

National Institutes of Health State-of-the-Science Conference Statement: Multivitamin/Mineral Supplements and Chronic Disease Prevention

NIH State-of-the-Science Panel*

National Institutes of Health (NIH) consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of 1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), 2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, 3) questions and statements from conference attendees during open discussion periods that are part of the public session, and 4) closed deliberations by the panel during the remainder of the second day and the morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the federal government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

At least half of American adults take a dietary supplement, the majority of which are multivitamin/multimineral (MVM) supplements. As more and more Americans seek strategies for maintaining good health and preventing disease, and as the marketplace offers an increasing number of products to fulfill that desire, it is important that consumers have the best possible information to make their choices. Assessing the available scientific evidence on the benefits of MVM supplement use for chronic disease prevention, identifying the gaps in the evidence, and recommending an appropriate research agenda to meet the shortfalls are subjects considered in this report.

The word *vitamine* was coined in 1912, as an abbreviated term meant to capture the notion of important factors in the diet, or "vital amines." This was preceded more than 150 years earlier by British navy physician James Lind's discovery—in the first recorded controlled trial—that citrus juice, a good source of what was found 2 centuries later to be vitamin C, could prevent scurvy in sailors.

In 1913, the first vitamin was isolated: thiamin, the deficiency of which caused beriberi. Thirteen vitamins and 15 essential minerals have now been identified as important to human nutrition.

Large-scale fortification of diets began in the United States with the addition of iodine to table salt in 1924 to prevent goiter, followed by the addition of vitamin D to milk in 1933 to prevent rickets and the addition of thiamin, riboflavin, niacin, and iron to flour in 1941. Multivitamin/multimineral products providing more than vitamins A and D became available in pharmacies and grocery stores in the mid-1930s. In the early 1940s, the first MVM tablet was introduced.

Although clinical deficiency of vitamins or minerals, other than iron, is now uncommon in the United States, growth in supplement use has accelerated rapidly with marketing spurred by claims—some based on scientific studies—that chronic conditions could be prevented or treated by supplement use. Annual sales of supplements to Americans are now reported at about \$23 billion, a substantial share of which is spent on vitamins and minerals.

Because of such widespread use of MVM, increasing public and medical confusion over apparently contradictory results from studies, and reports of possible adverse effects from overuse in certain circumstances, the Office of Dietary Supplements and the Office of Medical Applications of Research of the NIH convened a State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention, held on 15–17

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Appendix 2

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*Panel statement from an NIH State-of-the-Science Conference held on 15–17 May 2006 at the National Institutes of Health, Bethesda, Maryland. For a list of the members of the NIH State-of-the-Science Panel, see Appendix 1. For a list of other participants, see Appendix 2, available at www.annals.org.

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May 2006, in Bethesda, Maryland. The goal of the conference was to assess the evidence available on MVM use and outcomes for chronic disease prevention in the generally healthy population of adults and to make recommendations for future research. The conference focused on vitamins and minerals and did not deal with botanicals, hormones, or other supplements. It also did not address the treatment of vitamin or mineral deficiencies. Except for considerations of safety, the conference also did not review issues of primary relevance to pregnant women or children.

Specifically, the conference explored the following key questions: 1) What are the current patterns and prevalence of the public's use of MVM supplements? 2) What is known about the dietary nutrient intake of MVM users versus nonusers? 3) What is the efficacy of single vitamin/mineral supplement use in chronic disease prevention? 4) What is the efficacy of MVM in chronic disease prevention in the general population of adults? 5) What is known about the safety of MVM for the generally healthy population? and 6) What are the major knowledge gaps and research opportunities regarding MVM use?

During the first 2 days of the conference, experts presented information on each of the key questions. After weighing the scientific evidence, including the data presented by the speakers and a formal evidence report commissioned through AHRQ, an independent panel prepared and presented a draft of this state-of-the-science statement addressing the conference questions. The evidence report prepared for the conference is available at www.ahrq.gov/clinic/tp/multivittp.htm.

For the purpose of this statement, the term *MVM* refers to any supplement containing 3 or more vitamins and minerals but no herbs, hormones, or drugs, with each component at a dose less than the tolerable upper level determined by the Food and Nutrition Board—the maximum daily intake likely to pose no risk for adverse health effects. Our review also included studies of the relationship of single-nutrient supplements and 2-nutrient supplements to certain disease outcomes. The term *primary prevention* refers to preventing the development of disease in a person who does not have the disease in question. The chronic conditions assessed include cancer; age-related sensory loss; and cardiovascular, endocrine, neurologic, musculoskeletal, gastroenterologic, renal, and pulmonary diseases.

A word is warranted about the nature of the evidence base considered by the panel. The range of vitamins and minerals of possible interest was so broad that the conference planning committee chose to focus the evidence report on nutrients for which the potential for impact had been most strongly suggested and on conditions for which supplements were thought to have the most potential influence.

The planning committee also limited the scope of the evidence report to consideration of randomized, controlled trials (RCTs), which are generally considered the gold standard for evidence-based decision making. These are studies

in which participants are allocated by chance alone to receive or not to receive 1 of 2 or more clinical interventions. For example, while folate supplementation was initially shown to decrease the risk for neural tube defects in animal studies, outcome data in nonhuman models were not considered sufficient evidence on which to base policy recommendations. At the next level of evidence, observational studies in humans suggested efficacy of folate supplementation to prevent such defects. However, these were criticized because they were not randomized and were potentially subject to bias. Not until these findings were confirmed by RCTs in humans was public policy implemented, including fortification of cereal grains with folate.

An observational study is one in which the exposure or treatment of interest is not assigned to the participant by the investigator. Such studies suggested that β -carotene intake might protect against the development of some types of cancer. However, RCTs of β -carotene supplementation not only showed no benefit, they also found an increased risk for lung cancer in persons who smoked cigarettes or who were exposed to asbestos. These examples illustrate both the risk of relying only on observational studies and the advantage of RCTs in identifying both benefits and risks of MVM supplementation.

Limiting the focus of our statement to RCTs has some inherent limitations, given the potential of other types of studies to provide important insights. Observational studies, for example, are particularly useful for generating hypotheses, defining adverse effects, and documenting long-term treatment consequences. They are often essential precursors to the well-conducted RCTs important for policy formation.

Our principal recommendations focus on the compelling research activities that must be supported to better inform the decisions that millions of Americans are making each day to use or not to use MVM supplements to prevent chronic disease. At the same time, mindful of the constraints of the available evidence base, we have also taken care not to make premature recommendations about whether generally healthy Americans should or should not take MVM supplements. Because of the need for more reliable information on MVMs, we have made strong recommendations for research and for increased U.S. Food and Drug Administration (FDA) oversight of the MVM industry.

1. WHAT ARE THE CURRENT PATTERNS AND PREVALENCE OF THE PUBLIC'S USE OF MVM SUPPLEMENTS?

More than half of American adults take dietary supplements in the belief that they will make them feel better, give them greater energy, improve their health, and prevent and treat disease. The use of supplements has been steadily increasing, and growth appears likely to continue. Currently, users spend more than \$23 billion per year on sup-

plements, and among this supplement-using population, MVM is the major category of supplements, used by about one third of Americans. Uncertainty remains in estimating prevalence of use because of problems defining these products; increasing complexity in the formulation of supplements, including more non-MVM components and specialized formulas; and varying frequency of use.

It appears that use is higher among women and among the children of women who use supplements; in elderly persons; among people with more education, higher income, healthier lifestyles and diets, and lower body mass indices; and among residents of the western United States. Individuals with chronic illnesses or who are seeking to prevent recurrence of a serious disease (for example, cancer) also tend to be more frequent users. Many dietary supplement users perceive their health as better. Conversely, MVM use is lower among smokers and certain ethnic and racial groups, such as African-American persons, Hispanic persons, and Native Americans, while certain Asian ethnic groups appear to have higher MVM use. Ironically, populations at highest risk for nutritional inadequacy who might benefit the most from MVM are the least likely to use such products.

2. WHAT IS KNOWN ABOUT THE DIETARY NUTRIENT INTAKE OF MVM USERS VERSUS NONUSERS?

According to several studies, MVM supplement users (for example, adults, infants, toddlers age 12 to 24 months, adolescents, and elderly persons) also tend to have higher micronutrient intakes from their diet than nonusers. Consequently, MVM users have an increased intake and are more likely to exceed the upper level. The trend to “fortify” certain foods not required by law to be fortified with vitamins and minerals makes calculation of total intake more difficult. A recent industry report estimates that, in 2005, 65% of Americans used such fortified foods or beverages, worth \$36 billion, and that these sales are increasing rapidly.

The measurement of dietary vitamin/mineral intake and intake from supplements is uncertain, which undermines our ability to accurately assess the distribution of vitamin/mineral intake in the population, as well as our ability to use observational studies to detect effects of vitamin/mineral intake on chronic disease. In part, these uncertainties stem from individuals’ difficulty in identifying correctly what supplements they are actually taking and their frequency of consumption (for example, many products look alike but are very different in their composition). Moreover, the lack of databases of MVM composition limits the ability to translate supplement intake into amounts of various vitamins and minerals actually consumed. There are thousands of product labels, vast differences in the amounts of vitamins/minerals delivered by various products, and major variability within even the same product over time and across batches.

These methodologic difficulties should be resolved by 2 actions. The quality of self-reported data of MVM use should be improved to enhance accuracy and specificity of reported MVM intake, and new databases that detail the exact composition of MVM supplements need to be built and updated on a continuous basis.

3. WHAT IS THE EFFICACY OF SINGLE VITAMIN/MINERAL SUPPLEMENT USE IN CHRONIC DISEASE PREVENTION?

Few high-quality clinical trials have been conducted to determine whether single-use or paired vitamins/minerals prevent chronic diseases, and even fewer are generalizable to the U.S. population. In addition, much of the evidence derives from post hoc analyses for outcomes not originally chosen as study end points. These studies are reviewed in the evidence report.

Findings by Vitamin/Mineral

β -Carotene

Two large trials (1, 2) designed to test lung cancer prevention with β -carotene found a surprising increase in lung cancer incidence and deaths in smokers and male asbestos workers. There was no effect in preventing a number of other types of cancer, including gastric, pancreatic, breast, bladder, colorectal, and prostate cancer as well as leukemia, mesothelioma, and lymphoma. The overall mortality rate was elevated in women, but not men, treated with β -carotene throughout the intervention and postintervention period. A third large trial (3), in healthy American men, found no effect of β -carotene on cancer except an increased risk for thyroid and bladder cancer. Two other β -carotene trials (4, 5) on prevention of nonmelanoma skin cancer found no effect on subsequent skin cancer incidence. A large study of healthy American women also found no effect of β -carotene on cancer incidence (6). Four of these β -carotene trials (2, 3, 5, 7) also evaluated cardiovascular disease (CVD) and found no benefits. In healthy women, there was a suggestion of increased stroke risk in 1 study (6) and an increased risk for CVD in women smokers in the Carotene and Retinol Efficacy Trial (CARET) (8).

Vitamin A

No trials were found for vitamin A supplementation alone. When vitamin A was paired with β -carotene in 1 trial (2), lung cancer and CVD deaths were increased. When vitamin A was combined with zinc in another trial, there was no impact on esophageal or gastric cardia cancer, although noncardia stomach cancer decreased (9).

Vitamin E

Four trials tested vitamin E. One large study of healthy women, the Women’s Health Study (WHS), recorded decreased cardiovascular deaths, although there was

no effect on incidence of CVD events (10). Another trial found a decreased risk for prostate cancer (and a suggestion of decreased colorectal cancer risk) in male smokers, as well as a decreased risk for angina and thrombotic stroke (7, 11–14). No other effects were found on other types of cancer. There was a trend toward increased bleeding, subarachnoid hemorrhage, and hemorrhagic stroke among male smokers in this study (7), but in the WHS, no increase in hemorrhagic stroke was seen among women (10). Another trial (15) yielded inconclusive results for main cardiovascular end points because of small numbers and because the trial was stopped prematurely. Two trials examined development of age-related cataract (16) and lens opacity (14), respectively, and reported no effect of vitamin E supplementation.

Vitamin B₂ and Niacin

One large Chinese trial of vitamin B₂ and niacin found a decreased risk for nuclear cataracts (17). No effects were found on cortical cataracts, mortality rates, stroke, upper gastrointestinal dysplasia, or cancer.

Vitamin B₆

Two small, short-duration studies of vitamin B₆ to prevent cognitive decline in elderly men and women showed no effects (18).

Folic Acid with or without Vitamin B₁₂

Multiple studies have shown the effectiveness of folic acid use by women of childbearing age to prevent neural tube defects in offspring. Four small, short-duration studies of folic acid, with or without vitamin B₁₂, to prevent cognitive decline in older adults found no effects (19).

Selenium

Three trials tested selenium supplementation to prevent cancer. In 2 Chinese trials, selenium decreased liver cancer incidence in patients at high risk because of either a family history of liver cancer or hepatitis B exposure status (20). The reports of these trials, however, lack many important details. The third selenium trial was conducted in men and women who had a history of skin cancer (21). It found no decrease in skin cancer but reported reductions in total deaths from cancer and in the incidence of lung, prostate, and colorectal cancer (outcomes the study was not designed to investigate).

Calcium and Vitamin D

Multiple studies demonstrate that calcium increases bone mineral density in postmenopausal women but by itself does not decrease fracture risk. Vitamin D alone does not increase bone mineral density or decrease fracture risk, but it does work in combination with calcium to decrease the risk for hip and nonvertebral fractures in postmeno-

pausal women. Vitamin D and calcium may increase the risk for kidney stones. The single trial that tested the effect of calcium supplementation and vitamin D on colorectal cancer risk found no effect, but the doses may have been inappropriately low (22).

Summary

Few trials of individual or paired vitamins and minerals for the prevention of chronic disease produced beneficial effects. We found no evidence to recommend β -carotene supplements for the general population and strong evidence to recommend that smokers avoid β -carotene supplementation. In combination, calcium and vitamin D have a beneficial effect on bone mineral density and fracture risk in postmenopausal women.

On the basis of single studies and analysis of secondary outcomes, there is a suggestion that selenium may reduce risk for prostate, lung, and colorectal cancer; that vitamin E may decrease cardiovascular deaths in women and prostate cancer incidence in male smokers; and that vitamin A paired with zinc may decrease the risk for noncardiac stomach cancer in rural China. Trials of niacin; folate; and vitamins B₂, B₆, and B₁₂ produced no positive effect on chronic disease occurrence in the general population.

4. WHAT IS THE EFFICACY OF MVM IN CHRONIC DISEASE PREVENTION IN THE GENERAL POPULATION OF ADULTS?

Five RCTs conducted in the United States, the United Kingdom, China, and France studied the efficacy of MVM supplements in the primary prevention of cancer and CVD and in delaying the development or progression of cataract and age-related macular degeneration (9, 23–27). The 5 studies used combinations of 3 to 7 vitamins, minerals, or both in 1 or more intervention arms.

We noted some limitations in these studies. In the Chinese study, while the body mass index of study participants was within the normal range, there were indications of inadequate intake of some micronutrients, thus limiting the generalizability of this study's findings to the U.S. population (9). Three of these studies addressed eye disease, and all were performed in patients who had existing eye disease and were seen in ophthalmology clinics (25–27). One of these studies had only 71 patients and included several supplements other than vitamins and minerals in the intervention (27). A binational study of cataracts had different entry criteria in each country (25).

Findings by Disease

Cancer

Both trials that examined cancer end points found a reduction in cancer incidence, mortality, or both. In China, overall cancer incidence and mortality rates were significantly reduced, as were incidence and mortality rates for the 2 leading types of cancer, esophageal and gastric, in an arm of the study that included vitamin E, β -carotene,

and selenium (9). The decrease in esophageal cancer emerged as a statistically significant finding only after many years of follow-up. Another arm of the study, on zinc and vitamin A, was associated with a reduction in noncardia gastric cancer, although other gastric cancer and esophageal cancer were not reduced. In France, an intervention consisting of vitamin E, selenium, vitamin C, β -carotene, and zinc was associated with a reduction in overall cancer incidence in men only, but no individual type of cancer was clearly reduced (23). Overall mortality rates in men were also lower in the intervention group. No effect was seen in women. In China, younger persons in the intervention group had a lower incidence of esophageal cancer, but older persons had a higher incidence associated with treatment. Among men in the French study with normal prostate-specific antigen levels, the intervention was associated with a lower incidence of prostate cancer but prostate cancer incidence was higher among men with high prostate-specific antigen levels at baseline (24).

CVD

None of the reviewed studies showed any benefits or harm related to CVD resulting from MVM use in the studied populations.

Cataract

Mixed results emerged from studies in which cataract progression was the targeted outcome. Only modest and inconsistent effects were found in the 2 studies that reported any benefit (25, 26).

Age-Related Macular Degeneration

One study showed less progression of intermediate-stage age-related macular degeneration in persons receiving vitamins C and E, β -carotene, and zinc (26).

Summary

The uncertainty resulting from these trials suggests that multivitamin trials are unlikely to lead to generalizable knowledge. They cannot distinguish between the effects of individual components; they are likely to be contaminated by MVM use in the placebo group; they have a weaker biological basis than single-vitamin or single-mineral studies; they require very large sample sizes; and they will become outdated from a public health perspective because of the changing composition of commonly used MVMs.

There is evidence from 1 well-designed trial to consider use of antioxidants and zinc in adults with intermediate-stage age-related macular degeneration. Some suggestive evidence points to a possible benefit of selenium, vitamin E, or both in cancer prevention, especially in men. However, studies have also identified subgroups of the population whose cancer risk might increase with such supplementation. Trials currently in progress (for example, the Selenium and Vitamin E Cancer Prevention Trial [SE-

LECT] and the Physicians' Health Study II) should help determine the actual benefits and harms of such supplementation.

5. WHAT IS KNOWN ABOUT THE SAFETY OF MVM FOR THE GENERALLY HEALTHY POPULATION?

Most people assume that the ingredients in MVM supplements are safe. There is evidence, however, that certain ingredients in MVM supplements can produce adverse effects, including reports from RCTs that noted excess lung cancer occurring in asbestos workers and smokers consuming β -carotene. In addition, esophageal cancer excess was found with long-term follow-up of older Chinese patients treated with selenium, β -carotene, and vitamin E supplements (9). There was also evidence for gender difference in patterns of lung cancer and CVD risk related to β -carotene. In another study, patients with elevated prostate-specific antigen levels at baseline who were receiving an MVM intervention had higher incidence of prostate cancer (24). Vitamin D and calcium may increase the risk for kidney stones for certain people. These data raise safety questions both in general and in special populations. Although these studies are not definitive, they do suggest possible safety concerns that should be monitored for primary components of multivitamins.

The RCTs and observational studies on vitamin and mineral supplements have provided little information on the safety of single-vitamin, single-mineral, or MVM dietary supplements. Safety assessments were often limited to adverse reports from patients who dropped out of trials. The RCTs did not include assessments of well-known potential adverse end points. Issues that have not been adequately addressed include but are not limited to reproducibility of the MVM manufacturing process, characterization of the vitamin mix, demonstration of the absence of contaminants, stability, and interactions with other nutrients or drugs.

There is potential for adverse effects in individuals consuming dietary supplements that are above the upper level. This can occur not only in individuals consuming high-potency single-nutrient supplements but also in individuals who consume a healthy diet rich in fortified foods in combination with MVM supplements. Furthermore, by law, the listing of ingredient amounts on nutrient supplement labels is the minimum content; thus, higher intakes are probable. Data from prospective studies have shown that individuals taking MVM dietary supplements improved their nutritional adequacy with respect to several nutrients but also increased the proportion of their intakes above the upper level for several of the supplemented nutrients. With the strong trends of increasing MVM and other dietary supplement consumption, and the increasing fortification of the U.S. diet, we are concerned that a growing proportion of the population may be consuming levels

considerably above the upper level, thus increasing the possibility of adverse effects.

The FDA has insufficient resources and legislative authority to require specific safety data from dietary supplement manufacturers or distributors before or after their products are made available to the public. This lack of regulation exists despite the reality that many of the ingredients of MVMs would be subject to premarket approval if they were marketed as food additives and that in some cases the ingredients possess biological activities similar, if not identical, to those found in medications. The 1994 Dietary Supplement Health and Education Act (DSHEA) assumed that history of use of a given supplement was evidence for safety, thus grandfathering in all supplements on the market before the legislation. However, use of nutrients in foods and supplements in the United States is changing, and we are concerned that public safety cannot be assured. Adverse events from MVMs appear with some frequency in both the reports of the American Association of Poison Control Centers and the FDA's MedWatch system.

We found the primary recommendation of the 2005 Institute of Medicine committee report on dietary supplements compelling: "[T]he regulatory mechanisms for monitoring the safety of dietary supplements, as currently defined by DSHEA, [should] be revised. The constraints imposed on FDA with regard to ensuring the absence of unreasonable risk associated with the use of dietary supplements make it difficult for the health of the American public to be adequately protected." The FDA should have the authority to better inform consumers and health professionals regarding the existence of upper levels as well as the possible risks of exceeding those levels; develop a formal, mandatory adverse event reporting system for dietary supplements; and mandate provision of a MedWatch toll-free telephone number or Web site on product labels to facilitate reporting of adverse events. Furthermore, we recommend that health care professionals, consumers, and manufacturers use the FDA MedWatch adverse event reporting system to report adverse events associated with the use of dietary supplements. Finally, we recommend that Congress revise and update the law to reflect current knowledge.

6. WHAT ARE THE MAJOR KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES REGARDING MVM USE?

This review of the state of the science has identified important gaps in knowledge about the relationship between MVM use and chronic disease prevention in generally healthy adults. These deficiencies are attributable to shortcomings in data quality and a paucity of rigorously designed and conducted studies, especially RCTs. Hence, this report emphasizes the need and rationale for rigorous, state-of-the-art, methodologically and technologically forward-looking research to bridge these gaps. We strongly recommend the following actions.

1. Elicit more accurate information from individuals to improve the quality of self-reported data on MVM use. Capitalize on new electronic technologies, design and employ improved questionnaires, and develop new dietary and MVM recall methods, all to enhance accuracy and specificity of reported MVM intake.

2. Build new MVM databases that detail the exact composition of supplements, update them on a continuous basis, and assure their constant availability to the research community. A national database, such as that developed and maintained by the U.S. Department of Agriculture for food composition, will be a major improvement for determining potential impact, benefits, and harms of MVM.

3. Determine the most effective means to translate scientific information and improve communication about dietary supplements among consumers, health care providers, industry, scientists, and policymakers.

4. Develop a strategy to support the study of possible interactions of MVMs with nutrients or prescribed and over-the-counter medications.

5. Study populations that reflect the diversity of the United States ethnically, economically, and by age and sex. Focus on population segments previously underrepresented and on individuals at increased risk for chronic disease.

6. Capitalize on the rapidly progressing state of biomedical science to develop and apply techniques for assessing the basic biological mechanisms by which supplements may modify disease risks, for example, nutritional genomics, molecular imaging, and systems biology network approaches. The resulting knowledge may identify important new biomarkers, early in the disease process, that may inform observational studies and RCTs.

7. Design and conduct rigorous RCTs of the impact of individual supplements (or paired supplements, when biologically plausible) to test their efficacy and safety in prevention of chronic disease, using well-validated measures. Select the vitamins and minerals to be studied on the basis of their biological plausibility and outcomes of appropriate observational and pilot studies. Include in trials the most modern and validated biomarkers of exposure, bioavailability intermediary metabolism, and early disease. When possible, incorporate relevant genetic polymorphisms and other indices of individual physiologic characteristics into trial design. Randomized, controlled trials should employ such cost-effective and innovative methods as fractional factorial designs, which will permit the simultaneous evolution of multiple single supplements and their low-order interactions. Assure sufficient trial duration of both observational studies and RCTs during intervention and follow-up to determine important outcomes that may inform public policy decisions.

CONCLUSIONS

Use of MVMs has grown rapidly over the past several decades, and dietary supplements are now used by more

than half of the adult population in the United States. In general, MVMs are used by individuals who practice healthier lifestyles, thus making observational studies of the overall relationship between MVM use and general health outcomes difficult to interpret. Despite the widespread use of MVMs, we still have insufficient knowledge about the actual amount of total nutrients that Americans consume from diet and supplements. This is at least in part due to the fortification of foods with these nutrients, which adds to the effects of MVMs or single-vitamin or single-mineral supplements. Historically, fortification of foods has led to the remediation of vitamin and mineral deficits, but the cumulative effects of supplementation and fortification have also raised safety concerns about exceeding upper levels. Thus, there is a national need to improve the methods of obtaining accurate and current data on the public's total intake of these nutrients in foods and dietary supplements.

In systematically evaluating the effectiveness and safety of MVMs in relation to chronic disease prevention, we found few rigorous studies on which to base clear conclusions and recommendations. Most of the studies we examined do not provide strong evidence for beneficial health-related effects of supplements taken singly, in pairs, or in combinations of 3 or more. Within some studies or subgroups of the study populations, there is encouraging evidence of health benefits, such as increased bone mineral density and decreased fractures in postmenopausal women who use calcium and vitamin D supplements. However, several other studies also provide disturbing evidence of risk, such as increased lung cancer risk with β -carotene use among smokers.

The current level of public assurance of the safety and quality of MVMs is inadequate, given the fact that manufacturers of these products are not required to report adverse events and the FDA has no regulatory authority to require labeling changes or to help inform the public of these issues and concerns. It is important that the FDA's purview over these products be authorized and implemented.

Finally, the present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease. The resolution of this important issue will require advances in research and improved communication and collaboration among scientists, health care providers, patients, the pharmaceutical and supplement industries, and the public.

APPENDIX 1: NIH STATE-OF-THE-SCIENCE PANEL ON MULTIVITAMIN/MINERAL SUPPLEMENTS AND CHRONIC DISEASE PREVENTION

J. Michael McGinnis, MD, MPP (*Panel and Conference Chairperson*), Institute of Medicine, The National Academies, Washington, DC; Diane F. Birt, PhD, Department of Food Science and Human Nutrition, Center for Research on Botanical

Dietary Supplements, and College of Agriculture and College of Human Sciences, Iowa State University, Ames, Iowa; Patsy M. Brannon, PhD, RD, Division of Nutritional Sciences, Cornell University, Ithaca, New York; Raymond J. Carroll, PhD, Department of Statistics, Texas A&M University, College Station, Texas; Robert D. Gibbons, PhD, Center for Health Statistics, University of Illinois at Chicago, Chicago, Illinois; William R. Hazzard, MD, Department of Medicine, Division of Gerontology and Geriatric Medicine, University of Washington, VA Puget Sound Health Care System, Seattle, Washington; Douglas B. Kamerow, MD, MPH, Georgetown University and RTI International, Washington, DC; Bernard Levin, MD, University of Texas M.D. Anderson Cancer Center, Houston, Texas; James M. Ntambi, PhD, Departments of Biochemistry and Nutritional Sciences, University of Wisconsin–Madison, Madison, Wisconsin; Nigel Paneth, MD, MPH, College of Human Medicine, Michigan State University, East Lansing, Michigan; Douglas Rogers, MD, Section of Pediatric and Adolescent Endocrinology, The Cleveland Clinic, Cleveland, Ohio; Audrey F. Saftlas, PhD, MPH, Department of Epidemiology, The University of Iowa College of Public Health, Iowa City, Iowa; William Vaughan, Consumer's Union, Washington, DC.

From the National Institutes of Health, Bethesda, Maryland.

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APPENDIX 2

Speakers

Anthony J. Alberg, PhD, MPH, Department of Biostatistics, Bioinformatics, and Epidemiology, Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina; Bruce N. Ames, PhD, University of California, Berkeley, and Children's Hospital Oakland Research Institute, Oakland, California; Diane Benford, PhD, Chemical Safety Division, Food Standards Agency, London, United Kingdom; Benjamin Caballero, MD, PhD, Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Allen Dobson, PhD, The Lewin Group, Falls Church, Virginia; Peter Greenwald, MD, DrPH, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Rockville, Maryland; Robert P. Heaney, MD, Department of Medicine, Creighton University, Omaha, Nebraska; Han-Yao Huang, PhD, MPH, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, Maryland; Suzanne Murphy, PhD, RD, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii; Roy M. Pitkin, MD, University of California, Los Angeles, La Quinta, California; Ross L. Prentice, PhD, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington; Cheryl L. Rock, PhD, RD, Family and Preventive Medicine, Cancer Prevention and Control Program, University of California, San Diego, La Jolla, California; Irwin H. Rosenberg, MD, Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts; Johanna M. Seddon, MD, ScM, Epidemiology Unit, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts; A. Elizabeth Sloan, PhD, *Food Technology, Functional Foods & Nutraceuticals, and Flavor & The Menu*, Escondido, California; Meir J. Stampfer, MD, DrPH, Departments of Epidemiology and Nutrition, Harvard School of Public Health and Harvard Medical School, Boston, Massachusetts; Maret Traber, PhD, Linus Pauling Institute, Oregon State University, Corvallis, Oregon; Jason J.Y. Woo, MD, MPH, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling, and Dietary Supplements, Center for Food Safety & Applied Nutrition, U.S. Food and Drug Administration, College Park, Maryland; Elizabeth Yetley, PhD, Office of Dietary Supplements, National Institutes of Health, Bethesda, Maryland.

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Johanna Dwyer, DSc, RD, and Paul M. Coates, PhD (*Planning Committee Co-Chairpersons*), Office of Dietary Supplements, National Institutes of Health, Bethesda, Maryland; Mayada Akil, MD, Office of Science Policy and Program Planning, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland; David Atkins, MD, MPH, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, Rockville, Maryland; Barbara A. Bowman, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease

Control and Prevention, Atlanta, Georgia; Elsa A. Bray, Office of Medical Applications of Research, National Institutes of Health, Bethesda, Maryland; Emily Chew, MD, Division of Epidemiology and Clinical Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland; Gerald Combs Jr., PhD, Grand Forks Human Nutrition Research Center, U.S. Department of Agriculture, Grand Forks, North Dakota; Margaret Coopey, RN, MGA, MPS, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, Rockville, Maryland; Cindy D. Davis, PhD, Nutritional Science Research Group, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; James Everhart, MD, MPH, Epidemiology and Clinical Trials Branch, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; Judith A. Finkelstein, PhD, Neuroscience and Neuropsychology of Aging Program, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; Gilman D. Grave, MD, Endocrinology, Nutrition, and Growth Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; Laura Kettel Khan, PhD, Chronic Disease Nutrition, Division of Nutrition and Physical Activity, Centers for Disease Control and Prevention, Atlanta, Georgia; Marguerite A. Klein, National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, Maryland; Barnett S. Kramer, MD, MPH, Office of Medical Applications of Research, National Institutes of Health, Bethesda, Maryland; Molly Kretsch, PhD, National Program Leader for Human Nutrition, Agriculture Research Service, U.S. Department of Agriculture, Beltsville, Maryland; Catherine Loria, PhD, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; Kelli K. Marciel, MA, Office of Medical Applications of Research, National Institutes of Health, Bethesda, Maryland; J. Michael McGinnis, MD, MPP, The Robert Wood Johnson Foundation, Washington, DC; Joan A. McGowan, PhD, Musculoskeletal Diseases Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland; Linda D. Meyers, PhD, Food and Nutrition Board, Institute of Medicine, The National Academies, Washington, DC; Lata S. Nerurkar, PhD, Office of Medical Applications of Research, National Institutes of Health, Bethesda, Maryland; Malden C. Nesheim, PhD, Division of Nutritional Sciences, College of Human Ecology, Cornell University, Ithaca, New York; Lester Packer, PhD, Department of Molecular Pharmacology and Toxicology, University of Southern California School of Pharmacy, Los Angeles, California; Irwin H. Rosenberg, MD, Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts; Susan Rossi, PhD, MPH, Office of Medical Applications of Research, National Institutes of Health, Bethesda, Maryland; John Paul SanGiovanni, ScD, Division of Epidemiology and Clinical Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland; Paul A. Sheehy, PhD, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Rockville, Mary-

land; Pamela Starke-Reed, PhD, Division of Nutrition Research Coordination, National Institutes of Health, Bethesda, Maryland; Amy F. Subar, PhD, MPH, RD, National Cancer Institute, National Institutes of Health, Rockville, Maryland; Anne Thurn, PhD, Evidence-Based Review Program, Office of Dietary Supplements, National Institutes of Health, Bethesda, Maryland; Paula R. Trumbo, PhD, Division of Nutrition Programs and Labeling, U.S. Food and Drug Administration, College Park, Maryland.

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