also being collected on the physiological significance of measures used to assess vitamin K nutritional status.

The most common source of vitamin K in the diet is phylloquinone, which is found in plant sources like leafy greens and green seeds. Other forms include a series of menoquinones (MKs) such as MK-7 (form found in supplements) and MK-4 (found primarily in poultry products). All share the common napthoquinone ring but differ in the structure of their side chain. There is currently an inadequate understanding of the dietary sources and metabolic fate of phylloquinone from the diet. However, a new paradigm suggests that phylloquinone coverts to MK-4 in the body and may have several unique functions. There are still a number of questions surrounding the biochemical pathway for the transformation of

phylloquinone to MK-4. It is likely that the side chain is cleaved off, though exactly how this happens is not clear. The process is thought to produce menadione as a metabolite in the conversion. MK-4 has a highly specific tissue distribution and favors the brain, pancreas, and salivary glands. This specific tissue distribution supports the hypothesis that vitamin K has a much greater function than was previously thought. In addition to the clotting proteins, a number of additional proteins not involved in coagulation appear to be dependent on vitamin K. Examples include osteocalcin, nephrocalcin, and periostin. Other functions for vitamin K may exist independent of its role as an enzyme cofactor.

The vitamin K field is advanced when it comes to measurements of vitamin K status, but the physiologic corollaries are much more challenging to assess. This is because plasma concentration of vitamin K varies greatly, reflects recent consumption, and can be easily manipulated. Some forms of vitamin K are also not in detectable levels in circulation. The measures of vitamin K dependent proteins are difficult to interpret.

Sharing many parallels with vitamin D, it is thought that vitamin K status is linked to more diseases than previously suspected. Examples include coagulation disorders, osteoporosis, osteoarthritis, cardiovascular disease, Alzheimer's, hepatocellular cancer, and diabetes. There is much excitement about the relationship between vitamin K and diabetes, but this relationship is complex and rather confusing. It appears that osteocalcin plays a role in glucose metabolism by regulating the cells that produce insulin in the pancreas. In a recent study conducted at the Vitamin K Laboratory, men who received vitamin K supplementation had less progression in their insulin resistance by the end of the clinical trial. This was not the case with women in the study. This may have been due to the fact that there was a higher prevalence of overweight or obese women in the study compared to the male group. Because vitamin K is stored in fat tissue, if there is excess fat, vitamin K may not be readily available to cells that require it to process glucose. Because there are few studies of vitamin K and insulin resistance, further investigation is needed.

WEIGHT GAIN DURING PREGNANCY: REEXAMINING THE GUIDELINES

Dr. Ann Yaktine, Senior Program Officer at the Food and Nutrition Board of the Institute of Medicine, provided an overview of the new guidelines for weight gain during pregnancy. Since 1990, the last time the IOM released guidelines for pregnancy weight gain, many key aspects relating to the health of women of childbearing age have changed. For example, there has been an increase in prepregnancy body mass index and gestational weight gain (GWG) in all population subgroups. There are also high rates of overweight and obesity in population subgroups at risk for poor maternal and child health outcomes. In addition, due to the fact that more women are becoming pregnant at an older age, it is more common for them to enter pregnancy with pre-existing conditions such as hypertension or diabetes, which puts them more at risk for pregnancy complications. As a result of these concerns, sponsors asked the Food and

Nutrition Board of the IOM and Board on Children, Youth, and Families in the Division of Behavioral and Social Sciences and Education of the National Research Council to review the 1990 IOM recommendations for weight gain during pregnancy. The committee was specifically asked to look at both maternal and child health outcomes in relation to weight gain patterns before, during, and after pregnancy and to recommend revisions to existing guidelines if necessary. The committee was also asked to recommend ways to encourage adoption of these guidelines and to identify gaps in knowledge and recommend research priorities.

The framework for the recent IOM study differed from the 1990 examination because it included a lifecourse perspective, examined the trade-off between mother and infant, and included a quantitative risk analysis. The new guidelines also use BMI categories that are based on the World Health Organization cutoff points instead of categories derived from the Metropolitan Life Insurance Tables used in 1990. Based on analyses of both maternal and infant outcomes, the new guidelines include a specific, relatively narrow range of recommended weight gain for obese ($\geq$ 30.0 kg/m^2) women, 11-20 lbs. Recommendations for total weight gain have not changed in the other BMI categories: underweight (<18.5 kg/m^2), 28-40 lbs; normal weight (18.5-24.9 kg/m^2), 25-35 lbs; overweight (25.0-29.9 kg/m^2). Provisional guidelines were also provided to mothers of twins, but there were insufficient data to offer guidelines for women with greater multiples. As no differences were determined across various racial and ethnic groups, the recommendations are applicable to all subgroups in the American population.

The committee recognized several challenges ahead. Specifically, they emphasized the need to conceive at a normal prepregnancy BMI. This requires preconceptional counseling, contraception, and for some, weight loss. It is important to inform women and their health care providers of the guidelines and to provide the individualized assistance necessary to meet them.

Many research gaps were also identified in the new report. Examples include a need for routine surveillance of GWG and post-partum weight retention on a nationally representative sample of women; support for studies in large and diverse populations of women to understand how dietary intake, physical activity, food insecurity, and more broadly, the social, cultural and environmental context affect GWG; and support for studies that examine the association between GWG and glucose abnormalities and gestational hypertensive disorders and well as the development of glucose intolerance, hypertension and other CVD risk factors as well as mental health and cancer later in life.

The full report can be viewed from the National Academies collection by directly accessing the report:
(http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=napp&part=nap12584)
or from the main bookshelf page:
(http://www.ncbi.nlm.nih.gov/sites/entrez?db=books)

RCDC UPDATE
Due to time constraints and the absence of several critical discussants, the RCDC update will be presented at the July NCC meeting.

REPORTS FROM NCC MEMBERS AND LIASONS

1. Dr. John Milner, NCI, announced that the speaker for the next Stars in Nutrition and Cancer seminar, which will take place at the end of September, is Dr. Randy Jirtle. Dr. Jirtle is the Director of the Epigenetics and Imprinting Laboratory at Duke University.

2. Dr. Sharon Ross, NCI, reported on the success of the session: *Nanotechnology Research Applications in Nutritional Science*, which was held on April 21st at the Experimental Biology Meeting in New Orleans. The session was sponsored by the NIH Nanotechnology Subgroup. There were four speakers as well as a panel discussion on the research opportunities and challenges in nanotechnology, food, and health. A publication summarizing the meeting will be available by the end of July.

3. Dr. Cindy Davis, NCI, also alerted the NCC that there will be a STEP forum on nanotechnology and foods in January 2010.

4. Dr. Pam Starke-Reed, DNRC, shared a document sent on behalf of the National Center for Health Statistics (NCHS) regarding two issues that should be addressed when analyzing 25-hydroxyvitamin D from the National Health and Nutrition Examination Survey (NHANES). Please see Appendix C for the full document, which explains the data concerns.

UPDATE FROM THE DHHS OFFICE OF DISEASE PREVENTION AND HEALTH PROMOTION (ODPHP)
Ms. Kathryn McMurry provided several updates from ODPHP:

Dietary Guidelines for Americans 2010

- The third Dietary Guidelines Advisory Committee meeting was held on April 29 & 30 via webcast. Transcripts, minutes, and public comments are posted at www.dietaryguidelines.gov. For those who missed the meeting, the audio recording is available on the website.

- The Nutrition Evidence Library process is one of the primary resources for the Committee's deliberations, along with NHANES survey data and some modeling using the MyPyramid system.

- The next meeting will occur in the fall.

- The committee's report is expected in spring 2010, followed by agency and public review and publication of the 2010 Dietary Guidelines for Americans in fall, 2010.

Dietary Reference Intakes (DRIs)
Review of Dietary Reference Intakes for Vitamin D and Calcium

- The first meeting was held on March 26-27, during which the study sponsors presented their perspectives to the committee and analytical presentations were made.

- The second meeting will include an information-gathering open public presentation on the new AHRQ report, analytical issues, biomarkers, chronic disease endpoints, perspectives from the first DRI panel and other vitamin D and calcium experts on August 4. Registration will open on June 15, 2009. The draft agenda and registration for this session can be accessed at http://www.iom.edu/vitamind.

- The report is expected in May, 2010. The study is being cosponsored by multiple agencies and offices of Health Canada and the U.S. Departments of Agriculture (USDA), Defense (DoD), and Health and Human Services (HHS).

Healthy People 2020

- The timeline for the development of Healthy People 2010 objectives has been expanded and will include a public comment period in October/ November 2009 and Departmental clearance March/ April 2010. The launch is now targeted for September, 2010.

- The charter for the Secretary's Advisory Committee on National Health Promotion & Disease Prevention Objectives for 2020 is being submitted for renewal. Its next meeting, via webinar, is scheduled for July 10.

- Nutrition and Overweight, Food Safety, and Physical Activity Focus Areas have been working hard to prepare documentation memos for proposed objectives.

- General information is available at www.healthypeople.gov

Assistant Secretary of Health
The nomination for Assistant Secretary of Health in the Department of Health and Human Services has recently been named. It is Dr. Howard Koh, the Harvey V. Fineberg Professor of the Practice of Public Health at Harvard School of Public Health (HSPH) as well as the Associate Dean for Public Health Practice and Director of the Division of Public Health Practice at HSPH.

Dr. Koh has served as the Principal Investigator of multiple research grants related to community-based participatory research, cancer prevention, health disparities, tobacco control, and emergency preparedness. He is also Director of the HSPH Center for Public Health Preparedness.

Dr. Koh previously served as Commissioner of Public Health for the Commonwealth of Massachusetts (1997-2003) where he emphasized the power of prevention for the Massachusetts Department of Public Health, which included four public health hospitals and a staff of over 3,000 professionals.

Dr. Koh graduated from Yale College, Yale University School of Medicine and completed his postgraduate training and chief residencies at Boston City Hospital and Massachusetts General Hospital. He has earned board certification in internal medicine, hematology, medical oncology, and dermatology, as well as a Master of Public Health degree. He is an elected member of the Institute of Medicine and Chair of the Board of Scientific Counselors for the CDC's Coordinating Office for Terrorism Preparedness and Emergency Response. Dr. Koh has published over 200 articles in the medical and public health literature. He has received numerous awards and honors including the Distinguished Service Award from the American Cancer Society. President Bill Clinton appointed Dr. Koh to the National Cancer Advisory Board (2000-2002).

UPDATE FROM THE NIH OFFICE OF DIETARY SUPPLEMENTS (ODS)
Dr. Paul Coates, ODS, shared the following information with the NCC:

Vitamin D: As the result of a joint effort, ODS and the National Institute of Standards and Technology (NIST) announce the availability (June 2009) of a Standard Reference Material (SRM) for plasma 25-hydroxyvitamin D that can be used to standardize the methodology for measuring vitamin D status. Optimal levels of 25-hydroxyvitamin D, or 25(OH)D, for bone and general health throughout life have not been established and are likely to vary at each stage of life, depending on the physiological measures selected. A range of cut-points that have been proposed by various experts (from 16 to 48 ng/mL) reflect differences in the functional endpoints chosen (e.g., parathyroid hormone levels, bone fractures, cancer prevention). There is considerable public and scientific discussion of these issues. It has become evident, however, that there can be substantial variability in the results obtained by using different methods, by different laboratories, and even within the same laboratory at different times. A major reason for this issue of precision and variability is that no standard reference preparations or calibrating materials are available commercially to help reduce the variability of results between methods and laboratories. The SRM will provide a material with stable, well-defined levels of the analytes of interest and will serve as a reproducible point of comparison, of results across laboratories, and within a given laboratory over time. As part of this effort, investigators also have the opportunity to participate in an ODS-funded NIST quality assurance program for analysis of vitamin D metabolites (e.g., 25(OH)D_2 and 25(OH)D_3). NIST chemists will compile data and provide confidential feedback to laboratories on their performance relative to expected values. Participation in this quality assurance program will demonstrate the laboratory's proficiency for assessment of vitamin D status. We believe that this effort will enhance confidence that

measured levels of vitamin D are accurate and can be interpreted in a meaningful way.

Experimental Biology Session: ODS staff and NIH-funded investigators co-organized a session at Experimental Biology '09 in New Orleans this spring, entitled *Measurement Issues Related to Dietary Supplement Use*. At this session, investigators from the NCI/ODS-funded group in Hawai'i, from the USDA and the CDC, as well as from ODS and NCI, presented data on models for assessing dietary supplement intake and harmonizing these data with food intake data to obtain improved estimates of exposure to nutrients (such as folate) from all sources. The results of these studies have strong implications for public health policy.

Dietary Supplement Databases: The Dietary Supplement Ingredient Database (DSID) (http://dietarysupplementdatabase.usda.nih.gov), released at Experimental Biology '09, will help researchers improve estimates of the U.S. population's total nutrient intakes, because it is based not only on the beverages and foods people consume, but also on their dietary supplement intake. The database provides statistical estimates—based on chemical analysis—of the nutrient content of selected ingredients in dietary supplements, compared with label-reported ingredient levels. Currently, the DSID provides estimated levels of 18 vitamin and mineral ingredients derived from analytical data for 115 representative adult multivitamin/multimineral supplements. Additional dietary supplement ingredients will be included in future releases of the database. The DSID was planned and developed by the USDA Agricultural Research Service Nutrient Data Laboratory and ODS, along with other government collaborators.

In a related development, a Dietary Supplement Label Database (DSLD) is under development by ODS, in collaboration with NLM, that will contain information from the labels of all dietary supplements sold in the United States. A pilot project, building on an existing database at NLM, is near completion. If the project is deemed feasible, development will continue with funding for up to 4 additional years.

ODS 15th Anniversary Celebration: ODS will release its 3rd Strategic Plan at the beginning of 2010, which will also be the 15th anniversary of the creation of the Office. We are planning a day-long symposium that will feature major highlights of research in the field.

Caffeine: Is the Next Problem Already Brewing? ODS will co-sponsor this symposium with NIDA on July 7 and 8 at the Neuroscience Center. The symposium consists of scientific presentations on the following topics: a pharmacological primer on caffeine's rewarding and behavioral effects; caffeine's effects on cognitive performance; caffeine and human disease; and studies to address when caffeine use may become problematic. There will also be

discussion of a future research agenda for this substance. Registration for the symposium is now closed as all seats are filled, but one can sign up to be placed on a waitlist. To learn more about the symposium, visit the following website: http://www.sei2003.com/nida/1014049/index1.asp

UPDATE OF DNRC ACTIVITIES

Nutrition Education Subcommittee (NES). CAPT Jean Pennington, DNRC, provided an update of the activities of the NIH NCC NES. For the calendar year 2009, the NES has reviewed 12 documents, 9 from NIH (4 each from NHLBI and ODS and 1 from NCI) and 3 from FDA. Documents reviewed since the last NCC meeting are:

- *Vitamin D (Consumer Version)* (ODS)
- *Vitamin D (Easy-to-Read Version)* (ODS)
- *Zinc (Consumer Version)* (ODS)
- *Zinc (Easy-to-Read Version)* (ODS)
- *Keep the Beat: Deliciously Healthy Dinners* (NHLBI)
- *Pocket Guide to Maintaining a Healthy Weight While Eating On-the-Go* (NHLBI)
- *Portion Control Wallet Card (Z-Card)* (NHLBI)
- *Portion Distortion Quiz* (NHLBI)

The DNRC listing of NIH nutrition education materials is available on the DNRC website (http://dnrc.niddk.nih.gov/nutrition_education/index.shtml). NCC members are requested to check the information on the website and provide any updates or other changes to Ms. Karen Regan, DNRC. The DNRC would appreciate receiving 10-20 copies of newer NIH nutrition-related publications for display in the DNRC Office. Please send them through interoffice mail to CAPT Pennington, Democracy 2, room 629.

International Committee Information: Dr. Dan Raiten, NICHD, gave a brief report on the Micronutrient Forum, which was held May 12-15 in Beijing, China. The Forum focuses on the impact of micronutrient deficiencies on public health and development, concentrating specifically on populations that are deficient in vitamin A, iron, folate, iodine, and zinc. The conference acts as a meeting-ground for leading scientists, policy-makers, and programmers to collaborate and share new research and operational findings. A particular focus of this year's meeting was on creating private/public partnerships to address the global food crisis caused by natural events, high costs and global food shortages. At the Forum, Dr. Raiten conducted a satellite session on the NIH/Gates/WHO collaboration to address safety and effectiveness of currently available iron interventions in areas in endemic malaria and related co-infections. Dr. Raiten expressed his desire to see more NIH ICs get involved in the global food/nutrition agenda.

A related issue to the Micronutrient Forum is a new initiative that is being developed as a consequence of some preliminary conversations with FIC and USAID about enhanced collaborations around nutrition. The focus of the initiative

referred to as the BOND initiative (Biomarkers of Nutrition for Development) will be to coalesce the nutrition community's needs for biomarkers of nutrient exposure, status and functional consequence from the perspective of research, clinical care and program implementation and evaluation. Discussions currently include NICHD, FIC, ODS, NCI, the Bill and Melinda Gates Foundation, USAID, USDA, WHO and several private organizations. Dr. Raiten welcomed the participation of any of the NCC members to these discussions. For further information on BOND please contact Dr. Raiten (Daniel.Raiten@nih.hhs.gov).

Dr. Raiten also reminded the NCC of the upcoming International Congress of Nutrition, which will take place in Bangkok, Thailand on October 4-9, 2009. The NIH is slated to give a presentation on opportunities in international research. More details will follow.

NEXT NCC MEETING
The next meeting will be July 2, 2009

ADJOURNMENT
The meeting was adjourned at 4:05 PM

LIST OF APPENDICES
Appendix A: NIH NCC Meeting Agenda for June 4, 2009
Appendix B: NIH NCC Meeting Attendees for June 4, 2009
Appendix C: Analytical Note for NHANES 2000-2006 and NHANES III (1988-1994) 25-Hydroxyvitamin D Analysis

APPENDIX A: NIH NUTRITION COORDINATING COMMITTEE MEETING AGENDA

1. **Welcome**……..…….……..…….....Pam Starke-Reed

2. **Approval of Minutes of the March 5, 2009 meeting**.... Pam Starke-Reed

3. **Scientific Presentation**:

   "Vitamin K: an Update"
   Sarah Booth, PhD,
   Senior Scientist, Vitamin K Laboratory,
   Jean Mayer USDA HNRC at Tufts University

4. **Weight Gain During Pregnancy: Reexamining the Guidelines**
   …..…….....Ann Yaktine, FNB, IOM, NAS

5. **RCDC Update**……..……Jim Krebs-Smith & Karen Regan, DNRC

6. **Reports from NCC Members and Liaisons**…..……NCC Members

7. **ODPHP Activities Update**…….....Kathryn McMurry, ODPHP/OS

8. **ODS Activities Update**..……..……..…Paul Coates, ODS

9. **Current DNRC Update of Activities**…..……..…..DNRC Staff
   - Nutrition Education Subcommittee Update……..Jean Pennington*
   - International Committee Information……..Pam Starke-Reed/Dan Raiten*

9. **Next Meeting** - Tentative July 2, 2009

*** Updates will be included in the minutes of the meeting only**

APPENDIX B: NCC MEETING ATTENDEES FOR MARCH 5, 2009

	Members Present	Members Absent	Alternates Present
Chairperson:	V Hubbard		P Starke-Reed
NIH Members:			
NCI	J Milner		S Ross
NHLBI	D Danford		
NIDCR		R Nowjack-Rayner	
NIDDK	C Miles		
NINDS		M Mitler	
NIAID		M Plaut	
NIGMS		S Somers	
NICHD		G Grave	D Raiten
NEI		N Kurinij	
NIEHS		E Maull	
NIA		J Hannah	
NIAMS		J McGowan	T Smith
NIDCD		B Wong	
NIMH	W Riley		
NIDA		G Lin	
NIAAA		R Breslow	
NINR	P Cotton		
NCCAM		L Duffy	
NCMHD	D Tabor		
NCRR	K Arora		
FIC		M Levintova	
NHGRI	S Basaric		
NIH Liaison Members:			
CC	N Sebring		
CIT		J Mahaffey	
CSR		S Kim	
NLM		S Phillips	
OBSSR	L Bosco		
ODS	P Coates		
OD/ODP	B Portnoy		
OLPA			
ORWH			
PRCC		M Vogel-Taylor	
Agency Liaison Representatives:			
AHRQ		I Mabry-Hernandez	
CDC/NCCDPHP		H Blanck	
CDC/NCHS		M McDowell	
FDA	K Ellwood		S Blakely
HRSA	M Lawler	S Adamo	
IHS		T Brown	
ODPHP	K McMurry		
USDA		D Klurfeld	
DOD	K Friedl		

DNRC: N Bulger, R Fisher, S Frazier, W Johnson-Askew, C McDade-Ngutter, J Pennington, K Wade

Guests:, L Beker (FDA), S Booth (HNRC/Tufts), K Camp (OBA), C Davis (NCI), A Ershow (NHLBI), S Gerrior (USDA/CSREES), P Hans (NINDS); H McPeak (OS/ODPHP), C Reynolds (CMS), A Yaktine (NAS/IOM/FNB)

APPENDIX C

Analytical Note for NHANES 2000-2006 and NHANES III (1988-1994) 25-Hydroxyvitamin D Analysis

Data Advisory:

The purpose of this note is to inform users of serum 25-hydroxyvitamin D (25(OH)D) data from NHANES about two issues that should be addressed when analyzing these data. First, users are cautioned about making direct comparisons between serum 25-hydroxyvitamin D measurements from NHANES 2000-2006 (i.e., publicly released data for 2001-2006 and controlled-access data for 2000) and measurements obtained in NHANES III (1988-1994). NHANES III 25(OH)D data must be adjusted in order to make a valid comparison to the 2000-2006 NHANES survey years due to a reformulation of the DiaSorin radioimmunoassay (RIA) kit that resulted in shifts in assay results between the two time periods. Second, data users should also be aware that the 25(OH)D data from the 2000-2006 NHANES were most likely affected by drifts in the assay performance (method bias and imprecision) over time. These assay drifts are likely due to reagent and calibration lot changes in the reformulated DiaSorin assay. These QC drifts may affect comparability, and therefore interpretability, of the data from any combination of NHANES data from 2000-2006, even when comparisons are not being made with NHANES III. Therefore, users of these various NHANES data sets are cautioned that changes in 25(OH)D results over the time period 1988-2006 are affected by the two methodological issues described above and both should be considered when evaluating whether, and how much, differences over time are due to true changes in the vitamin D status of the US population.

Background

Measurements of serum 25-hydroxyvitamin D were performed as part of the nutrition biomarker component of NHANES III (1988-1994) and in the years 2000-2006 of NHANES. These 25(OH)D data are available on public use data files on the NCHS/NHANES website for NHANES III and NHANES 2001-2002, 2003-2004 and 2005-2006. The 25(OH)D data collected in 2000 are available through the NCHS Research Data Center (not available in public data sets) because of a disclosure risk of confidential information for a single-year data release. Readers should be aware that all issues discussed below in regard to the publicly available data for 2001-2006 also apply to the controlled-access data from 2000.

Measurements of serum 25(OH)D were performed in NHANES III (1988-1994) and NHANES 2000-2006, at the National Center for Environmental Health, CDC, Atlanta, GA using the DiaSorin RIA kit (Stillwater MN). The DiaSorin assay kit had been reformulated by the manufacturer between 1994 and 2000 by introducing an antibody that provided improved binding. On average, 25(OH)D values from the reformulated RIA assay used in NHANES 2000-2004 were 12% lower than the original RIA assay values from NHANES III. In addition, drifts in the serum 25(OH)D assay performance (as reflected in QC pool shifts in the mean, up or down, by up to 10%) due to changes in reagent and calibrator lots over the period of 2000-2006 have been observed in the CDC laboratory.

Preliminary steps have been taken to address the changes in assay method between NHANES III and NHANES 2000-2004. A method comparison

study between NHANES III and NHANES 2000-2004 was conducted, which is described in detail in Appendix 1 that accompanied a paper published in the American Journal of Clinical Nutrition.1 This appendix is available on the AJCN website but not in the printed version of the paper, so it is briefly summarized here. To assess the magnitude of assay changes that might have an impact on any observed trends in serum 25(OH)D in the population, the CDC laboratory reanalyzed a subset of 150 banked serum samples from NHANES III using the reformulated version of the RIA assay. The serum samples were selected to represent the entire distribution of serum 25(OH)D values in NHANES III. The NHANES III results as measured with the reformulated assay were regressed on the NHANES III values obtained with the original assay for these 150 specimens. The average difference between the reformulated and original RIA was -12% and is described by the following equation:

NHANES III 25(OH)D2000-2004 RIA assay =
(0.8429* NHANES III 25(OH)D 1988-1994 RIA assay) + 2.5762 nmol/L (r = 0.8966).

This adjustment equation was generated after first accounting for the assay drifts during 2000-2004 with the reformulated DiaSorin assay.

Impact of assay variation on serum 25(OH)D measurements from the NHANES 2000-2006

The weighted mean of 25(OH)D for NHANES 2001-2006 was 59.0 nmol/L, with a range of single-year means of 52.5-66.8 nmol/L. As indicated above, the variation between single years appeared to be due to method variation (arising from method bias and imprecision) over time that results from reagent and calibration lot-to-lot variation.

An approach to address the observed methods variations of 25(OH)D over time in NHANES is currently being developed. However, because this approach will likely take many months to complete, an interim approach was used to assess the potential impact of including data from time periods with greater assay variability on means and prevalences. This approach repeats analyses published in AJCN (Looker et al), which included the data with greater variability, by excluding the data of concern.

Results from these analyses indicated that the impact of including the data from the time period of concern was minimal on results calculated for NHANES 2000-2004. In specific, excluding the time period of concern produced means for NHANES 2000-2004 that were lower on average by -1.3 to -1.9 nmol/L (range -3.1 to +1.1 nmol/L) than means presented in the AJCN article. Percentile data from NHANES 2000-2004 were also minimally affected when excluding the time period of concern: 5th percentile values were higher on average by 0.6 nmol/L (range -1.8 to +4 nmol/L), 50th percentile values did not differ (range -2.5 to +2.4 nmol/L) and 95th percentile values were lower by -1.5 nmol/L (range -6.2 to +5.7 nmol/L). Finally, when the time period of concern was excluded, prevalence estimates for values below cut-points from NHANES 2000-2004 were slightly higher on average than the prevalences presented in the AJCN article. For example, estimates of the prevalence < 25 nmol/L were higher, on average, by 0.25 percentage points (range -0.1 to +0.6). Estimates of the prevalence < 37.5 nmol/L to < 75 nmol/L were higher, on average, by 1.5 to 2.2 percentage points (range -3.3 to +6.4).

In summary, excluding the data from the time period of concern resulted in means and percentiles for NHANES 2000-2004 that were slightly lower and prevalence estimates that were slightly higher than those originally obtained when the entire 2000-2004 dataset was used.

Analysis Recommendations:

Based on the above information and analyses, NCHS strongly urges data users to follow the following recommendation before comparing serum 25(OH)D data from NHANES IIII with serum 25(OH)D data from NHANES 2000-2006: Serum 25(OH)D data from NHANES III should be adjusted using the following equation if comparisons with 25(OH)D data from the full combined 2000-2006 NHANES are being made:

NHANES III 25(OH)D2000-2004 RIA assay =
(0.8429* NHANES III 25(OH)D 1988-1994 RIA assay) + 2.5762 nmol/L

Readers should be aware that this equation allows an approximation of NHANES III results to the level of the reformulated assay used in NHANES 2000-2004. However, it is imperfect in that it cannot simultaneously adjust for drifts in assay performance that may have occurred after 2004. As a result, it should be employed with caution when making comparisons between NHANES III and the publicly available NHANES 2001-2006 25(OH)D data.

Based on the above information and analyses, NCHS strongly urges data users to follow the recommendations below when comparing serum 25(OH)D data for the 2000-2006 NHANES survey period:

1) NCHS strongly discourages analysis of, or comparisons between, any of the two-year NHANES 2001-2006 25(OH)D data due to method variability and sample design limitations. Users are discouraged from using a four-year dataset based on 2001-2004 due to a higher possibility that results may be affected significantly by assay variability.

2) NCHS recommends the use of a data set which combines all years of data (2001-2006 or 2000-2006) to provide more stable estimates of means, percentiles, and prevalence estimates for 25(OH)D. Users should note the possibility of assay variability in their results from the combined dataset as a study limitation.

3) Given the observed QC data variability, users should exercise caution when analyzing and interpreting inter-relationships between 25(OH)D and other NHANES variables using the 2000-2006 NHANES dataset. At a minimum, users should note the possibility of variability due to laboratory methods issues in their results as a study limitation. This variability may be more of an issue for population subgroup analyses.

4) Some variables of interest relative to 25(OH)D were only collected in NHANES 2003-2006 (i.e. parathyroid hormone and sun exposure variables). Interpretation of any analyses conducted on this four-year data set may not be affected in any significant way by the observed

variation in 25(OH)D data during this time period, but users should be aware of, and, at a minimum, list this issue as a potential limitation of analyses and findings conducted using this four-year data set.

5) Additional variables of interest relative to 25(OH)D, geography and seasonality, are only accessible through the NCHS Research Data Center (due to increased disclosure risk) and are subject to the analytic limitations of data used in that setting.

Future Plans

At present, there is no gold standard method for measuring serum 25(OH)D, so that no 25(OH)D data are accuracy-based regardless of the assay used. The National Institute of Standards and Technology (NIST) will soon provide standard reference materials for 25(OH)D assays with certified values assigned by use of isotope dilution tandem mass spectrometry (LC-MS/MS) candidate reference measurement procedures.2 CDC intends to generate regression equations that will permit the adjustment of the 25(OH)D data from various NHANES survey years to the NIST accuracy-based standard by reanalyzing subsets of specimens from NHANES 1988-1994 and 2000-2006 using a candidate LC-MS/MS method. This will improve the ability to analyze the 25(OH)D data from NHANES 2000 and beyond for all types of analyses, including comparisons between NHANES 2000-2006 and NHANES III. When these equations become available, this analytical note will be updated with a revised analytical note.

References

1) Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. *Am J Clin Nutr* 2008 December 1;88(6):1519-27.

2) Phinney KW. Development of a standard reference material for vitamin D in serum. *Am J Clin Nutr* 2008 August 1;88(2):511S-512S