National Program 107
Human Nutrition

Accomplishment Report 2000-2006

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BACKGROUND AND GENERAL INFORMATION

Human nutrition research is clearly important to improving life at all stages. While deficiency diseases are no longer the public health problem they used to be, much work remains on tracking changes in the food supply and dietary habits, defining optimal levels of nutrient intake, discovery of novel health-promoting compounds in foods, nutrient interactions, and maintenance of health, with special interest on the prevention of obesity and related conditions.

The vision for the USDA/Agricultural Research Service National Program 107 (NP 107), Human Nutrition, is that well-nourished Americans will make health-promoting diet choices based on scientific evidence. Consequently, our mission is to define the role of food and its components in optimizing health throughout the life cycle for all Americans by conducting high national priority research. The National Program's mission follows from the USDA/ARS Strategic Plan (http://www.ars.usda.gov/aboutus/docs.htm?docid=1766) which, in turn, is directed towards achieving the goals mandated by the USDA Research, Education, and Extension Mission Area Strategic Plan and the USDA Strategic Plan (http://www.usda.gov/ocfo/usdasp/usdasp.htm).

The products of NP 107's research contribute toward broader goals (termed "Actionable Strategies") associated with three specific Performance Measures from the ARS Strategic Plan for 2003-2007 Goal 4: Improve the Nation's Nutrition and Health. The measures are:

Performance Measure 4.1.1: Scientifically assess the efficacy of enhancements to the nutritional value of our food supply and identify, conduct, and support intramural and extramural research to develop, test, and evaluate effective clinical and community dietary intervention strategies and programs for modifying diet, eating behavior, and food choices to improve the nutritional status of targeted populations. A special emphasis is to prevent obesity and promote healthy dietary behaviors.

Performance Measure 4.1.2: Define functions, bioavailability, interactions, and human requirements (including effects such as genetic, health status, and environmental factors) for known, emerging, and new classes of nutrients. Determine the abundance of known, emerging, and new classes of nutrients in the food supply and provide that information in databases.

Performance Measure 4.1.3: Determine food consumption patterns of Americans, including those of different ages, ethnicity, regions, and income levels. Provide sound scientific analyses of the U.S. food consumption information to enhance the effectiveness and management of the Nation's domestic food and nutrition assistance programs.

PLANNING AND COORDINATION FOR NP 107

USDA/ARS National Programs follow a five-year program cycle, initiated by a Customer/Stakeholder Workshop. The first NP 107 National Program Cycle began with a workshop in March, 2000, in Beltsville, Maryland. ARS scientists and administrators met with customers, stakeholders, and partners to discuss major nutrition issues and research priorities.

Based on those in-depth discussions, seven major Research Components for this National Program were identified prior to developing the NP 107 Action Plan that can be viewed at: (http://www.ars.usda.gov/research/programs/programs.htm?np_code=107&docid=277).

The NP 107 Action Plan was drafted by ARS scientists and members of the USDA/ARS National Program Staff (NPS). The writing team combined input from the workshop, their own knowledge of the subject matter area, and input from other ARS scientists and their cooperators to identify the key, priority needs that could be addressed by ARS research. These Researchable Issues were aggregated into NP Research Components.

Once the Action Plan was completed, specific research Project Plans were written by individual scientists or teams of scientists. Project Plans included statements of research objectives, the experimental approach, information to be generated by the Project, how the research contributes to solving the larger National Program Problem Areas, and time lines and milestones for measuring progress toward achieving the Project goals. All Project Plans associated with NP 107 were then evaluated for scientific quality by external peer panels. The project peer reviews were handled by the ARS Office of Scientific Quality Review. Project Plans were approved or revised in response to peer panel recommendations, and then implemented; those plans that did not receive passing scores after a second review were terminated and funds reallocated. Since the first NP 107 Customer-Stakeholder Workshop was held in 2000, it is now time for the progress achieved in attaining the Action Plan goals to be evaluated by an external assessment panel. This assessment is in preparation for the beginning of the next five-year National Program Cycle.

It should be noted that there was no permanent National Program Leader for more than two years during 2002-2004. This is relevant because the Action Plan was rewritten by the two current NPL's soon after they were appointed in mid-2004. While the components of the original Action Plan from 2000 were not changed, they were reworded, reordered, and newly justified to produce a more coherent and contemporary set of goals. In addition, the NPL's have placed greater emphasis on certain components of the Action Plan in response to recent priorities of ARS and its stakeholders, such as obesity prevention.

NP 107 is the fourth largest of ARS' National Programs and includes six Human Nutrition Research Centers, three of which are operated cooperatively with universities, and locations at other sites throughout the country. The Centers and other locations are given in Appendix 3. The Program requires ongoing direction, oversight and coordination at the national level which is the responsibility of the National Program Leaders.

HOW THIS REPORT WAS CONSTRUCTED AND WHAT IT REFLECTS

In this Report, information about National Program 107 achievements and their impact or potential benefit is organized according to seven National Program Research Components. The report first outlines the components, problem areas, examples of researchable issues and sample goals. These are followed by selected accomplishments achieved since the last Stakeholder Workshop and by the impact of those achievements on solving the problems and meeting the

high priority needs identified by customers/stakeholders in the NP 107 Action Plan.

For the most part, the content of this report is derived from responses to a recent survey of the scientists assigned to NP 107, who were asked to summarize their project's major accomplishments since 2000, their impact, and key references documenting the accomplishments. A writing team comprised of fourteen NP 107 scientists selected high-priority accomplishments from the summaries and wrote the first draft which was reviewed by the NP 107 Center Directors. Consequently, this report does **not** include **all** accomplishments achieved by each NP 107 research project but, rather, only those **selected** by the writing team and the National Program Leaders, who are ultimately responsible for the content of the final report.

NP 107 encompasses 62 current research projects, some of which have multiple subprojects. The titles of all individual projects initiated since the last stakeholder workshop in 2000 are listed in **Appendix 3 – Research Projects**, which is organized according to the geographical location of the research unit. Note in Appendix 3 that the individual research projects may address more than one Research Component. Also note that all existing projects began more recently than the initiation of the first NP 107 National Program Cycle in 2000.

NP 107 Research Component 1 addresses the composition of foods via updating and maintenance of the National Nutrient Databank as well as the development of new food composition analytical methods. Component 2 includes the bioavailability of nutrients and non-nutrient food components. The third Component deals with nutrition monitoring, primarily through conduct of the nationally representative "What We Eat in America" survey which is part of the National Health and Nutrition Examination Survey (NHANES). Component 4 addresses nutrient requirements including energy, vitamins, minerals, and macronutrients across the lifecycle. The fifth Component encompasses study of the health promoting properties of plant and animal foods. Component 6 includes study of prevention of obesity and disease along with the relationship between diet, genetics, and lifestyle. The final, seventh Component addresses health promoting intervention strategies for targeted populations, including children, rural poor, and those of other high-risk groups.

Finally, a word about how NP 107 achievements are documented. Selected examples in the narrative are referenced by numerical citation [e.g., (1)] to references presented in **Appendix 1,** which is organized according to the seven NP 107 Components. Just as only selected accomplishments are reported, the details of those endeavors are documented selectively to illustrate the overall variety of knowledge generated by this National Program. In the report, representative achievements of scientists in NP 107 that demonstrate acknowledgment of peers are cited in **Appendix 2.** These include major awards from national/international organizations, election to office of national, professional organizations, service on major national/international nutrition committees, service on editorial boards of nutrition or biomedical journals, and documentation of highly cited authors who are part of NP 107. **Appendix 3** is a listing of all projects by location funded under NP 107 during the review period.

Component 1 -- Composition of Foods

Problem Area: ARS is the primary source of food nutrient composition information for the public and private sectors in the United States, as well as serving as the foundation for many databases throughout the world. To reflect the dynamic nature of the American diet, the USDA National Nutrient Databank must be continually updated to include the changing array of foods eaten in the United States from both domestic and international sources. No other facility does this and this database is considered the "gold standard" for all others in the world. Besides the need for information on essential nutrients, there is a growing need for new data on food components known to impart health benefits in people. Identification of these health promoting compounds is inextricably interwoven with the development of new analytical methodology to quantitatively measure the food constituents found in the American diet. Following identification and analysis, values are incorporated into computer databases and publicly released for use by consumers, professionals, universities, government agencies, and private industry.

Examples of Researchable Issues: Analysis of key foods, defined as the major contributors of calories and nutrients in the Nation's diet, is required because food composition and food choices change over time. For example, the amount of fat in beef and pork has decreased over time as a result of changes in production and processing methods. Changes in agricultural practices like selecting faster maturing crops can alter the amount of nutrients in the final product. Likewise, changes in manufactured foods such as breakfast cereals and crackers have resulted in increased fiber and decreased trans-fatty acids, respectively. In order to assess the contribution of these foods to health, it is essential to have current data on the composition of the foods. In addition, as analytical instruments and methods are improved and become less expensive, more accurate and more specific tests for the nutrients of interest are developed.

Sample Goals:

- Yearly updates to the food composition values in the USDA National Nutrient Database for Standard Reference
- Production of special interest databases on specific nutrients such as choline, fluoride, and a variety of health-promoting constituents found in foods
- Generation of a Dietary Supplement Ingredient Database
- Development of new and more accurate analytical methods for measuring components in foods

Selected Accomplishments:

*National Nutrient Database for Standard Reference***:** The complexity of the human diet presents a daunting challenge to those tasked with its analysis. Not only must the foods and their constituents be continually updated but the process and software underlying such improvements must be continually scrutinized to ensure a state-of-the-art system for the Nation's premiere source of food composition data. Since 2000, key improvements in both areas have occurred. The USDA National Nutrient Database for Standard Reference (SR) currently contains data for 7,146 foods and up to 136 food components. In 2001, ARS instituted annual SR update releases that have continued to date (1). Over 700 foods have been added or updated in the SR database

including new information for select cuts of pork and beef as well as starch, different forms of vitamin K (2-8), individual sugars, fatty acids (including *trans* fatty acids), folate, tocopherols, and phytosterols. In addition, pertinent statistical data (e.g. means and error bounds) and data source information have been added to SR, and nutrient forms and units of measure have been updated to comply with recent releases of the Dietary Reference Intakes (9). The National Food and Nutrient Analysis Program (NFNAP), a highly successful partnership between the ARS and National Institutes of Health (NIH), supported many of the SR updates.

During this time period, technology and system updates were also implemented. Under NFNAP, a standardized and rigorous SR update process was developed that includes: identification and prioritization of updates based upon key foods (the most commonly consumed foods) and nutrients of public health significance (10), development of a nationally representative food sampling plan (11) with specialized sampling plans for ethnic groups (12, 13), examination of analytical methodology to ensure the proper assay, food composition analyses using quality control materials and procedures (14, 15), and data compilation into a variety of formats to maximize technology transfer. Also since 2000, ARS has released SR updates in CD-ROM, Web, PC, and personal digital assistant (PDA) formats, the latter products resulting from a partnership between ARS and a commercial software developer (16, 17). Because of these technological advances, usage of the National Nutrient Databank now extends beyond professionals to the general public.

Special Interest Databases on Specific Nutrients: ARS produced and released databases for choline (18, 19), fluoride (20, 21), flavonoids, isoflavones, proanthocyanidins (monomeric and polymeric) (22-26) and antioxidant capacity (ORAC) (27). The databases have between 100 and 450 foods with food constituent values for individual classes and specific components (e.g., flavonoids), when appropriate. The USDA Data Quality Evaluation System (15) was used to determine the quality of the analyzed values and the databases include the mean, standard error when possible, number of samples analyzed, and a confidence code (the indicator of data quality) for each value. Also, a Special Interest Database for added sugars was released in 2006 for 2,041 commonly consumed foods. The values are calculated estimates based upon an established algorithm. Most of these databases are the result of successful partnerships with other ARS laboratories, universities, and private industries. Special Interest Databases are the first step in establishing food composition research priorities for specific food components.

Dietary Supplement Ingredient Database: ARS and the NIH Office of Dietary Supplements are collaborating on the development of a Dietary Supplement Ingredient Database (DSID) for products consumed in the United States (28). The database will include data on supplement components and their analyzed amounts. To date, market share, sampling procedures (e.g. purchasing, storing, and shipping), qualified analytical laboratories, methods for handling and analyzing samples, and quality control procedures for 12 vitamins and 11 minerals have been ascertained. Also, label and analytical value agreement for nutrients in ~ 220 products have been assessed and nutrient variability among and within dietary supplement products evaluated.

New and More Accurate Analytical Methods:

Water-Soluble Vitamins. ARS scientists developed new methods for quantifying the water soluble vitamin content of foods, in some cases replacing out-dated, microbiological methods with chromatographic methods. New methods include: a method for measuring cobalamin (vitamin B_{12}) species in foods plus a rapid screening method for cyanocobalamin (the common food fortificant in the U.S.) in fortified foods and supplements (29, 30); a method for definitive quantification of folic acid and 5-methyl-tetrahydrofolic acid (the common fortificant and dominant natural food folate, respectively) in foods and serum (31), a second less expensive and more robust method for the determination of the natural food folate, 5-methyl tetrahydrofolic acid (32) and a third method for folic acid to generate data for 300 food samples obtained from the NFNAP program (33); and a method, to measure niacin in infant formula and wheat flours that has been approved as a Peer Validated Method by AOAC International (34). These methods have been applied to measure these vitamins in the new multi-vitamin Standard Reference Materials (SRMs), being jointly developed with National Institute of Standards and Technology (NIST) and the NIH Office of Dietary Supplements (ODS).

Phenolic Phytochemicals. ARS scientists developed and successfully applied new analytical methods to measure the flavonoid, phenolic acid, proanthocyanidin, and anthocyanidin content of foods. One method quantifies 20 flavonoids from the 5 major subgroups (flavones, flavonols, flavanones, catechins, and anthocyanidins) as aglycones (35, 36), and was used to measure the flavonoid content of selected fruits, vegetables, and nuts for the USDA Special Interest Database on flavonoids. A second method quantifies 16 phenolic acids and their analogs in foods and was used to assess phenolic acids in selected foods (37, 38). A third method determines and quantifies proanthocyanidins, oligomeric as well as polymeric forms (39), and a fourth method determines and quantifies anthocyanins using the glucoside forms of the 6 major anthocyanidins (40, 41).

Unbound Coded and Non-Coded Amino Acids. ARS scientists developed an analytical method for the determination of unbound, coded amino acids (genetically specified) and non-coded amino acids (secondary amino acid metabolites such as S-methyl-cysteine, S-ethyl-cysteine, S-methyl-cysteine sulfoxide, S-allyl-cysteine sulfoxide, Se-methyl-Se-cysteine, and Se-ethyl-Se-cysteine) (42). This new method determines thiosulfinate precursors found in alliums (e.g. garlic) and brassica (e.g. broccoli and cauliflower) as well as secondary amino acid metabolites produced when plants are stressed by excess selenium in the soil (43).

Standard Reference Materials. ARS scientists provided leadership to the development of food-based standard reference materials (SRMs) that are essential to generating accurate food composition data for the National Nutrient Databank (14). In collaboration with the National Institute of Standards and Technology (NIST), the U.S. Pharmacopoeia, the NIH, and the National Research Council of Canada, reference materials were developed for total trace metals and selenomethionine (44). Also, ARS supported the NIH water fluoride survey by developing a fluoride control material (45), and supported NIST in the development of reference materials by characterizing trace metals in SRM 1598a bovine serum, SRM 1548a Mixed Diet, RM 8431 Total Diet, SRM 1570a Spinach Leaves, SRM 2387 Peanut Butter, and SRM 1946 Fish Tissue

(46). ARS worked with the Technical Division on Reference Materials of the AOAC International to establish a new program to evaluate and officially recognize the use of SRMs with Official Methods of Analysis (47).

Impact:
ARS' provision of new, up-to-date, and accurate food composition data for nutrients and other food constituents have impacted our understanding the role of food and nutrients have in promoting health and preventing disease, the science-based nutrition and health policies emanating from such discoveries, the integrity of federal food assistance, nutrition education, food labeling, and food consumption monitoring programs, as well as the usage of such information by professionals and consumers. For example:

The National Nutrient Database underpins diet and health research by federal (USDA, Department of Health and Human Services (DHHS), Department of Defense, and Environmental Protection Agency) and academic scientists, particularly those engaged in human intervention and epidemiologic research. Accurate food composition information strengthens research conclusions and new nutrient and/or bioactive food composition information makes possible new discoveries. For example, release of Special Interest Databases led to research on the health benefits of choline in preventing neural tube defects and in managing trimethylaminuria (48, 49), vitamin K in promoting bone health, and flavonoids, proanthocyanins, and anthocyanins in conferring protective cardiovascular and cognitive benefits.

The National Nutrient Database is the source of food composition information for the dietary assessment arm of the NHANES national survey, i.e., "What We Eat in America." Without this food composition information, national nutrition monitoring would not be possible. Also, the National Nutrient Database was used extensively to develop the USDA and DHHS 2005 Dietary Guidelines for Americans, the primary food and nutrition policy for the United States, and in establishing the new Dietary Reference Intakes, the nutrient recommendations for the U.S. and Canada. Also, ARS provides the food composition database for the new interactive, computerized MyPyramid.gov nutrition guidance tools developed by the USDA's Center for Nutrition Policy and Promotion (CNPP) to aid the public in implementing the Dietary Guidelines.

The Nation commits over $56 billion to Federal food and nutrition assistance and education programs designed to maintain and improve the health of millions of Americans. ARS food composition information is the basis by which USDA agencies charged with food assistance, labeling, and nutrition education responsibilities (i.e. the FNS, CNPP, ERS, CSREES, FSIS, AMS, and NAL) can ensure federal programs adhere to the 2005 Dietary Guidelines for Americans and the Dietary Reference Intakes. Similarly, other federal agencies such as the Department of Health and Human Services (FDA, CDC, NIH, and ODPHP) as well as the Department of Defense and the Environmental Protection Agency require accurate food composition information for food labeling enforcement, nutritional status and health monitoring, nutrition education, and military feeding program planning and evaluation purposes.

The National Nutrient Database is also widely used by academia, healthcare professionals, and consumers for planning and evaluating diets. Because the databases are freely available via the Internet and in formats for PCs and PDAs, the data are easily accessible to all interested parties. In fact, the public release of these databases spawned development of the nutrition analysis software industry. Examples include: Minnesota Nutrient Data System, Food Processor, CBORD Group Inc., and Princeton Multimedia Technologies Inc., and others.

ARS scientists are established world leaders in the development of new analytical food composition methods and reference materials for essential nutrients and health-promoting components in foods. In fact, the USDA Food Composition Laboratory is the only laboratory in the United States devoted exclusively to development of analytical methods for this purpose. The methods are used worldwide by scientists in government, academia, and industry to analyze foods for essential nutrient and other food constituent content. Noteworthy is the replacement of non-specific and out-dated microbiological methods with precise and accurate LC-MS methods for the analysis of folates and several other water-soluble vitamins. Also of note are analytical achievements that provide the ability to definitively analyze specific bioactive compounds such as flavonoids, phenolic acids, proanthocyanidins, anthocyanidins, and amino acid secondary metabolites. In many cases, these methods produced the first systematic data on the concentration of these bioactive compounds in foods making possible human intervention and epidemiological studies to assess the true health benefits of these food constituents. Of particular significance is the establishment of food-related standard reference materials that permit the harmonization of food composition analyses around the country and the world resulting in more reliable analytical results.

Although still under development, the Dietary Supplement Ingredient Database will for the first time permit determination of total dietary intake based upon both food and dietary supplement analyzed composition information. Presently, dietary supplement ingredient information is based solely upon commercial label information—not analyses. In view of the fact that dietary supplements often contain nutrient quantities 100x or 1000x that found in foods, dietary supplement label errors can radically affect the interpretation of dietary intake data. Thus, the development of this new Dietary Supplement Ingredient Database will be a true milestone for the field of dietary assessment as well as helping healthcare professionals/consumers in making informed dietary supplement recommendations/choices.

Component 2 -- Bioavailability of Nutrients and Food Components

Problem Area: Bioavailability is one of the factors that determine nutrient requirements because it affects how much of a nutrient must be consumed to meet the true requirement. Not all nutrients in foods are fully absorbed in the intestine and available for use in the rest of the body. Numerous food-based factors affect biological availability and these differ for each compound of interest. The dietary habits, health status, sex, and life stage of an individual also influence their ability to absorb and utilize nutrients. Unfortunately, there is still much to learn about the bioavailability of many food components, especially when these are consumed in a whole, complex diet. Thus, critical goals in this area are to provide valid information on the absorption

and metabolism of essential nutrients and other health-promoting food constituents in diverse populations, such that informed dietary recommendations can be conveyed to consumers. Novel approaches are required for these studies and efforts are underway to develop and validate new methods. Research is also necessary to understand the molecular and environmental factors that contribute to the phytochemical and mineral content of crop plants, such that a highly nutritious food supply can be guaranteed for the public.

Examples of Researchable Issues: It is unknown the extent to which many of the recently discovered health-promoting compounds in plants are absorbed by humans. There are also few studies on the metabolic fate of these compounds after uptake from the intestine. Research required to address these problems includes identification and characterization of new the health-promoting compounds and metabolites, plant growth/nutrient accumulation studies, intestinal cell culture and animal model investigations, human feeding trials, and kinetic mathematical modeling studies. For example, mineral bioavailability from plants encompasses research on chemical form, absorption by plant roots, transport to and deposition in edible parts of the plant, identification of genetic factors controlling accumulation in the plant, and identification of promoters and inhibitors altering bioavailability in humans.

Sample Goals:

- Identification of soil and growing conditions that optimize uptake and deposition of minerals into edible plants
- Determination of genetic traits of plants that affect concentration of target compounds
- Investigation of dietary factors that promote or inhibit intestinal absorption of essential nutrients and other food constituents
- Discovery of pathways used by intestinal cells to absorb and metabolize food constituents for distribution throughout the body

Selected Accomplishments:

Bioavailability of Phytochemicals: ARS scientists have been instrumental in providing data on the absorption and metabolism of several essential and/or health-beneficial phytochemicals. Studies have focused on various common foods in an effort to broaden our understanding of how different fruits and vegetables of unique composition and matrix characteristics are able to supply important nutrients in our diet. The absorption of β-carotene and the efficiency of its conversion to vitamin A have been studied in spinach, carrots, and kale (1, 2), with results demonstrating a β-carotene conversion that is less efficient than the current 12:1 factor established by the National Academy of Science's Food and Nutrition Board. Additional metabolic studies, using stable and radioisotopically labeled β-carotene and retinol, have also confirmed poorer conversion efficiencies and demonstrated considerable variability in healthy male and female adults, even when the pure forms were fed (3, 4). The absorption and metabolism of other carotenoids and xanthophylls, such as lycopene (believed protective against prostate cancer) and lutein and zeaxanthin (important antioxidant compounds localized to the macular pigment in eyes) have also been investigated. Lycopene absorption was measured from tomato and watermelon (5, 6) and demonstrated a saturating effect such that high doses did not lead to higher levels of lycopene absorption (5, 7). Similarly, ARS researchers developed novel

isotopic methods and demonstrated that lutein absorption could be measured from spinach, kale, and collard greens in humans (1, 8). Lutein and zeaxanthin supplementation studies with primates provided data on the accumulation of these xanthophylls in serum and macular pigment (9). Methods were developed to measure the absorption of vitamin K from different food sources. Physiologic doses of vitamin K in broccoli or collard greens were shown to be well absorbed, but to have a very rapid clearance from circulation (10, 11). Oil-based sources of this fat-soluble vitamin were shown to support higher rates of absorption, relative to vegetables (12). The absorption of anthocyanins, a group of plant pigments associated with cancer protection and improved brain function, were studied in humans. Anthocyanins were absorbed intact from purple carrots but high intakes of anthocyanins can limit absorption efficiency (13). Also, the aglycone and sugar moiety portions of anthocyanins greatly alter bioavailability and the extent of conjugation and methylation that occurs post-absorption (14-16).

Bioavailability of Minerals: Most plant- or animal-derived foods contain essential minerals required by humans, although amounts vary and promoters or inhibitors in these foods alter mineral absorption. Thus, research is needed to quantify mineral bioavailability from foods to understand how these factors contribute to, or detract from, mineral absorption and utilization from a mixed diet. Since 2000, ARS scientists have expanded our scientific understanding of the bioavailability of several dietary minerals including iron, calcium, zinc, copper, cadmium and selenium. Research efforts focused on human studies, when possible, using diverse population groups. However, ARS scientists also have taken advantage of animal and *in vitro* cell culture systems to move the science forward at a more rapid pace. Clinical trials demonstrated that subjects who carried one copy of a mutation associated with the iron overload disorder, hemochromatosis, did not exhibit excessive iron absorption, even from foods highly fortified with iron and the promoter compound, ascorbic acid (17). Human studies also showed that soybeans containing high levels of phytoferritin can provide highly bioavailable iron, even though they contain appreciable levels of the anti-nutrient, phytate (18). Phytoferritin is the predominant iron storage protein found in plant foods and phytate accumulates in many seed crops. Using a pig model, it was shown that when the non-digestible carbohydrate was added to a maize-and soybean-based diet, this prebiotic promoted iron incorporation into hemoglobin in anemic animals (19) that enabled researchers to screen a multitude of factors that can affect iron bioavailability, and to do so in a rapid and cost-effective manner (20, 21). Deprivation of copper was shown to reduce the intestinal expression of hephaestin, the ferroxidase that is essential for the enteric absorption of iron, thus explaining the well known reduction of iron utilization by copper deficiency (22, 23). Also, dietary copper supplied in the form of pinto beans is at least as, or more, effective than inorganic copper in reversing the biomarkers of copper deficiency in the rat model, and daily consumption of a combination of prebiotic short- and long-chain inulin-type fructans significantly increases calcium absorption and enhances bone mineralization during pubertal growth (24). ARS research on zinc absorption led to the discovery and characterization of new zinc transporters that are important for moving this metal across intracellular membranes in mammalian cells (25, 26). A study of selenium bioavailability from foods such as broccoli, wheat, buckwheat, and meat demonstrated that it depends both on the food source and the chemical nature of the seleno-compounds (27, 28). Also, studies on the bioavailability of cadmium from confectionary sunflower seeds grown in eastern North Dakota demonstrated that

it was nearly unavailable to experimental animals (30) but completely unavailable to humans (31, 32).

Nutritional Enhancement of Food Crops: Because our health and well-being are dependent on the availability of nutritious foods, ARS scientists are investigating the molecular, physiological, and environmental factors that contribute to phytonutrient synthesis and mineral accumulation in crop plants. This information is being used to predict how plant nutritional quality might be affected by global climate change or how plants might be manipulated to enhance their nutritional value. Research with soybeans has shown that moderately elevated temperatures during seed development caused changes in tocopherols and isoflavones in seeds (33). The proportions of alpha-, gamma-, and delta-tocopherol changed at the elevated temperatures, with no effect on total tocopherols, while total isoflavones decreased by 67%. Results also demonstrated that increased concentrations of atmospheric carbon dioxide, to levels expected at the end of this century, reduced the effect of temperature on both tocopherols and isoflavones. (These findings are also applicable to Component 5 of this report.) Studies utilizing mutagenized populations of a model legume allowed scientists to identify several plant mutants defective in calcium oxalate formation (34). Characterization of these mutants has provided information on the function and storage of calcium in plants that could facilitate breeding of high-calcium crops. Bioengineering approaches, involving the gene for a specific plant calcium transporter, were used to generate proof-of-concept transgenic tomatoes, potatoes, and carrots with elevated concentrations of available calcium (35, 36). Bioinformatic approaches were used to identify several new genes involved in iron and zinc transport and homeostasis in plants, and provided the means to assess the roles of these genes and their gene products in the movement of metal ions from the soil to edible plant tissues (37). Supplemental ultraviolet radiation at levels not detrimental to plant growth increased phenolic acids and flavonoids by as much as 8-fold in green leafy vegetables such as lettuce and kale (38). These results are relevant to vegetable production in greenhouses or hightop shelters in the field.

Isotopic Methods for Bioavailability Studies: As demonstrated in the accomplishments above, investigations to determine nutrient bioavailability require novel, state-of-the-art approaches, and ideally should focus on whole foods. ARS scientists have been world leaders in the development of stable- and radioisotopic techniques to facilitate these studies. Atmospheric enclosures and growth parameters have been optimized to produce carbon-13 labeled organic nutrients in kale and barley (39, 40) that have enabled phytochemical absorption and carbohydrate utilization studies in humans. Methods have been developed to provide heavy water (deuterium oxide) to plants, in order to label hydrocarbons with a heavy form of hydrogen (2, 11). These labeled foods have been used to investigate carotenoid, xanthophyll, and vitamin K absorption and metabolism. In parallel with the availability of these labeled plants, ARS scientists have developed and validated new mass spectrometry approaches, including using a nuclear accelerator as a mass spectrometer, for analysis of absorbed or metabolized nutrients in biological samples (10, 41, 42). Cell culture system techniques have also been perfected to label unique phytochemicals, such as flavonoids and anthocyanidins, with radioactive carbon-14 for animal studies (43, 44).

Impact:
Bioavailability of Phytochemicals: The development of valid dietary recommendations for specific nutrients or health-beneficial compounds requires a thorough understanding of their absorption and metabolism in healthy Americans. For instance, the conversion factor for dietary β-carotene to vitamin A was set at 6:1 in the 1980s and was adjusted to 12:1 in 2001 by the Food and Nutrition Board, Institute of Medicine of the National Academies of Science, but with an acknowledgement that additional quantitative determinations were needed in humans. ARS scientists responded to this need by developing new methods and executing advanced approaches to determine the conversion factors for provitamin A carotenoids. These results are likely to lead to future revisions in dietary recommendations. In a similar manner, state-of-the-art approaches to study other carotenoids, xanthophylls, vitamin K, and anthocyanins, from a range of common foods, are providing science-based evidence on the absorption and whole-body utilization of these important dietary compounds. Phytochemical absorption information from foods benefits U.S. farmers by providing marketing opportunities for the promotion of "value-added" commodities and helps direct plant breeders towards the best targets in their efforts to develop nutritionally enhanced cultivars. It also has been instrumental in growing the functional foods segment of the food industry, which is now one of the fastest growing sectors in the industry. These ARS results are also essential information for nutritionists, dietitians, and health workers in order to deliver reliable information to the U.S. and international public.

Bioavailability of Minerals: Research on individuals carrying a hemochromatosis-associated allele provides evidence that public policies allowing food fortification with iron and ascorbic acid are unlikely to adversely increase body iron accumulation in this group, who comprise 10% of the white, non-Hispanic U.S. population. Encouraging results with phytoferritin, a bioavailable source of iron, offer confidence to plant scientists that breeding plants with high levels of phytoferritin iron will have a positive impact on the health of target consumers. The inulin results show that the activity of colonic microorganisms, and foods that promote their growth, can have a dramatic effect on iron bioavailability as well as on calcium absorption, especially in plant foods high in antinutrients. These findings have alerted the scientific community of the need to expand human nutrition research into the area of colonic microbial ecology, in order to assess the effects of prebiotics on bioavailable iron and calcium, as well as other mineral nutrients. The Caco-2 *in vitro* model has been used to identify both antinutrients and promoter substances in foods, and is providing critical information to the food industry and others about ways to develop new foods and food crops with enhanced iron nutritional value. The discovery of new mammalian zinc transporters offers new targets for scientists who are attempting to decipher how cells regulate their internal zinc levels, especially when challenged with excess zinc. The finding that copper in pinto beans is bioavailable identifies beans as a potential food source beneficial to cardiovascular health, thus providing nutrition knowledge to health professionals, the food industry, and the consumer. The investigations of selenium bioavailability and the potential health effects of high-selenium foods have prompted the South Dakota Wheat Commission to study the feasibility of segregating high-selenium wheat for sale to specialty markets. The findings of low cadmium bioavailability in sunflower seeds was cited by the EU as justification for not placing importation restrictions on U.S. confectionary sunflower seeds, as had been proposed on the basis of the cadmium content of this crop. This

decision, which was based primarily on ARS research, prevented loss of a major export market for the U.S. sunflower industry.

Nutritional Enhancement of Food Crops: Our plant-based food supply is comprised of unique varieties that have been developed by breeders to have the highest yield, best disease resistance, and are optimized for particular environmental conditions. As our climate changes and new disease pressures arise, breeders will continue to select and introduce new varieties to ensure an adequate supply of food. ARS research in plant nutritional value is providing important predictive information to help breeders also monitor and safeguard the nutritional value of these new varieties. Similarly, research in plant mineral nutrition is offering strategies and proof-of-concept approaches to enhance the availability of essential minerals, like calcium, iron and zinc. Nutritionally improved crops can enhance the dietary intake of U.S. and foreign consumers of our nation's farm products.

Isotopic Methods for Bioavailability Studies: Collaborative efforts between plant and human nutritionists in National Program 107 have been instrumental in enabling many of the bioavailability studies performed by ARS scientists and their non-ARS colleagues. The availability of intrinsically labeled plant products, generated in a cost-effective manner, has opened up several new avenues of research, especially involving healthy, nutrient-replete subjects. The isotopically tagged phytochemicals, along with analytical methods to measure them, provide a means to detect phytochemicals from a given food in a single meal, and to discern them from endogenous unlabeled compounds already in the body. Thus, their use does not require subjects to be put on a depletion diet to lower their levels of a given nutrient prior to a study. Feeding isotopes directly to whole plants or specialized cell cultures often provides the sole means of generating labeled, complex phytochemicals (e.g., flavonoids, polyphenolics), if there are no chemical syntheses available to introduce isotopic tags to these compounds.

Component 3 – Nutrition Monitoring

Problem Area: The USDA's "What We Eat in America" survey (WWEIA) provides continuous monitoring of the energy, nutrients, and foods consumed by the American population. From this cross-sectional survey, usual food and nutrient intakes of the American population are measured and nutritional adequacy is assessed. This is the only nationally representative diet survey conducted in the United States, including Americans of different ages, ethnicity, income levels and geographic regions. Currently, 5,000 Americans participate in this dietary arm of the National Health and Nutrition Examination Survey (NHANES). Linkage of dietary data to health endpoints in the same population generates useful information for researchers studying diet and health. A further goal is to provide sound scientific analyses of the U.S. food consumption information to enhance the effectiveness and management of the Nation's domestic food and nutrition assistance programs.

Examples of Researchable Issues: Dietary assessment methods are widely debated by scientists nationally and internationally in light of the vulnerability of such methods to misreporting. Thus,

it is essential that the national dietary survey be based upon methodology validated for accuracy with appropriate criterion measures. A major outcome of the survey's dietary component is to determine the dietary and nutritional adequacy of Americans, including those of different ages, ethnicity, regions, and income levels. Another goal is to provide sound scientific analyses of the U.S. food consumption information to enhance the effectiveness and management of the Nation's domestic food and nutrition assistance programs.

Sample Goals:

- Develop and validate methods to accurately measure food and nutrient consumption in the United States
- Compile and release food consumption data on Americans every two years
- Provide reports on the nutritional adequacy of the American diet, including population subgroups of varying ages, ethnicities, regions, and income levels
- Interpret food consumption information to enhance the effectiveness and management of the Nation's domestic food and nutrition assistance programs, policy decisions, and to provide consumers with information to improve their food choices

Selected Accomplishments:

Methods to accurately measure food and nutrient consumption: The USDA Multiple-Pass Method (AMPM) is the 5-step computerized dietary recall instrument developed for the USDA "What We Eat in America/NHANES" survey. Using doubly labeled water (DLW) total energy expenditure and 14-d food record absolute nutrient intakes as criterion measures, ARS scientists demonstrated that the AMPM provides accurate group energy intake (without bias and within 4% of DLW) and absolute nutrient intakes statistically equivalent to the criterion measures in women (1). Also, the AMPM has been evaluated in a large-scale study with a diverse sample of adults using DLW for energy intake and 24-hour urinary nitrogen for protein intake as criterion measures. Results are pending (2). The AMPM was built upon an earlier paper and pencil multiple pass method also developed and validated in observational studies conducted by ARS scientists during this timeframe (3, 4). However, attaining accuracy in less time and with less subject burden is a clear advantage of the computerized AMPM over the earlier manual method.

Food consumption database releases: The National Nutrition Monitoring and Related Research Act of 1990 mandated a coordinated national survey effort between USDA and the Department of Health and Human Services (DHHS). After comprehensive planning, USDA and DHHS combined their respective dietary survey operations in 2002 to establish a single joint, national food and nutrition survey (5). The highly successful integrated survey, now called "What We Eat in America /NHANES" (WWEIA/NHANES), collects dietary data on a national sample of approximately 5,000 individuals each year. The first joint USDA/DHHS data release occurred in 2004 (WWEIA/NHANES 2001-02) and again in 2006 (WWEIA/NHANES 2003-04) with new releases planned for every two years (6).

The Food and Nutrient Database for Dietary Studies (FNDDS), the food composition database system used for processing the "What We Eat in America/NHANES" survey, and the FNDDS search tool were updated and publicly released in 2004 and again in 2006 (7). FNDDS includes

survey food descriptions, food codes, food composition values (energy and 61 food components), and gram weights for approximately 30,000 food portions. The underlying food composition data are from the USDA Nutrient Database for Standard Reference (SR) but in many cases the foods are converted through recipe calculations to those consumed by the American public (8). Also, the FNDDS search tool, "What's in the Foods You Eat?", provides easy access to FNDDS foods, portions, and nutrients and is available through the World Wide Web or downloaded for use on a PC.

Also, updates to the Food Link database, a new search tool, as well as several other data tables were publicly released on the World Wide Web during this timeframe (9, 10). A major use of the Food Link Database System is to translate foods eaten by the American public into MyPyramid food servings. Without this new database, it would not be possible to monitor the extent of adherence by the American public to the Dietary Guidelines for Americans, the national food and nutrition policy.

Reports on the nutritional adequacy of the American diet: ARS researchers used data from the "What We Eat in America/NHANES 2001-2002 survey to establish benchmark data on national estimates of "usual nutrient intake" distributions for 24 nutrients/food components and compared the estimates to the new Dietary Reference Intakes (DRIs) (11). Vitamins A, E, C and magnesium intakes had a high prevalence of inadequacy for most gender/age groups. Other problem nutrients included vitamin B6 for older adult females, zinc for older adult males and females and teenage females, and phosphorus for preteen and teenage females. Vitamin K, calcium, potassium and dietary fiber may also be problematic but Estimated Average Requirement values (EARs) have not been established for these nutrients. This is the first application of the new DRIs to evaluating the national dietary survey data. For the above, "usual nutrient intakes" were estimated from one day of dietary recall data collected in the national dietary survey. This required the use of sophisticated statistical techniques and numerous well-reasoned assumptions for which there is no clear-cut precedence. A report published in 2005 contains a detailed description of the method used to generate the estimates, and is accompanied by within-individual variance estimates that can be used by researchers interested in conducting similar analyses (12). On-line access is provided to the above datasets including detailed statistical tables, summary graphs, and bulleted highlights that make the information useful to a broad range of users with differing levels of expertise. The variance estimates accompanying the report make it possible for other researchers to conduct similar analyses using the data set for the "What We Eat in America" survey 2001-2002.

Food survey information analyses and interpretation: Data from the 1977-78 Nationwide Food Consumption Survey and the 2001-2002 What We Eat in America, NHANES were analyzed to identify trends in eating patterns food and nutrient intakes over the past quarter century (13-15). Also, data from the CSFII 1994-1996, 1998; Diet Health Knowledge Survey 1994-1996; and NHANES 1999-2001 data were analyzed to determine relationships between diet, physical activity, and other behaviors on health outcomes among diverse population groups (16-20). Salient findings include: In adults, the dietary practices that promoted good nutrition included eating a diet with 45% or more total calories from carbohydrate, less than 12% calories from

added sugars, eating fruit and non-starchy vegetables, reading food labels, and adopting fat reduction strategies such as use of low fat or lean foods, removing chicken skin, and not adding table fats to cooked vegetables. On the other hand, breakfast skipping, eating fast food, and watching more than 2 hours television a day were associated with being overweight or obese, eating a low nutritious diet that was high in saturated fat and added sugars, and deriving more calories from snacks and supper. Consumption of fast food by U.S. children was found to adversely affect diet quality in ways that elevate their risk for obesity. They consumed more total energy and energy dense foods; more fat, carbohydrate, and added sugars; more sweetened beverages; and less fiber, milk, fruits and nonstarchy vegetables than children not eating fast food. Dietary patterns and other behaviors of African Americans were assessed and published as *Food Counts in the African American Community, Chartbook 2001* (21, 22). Findings indicated that only 42% of all African Americans 2 years and older eat at least 3 servings of vegetables per day. Less than 50%, regardless of income, consume the recommended fruit servings per day. And 40% of males and 55% of females aged 40-59 years rarely exercise.

Impact:
Nutrition monitoring is essential for tracking the health and well being of the American population and for observing health trends in the Nation. The "*What We Eat in America/NHANES"* survey is the only source of nationally representative dietary intake data. The linkage of this dietary data to demographic, socioeconomic and health information in the NHANES survey dramatically increases the value of this information by providing information to study relationships between eating patterns and health/disease. The information's impact is substantial and broad and is used extensively throughout the federal government by program and policy decision makers. Important uses include: determining the nutritional adequacy of the American diet and food supply, measuring the impact of food fortification on nutrient intakes, developing dietary guidance policy (e.g. the Dietary Guidelines for Americans), estimating exposure of population groups to food contaminants such as pesticide residues (Environmental Protection Agency) as well as other industrial chemicals and toxic elements (FDA's Total Diet Study), evaluating the nutrition impact of USDA food assistance programs (USDA Food and Nutrition Service and Economic Research Service) and assessing the demand for agricultural products and the effect on trade (USDA, Agricultural Marketing Service and the State Department). Another key use of the data is by the Food and Nutrition Board of the Institute of Medicine, National Academies of Science to establish the Dietary Reference Intakes (DRIs). Also, the Food and Nutrient Database for Dietary Studies (FNDDS) and its search tool provide health professionals and the general public with easy-to-use information about the energy value and nutrient content of the foods eaten in the U.S. and to help individuals make informed decisions about food choices.

FoodLink is also a high impact database used for research, nutrition education and policy programs. The USDA Center for Nutrition and Policy Promotion uses the database for the development of: 1) the Thrifty Food Plan, which forms the basis of the Food Stamp Program, a more than $35 billion annual program; 2) the Healthy Eating Index, a population-based dietary status score used for policy research; and 3) the USDA MyPyramid Tracker, a web-based consumer assessment and education tool. The NIH National Cancer Institute also uses the

database system for epidemiologic and dietary patterns research and the Environmental Protection Agency uses a special database from the system to evaluate pesticide residue exposures.

Good programs and policy are dependent upon quality data. The Automated Multiple Pass Method (AMPM) developed and validated by ARS research is now recognized as the gold standard for collecting complete and accurate 24-hour dietary recalls. Not only is the AMPM the method of choice for the "What We Eat in America/NHANES" survey but it is also used for the Canadian Community Health Survey. To date some 40,000 Canadians have been surveyed using the AMPM method.

Component 4 -- Nutrient Requirements

Problem: Although Dietary Reference Intakes (DRIs) have been established for many nutrients, knowledge gaps remain and updates are required as new research becomes available. In particular, there is a clear need for more information to set DRIs for children, the elderly, and other at-risk groups. Also, with scientific advancements the most appropriate parameter(s) for assessing nutrient or health status can change, e.g., long-term changes in bone density or incidence of fractures in older women instead of short-term calcium balance studies. Significant research findings are used by the Food and Nutrition Board of the National Academies of Science to update and establish nutrient recommendations for the United States and Canada.

Examples of Researchable Issues: Essential nutrient requirements for human health at various stages of life still need to be established, particularly for children and the elderly. Optimal levels of energy, protein, carbohydrate, lipid, fiber, vitamins and minerals are being studied. Some specific examples include the following: The dietary requirement for calcium is affected not only by the amount of calcium in the diet and the age of the individual but by other components of the diet including protein, vitamin D, magnesium, copper and zinc. In addition, vitamin K levels in food and its bioavailability have an impact on bone density. Another issue is that protein requirements in the elderly may be higher than currently recommended by the DRI's in order to prevent a decline in muscle mass that often accompanies aging.

Sample Goals:

- Determine nutrient requirements essential for bone health such as calcium, protein, magnesium, copper and zinc
- Study the requirement of vitamin D for older men and women
- Assess the amount of vitamin K in foods, its bioavailability and impact on bone density
- Investigate the dietary protein requirement to help prevent muscle mass loss in older men and women

NOTE: Except for targeted research interventions, covered under component 7 of this report, all other Program research contributes in some way to setting nutrient requirements. Thus, some research relevant to nutrient requirements is highlighted here but it should be understood that the

breadth of information drawn upon in establishing nutrient recommendations includes research reported under other report components as well.

Selected Accomplishments:
Nutrient Requirements related to Bone Health: Calcium and vitamin D supplementation of men and women aged 65 years and older reduced their risk of bone fractures by lowering the rate of bone loss that accompanies aging. In fact, older women had only half the risk of falling as those receiving a placebo (4). Also, there appears to be a synergistic effect between high calcium intake and dietary protein in enhancing bone mineral density (1, 2), and higher blood levels of vitamin D are linked with better muscle function in older men and women (5, 6). Meta-analysis of randomized, placebo-controlled vitamin D intervention studies revealed that vitamin D lowered risk of falling by 22% (7) and significantly lowered risk of fractures (8). However, cessation of calcium and vitamin D supplementation reversed the positive gains in bone mineral density within one to two years (3). Thus, ensuring sufficient calcium and vitamin D intake on an ongoing basis is essential for maintaining bone health and muscle function, reducing the risk of falling, and lowering the risk of fracture in older people.

The vitamin D receptor (VDR) gene has been implicated as one of the major genetic components of osteoporosis. Findings by NP 107 scientists suggest a substantial relationship between the VDR gene and bone metabolism at one or more levels, including dietary absorption of calcium and bone mineral density in growing children (9)

Vitamin K also plays a role in bone and cartilage health. NP 107 scientists demonstrated that high dietary intakes of vitamin K are associated with a reduced risk for hip fracture, low bone mass (10, 11), and osteoarthritis (12) in both men and women. Further, dietary intakes of vitamin K were found to be lower in U.S. adults than previously assumed (13). This research on vitamin K would not have been possible without the vitamin K food composition analyses conducted by ARS researchers (see Component 1). More than 2000 foods and food ingredients were analyzed for three forms of vitamin K: phylloquinone (the primary dietary source of vitamin K in the U.S.), dihydrophylloquinone (the hydrogenated form), and menaquinone-4.

Moderately high meat intakes (~ 20% of energy as protein) do not adversely affect calcium retention or bone metabolism in healthy postmenopausal women compared to a low meat diet (14). Chronic dieting to control body weight was found to adversely affect bone mineral content in premenopausal women. That is, high dietary restraint was associated with increased bone turnover (loss) and a high incidence of osteopenia or osteoporosis (20, 21). Boron in the diet strengthens bones and helps maintain bone internal structure in animal models in ways similar to calcium and magnesium (15). Further, dietary copper (16), zinc (17), silicon (18) and fat (19) were linked to bone development and metabolism in animals and humans.

Hypothesizing a relationship between appetite and bone mass, NP 107 scientists discovered that leptin, which appears with the bony skeleton during development, is a regulator of bone mass (22). Specifically, leptin regulates bone formation, following its binding to hypothalamic neurons, and uses the sympathetic nervous system to mediate this action. The sympathetic tone

acts on osteoblasts via beta2 receptors to limit their proliferation (23). Sympathetic tone uses clock genes that down regulate C-myc and cyclin D1 expression and thereby osteoblast proliferation (24). In addition, leptin negatively regulates bone resorption by the sympathetic tone.

Nutrient Requirements related to Cardiovascular Disease and Immune Function: ARS scientists made significant progress in determining the role of copper in cardiovascular function using experimental animals. Both severe and marginal copper deficiencies were investigated and a maternal/neonatal model of copper deficiency and cardio-respiratory function was introduced. Studies conducted with marginal dietary copper levels, approximately equal to copper levels consumed by some Americans, demonstrated that as early as 6 months into the feeding regimen cardiovascular deficits (heart structural and functional impairment; blood vessel dysfunction) occurred similar to those of copper-deficient rats (25, 26). Also, the importance of adequate copper nutrition during pregnancy was demonstrated in a maternal/neonatal model of dietary copper deficiency. Pregnant dams fed a marginally copper-deficient diet with offspring weaned to a diet adequate in copper resulted in offspring that were unable to recover essential respiratory enzyme function in their hearts even after 9 months (27, 28). ARS scientists found new evidence that a long-term high copper intake, but less than the current DRI upper level, appears to adversely affect antioxidant defense and immune function in men (29). Further, it was demonstrated that the homeostatic mechanisms controlling copper retention in humans are not sufficient to prevent accumulation of copper when intake is high (30). These findings suggest that the current upper DRI level for copper is higher than desirable, and consideration should be given to establishing a reduced upper amount. Also, it was shown that vitamin C and E intakes at or near the RDA level were adequate to protect against significant oxidative stress incurred by HIV infection in adolescents and young adults (31).

Nutrient Requirements related to Physical Activity and Performance: Since 2000, NP 107 scientists made significant progress in determining the roles of nutrients in physical activity and performance. Dietary zinc fed at levels commonly consumed by physically active adults in the U.S. resulted in impaired physical performance, including altered cardio-respiratory function during maximal and endurance exercise and reduced endurance performance in men (32). Low magnesium intakes adversely affected cardiovascular function and energy metabolism during submaximal exercise in postmenopausal women (33). These physiological aberrations were associated with decreased muscle concentrations of magnesium and an overall loss of magnesium from the body. Also, abnormal motor function appears to be a permanent impairment even after long-term recovery from perinatal copper deficiency in rats (34). In addition, NP 107 scientists determined the control of protein turnover during exercise by examining the effect of age on the regulation of metabolic pathways that turn on muscle protein synthesis in response to muscle action or contraction (35). Using a well-characterized animal model for skeletal muscle aging, adult and aged rats were studied before and after activation (contraction) of their hind limbs designed to mimic a weightlifting protocol in humans. Metabolic signals associated with turning on protein synthesis in the muscle cells were increased after activation in adult animals but not in aged animals. These observations suggest that protein

synthesis in response to muscle contraction is attenuated with aging and may contribute to the limited capacity of muscle growth with aging.

Nutrient Requirements for Optimal Growth and Development: NP 107 scientists demonstrated that retinoic acid controls endothelial cell proliferation and blood vessel formation and patterning (36). Findings provide new fundamental information about the role of retinoic acid to control aberrant vascular formation and tumorigenesis (37) in the regulation of growth, development and function. Also, a high rate of muscle growth in neonatal pigs results from an enhanced sensitivity of muscle protein synthesis to the rise in amino acids and insulin after a meal (38, 39). Nutrient and growth factor signaling proteins and translation initiation factors that regulate this response have also been identified (40, 41). Enteral nutrition was demonstrated to be crucial to maintain normal neonatal intestinal growth (42), nutrient absorption (43), and barrier function (44), and the gut hormone, GLP-2, was shown to play an important role in these processes (45, 46). Also, amino acid requirements for intestinal growth were defined (47).

Impact:

Nutrient Requirements related to Bone Health: New evidence of the functional outcomes for nutrients is the first step in setting nutrient requirements. Bone loss and muscle wasting accompany aging. More than 10 million Americans over the age of 50 years have osteoporosis and another 33 million have osteopenia or low bone mass. Muscle mass declines at an average rate of 2.0 kg per decade after age 50, and together, bone and muscle loss lead to weakness, falls, fractures, disability, and loss of independence. In fact, in the U.S., one in three persons over the age of 65 falls each year and of those who fall, 20 to 30% sustain moderate or severe injuries, at least half of which are fractures. While the causes of bone and muscle loss are multi-factorial, there is now evidence that these problems can be mitigated by increasing the calcium, vitamin D, and the vitamin K content of American diets. These findings significantly advance the evidence base for setting dietary intake requirements for calcium and vitamin D, which have been primarily based upon their direct effects on bone tissue but now include their effects on muscle performance and the risk of falling. In fact, the National Osteoporosis Foundation used these findings as a basis for its vitamin D intake recommendation. Historically, vitamin K requirements were set based exclusively on its role in blood coagulation. ARS' contribution to characterizing the dietary forms of vitamin K in the food supply, determining dietary intakes of vitamin K by Americans, and advancing the knowledge base of the role of vitamin K in preventing bone loss and abnormal cartilage development provide the kind of scientific evidence needed to establish Dietary Reference Intakes for vitamin K.

Establishing nutrient requirements also requires knowledge of other influencing factors, such as nutrient interactions, bioavailability of nutrients, etc. The high protein content of the Western diet is often cited as a risk factor for osteoporosis or bone fractures. The ARS finding that calcium retention is not reduced when people consume a high protein diet from meat is important to setting future calcium requirements in the context of a society that derives most of its protein from meat sources. Also, with over 50 million Americans currently estimated to have osteoporosis, the negative effect of routinely restricting energy intake on bone health is a new discovery opening up a new avenue of research. National campaigns to reduce obesity could have the inadvertent effect of increasing the incidence of osteopenia and osteoporosis in this

country. Also, the novel finding of the role of leptin in bone formation and osteoblast proliferation is an important finding also creating a new research area. Dietary factors that influence leptin levels could indirectly affect bone health in children and adults.

Nutrient Requirements related to Cardiovascular Disease and Immune Function: The copper research provides new knowledge on the cardiovascular system under conditions of severe and moderate copper deprivation thereby extending the evidence base for copper requirements. In particular, the finding that copper deficiency during pregnancy produced sustained negative effects on the cardiovascular health of the offspring is a novel discovery. While many of the defects of copper deficiency instituted at weaning or later are known to be reversible, copper deficiency during pregnancy and lactation imposes a handicap on the offspring that is not reversible, at least through middle age. This is especially important in view of the fact that many women of child-bearing age do not consume adequate copper. Also, new evidence on the functional effects of a high copper intake in humans is essential to establishing a safe, upper DRI level for copper. This kind of evidence is greatly lacking for most nutrients.

Nutrient Requirements related to Physical Activity and Performance: These findings are used to establish nutrient requirements to achieve optimal physical activity and performance. Findings have already been used by the Institute of Medicine (IOM), Committee on Military Nutrition to determine the adequacy of rations to support military personnel during deployment and combat operation conditions (48) and in setting the nutritional requirements for military personnel (49, 50). The World Health Organization used this information to recommend the addition of magnesium to purified drinking water. Also, much of our knowledge about the regulation of muscle protein degradation and synthesis comes from studies of acute exercise, which generally causes muscle injury and initiates inflammatory reactions. NP 107 research helps to characterize the molecular landscape that controls the balance between skeletal muscle protein synthesis and breakdown. In particular, understanding the metabolic controls of skeletal muscle protein turnover and the impact of aging may help in the development of novel preventive strategies to attenuate the age-associated loss of skeletal muscle mass (sarcopenia).

Nutrient Requirements for Optimal Growth and Development: NP 107 scientists have generated fundamental information about the role of specific nutrients and diet in the regulation of growth and development. Cell culture, animal models, and studies with children have been used to determine the roles of nutrients in the regulation of gene expression, in the development of specific cells and tissues, and in metabolic function relevant to growth and development. In particular, establishment of the biological basis for amino acid requirements in infants and the identification of GLP-2 as a new therapeutic agent for the treatment of gastrointestinal disease are key aspects of this research. This research provides important new information that will lead to strategies to improve the nutritional health of infants and children and help set nutrient requirements for this age group. Further, professionals in the infant formula industry can use these findings to develop new targeted nutritional products for premature infants.

Component 5 – Health Promoting Properties of Plant and Animal Foods

Problem Area: A more nutritious food supply can be developed by lowering caloric density and increasing nutrients and health-promoting non-nutrient constituents of the diet. This can be achieved by traditional breeding or genetic modification of crops and animals, changes in food production or processing, and development of new foods or processing methods for commonly eaten foods. This problem area includes the following researchable issues.

Examples of Researchable Issues: Changes in water availability, temperature, atmospheric carbon dioxide and other factors affect the nutritional value of crops. Only when the impact of such alterations is quantified will food producers and researchers understand how environmental changes affect nutrient concentration in crops. Scientists in this national program are studying a number of specific foods or extracts from foods. Examples include: effects of barley on glucose utilization and insulin sensitivity as well as risk factors for cardiovascular disease (CVD) and weight loss; whether different types of tea reduce inflammation and risk for CVD; how beneficial bacteria called probiotics, found in yogurt and other fermented dairy foods, modify the immune response and prevent infection by pathogenic bacteria like Salmonella; and if compounds found in berries, tea and other antioxidant-rich foods reduce the risk of age-related eye disease and cognitive decline.

Sample Goals:

- Determine effects of changes in agricultural conditions on nutrients in crops
- Assess the influence of consuming barley, tea, berries, vitamin E, and probiotic bacteria on reducing the risk for common chronic diseases or for infections
- Ascertain if following the Dietary Guidelines for Americans reduces the risk of eye disease commonly associated with aging

NOTE: A considerable number of these issues overlap with those identified under Component 6 (Prevention of Obesity and Disease: Relationship between Diet, Genetics, and Lifestyle) and both Components 5 and 6 relate to the knowledge base for Component 4 (Nutrient Requirements). Some issues, like the final sample goal above, were erroneously placed in this component under the original Action Plan in 2000.

Selected Accomplishments:
NP107 scientists have studied a wide range of plant and animal foods for health benefits. Selected examples of the more promising findings are described here but the total research portfolio includes: development and refinement of analytical assays, measurement of these compounds in food, bioavailability studies, *in vivo* metabolism of the compounds, health effects in animals and humans, and elucidation of mechanisms responsible for the effects. Several of these areas are documented under other components of the National Program review, including development of a database for proanthocyanidins and other antioxidants in foods, an essential first step in stimulating research using those foods.

Changes in agricultural conditions and nutrients in crops: NP 107 scientists documented changes in nutrient content of crops as a result of environmental variation. Vitamin E and isoflavone content of soybeans are significantly affected by temperature, carbon dioxide and water stress; the range of total isoflavone content was 10-fold, dependent on growing conditions (1). Selenium concentration in broccoli can be modulated 800-fold by application of a Se-rich fertilizer but this practice results in marked declines of sulfurophane and phenolic acids (2). These experimental results demonstrate that climate change can greatly alter specific nutrient content of crops and that increases in one nutrient may lead to unexpected and undesirable declines in other bioactive compounds.

Reducing the risk for common chronic diseases or for infections with specific foods: The consumption of barley by volunteers was studied for influence on risk factors for heart disease and diabetes in two trials carried out in mildly hypercholesterolemic men and women. Total and LDL-cholesterol concentrations, triglycerides and fasting glucose were significantly reduced, without a significant reduction in HDL-cholesterol, compared to pre-study values by the inclusion of 3 or 6 g beta-glucan/day in men and postmenopausal women while declines in pre-menopausal women were modest. Barley consumption has the same health benefits previously reported after the consumption of oats containing equivalent amounts of beta-glucan (3, 4). This research led directly to FDA approval in May 2006 of a health claim for barley based on its soluble fiber content.

Tea is one of the most widely consumed beverages and its polyphenol content has been related to a variety of health effects in epidemiologic and experimental studies. NP107 scientists demonstrated that tea consumption resulted in improved serum lipid profiles (5). Also, the program showed that green tea and its primary catechin, epigallocatechin gallate (EGCG), inhibit endothelial cell signaling.

Another food group rich in polyphenols is berries and NP107 has been a leader in demonstrating potential health benefits as a result of eating berries. For example, scientists have related blueberry intake by aging rats to significantly improved cognition in a series of experiments from our program (6). This finding led to additional research indicating that fruits and vegetables high in polyphenols, such as strawberries, grapes and spinach, can protect against ionizing radiation, neuronal decline associated with aging, and oxidative stress; in addition to the gross behavioral observations, our scientists demonstrated that these compounds cross the blood-brain barrier and have pursued the molecular mechanisms by which polyphenols exert their benefits (7-9).

Cherry consumption has been shown by NP107 to reduce serum uric acid as well as levels of several markers/mediators of inflammation including C-reactive protein, regulated upon activation, normal T-cell expressed and secreted (RANTES) and nitric oxide in humans (10, 11). While oats have been studied by other researchers primarily for cholesterol-lowering benefit derived from their soluble-fiber content, ARS scientists identified avenanthramides, a type of polyphenol found uniquely in oats, as having antioxidant activity. NP107 investigators demonstrated antioxidant activity *in vitro* and *in vivo* along with inhibition of vascular smooth muscle cell proliferation (12, 13), indicating potential anti-atherosclerotic activity.

Other projects in NP 107 have examined effects of phenolic phytochemicals on markers for heart disease or cancer, including inhibition of P-selectin, platelet-leukocyte interactions, tyrosine kinase activity (14) and blood pressure (15). One important study showed that supplementation with vitamins C and E plus folate did not improve oxidant biomarkers in healthy young men who had a low intake of fruits and vegetables, indicating the non-nutrient compounds play a significant role in protecting against oxidative damage (16).

Program scientists identified cinnamon as an insulin mimetic several years ago and have exploited this finding to achieve several goals. Active ingredients have been identified, the most potent of which is methylhydroxychalcone (17). This has led to a clinical trial showing cinnamon ameliorates the glucose intolerance in type 2 diabetics principally by increasing insulin sensitivity and lowers serum lipids significantly (18).

Soy is perhaps the food that has garnered more interest in providing potential health benefits than any other in the past 20 years. NP107 scientists have made major contributions to the scientific base and are conducting studies that are expected to have a most important impact on the general use of soy-based formulas for infant feeding. The isoflavonoids in soy have been studied extensively; NP107 scientists have identified glyceollins as additional members of that family produced in response to stress and have demonstrated biological activity against breast cancer cells mediated via their interaction with estrogen receptors (19). Follow-up studies are underway to modulate levels on glyceollins in edible portions of the plant and to study the biological effects of exposure to them. Many other soy studies conducted by the program are either documented under other components of this report or not selected for presentation.

In an NP107 study comparing high-isoflavone soy protein and beef in diets of postmenopausal women, these two protein sources were equivalent when markers of calcium loss and bone health were assayed (20). It was also demonstrated that high meat intake was not detrimental to bone status in the presence of adequate calcium intake (21).

A study currently underway and expected to have major impact has recruited about a third of the anticipated 600 children and is comparing development of infants given one of three feeding regimens: breast feeding, soy formula feeding, or cow's milk formula feeding during the first six months. Children will be followed through puberty and studied for growth, body composition, bone mineral content, metabolism and pharmacokinetics of isoflavones, brain development, cognitive function, language acquisition, learning and attention. Relevant to this trial and this area of research, a number of NP107 scientists are studying potential mechanisms by which soy protein/isoflavones modulate gene expression, monocyte adherence to endothelium, hypercholesterolemia and other markers of health.

The program has been among the leaders in research on the potential of vitamin E for reducing risk of chronic diseases and infections. Most of this work is described under Component 6. The most significant finding is that supplements of vitamin E administered to elderly nursing home

residents resulted in significantly fewer upper respiratory infections and those infections were also of shorter duration (24).

Probiotic bacteria in the form of combined lactobacilli and bifidobacteria are being studied for a variety of health outcomes by the program. The major accomplishment related to this area has been development of a neonatal swine model that recapitulates most of the pathophysiology found in humans with allergy (25). Both FDA and NIH have identified a non-rodent model for dietary allergens repeatedly as a high priority. Research accomplishments in this area also include testing of human-derived probiotics in the swine model (26) and establishing parameters of the immune response. The immune studies on these animals have identified interactions with intestinal parasites and established the basis for successful therapy in a number of immune-mediated conditions including Crohn's disease and ulcerative colitis, with a majority of patients experiencing remission (27, 28).

Diet and risk of eye disease commonly associated with aging – The potential for diet to modulate eye disease has been recognized relatively recently. Our program has been central in conducting epidemiologic studies, interventions and basic research on how various nutrients influence the eye. Our labs have identified several modifiable risk factors for cataract and age-related macular degeneration (AMD) (29). In addition to participation in the Age Related Eye Disease Study (AREDS), which tested vitamins C and E, beta-carotene and zinc in treatment of AMD, the program is involved with AREDS 2, which will begin shortly and is an NIH-funded multi-center trial of lutein, zeaxanthin and omega-3 fatty acids against AMD. In response to the NP107 Action Plan, it was found that adherence to the Dietary Guidelines for Americans is associated with significantly reduced risk for cataracts (30).

Impact: Research conducted under this component of health promoting properties of plant and animal foods had impacts at multiple levels. This included stimulation of additional research in many areas. Perhaps the most pertinent example is the demonstration that blueberries fed to laboratory animals ameliorated signs of aging of the central nervous system. Not only has this line of research spawned numerous studies by other scientists, it has increased consumer demand strikingly for blueberries and other polyphenol-rich commodities in the U.S. and other countries (31). This has fostered research by many other scientists to exploit a variety of other phytonutrient-rich foods and examine additional end-points in animal models. Furthermore, this research has been remarkably beneficial to the food industry, opening up new marketing campaigns for crops such as cranberries, strawberries and pomegranates in the U.S. and abroad. While there has been only slight increase in fruit and vegetable intake by Americans over the last several years, products identified by this research have shown marked increases in consumption.

The research finding that high meat diets actually enhanced bone mineral density in women was important to the meat industry as many women have reduced meat intake based on the supposition that high animal protein intake reduced calcium retention and bone density.

The vitamin E study in institutionalized elderly can improve quality of life for this population. Since respiratory infections are the major cause of both morbidity and mortality in this

population, this inexpensive intervention has potential for saving health care costs and improving the quality and quantity of life for those individuals.

Research studies on probiotics and related work on intestinal immunity have spun off a number of innovative areas of treatment. One of the hindrances to more concerted work in this field has been the absence of a yogurt manufacturer that will certify their products according to FDA standards. However, a 2-day international conference sponsored by the Drug Information Association is scheduled for October 16-17, 2006 at the University of Maryland to stimulate regulatory agencies and the private sector to jointly work toward establishment of production standards for food products containing probiotics. The basic intestinal immunity discoveries from these projects have the potential for completely revolutionizing therapy of conditions that are very difficult to treat, such as Crohn's disease, ulcerative colitis and round worm infections common in much of the developing world.

The impact of our studies on age-related pathology of the eye in relation to diet cannot be overestimated. More than 50% of the elderly in the U.S. will develop a cataract or age-related macular degeneration. The latter is the most common cause of blindness in people over 65. Factors identified by our scientists are being tested in the NIH-sponsored AREDS 2 study, which began in July 2006.

Studies of the health-promoting properties of cinnamon have resulted in considerable interest from the private sector, which has translated into establishment of Cooperative Research and Development Awards totaling over 1.7 million dollars. Attempts at finding patentable derivatives of active agents found in cinnamon may result in additions to the pharmacopeia for treatment of diabetes and dyslipidemias.

Another indicator of impact for this component is the citation impact factor produced by Thomson Scientific. Recently published rankings for agricultural sciences shows Drs. Ronald Prior and Guohua Cao, from this program, as the first and fourth most highly cited authors in this discipline. Dr. Prior published 41 papers from 1996-2006 and received 2026 citations for a mean of over 49 citations per paper. Both of these scientists developed an automated version of the oxygen radical absorbance capacity (ORAC) assay and this has been used to quantify antioxidant capacity of a variety of foods and in plasma following consumption of test foods. Although this applies to the health promoting effects of plant foods, much of this work is also described under Component 1, Composition of Foods.

The ongoing longitudinal study comparing children who are breast-fed, milk formula-fed, or soy formula-fed is expected to become the definitive survey of whether feeding choice affects multiple parameters outlined in the narrative above. The New Beginnings study of formula feeding either soy or milk compared with breast-feeding will address the considerable controversy surrounding the safety of soy protein feeding to infants, which has led to recommendations against consumption of soy formula by the governments of Australia, New Zealand and Israel as well as major conferences and governmental hearings in other countries. Although only it its earliest phase, preliminary results have shown no differences between infants

fed the two types of formulas but more rapid growth than those who were breast-fed (22, 23). Given that other countries have begun to recommend against soy feeding for infants save for exceptional circumstances in the absence of adequate data, the need for these results is obvious and has very high potential impact on the soy industry and consumer health and safety.

Component 6 – Prevention of Obesity and Disease: Relationship between Diet, Genetics, and Lifestyle

Problem Area: There is considerable variation in health status of populations in response to consumption of specific types and amounts of nutrients. Some of the reasons for this are genetic diversity, gender, behavior, and lifestyle. Genetic variation as a factor in modifying response to nutrients is an area of intense research because studies have demonstrated the body responds to environmental factors such as diet and tobacco use as a result of single or multiple gene changes.

Examples of Researchable Issues: Some of the genetic differences being studied by researchers in this national program include: those that modify metabolism of the B vitamin folic acid which alter the risk for both cardiovascular disease (CVD) and cancer; those that contribute to intestinal resistance to the hormonal actions of vitamin D on calcium absorption; markers for CVD and obesity in the U.S. population and other countries; and genes that affect development of obesity in Hispanic children. Dietary components that affect disease under study in this program include: types of fatty acids for effects on the inflammatory response; selenium as a protective agent against cancer; nutrient regulation of hormone receptors implicated in a variety of health conditions; and breast versus formula-feeding, school meals, and phytochemicals in fruits for effects on neurophysiological and psychological development in infants and children. Finally, the effects of physical activity on long-term food intake and maintenance of healthy weight are being assessed.

Sample Goals:

- Identify the effects of genetic variation on response of various risk factors for chronic disease to differences in diet
- Determine how genetic factors affect development of obesity in children from an ethnic minority
- Assess whether infant or childhood feeding practices alter brain development and function
- Provide data that bear on whether selenium, vitamin A and other antioxidants reduce cancer risk or improve resistance to infection
- Understand whether changes in physical activity alter long-term food intake and maintenance of healthy weight

NOTE: A considerable number of these issues overlap with those identified under Component 5 (Health Promoting Properties of Plant and Animal Foods) and both Components 5 and 6 relate to the knowledge base for Component 4 (Nutrient Requirements).

Selected Accomplishments:
Genetic variation and diet: Many of our scientists are studying genes in children, adults or model systems that interact with diet and correlate with susceptibility to diseases such as cancer, heart disease and obesity. In addition, other program researchers are examining dietary influences on epigenetic processes and age as factors in multiple paradigms. Several selected examples follow. Perilipin, a protein that coats intracellular lipid droplets within adipocytes and regulates their lipolysis, was identified by the program in the early 1990's and work within the review period of this report focused on several polymorphisms of the perilipin gene which appear strongly related to obesity (1, 2). This has been shown in a study of over 800 Caucasian women, but not men, in the U.S., and in over 4,000 Singaporeans of Chinese, Indian and Malay ethnicities. A common mutation in the perilipin gene was significantly associated with body weight, serum glucose and triglyceride concentrations, suggesting that these metabolic variables are causally related to increased body weight. In addition, another less common perilipin polymorphism was strongly associated with successful weight loss after a low-calorie diet up to 12 months (3).

The program has been at the forefront of research linking high levels of homocysteine with a variety of health endpoints for many years. During the review period, scientists identified the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, which interacts with folate status, as responsible for high plasma homocysteine, global DNA hypomethylation, and non-methylated folate levels in erythrocytes (4). In addition, a new HPLC method was developed to analyze folate in foods and this allowed contribution of folate values for more than 300 foods in the USDA National Nutrient Databank (5); information on this is found under Component 1. Much of the evidence FDA evaluated as justification for mandated folate fortification of grain products came from NP 107. Follow-up work by the program has shown that folate intake in the U.S. exceeds predicted values and health effects of this are being monitored (6). Mechanistic studies on this subject have revealed that vitamin B12 deficiency alters methylation of DNA suggesting an important role in cancer and perhaps aging (7). Further work showed that homocysteine levels and plasma concentrations of B vitamins have robust value in predicting risk of subsequent cognitive decline, progression to dementia, and morphological changes in the brain (8, 9).

Additional genetic polymorphisms were found that explain the heterogeneic response of plasma HDL-cholesterol (HDL-C) to consumption of polyunsaturated fatty acids (PUFA) (10, 11). About 20% of the U.S. population has an apoA1 polymorphism that increases HDL-C in response to more dietary PUFA while those without it show a decrease in HDL-C (12).

Genetic factors and obesity in children from an ethnic minority: Analysis of obese and non-obese Hispanic children has differentiated effects of environment from genetics for a variety of traits including serum IGF binding proteins, insulin, cholesterol, and adiponectin (13, 14). Work done in parallel has resulted in establishment of a contemporary reference database for body composition from infancy to early adulthood for European, African, and Hispanic ethnicities in the U.S. (15). This database is available on the Web to researchers and has over 240 registered users. Related methodological work has been done to examine the techniques used to quantify body composition, particularly bioelectrical impedance analysis, and our program has been a

leader in this area studying children, adults and laboratory animals using several methods (16-18).

A polymorphism in the vitamin D receptor was identified that modulates calcium absorption and bone accretion during the pubertal growth phase (19). Another mutation in epithelial cell calcium-channel was identified as modulated by vitamin D, which may be an important determinant of intestinal calcium absorption (20).

Feeding practices effects on brain development and function: The outcome of assessing infant and childhood feeding practices for effects on brain development and function is being addressed by a large longitudinal study currently underway that is expected to be the definitive study on feeding practices and neurological development; it is described in detail under Component 5.

A*ntioxidants and cancer or resistance to infection:* The program has many projects under the theme aimed at elucidating the role of selenium, vitamin A, and other antioxidants in the development of chronic disease or resistance to infections; some relevant studies are also described under Component 5. Studies have been performed in cell culture, animal models and in human volunteers. The program has been a major contributor in linking selenium to cancer prevention (21) and resistance to infections (22). While the former is generally well known and is being studied in large clinical trials, the latter may have equally important public health implications. Deficiencies of selenium or vitamin E have been shown to increase susceptibility of mice to several viral infections and to increase the rate of viral mutation in infected hosts. The latter phenomenon may be one of the reasons that important influenza mutations frequently originate in Asia, where selenium status is often compromised. These nutrients may also play a significant role in mucosal immunity (23). Vitamin E supplementation of elderly nursing home residents for 12 months led to significant reductions in upper respiratory infections and this effect was shown to be mediated via improved CD4+ T cell function (24, 25). This was modeled in aged mice supplemented with vitamin E that had significantly lower viral lung titers and better function T cells compared to mice consuming the required amount. A final example in this area is the demonstration that ∃-carotene in low dose is able ameliorate cigarette smoke-induced activation of several oncogenes (26). This latter finding has been extended to other tumor models, additional tumor markers and is directly relevant to supporting the dietary recommendation of increasing fruit and vegetable consumption, particularly for prevention of chronic diseases.

Numerous other nutrients that do not exhibit antioxidant activity also affect the carcinogenic process. Using animal models, we have established that the colonic epithelium of aged animals is more susceptible to depletion of folate then the colon of young adults (27). At the other end of the lifespan, intake of methyl groups by pregnant animals affects methylation status of their offspring by epigenetic mechanisms (28). This phenomenon also results following consumption of genistein (29).

Long-term food intake and maintenance of healthy weight: Study of food intake, physical activity and weight maintenance has been a focus of several of the Human Nutrition Research

Centers. One of the more important accomplishments in this area was the comparison of four popular diets for weight loss in overweight and obese individuals over a one year period leading to the conclusion that the most important factors were adherence to the diet, rather than the macronutrient profile of the diet plans, and that fad diets had lower compliance (30).

Other meaningful accomplishments: In addition to the genetic markers for cardiovascular disease described above, the program has several projects relevant to reducing risk for this major cause of death in the U.S. We reported that older men respond better than women to a cholesterol-lowering diet (31), that hydrogenated fats adversely affect lipoprotein metabolism (32) and that intake of soy protein has a real, but limited, effect on serum cholesterol levels (33). FDA considered the two latter findings in requiring *trans* fatty acids on the Nutrition Facts label and approving a health claim for soy protein.

ARS scientists have tracked longitudinal changes in body composition (34), determined how much muscle loss is tolerated without clinical deterioration (35) and devised an exercise protocol that improved glycemic control in older Hispanics with type 2 diabetes (36). In order to devise effective interventions to reduce muscle loss during aging we must understand the basic process. To that extent, we found that human muscle senescence disrupts the coordinated expression of (catabolic) inflammatory and (anabolic) anti-inflammatory cytokines that follow a period of exercise (37). Study of dietary factors altering the inflammatory response is a theme that cuts across multiple projects and much of this is reported under Component 5.

Individual foods and nutrients have been tested for a variety of health endpoints related to prevention of chronic disease in humans and in a variety of model systems. We have shown that consumption of cherries has demonstrable anti-inflammatory effects as described under Component 5 (38). Much research effort has been devoted to categorizing the immune alterations following intake of different fatty acids: linoleate, arachidonate, *trans* fats, conjugated linoleate (CLA), and omega-3 fats. Similar studies on immune response have been conducted in which the variable was mineral status for copper, zinc, or selenium. Additional research on fatty acids has linked them to activation of toll-like receptors, which are now thought to play a pivotal role in inflammatory responses to infection and various endogenous stress molecules. Our studies demonstrated that saturated fatty acids activate Toll-like receptors and n-3 polyunsaturated fatty acids suppress them (39).

In addition, response of the gastrointestinal (GI) immune system in swine to feeding of probiotics has been examined (40). Related to this work is development of the Porcine Immunology and Nutrition database that includes about 2,600 genes and is freely available to any researcher via the Web (41). This project has led to the conclusion that the pig immune system is more similar to that of humans for >80% of variables while only 10% of rodent immune variables are more comparable to humans. The swine model, and its comparison with rodents, has played an important role in studying the GI immune response, resistance to GI infections, food allergies, and successful experimental treatments for conditions such as Crohn's disease and ulcerative colitis (42-44).

Our program has generated epidemiological studies that link dietary practices with health outcomes. In addition to the bone studies described in earlier sections, we have shown in observational studies that relatively high protein was associated with higher bone mineral density (45). Other nutrients, including vitamin K, silicon and B vitamins, particularly B12, were associated with bone mineral density (46). Other research found that people who ate three or more servings per day of whole grains were less insulin resistant, less likely to have metabolic syndrome, and had lower mortality (47).

Finally, a number of advancements in the area of growth and nutrition have been made by NP 107 scientists. The program was an early leader in identification of the omega-3 fatty acid, DHA, as important in neurodevelopmental status of infants and conducted several studies in this area (48, 49). Markers of oxidant damage were correlated with fatty liver and negatively associated with glutathione synthesis, suggesting that oxidant damage to mitochondria may underlie impaired lipid oxidation in children with kwashiorkor (50). Elucidation of the precise role of lactoferrin was hampered by the lack of a suitable animal model until NP 107 scientists generated a knockout mouse and discovered that milk-derived lactoferrin protected against iron overload in the intestine and modulated neutrophil oxidative burst (51).

Impact: This component has more projects under it than any other portion of the program. The genetic information generated by the program has been instrumental in bringing diet-gene interactions to the forefront of research on nutritional requirements and susceptibility to disease. This research will lay the foundation for more individualized nutrition requirements, a direction that is presaged by the individualization of USDA dietary guidance for total energy in MyPyramid. Few impacts can be documented for nutrigenomics work yet but the potential dividends are great and high levels of interest exist among researchers, funding agencies, and the food industry. The Porcine Immunology and Nutrition database has immediate applicability to prevention of swine diseases, more efficient production of swine as a commodity and serves as a template for researchers doing similar work in chickens, cows, rabbits and fish.

One of the most important findings from the program was the apoA1 polymorphism that explains the heterogeneous response of HDL-cholesterol to polyunsaturated fat intake. Not only does this finding explain a lack of reliable response to diet, it is a major discovery in the potential development of more individualized dietary recommendations that eventually will be based on accumulation of a panel of genetic polymorphisms that modulate response to diet.

Identification of gene polymorphisms that relate to weight loss/maintenance will help in the design of interventions that are more successful over the long term – an area that is woefully inadequate. This nascent field has the potential to revolutionize dietary guidance for the entire population.

A number of nutrients and specific foods have been identified by the program as playing a major role in host resistance to infection and to several chronic diseases. Some of the research in this category will undoubtedly be considered when the Dietary Reference Intakes for relevant

nutrients are revised. One of the genuine challenges in this area is to instigate behavioral changes that will lead to diet and activity differences identified as health-promoting.

Research from the program was used by FDA for a variety of purposes including adding *trans* fat to the Nutrition Facts label, requiring folate fortification of grain products, and approval of health claims for soy protein and barley. The approved soy health claim has been one factor in greatly increased sales of soy products to the American consumer. Described under Component 5 was the ARS research that led to FDA extending the health claim for oats to barley.

The observational studies on diet and bone density, insulin resistance, metabolic syndrome and diabetes will influence the next Dietary Guidelines for Americans advisory committee and likely play a role in revision of the appropriate DRI's.

One of the most profound changes in infant formulas over the past few decades has been the addition of the long chain omega-3 fatty acid, DHA, to most formulas in attempts to more closely mimic human milk and stimulate neuronal development. Additional findings in malnourished children have led to reformulation of the early maintenance diet used to treat malnourished children with hepatic steatosis. The findings on lactoferrin will lead to additional research studies and may stimulate changes in infant formulas for preterm and low birth weight infants.

Component 7 – Health Promoting Intervention Strategies for Targeted Populations

Problem Area: Although nutrition knowledge is necessary to implement strategies to maintain healthy weight and meet other nutritional requirements, this information alone does not ensure proper nutrition for a variety of reasons including inadequate access to recommended foods, low income, low literacy, cultural beliefs and a variety of other factors. Dietary interventions need to be created and tested that will improve the health of Americans. Research on the endpoints of interest is needed to identify effective ways of communicating food and nutrition knowledge to individuals and populations to elicit changes in food intake and other behaviors that are based on scientific evidence.

Researchable Issues: Several approaches to this problem are taken by scientists in the national program. Development of databases on food consumption and use of them in identification of practical diet practices to avoid obesity, diabetes, osteoporosis and other chronic conditions is being done. Comparison of a diet and exercise program with physical activity alone is required to address the issues of whether fitness at any weight is as healthy as being in a specified healthy weight range and what interventions are sustainable over the long term. It is also necessary to address nutrition interventions in the context of local community issues because different demographic backgrounds will necessitate interventions of varying types.

Sample Goals:

- Develop databases that can be used to identify diet practices to avoid obesity and other chronic health conditions
- Show that an exercise program without intent to lose weight improves insulin sensitivity
- Identify, implement and test nutrition and physical activity interventions in low-income communities

Selected Accomplishments:

Databases for targeted populations: In order to develop appropriate interventions and evaluate their effectiveness, it is critical to know what Americans, and more specifically high-risk sub-populations, currently eat. Accomplishments in this area are described in more detail in Component 3: Nutrition Monitoring primarily in relation to the nationally representative diet survey conducted by NP 107 as part of NHANES. Since NHANES only surveys the U.S. in areas of adequate population density, the need to determine if rural diets mirror those of urban and suburban areas should be obvious. Program scientists have developed databases on the normal dietary intakes of individuals in several geographic regions. These data have been used to develop and validate population specific food frequency questionnaires (FFQ) designed for use with older adults living in the rural northeast and for adults in the rural Mississippi Delta region where dietary intakes are quite different from the average intake in the rest of the United States (1). A representative, cross sectional telephone survey, Foods of Our Delta (FOODS 2000), was completed for a 36 county area of the lower Mississippi delta region in Arkansas, Louisiana, and Mississippi and found a higher prevalence of diet and nutrition related chronic diseases than found elsewhere in the United States (2). This was the first data to be collected for the Lower Mississippi Delta population that included food intake, health/disease perceptions, food insecurity status, and quality of life issues (3).

Exercise program without intent to lose weight: NP 107 scientists showed that a novel "health centered" non-diet wellness program for obese women who were chronic dieters compared with a traditional weight loss program produced improvements in blood pressure, blood lipids, self-esteem and eating behavior, and increased caloric expenditure; in addition, attrition was only 8% in the wellness program compared with 41% in the diet group (4). Weight loss and regain occurred in the diet group without any weight loss in the wellness group but the differences in risk factors were sustained at 2 years (5).

Nutrition and physical activity interventions in low-income communities: The largest share of resources under this Component is devoted to assessment of the nutrition and health needs in the lower Mississippi Delta region and development of interventions that will ameliorate those conditions among some of our country's poorest residents. This project was established in 1995. A food frequency questionnaire was developed for use in this region, validated and used to identify nutrients of concern (6). High rates of food insecurity have been identified and linked to poor health status, even when controlling for income and race (7). Residents of small towns in Arkansas, Louisiana and Mississippi have been surveyed and groups are participating in pilot interventions developed under the rubric of community-based participatory research. One pilot group had high retention (90%) at 6 months, a small but significant weight loss and demonstrated

that non-professional church members could be trained to conduct such an intervention successfully (8).

A much smaller project, ongoing since 1988, intended to assess the nutritional status of older adults in a rural setting in the northeast is situated in north central Pennsylvania. The Geisinger Rural Aging Study is a longitudinal cohort of >20,000 people over 65 years old living in small towns with a subset evaluated for diet. This study has found higher prevalence of overweight and obesity among this population than average along with evidence that high nutrient density diets are associated with weight in the healthy range (9).

Interventions targeting children are one of the key foci of this component. The program found that children who skip breakfast exhibit cardiovascular signs of increased parasympathetic activity (10) in addition to performing less well on a variety of cognitive tests. When children gained access to school snack bars and ala carte menus, the quality of their diet declined (11, 12). This finding was made in the Houston school district and formed the basis for revamping the Texas state school foods policy (13). An interactive multimedia game aimed at increasing fruit and vegetable intake was developed that helped children increase their consumption within 5 weeks (14) as well as an Internet-based merit badge program for Boy Scouts that supplemented time on this topic spent at troop meetings led to increased fruit consumption and decreased inactivity (15) are examples of a number of youth-centered interventions developed by NP 107 scientists.

At the opposite end of the age spectrum, the program also developed interventions in older adults. Among Hispanic older adults with poorly controlled type 2 diabetes, a progressive resistance exercise program resulted in improved glycemic and metabolic control (16). A number of other interventions in older people are described under other components of this report.

Impact: The biggest demonstrable impact of research under this component is the change in Texas school food policy following the first longitudinal study of food choices in school by children gaining access to foods not in USDA-approved lunch programs. This change in policy became a model for many other states that have modified their policies on sale of foods and soft drinks in school.

It is hoped the interventions being piloted in the lower Mississippi Delta will be useful in other, similar communities after full-scale intervention studies are conducted. The five questions for determining food insecurity in older children developed by ARS researchers have been incorporated into the NHANES. The Food Frequency Questionnaires and the Dietary Quality Screener developed by ARS researchers are being used in broad-based community interventions and clinical health screenings. These tools have shown that obesity is a risk factor for functional decline and for reporting homebound status in older persons and could ultimately change the paradigm of care for older persons.

APPENDIX 1 – DOCUMENTATION OF SELECTED ACCOMPLISHMENTS FROM NP 107 RESEARCH

Component 1 – Composition of Foods

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Component 5 – Health Promoting Properties of Plant and Animal Foods

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Component 6 – Prevention of Obesity and Disease: Relationship between Diet, Genetics, and Lifestyle

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Component 7 – Health Promoting Intervention Strategies for Targeted Populations

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APPENDIX 2 – SELECTED SUPPORTING INFORMATION ON IMPACT OF NP107 SCIENTISTS

Major Awards from National and International Organizations – 16 scientists received 20 awards. Examples include:

David Baer, BHNRC*, Pan-American Prize in Nutrition, 2004
Irwin Rosenberg, HNRCA, FDA Commissioner's Medal, 2000; ACN Annual Award, 2000; ASN Conrad Elvehjem Award, 2006
Margaret Bogle, Delta NIRI, Marjorie Hulsizer Copher Award, Am Dietetic Assn, 2002
James Joseph, HNRCA, Harman Research Award, Am Aging Assn, 2004
Morey Haymond, CNRC, Lifetime Achievement Award, Juvenile Diabetes Res Foundation, 2005
Robert Russell, HNRCA, Human Nutrition Award, DSM, 2005

Elected Officers of National/International Organizations – 10 scientists held 10 offices. Examples include:

Lindsay Allen, WHNRC, President, American Society for Nutritional Sciences
Simin Meydani, HNRCA, President, American Aging Association
Curtiss Hunt, GFHNRC, President, Intern Soc Trace Element Res in Humans
Dennis Bier, CNRC, President, American Society for Nutrition
Thomas Baranowski, CNRC, President, Intern Soc Behavioral Nutr & Physical Activity

Service on Major Committees – 18 scientists served on 35 committees. Examples include:

Joan Conway, BHNRC, WHO/FAO Panel on Vitamin & Mineral Requirements
Gary Beecher, BHNRC, NAS/IOM Panel on Antioxidants
Thomas Badger, ACNC, Scientific Advisory Board, Keck School of Medicine, USC
Robert Russell, HNRCA, NAS/IOM Food and Nutrition Board, Chair
Gerald Combs, Jr., GFHNRC, WHO Panel on Desalination of Drinking Water, NAS/IOM Committee on Mineral Requirements for the Military
Lindsay Allen, WHNRC, NAS/IOM, Dietary Reference Intake Committee
Janet King, WHNRC, NAS, Board on Agriculture and Natural Resources
Theresa Nicklas, CNRC, NAS/IOM, Dietary Guidelines Advisory Committee
Nancy Butte, CNRC, WHO Working Group on Energy and Protein Requirements

Editorial Boards – 47 scientists served on 74 editorial boards. Examples include:
Joseph Urban, BHNRC, J Immunol, Infect Immun, Vet Parasitol, Parasit Immunol, Exp Parasitol
Wayne Wolf, BHNRC, AOAC International, Food Testing & Analysis
Martin Ronis, ACNC, Exp Biol Med

Frank Simmen, ACNC, Endocrinology
Robert Russell, HNRCA, Am J Clin Nutr, Nutr Rev (Editor-in-Chief)
Ernst Schaefer, HNRCA, Atherosclerosis (US Editor)
Forrest Nielsen, GFHNRC, Biofactors, Biol Trace Element Res, J Trace Elements Exp Med
Daniel Hwang, WHNRC, J Biol Chem
Darshan Kelley, WHNRC, Lipids, Nutr Res
Charles Stephensen, WHNRC, Am J Clin Nutr, Nutr Rev
Douglas Burrin, CNRC, J Nutr, Domestic Anim Endocrinol
Teresa Davis, CNRC, J Nutr, J Anim Sci

Highly Cited Scientist Lists
The July/august 2006 issue of ScienceWatch, published by Thomson Scientific, lists the 25 most cited authors in Agricultural Science (ranked by total citations) for 1996-2006. Two scientists from NP107, Ronald Prior and Guohua Cao, were listed as numbers 1 and 4, respectively with 2,025 and 1,509 citations each.

Thomson Scientific also maintains a Web site (http://isihighlycited.com) that lists 276 scientists in the field of Agricultural Sciences. Five current or former scientists from NP107 are listed:
Gary Beecher, BHNRC
Ronald Prior, ACNC
Forrest Nielsen, GFHNRC
Peter Reeds, CNRC
Philip Reeves, GFHNRC

Comprising 2% of the scientists in this database, NP107 represents <0.001% of scientists working in this field.

*Center Abbreviations:
BHNRC: Beltsville Human Nutrition Research Center
HNRCA: Human Nutrition Research Center on Aging at Tufts University
GFHNRC: Grand Forks Human Nutrition Research Center
ACNC: Arkansas Children's Nutrition Center
CNRC: Children's Nutrition Research Center at Baylor College of Medicine
WHNRC: Western Human Nutrition Research Center

Appendix 3 – Research Projects

This listing includes all research projects funded under NP 107 since the last Stakeholder Workshop held in March, 2000. Projects in ARS have a life of no more than 5 years so start and end dates have been provided for reviewers to see the topics covered by the 107 projects initiated since 2000; of those, 62 are currently active. Some projects were terminated due to changes in scientific personnel while other projects continued previous research work.

Arkansas Children's Nutrition Center, Little Rock, AR		
Title	**Start Date**	**End Date**
DIETARY FACTORS EARLY IN HUMAN DEVELOPMENT: HEALTH CONSEQUENCES OF PHYTOCHEMICAL INTAKE	10/01/2004	04/30/2009
EFFECTS OF DIET AND NUTRITION ON PSYCHOLOGICAL/PSYCHONEUROPHYSIOLOGICAL FUNCTIONING IN CHILDREN	05/01/2004	04/30/2009
DIETARY FACTORS EARLY IN HUMAN DEVELOPMENT: HEALTH CONSEQUENCES OF PHYTOCHEMICAL INTAKE	04/02/2002	09/30/2004
Beltsville Human Nutrition Research Center, Beltsville, MD		
Title	**Start Date**	**End Date**
METABOLISM, FUNCTION, AND INTERACTIONS OF MINERALS USING STABLE ISOTOPES	06/19/2002	12/16/2002
DETERMINATION OF PHYTONUTRIENTS IN FOODS	07/03/2002	02/21/2004
DETERMINATION OF BIO-ORGANIC NUTRIENTS IN FOODS	07/03/2002	02/21/2004
THE ROLE THAT OXIDATIVE STRESS PLAYS IN ELEVATING RISK-FACTOR METABOLITES ASSOCIATED WITH HEART DISEASE	10/01/2003	04/01/2004
DETERMINATION OF SELECTED TRACE ELEMENTS AND ELEMENTAL SPECIES IN FOODS	07/16/2002	02/21/2004
DEVELP. & ADAPTATION OF NEW & EXISTING ANALYTICAL TECHNOL. FOR THIS DETERMINATION OF FOOD COMPONENTS	07/16/2002	02/21/2004
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PHYTOCHEMICALS AND CANCER PREVENTIVE PATHWAYS: EFFECTS OF GENETIC AND EPIGENETIC FACTORS	04/12/2005	04/30/2009
METHODS FOR IDENTIFICATION AND DETERMINATION OF S AND SE CONTAINING COMPOUNDS IN FOODS	02/22/2004	02/21/2009
INFLUENCE OF PHYSICAL ACTIVITY ON LONG-TERM VOLUNTARY FOOD INTAKE AND MAINTENANCE OF A HEALTHY WEIGHT	02/16/2004	02/15/2009

LIQUID CHROMATOGRAPHIC AND STABLE ISOTOPE DILUTION MASS SPECTROMETRIC METHODS FOR THE DETERMINATION OF WATER-SOLUBLE B VITAMINS IN FOODS ...	02/22/2004	07/11/2006
CHROMIUM AND POLYPHENOLS FROM CINNAMON IN THE PREVENTION AND ALLEVIATION OF GLUCOSE INTOLERANCE	11/18/2004	04/30/2009
CAROTENOIDS FROM FOODS: BIOAVAILABILITY, TRANSPORT AND ANTIOXIDANT ACTIVITY	08/04/2000	05/19/2004
CHROMIUM & OTHER INSULIN POTENTIATORS IN THE PREVENTION AND ALLEVIATION OF GLUCOSE INTOLERANCE	07/18/2000	11/18/2004
MEASURING MUCOSAL DERIVED IMMUNITY IN SWINE WITH DIFFERENT VITAMIN A STATUS TO YIELD BIOMARKERS OF HUMAN NUTRIENT/DISEASE INTERACTIONS	05/25/2005	04/30/2009
DIETARY MODULATION OF MARKERS OF INFLAMMATION AND OXIDATION AS RISK FACTORS OF CHRONIC, DEGENERATIVE DISEASES	05/20/2004	04/30/2009
THE EFFECT OF DIETARY PROBIOTICS ON IMMUNE AND GASTROINTESTINAL FUNCTION	04/02/2004	04/01/2009
QUANTITATIVE AND QUALITATIVE ASSESSMENT OF COMMUNITY BASED NUTRITION PROGRAMS AND INTERVENTIONS	01/05/2004	01/04/2009
IMPROVE AND CONDUCT THE COLLECTION, ASSESSMENT, AND DISSEMINATION OF FOOD CONSUMPTION AND RELATED DATA OF AMERICANS	01/31/2004	01/30/2009
RESEARCH TO IMPROVE & CONDUCT THE COLLECTION, ASSESSMENT, & DISSEMINATION OF FOOD CONSUMPTION...	08/16/2000	01/30/2004
EFFECTS OF PHENOLIC PHYTOCHEMICALS ON CANCER: ABSORPTION, MOLECULAR ACTIONS AND GENE RESPONSE	10/01/2004	04/30/2009
MOLECULAR BASIS OF ABSORPTION, INTERACTION, AND FUNCTINS OF FLAVONOIDS IN HUMAN CELLS	10/01/2004	04/11/2005
LIQUID CHROMATOGRAPHIC & STABLE ISOTOPE DILUTION MASS SPECTROMETRIC METHODS FOR THE DETERMINATION OF WATER-SOLUBLE & LIPID ... SUPPLEMENTS	07/12/2006	04/30/2009
DEVELOPMENT OF ANALYTICAL METHODS FOR TRACE ELEMENTS AND ELEMENTAL SPECIES IN FOODS	02/22/2004	02/21/2009
EFFECT OF DIETARY INDUCED OXIDATIVE STRESS ON INTESTINAL PHYSIOLOGY AND THE DEVELOPMENT OF MUCOSAL IMMUNITY TO ENTERIC PATHOGENS	03/28/2004	03/27/2009
BENEFICIAL HEALTH EFFECTS OF CONSUMPTION OF BARLEY AND BARLEY COMPONENTS BY HUMANS	04/08/2004	04/07/2009
IMPACT OF NUTRITIONAL STATUS ON IMMUNE-INDUCED CHANGES IN GUT FUNCTION	03/28/2004	03/27/2009

THE USDA NATIONAL NUTRIENT DATABANK: ACQUISITION, EVALUATION & COMPILATION OF NUTRITIONAL SUPPLEMENT DATA	02/20/2004	02/19/2009
DEVELOPMENT OF ACCURATE AND REPRESENTATIVE FOOD COMPOSITION DATA FOR THE U.S. FOOD SUPPLY	02/20/2004	02/19/2009
ANALYTICAL METHODS FOR THE DETERMINATION OF PHENOLIC PHYTONUTRIENTS IN FOODS	02/22/2004	02/21/2009
BIOAVAILABILITY AND METABOLISM OF PHYTOCHEMICALS AND MICRONUTRIENTS	02/06/2004	02/05/2009
REDUCING THE HEALTH RISKS OF OBESITY USING FIBER COMPONENTS	06/05/2000	12/31/2002
PROTECTIVE EFFECTS OF DIETARY SELENIUM AND VITAMIN E AGAINST HUMAN DISEASE	05/27/2004	04/30/2009
METABOLISM OF VITAMIN A AND CAROTENOIDS	02/13/2004	02/12/2009
QUANTIFYING NUTRIENT METABOLISM WITH MATHEMATICAL MODELING	02/03/2002	02/05/2004
ESTIMATION OF ENERGY INTAKE AND PHYSICAL ACTIVITY IN FREE-LIVING ADULTS	02/03/2002	05/19/2004
THE IMPACT OF VITAMIN E AND SELENIUM IN HUMAN DISEASE PREVENTION	06/10/2002	05/24/2005
HEALTH BENEFITS OF DIETS HIGH IN BARLEY AND OATS	06/20/2002	04/07/2004
INTAKES OF VEGETABLES, FRUITS AND TEAS AS RELATED TO HUMAN HEALTH	07/04/2001	02/12/2004
Children's Nutrition Research Center, Houston, TX		
Title	**Start Date**	**End Date**
CHILDHOOD EATING BEHAVIORS: PREVENTION OF CHILDHOOD OBESITY AND CHRONIC DISEASES	05/21/2004	04/30/2008
PHYTONUTRIENT BIOCHEMISTRY, PHYSIOLOGY, AND TRANSPORT	05/21/2004	04/30/2008
NUTRITIONAL REGULATION OF CELL AND ORGAN GROWTH, DIFFERENTIATION, AND DEVELOPMENT	05/21/2004	04/30/2009
NUTRIENT - GENE INTERACTIONS	05/21/2004	04/30/2009
CHILDHOOD OBESITY: REGULATION OF ENERGY BALANCE AND BODY COMPOSITION	05/21/2004	04/30/2009
NUTRITION DURING PREGNANCY, LACTATION, INFANCY, AND CHILDHOOD	05/21/2004	04/30/2009
DEVELOPMENTAL ORIGINS OF OBESITY, CARDIOVASCULAR DISEASE, AND OTHER CHRONIC DISEASES OF NUTRITIONAL LINEAGE	05/21/2004	04/30/2009
ABSORPTION AND METABOLISM OF ESSENTIAL MINERAL NUTRIENTS	05/21/2004	04/30/2009
Grand Forks Human Nutrition Research Center, Grand Forks, ND		
Title	**Start Date**	**End Date**
DIETARY TRACE ELEMENTS AND PHYSIOLOGY OF THE CARDIOVASCULAR AND RELATED SYSTEMS	02/11/2001	02/21/2002

BIOCHEMICAL, PHYSIOLOGICAL, AND NUTRITIONAL ROLES OF CERTAIN ULTRATRACE ELEMENTS	03/04/2001	02/21/2002
MICRONUTRIENT ROLES IN PHYSIOLOGY AND HEALTH	04/03/2004	04/02/2009
OPTIMAL MINERAL NUTRITION FOR PHYSIOLOGICAL AND PSYCHOLOGICAL DEVELOPMENT, FUNCTION AND HEALTH	02/22/2002	04/02/2004
MINERAL UTILIZATION & BIOAVAILABILITY IN THE 21ST CENTURY, WITH CHANGING DIETS & AGRICULTURAL PRACTICE	02/23/2002	01/14/2004
EFFECTS OF COPPER DEPLETION ON CARDIOVASCULAR FUNCTION AND METABOLISM	03/04/2001	02/21/2002
MINERAL ELEMENT NUTRITION, NEUROPSYCHOLOGICAL FUNCTION AND BEHAVIOR	03/15/2001	02/21/2002
BIOAVAILABILITY OF TRACE ELEMENTS, ESPECIALLY IRONFROM FOOD, & ITS INFLUENCE ON NUTRITURE & FUNCTION	03/29/2001	02/22/2002
HOMEOSTASIS AND BIOAVAILABILITY OF TRACE ELEMENTS IN HUMANS AND ANIMALS	04/12/2001	02/22/2002
DEVELOPMENT AND EVALUATION OF METHODS FOR THE CLINICAL EVALUATION OF MINERAL NUTRITIONAL STATUS	05/30/2001	02/21/2002
ROLE OF DIETARY MINERALS ON GENE EXPRESSION, CELL CYCLE AND MOLECULAR MECHANISMS IN CANCER RISK	02/22/2002	07/20/2004
MINERAL ELEMENTS, PHYSIOLOGICAL FUNCTION AND PERFORMANCE AND BODY COMPOSITION	03/04/2001	02/21/2002
MINERAL ELEMENT REQUIREMENTS FOR OPTIMAL CARDIOVASCULAR FUNCTION AND HEALTH	02/22/2002	07/20/2004
MINERAL INTAKES FOR OPTIMAL BONE AND JOINT DEVELOPMENT AND HEALTH	02/22/2002	07/31/2005
MINERAL UTILIZATION AND BIOAVAILABILITY IN THE 21ST CENTURY, WITH CHANGING DIETS AND AGRICULTURAL PRACTICES	01/15/2004	01/14/2009
ROLE OF DIETARY SELENIUM ON GENE EXPRESSION, CELL CYCLE AND MOLECULAR MECHANISMS IN CANCER RISK	07/21/2004	04/30/2009
DIETARY COPPER REQUIREMENTS FOR OPTIMAL CARDIOVASCULAR FUNCTION AND HEALTH	07/21/2004	04/30/2009
MINERAL INTAKES FOR OPTIMAL BONE DEVELOPMENT AND HEALTH	08/01/2005	04/30/2009
HUMAN MINERAL ELEMENT REQUIREMENTS AND THEIR MODIFICATION BY STRESSORS	05/13/2001	02/21/2002
Human Nutrition Research Center on Aging at Tufts University, Boston, MA		
Title	**Start Date**	**End Date**
NUTRITION, CARDIOVASCULAR HEALTH AND GENOMICS	10/01/2001	04/30/2004

DIETARY ASSESSMENT OF RURAL OLDER PERSONS (GEISINGER)	01/01/2001	07/02/2004
DIETARY ANTIOXIDANTS, AGING AND OXIDATIVE STRESS STATUS	11/01/2004	04/30/2009
EPIDEMIOLOGY APPLIED TO PROBLEMS OF AGING AND NUTRITION	05/01/2004	04/30/2009
NUTRITION, CARDIOVASCULAR HEALTH AND GENOMICS	05/01/2004	04/30/2009
DIET-GENE INTERACTIONS AND MICRONUTRIENT STATUS	05/01/2004	04/30/2009
B VITAMIN METABOLISM AND AGING	05/01/2004	04/30/2009
NUTRITION, EXERCISE CAPACITY, AND SARCOPENIA IN THE ELDERLY	04/13/2006	04/30/2009
NUTRITION AND CANCER PREVENTION	05/01/2004	04/30/2009
NUTRITIONAL MODULATION OF BRAIN AGING AND COGNITIVE DECLINE	05/01/2004	04/30/2009
DETERMINATION OF ENERGY REGULATION IN AGING	10/01/2004	04/30/2008
NUTRITION, AGING AND VISUAL FUNCTION	05/01/2004	04/30/2009
DIET, LIPOPROTEINS AND CARDIOVASCULAR RISK	05/01/2004	04/30/2009
NUTRITION AGING, IMMUNE FUNCTION, AND INFLAMMATORY RESPONSE IN HEALTH AND DISEASE	05/01/2004	04/30/2009
BONE HEALTH IN THE ELDERLY	05/01/2004	04/30/2009
NUTRITION AND CANCER PREVENTION	06/05/2002	04/30/2004
DIETARY EFFECTS ON NEURONAL SIGNALING	10/01/2001	04/30/2004
NUTRITION, EXERCISE AND SARCOPENIA IN THE ELDERLY	06/11/2004	04/12/2006
GEISINGER RURAL AGING STUDY	07/03/2004	04/30/2009
Western Human Nutrition Research Center, Davis, CA		
Title	**Start Date**	**End Date**
INFLUENCE OF DIETARY INTERVENTION ON MINERAL HOMEOSTASIS	10/01/2001	01/28/2004
DIET GENE INTERACTIONS	09/24/2003	10/19/2004
U.S. DIETARY GUIDELINES AND HEALTHY BODY WEIGHT	04/14/2006	04/30/2009
INFLUENCE OF DIETARY FATTY ACIDS ON HUMAN HEALTH WITH EMPHASIS ON IMMUNE AND INFLAMMATORY RESPONSES	05/01/2004	04/30/2009
EVIDENCE-BASED REDUCTION OF PROSTATE CANCER PROGRESSION THROUGH NUTRITION	10/20/2004	04/30/2009
MICRONUTRIENTS AND IMMUNE FUNCTION	01/18/2004	01/17/2009
HEALTH EFFECTS OF DIETARY FATTY ACIDS AND THE MECHANISMS INVOLVED	11/25/2001	04/30/2004
DIETARY PATTERNS, MINERAL AND VITAMIN METABOLISM	01/29/2004	01/28/2009

METABOLIC AND FUNCTIONAL CONSEQUENCES OF ENERGY RESTRICTION	10/01/2001	04/13/2006
MECHANISMS AND BIOMARKERS OF CANCER PREVENTION WITH MICRONUTRIENTS	10/01/2001	10/19/2004
Other ARS location Albany, CA		
Title	**Start Date**	**End Date**
PROCESSING AND BIOTECHNOLOGICAL IMPROVEMENT OF FOODS TO PREVENT OBESITY RELATED AND OTHER DEGENERATIVE DISEASES	06/04/2004	06/03/2009
Other ARS location Ithaca, NY		
Title	**Start Date**	**End Date**
UNDERSTANDING SOIL-PLANT-HUMAN/ANIMAL FOOD SYSTEMS AND NUTRIENT BIOAVAILABILITY TO IMPROVE HUMAN HEALTH	01/29/2004	01/28/2009
IMPROVING HUMAN HEALTH THROUGH UNDERSTANDING SOIL-PLANT-HUMAN/ANIMAL FOOD SYSTEMS AND NUTRIENT BIOAVAILABILITY	10/01/2002	01/28/2004
Other ARS location Little Rock, AR		
Title	**Start Date**	**End Date**
NUTRITION INTERVENTION RESEARCH IN THE MISSISSIPPI DELTA OF AR, LA, AND MS	06/01/2004	04/30/2009
Other ARS location New Orleans, LA		
Title	**Start Date**	**End Date**
DIETARY, BIOLOGICAL, BEHAVIORAL, AND ENVIRONMENTAL PREDICTORS OF WEIGHT GAIN IN A HEALTHY, YOUNG, ETHNICALLY MIXED POPULATION	10/01/2004	07/20/2006
IDENTIFY MECHANISMS OF ISOFLAVONOID INDUCTION IN LEGUMES AND THEIR PHYTOESTROGENIC EFFECTS	03/20/2001	03/19/2006
PHYTOESTROGENIC EFFECTS OF FUNGALLY INDUCED ISOFLAVONOIDS IN LEGUMES	03/20/2006	04/30/2009
Other ARS location Stoneville, MS		
Title	**Start Date**	**End Date**
DELTA HUMAN NUTRITION RESEARCH	02/02/2006	04/30/2009