



## **BENEFITS** & SAFETY OF

# DIETARY SUPPLEMENTS

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## WHITE PAPER

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# Executive Summary

The purpose of this paper is as follows:

- 1) To improve the understanding of the relatively small risk and substantial benefits associated with consumption of dietary supplements;
- 2) To review the most current science on the safety and efficacy of dietary supplements;
- 3) To provide perspective on the relative safety of dietary supplements, compared to risks of other hazards facing the American public;
- 4) Alert the public, media and legislators to an unwarranted bias that exists regarding the safety of dietary supplements;
- 5) Alert the public and legislators to much more serious health issues that are adversely affecting the health of millions of Americans;
- 6) Promote good public policy and regulations for dietary supplements that are based upon fact rather than misinformation and exaggeration.

Over 100 million Americans have adopted the use of dietary supplements, and numerous research studies are now validating the efficacy and safety of supplement use. The current dietary supplement research suggests an important health promotion role for dietary supplements which may be helpful to counter the effects of the pandemic lifestyle diseases such as Type II diabetes, obesity, heart disease, and cancer. Unfortunately, current patent law and high research costs limit private investment in “new drug approval” types of clinical research for dietary supplements. A lack of understanding of the current body of scientific literature, limited private investment in dietary supplement research, along with limited government funding of research has resulted in misperceptions and biases in the media regarding safety and efficacy of these products. It is important that the public and legislators understand the facts regarding dietary supplements in order to make informed decisions, rather than over-react to exaggerated misinformation perpetuated by those with a lack of knowledge, ideological differences or a commercial conflict of interest.

Public policy based on facts is important to constituents who rely on dietary supplements to support their health. Consumers of dietary supplement do not want dangerous

products on the market nor do they want safe and effective products removed from the market because of exaggeration and overreaction.

## ***Overview of Dietary Supplements***

Dietary Supplements have a rich and well-documented history of safety and benefit in supporting human health. Scientific research has consistently documented the importance of adequate nutritional intake to maintain proper health, and has linked the consumption of between 5 and 9 servings of fruits and vegetables per day to meet this baseline for nutritional health (Hyson, National Cancer Institute). However, surveys conducted by the CDC and the USDA show that, on average, less than 25% of all Americans are consuming the minimum recommended 5 servings each day of fruits and vegetables (CDC). In addition, there are other factors, such as variable genetic requirements and low nutritional value of over processed junk foods that are impacting Americans' nutritional status (Eaton and Konner) (Williams) (Muller and Kersten). For many, diet alone may not be meeting their needs. Dietary supplements can play an important role in assisting Americans in bringing their nutritional intake at least up to minimum standards.

There are numerous examples of how dietary supplements can have an important health benefits. According to the March of Dimes and the Centers for Disease Control and Prevention, folic acid taken *before* pregnancy and during the first trimester can greatly reduce the risk of having a baby with neural tube birth defect such as spina bifida (CDC). Middle-aged and older adults slowly lose bone as they age and the longer they live the more likely they are to develop osteoporosis. High calcium intakes, preferably with supplemental vitamin D, magnesium, and boron can slow the rate of bone loss and help protect against fractures. Studies also suggest that people who take vitamin E and vitamin C on a regular basis may get some protection against diseases or conditions caused by oxidative damage, such as heart disease, cancer and cataracts (Fletcher and Fairfield, CRN).

Supplements are easy to add to the daily diet, and are often the first step consumers take toward greater nutritional awareness and the adoption of other healthy lifestyle choices.

## ***The Health Benefits of Dietary Supplements***

Dietary supplements perform several health roles in our lives. At a minimum, they can provide the nutritional support to help us in meeting the optimal levels of nutrients to ensure baseline health. Whether these levels are not being met due to dietary insufficiencies or as a result of genetic variation, many people are consuming dietary supplements to close the gap between their existing levels and the baseline levels of nutrient intake. History and more recent studies are demonstrating the value of dietary supplements, whether to defend against the past afflictions of scurvy, rickets and beri beri, or protect against today's more pressing problems of heart disease, osteoporosis, and neural tube defects.

Throughout this document, we will be describing dietary supplements in each of these roles, since Americans consume dietary supplements for all of the above reasons, and we believe it is essential provide a comprehensive view of their proven, and growing, list of benefits.

### ***Safety***

Safety data for vitamins and minerals are available and documents a remarkable record. The number of incidents of serious adverse events resulting from consumption of dietary supplements is extremely low even though over 100 million Americans regularly consume dietary supplements. Results of clinical trials show minimal adverse reactions due to exposures from dietary supplements, with most complications being easily reversed or remedied through lowering intake levels. 2002 data from the Poison Control Centers Toxic Exposure Surveillance System (TESS) revealed only 7 deaths due to vitamin and mineral overdoses and only 3 deaths due to botanicals, a remarkably small number (Watson, et. al.).

Controversy surrounding the safety of botanical products containing Ephedra has recently driven the issue of dietary supplement safety in the United States, somewhat blurring in the minds of many the important distinction between the safety of two quite distinct

categories of dietary supplements, namely botanical herbs and nutrients. Ephedra has been used extensively both as a dietary or herbal supplement and has also been synthesized as the drug ephedrine. Ephedra and ephedrine have been used in the U.S. since 1927 when the AMA originally approved ephedrine for use as an OTC drug. Under the terms of the Dietary Supplement Health and Education Act (DSHEA), Ephedra was, prior to 2004, allowed to be used as a dietary supplement, while ephedrine is not since OTC drugs are expressly prohibited for sale as dietary supplements. Some dietary supplements had been found to be adulterated with ephedrine and removed from the market by the FDA. Whether or not the adverse reactions attributed to Ephedra were caused by products adulterated with ephedrine is not clear. Even if the data are skewed by Ephedra which has been adulterated with ephedrine, the incidence of adverse events is extremely low when compared with adverse events even for foods which have been estimated to cause some 76 million illnesses, 325,000 hospitalizations, and 5,000 deaths in the United States each year (Mead, et al.).

A 2003 RAND report examined safety data on adverse events for Ephedra and ephedrine from clinical trials and case reports published in the literature, submitted to the FDA, and reported to Metabolife, a manufacturer of Ephedra-containing supplement products. Their conclusions were that the controlled trials studied relatively few people and in aggregate were insufficient to evaluate events with a risk of less than 1 per 1000. They also found that the majority of the case reports were insufficiently documented to make an informed judgment about the relationship between the use of ephedrine or Ephedra-containing dietary supplements and the adverse event in question (Shekelle, M.D., PhD., et. al.). The number of deaths reported in the TESS system for the botanical category including Ephedra products for 2002 was three; omitting Ephedra it was zero (Watson, et. al.).

Some believe that dietary supplements should fall under the same legislative standards of approval as those for conventional drugs. With this in mind, we examined the relative safety of conventional medicines against dietary supplements to determine if FDA “drug regulatory standards” are appropriate.

There is a substantial body of research documenting a relatively high frequency of serious adverse events from pharmaceuticals resulting in substantial harm and a large

number of deaths. The data are clear and demonstrate that the danger of “conventional drugs” is far greater than that of dietary supplements which raises legitimate questions whether the drug regulatory standards should be applied to dietary supplements. A few key findings include:

- A study published in the *Journal of the American Medical Association (JAMA)* reported that 106,000 people died and over 2 million were hospitalized from adverse drug reactions to FDA approved drugs administered by physicians in hospitals, ranking adverse drug reactions (ADRs) between the 4<sup>th</sup> to 6<sup>th</sup> leading cause of death in the U.S. (Lazarou);
- The New England Journal of Medicine reports that 16,500 arthritis patients die every year from the adverse effects of pain and non-steroidal anti-inflammatory drugs (NSAIDs), making them the 15<sup>th</sup> leading cause of death in the U.S. (Singh);
- The incidence of emergency department (ED) visits related to narcotic analgesic abuse reached over 90,000 in 2001, more than doubling since 1994 (DAWN);
- In the 2002 Poison Control Center data, the total number of adverse outcomes for pharmaceuticals was over 300,000, or nearly 27% of all reported exposures. Most sobering was that the Poison Control Center data indicate that nearly *1,900 people died from exposure to a variety of pharmaceutical drugs in 2002.* (Watson, et. al.).

Overall, in terms of safety, the following chart provides relative risks to death every year for Americans by various types of hazards.

<i>Type of Incident</i>	<i>Number of Deaths</i>
Dietary Supplements	10
Fireworks	13
Shark injuries	18
Hornet, wasp and bee stings	46
Lightning	63
Bathtub Accidents	337

Foods	5,000
Firearm Homicides	11,348
NSAID-related Deaths	16,500
Auto Accidents	42,443
Deaths from Adverse Drug Reactions	106,000

*Sources: American Association of Poison Control Centers, CDC, Mead, Singh, Lazarou, Sims.*

Considering the fact that over 100 million Americans are regular consumers of dietary supplements, they stand out as very safe when compared with other risk factors, even those associated with the consumption of food. The perception that dietary supplements in general are dangerous is clearly not supported by the facts.

Most of the very limited harm caused by dietary supplements has been associated with the low quality of products or the presence of contaminants. Dealing with quality assurance as a means of improving safety would be substantially more effective, as well as cost-effective, than forcing dietary supplements through a drug regime which, in itself, has not been shown to guarantee product safety.

Since dietary supplements have been shown to provide a wide variety of health benefits such as preventing birth defects, blindness, osteoporosis etc., the risk/benefit relationship for dietary supplements is very favorable. One could not say the same thing regarding fireworks which are responsible for 13 deaths per year, since they provide little benefit other than entertainment value. Nor could a case be made for the risk/benefit justification of bathtubs which kill 337 every year when a safer alternative, “the shower,” could be used instead. However the massive number of deaths associated with pharmaceutical drugs, over 106,000 per year, raises serious questions about their risk/benefit profile.

It is curious why dietary supplements have become such a hot political issue when other more serious risk/benefit issues are being ignored.

## ***Efficacy of Dietary Supplements***

Numerous clinical trials have been conducted in an attempt to determine the efficacy of dietary supplements. While additional research is required to answer all the questions regarding the efficacy of dietary supplements, there is a large and growing body of evidence that supports the use of dietary supplements for health promotion. This paper highlights the major findings from a representative collection of these studies and provides references at the end for those wishing to obtain greater detail on this research.

## ***Costs***

The biggest challenge to date has been in the area of quantifying the actual cost effectiveness associated with the use of dietary supplements. The Lewin Group, Inc. found that through providing older adults with a daily multivitamin, the potential savings over a five year period resulting from a reduction in the relative risk of coronary artery disease and improved immune functioning was approximately \$1.6 billion (Dobson, et. al.). Another article provides information that, for health issues where dietary supplements are useful, the daily cost often runs from 10% to 25% of pharmaceutical alternatives (Snow). Given earlier data which outlined the potential efficacy, and lack of risks in taking dietary supplements in general, we can conclude that the cost/benefit ratio of using dietary supplements is very favorable.

We once again review the comparison between dietary supplements and pharmaceutical products, this time for costs. The cost of adverse events due to dietary supplements is relatively miniscule compared with pharmaceuticals since there are so few serious adverse events. The exact toll of adverse drug events (ADEs) on individuals is difficult to quantify, in part because there are so many elements to consider. In the U.S. overall, some studies suggest that hospital costs alone could reach \$4.2 billion, between \$2600 and \$3300 per ADE, and the national excess hospital length of stay attributed to ADEs would exceed 1.5 million days (Bates, et. al.) (Einbinder). Others estimate that costs associated with drug-related morbidity and mortality range from \$30.1 billion for the

more conservative end of the range of negative therapeutic outcomes to \$136.8 billion in a worst-case scenario, not including societal costs such as loss of productivity. These same researchers attempted to estimate total costs including the societal impact and believe the overall costs of ADE's to the U.S. economy range from \$138 to \$182 billion per year (Johnson and Bootman). Adding up all the various ADE elements associated with the use of pharmaceuticals, the potential costs both to individuals and to our society are substantial. The costs associated with adverse events due to dietary supplements are less than a rounding error compared with the costs associated with pharmaceuticals.

### ***Benefits and Risks of Dietary Supplements***

To assess the actual benefit/risk profile of dietary supplements, we need to look at two key measures of risk: frequency and severity, along with the potential benefit that may flow from the action. Wrapped around the whole benefit/risk profile is the component of cost which plays a key part in our overall analysis. If taking a dietary supplement has a high probability of providing a measurable health benefit, and the potential negative consequences are mild, then the only question is: "Is the reward good enough to make it worth the cost?" However, if the chances of success on any one use are small, and the consequences or costs of failure are severe, then the benefit/risk profile is in question.

In our final analysis, because of the significant benefit of taking dietary supplements, the relatively low frequency and severity of risk, and the overall cost/benefit equation, the perception that dietary supplements, in general, are dangerous or not generally appropriate for health promotion purposes is clearly not supported by the facts.

The need for applying pharmaceutical regulatory standards and associated regulatory expenses to dietary supplements does not seem to be justified when comparing the relative risks and costs of drugs to those of dietary supplements. Considering the fact that over 100 million Americans are regular consumers of dietary supplements, they easily stand out as the safest group of products consumed orally, and among the safest products known.

## ***Medical Bias and Research Tactics***

There are numerous aspects of bias with regard to health care and the negative views which commonly impact dietary supplement acceptance. Physician bias occurs when he or she is confronted by the patient regarding alternative approaches to health care, and is placed in the situation of either recommending an unfamiliar therapy or of rejecting the therapy out of hand, simply out of lack of knowledge (Sierpina). “Publisher bias” can be seen in magazines and journals which are industry funded and reviewed by scientists or physicians with industry ties. In fact, according to an article in the *New England Journal of Medicine*, “researchers serve as consultants to companies whose products they are studying, join advisory boards and speakers' bureaus, enter into patent and royalty arrangements, agree to be the listed authors of articles ghostwritten by interested companies, promote drugs and devices at company-sponsored symposiums, and allow themselves to be plied with expensive gifts and trips to luxurious settings (Angell).”

These biases may undermine objective research and promote criticism of effective methods of treatment by those with conflicts of interest. These experts often serve as experts for the media, thereby extending their biases into the public press and publishing them as objective reporting to an unsuspecting public. For example, a study published in the *Journal of the American Medical Association* reviewed data from 37 peer-reviewed studies published between 1980 and 2000 and found that 25% of biomedical researchers at universities had commercial ties "serious enough to raise questions of financial conflict" and in many cases, "enough to skew their research.” Using these results, the study estimates that industry-sponsored research is 3.6 times more likely to have results favorable to the company that funded the research. Drug industry funds have become the "lifeblood" of biomedical research accounting for 62% of U.S. expenditures on prescription drug research in 2000 (Bekelman, et. al.).

Our nation’s health should be approached in a patient-centered manner, considering the needs and desires of each individual without the influences of biases that have permeated clinical studies, our institutions of education, or have resulted from the emotional ranting by the media.

## **Conclusion**

- Dietary supplements are safe: over 100 million Americans are purchasing and consuming dietary supplements without significant numbers of adverse events, making the risk/benefit profile of supplements very favorable.
- The ingredients of many dietary supplements are critical to the basic, healthy functioning of each human being and furthermore are proven to provide additional important health benefits such as folic acid to reduce the risk of having a baby with a neural tube birth defect, high calcium intakes to slow the rate of bone loss and help protect against fractures, and taking vitamins E and C on a regular basis to protect against heart disease, cancer and cataracts.
- If dietary supplement companies introduce harmful dietary supplements to the market, the FDA currently has full regulatory authority under DSHEA, the existing law applicable to dietary supplements, to remove harmful dietary supplements from the market, if necessary. DSHEA needs to be enforced.
- The current cost of dietary supplements makes it possible for the majority of people, of all ages, to have access to and reap the health benefits of dietary supplements.
- Attempting to over-regulate dietary supplements unnecessarily could limit access to effective, inexpensive and safe products the average American can use to maintain good health and reduce health care costs.

We must not increase costs for consumers to purchase dietary supplements by enforcing a drug regulatory system on products with little safety risk, but instead should appropriately enforce the existing law to assure the public is properly protected.

# Introduction

## ***Purpose***

The purpose of this paper is as follows:

- 1) To improve the understanding of the relatively small risk and substantial benefits associated with consumption of dietary supplements;
- 2) To review the most current science on the safety and efficacy of dietary supplements;
- 3) To provide perspective on the relative safety of dietary supplements, compared to risks of other hazards facing the American public;
- 4) Alert the public, media and legislators to an apparent unwarranted bias that exists regarding the safety of dietary supplements;
- 5) Alert the public and legislators to much more serious health issues that are adversely affecting the health of millions of Americans;
- 6) Promote good public policy and regulations for dietary supplements that are based upon fact rather than misinformation and exaggeration.

## ***The Importance of this Paper***

Over 100 million Americans have adopted the use of dietary supplements for many years, relying on their properties for the promotion of health. Supplements have a very good history of safety producing only a small number of negative reactions to those who consume them. Most supplements have a long history of safe and effective use from around the world, and many studies exist – well supported by a growing body of both scientific and traditional empirical literature – demonstrating their benefits. These studies, such as those conducted by Drs. Dean Ornish, Karen Soeken, James Anderson and many others are referenced and described in the health benefits section of this paper. In balance, when comparing the known benefits with the known dangers of dietary supplements, there is substantial evidence suggesting that the benefits of supplement usage far outweigh the negatives. Yet the perceptions of the benefits versus the safety of

dietary supplementation have largely been misrepresented in the media as well as by other groups.

The risks in taking dietary supplements compared to various other hazards faced by the American public are extremely low. Compare these statistics:

- The Poison Control Center Toxic Exposure Surveillance System (TESS) reported a total of 7 deaths out of 76,600 exposures to vitamin and mineral supplements in 2002. By comparison, TESS reported 32 deaths due to exposures from household cleaning products, 18 from pesticide exposures and approximately the same number of deaths due to insect and snake bites (6) as from dietary supplements (Watson, et. al).
- Including Ephedra products, a total of 3 deaths in the botanicals category were reported via TESS. Without Ephedra products, the total number of deaths in this category was zero.
- 2001 data from the National Center for Health Statistics revealed deaths from auto accidents at 42,443, firearm homicides at 11,348, and deaths due to alcoholic liver disease at 12,207 (National Center for Health Statistics).
- In overall deaths reported in the TESS reporting system, the number 1 cause of death was due to analgesics, for a total of 659 deaths, followed by sedative/hypnotics/psychotics as the number 2 cause (364), and antidepressants (318) coming in at number 3. In fact, the total number of deaths due to pharmaceutical drugs in the TESS 2002 report was 1,878 (Watson, et. al). These data are supported by numerous scientific studies that point to over 100,000 deaths due to adverse drug events each year, ranking anywhere from the 4<sup>th</sup> – 6<sup>th</sup> leading cause of death in the U.S. (Lazarou).

The comparison between dietary supplements and pharmaceutical products is important, simply because some believe that dietary supplements should fall under the same standards of approval as those for conventional drugs. Because most supplements have not yet been placed through the same stringent studies and large scale clinical trials

required for FDA drug approval as have most (but not all) prescription or over-the-counter medicines, the lack of “new drug approval” data has led many people to unfairly criticize and condemn dietary supplements, without fair consideration of the studies that have been done and the history of safe use of the ingredients in these products. Consequently, the remarkable safety record of dietary supplements is often overlooked. This paper will demonstrate that the lack of “new drug approval” evidence does not necessarily mean that dietary supplements are unproven, lack efficacy or are unsafe.

It is our hope that by sharing the most recent research in this paper, we can dispel some of the most common misperceptions and biases that currently exist. It is essential that legislators and policy making bodies understand the issues surrounding the dietary supplement industry, in order to make decisions based on facts, not exaggerations, and to effectively support the millions of constituents that rely on dietary supplementation to support their health.

# Overview of Dietary Supplements

## *Review of Current Legislation*

The media in their “investigative reporting” as well as others seeking information on the prevalence of adverse events for nutritional products claim that the public is at risk by taking “unregulated” dietary supplements. In fact, dietary supplements *are* regulated as is well known by those familiar with the Dietary Supplement Health and Education Act of 1994 (DSHEA, Public Law 103-417, October 25, 1994).

Millions of people believe that dietary supplements are an effective avenue for meeting basic nutritional needs, as well as for promoting health. In an effort to support Americans in their increasing demands for these products, Congress' enacted DSHEA, which addressed the concerns of both consumers and manufacturers and regulated the manner in which safe and appropriately labeled products were made available to the consumer.

These specific provisions of the DSHEA are described below. Much of the following information was taken verbatim from the Web site of the Food and Drug Administration's Center for Food Safety and Applied Nutrition (CFSAN).

## **DEFINITION OF DIETARY SUPPLEMENT**

The DSHEA established a formal definition of "dietary supplement" using several criteria. A dietary supplement:

- is a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.
- is intended for ingestion in pill, capsule, tablet, or liquid form.
- is not represented for use as a conventional food or as the sole item of a meal or diet.

- is labeled as a "dietary supplement."
- includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

It can also be in other forms, such as a bar, as long as information on its label does not represent the product as a conventional food or a sole item of a meal or diet. Whatever their form may be, DSHEA places dietary supplements in a special category under the general umbrella of foods, not drugs, and requires that every supplement be labeled a dietary supplement.

## **SAFETY**

Because dietary supplements are under the umbrella of foods, FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for the agency's oversight of these products. FDA's efforts to monitor the marketplace for potential *illegal* products (that is, products that may be unsafe or make false or misleading claims) include obtaining information from inspections of dietary supplement manufacturers and distributors, the Internet, consumer and trade complaints, occasional laboratory analyses of selected products, and adverse events associated with the use of supplements that are reported to the agency.

Under DSHEA, once a dietary supplement is marketed, FDA has the responsibility for showing that a dietary supplement is unsafe before it can take action to restrict the product's use. This was the case when, in June 1997, FDA proposed, among other things, to limit the amount of ephedrine alkaloids in dietary supplements (marketed as Ephedra, Ma huang, Chinese Ephedra, and ephedronin, for example) and provide warnings to consumers about hazards associated with use of dietary supplements containing the ingredients. The proposal stemmed from FDA's review of adverse event reports it had received, scientific literature, and public comments. Individual states can also take steps to restrict or stop the sale of potentially harmful dietary supplements within their jurisdictions. The Secretary of HHS may also declare that a dietary supplement or dietary ingredient poses an imminent hazard to public health or safety. However, like

any other foods, it is a manufacturer's responsibility to ensure that its products are safe and properly labeled prior to marketing.

## **LITERATURE**

The DSHEA provides that retail outlets may make available "third-party" materials to help inform consumers about any health-related benefits of dietary supplements. These materials include articles, book chapters, scientific abstracts, or other third-party publications. These provisions stipulate that the information must not be false or misleading; cannot promote a specific supplement brand; must be displayed with other similar materials to present a balanced view; must be displayed separate from supplements; and may not have other information attached.

## **NUTRITIONAL SUPPORT STATEMENTS**

The DSHEA provides for the use of various types of statements on the label of dietary supplements, although claims may not be made about the use of a dietary supplement to diagnose, prevent, mitigate, treat, or cure a specific disease unless approved under the new drug provisions of the Food, Drug, and Cosmetic Act. For example, a product may not carry the claim "cures cancer" or "treats arthritis." Appropriate health claims authorized by FDA – such as the claim linking folic acid and reduced risk of neural tube birth defects and the claim that calcium may reduce the risk of osteoporosis – may be made in supplement labeling if the product qualifies to bear the claim. Under DSHEA, firms can make statements about classical nutrient deficiency diseases as long as these statements disclose the prevalence of the disease in the United States. In addition, manufacturers may describe the supplement's effects on "structure or function" of the body or the "well-being" achieved by consuming the dietary ingredient. To use these claims, manufacturers must have substantiation that the statements are truthful and not misleading and the product label must bear the statement "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." Unlike health claims, nutritional support statements need not be approved by FDA before manufacturers market products bearing the statements, however, the agency must be notified no later than 30 days after a product that bears the claim is first marketed.

## **INGREDIENT AND NUTRITION INFORMATION LABELING**

Like other foods, dietary supplement products must bear ingredient labeling. This information must include the name and quantity of each dietary ingredient or, for proprietary blends, the total quantity of all dietary ingredients in the blend. The label must also identify the product as a "dietary supplement." Labeling of products containing herbal and botanical ingredients must state the part of the plant from which the ingredient is derived.

Labels also must provide nutrition labeling. This labeling must first list dietary ingredients for which FDA has established daily consumption recommendations followed by dietary ingredients with no daily intake recommendations. The nutrition labeling must include the quantity per serving for each dietary ingredient (or proprietary blend) and the source of a dietary ingredient.

## **NEW DIETARY INGREDIENTS**

Supplements may contain new dietary ingredients, those not marketed in the United States before October 15, 1994, only if:

- 1) those ingredients have been present in the food supply as an article used for food in a form in which the food has not been chemically altered, or;
- 2) there is a history of use, or some other evidence of safety exists that establishes that there is a reasonable expectation of safety when the product is used according to recommended conditions of use.

Supplement manufacturers must notify FDA at least 75 days before marketing products containing new dietary ingredients, providing the agency with the information on which the conclusion that a dietary supplement containing the new dietary ingredient "will reasonably be expected to be safe" was based. Any interested party, including a manufacturer of a dietary supplement, may petition FDA to issue an order prescribing the conditions of use under which a new dietary ingredient will reasonably be expected to be safe.

## **GOOD MANUFACTURING PRACTICES (GMPs)**

DSHEA grants FDA the authority to establish GMP regulations governing the preparation, packing, and holding of dietary supplements under conditions that ensure their safety. These regulations are to be modeled after current good manufacturing practice regulations in effect for the rest of the food industry. GMP regulations have never been finalized by FDA despite the 10 years the agency has had to follow through on the DSHEA legislation which authorized FDA to create GMP regulations for dietary supplements. This failure of FDA to act in a reasonable time period is reprehensible.

## **COMMISSION ON DIETARY SUPPLEMENTS**

The DSHEA requires the formation of a Commission to conduct a study and make recommendations on the regulation of label claims and statements for dietary supplements and procedures for the evaluation of the claims. The members of the Commission will evaluate how best to provide truthful, scientifically valid, and not misleading information to consumers so that they can make informed and appropriate health care choices. The Commission will be composed of seven members, appointed by the President, with experience in dietary supplements and in the manufacture, regulation, distribution, and use of supplements. Three members must be qualified by scientific training and experience to evaluate supplements' health benefits, and one of these must be trained in pharmacognosy, medical botany, traditional herbal medicine, or other related sciences. All Commission members and staff should be unbiased about supplement use. This commission has been appointed and is providing guidance to the dietary supplement industry.

## **OFFICE OF DIETARY SUPPLEMENTS**

In compliance with DSHEA the HHS Secretary has established an office within the National Institutes of Health to explore the potential role of supplements to improve health care in the U.S. The office will also promote scientific study of supplements and their value in preventing chronic diseases; collect and compile scientific research, including data from foreign sources and the NIH Office of Alternative Medicine; serve as a scientific adviser to HHS and FDA; and compile a database of scientific research on supplements and individual nutrients.

## **EFFECTIVE DATE**

DSHEA's provisions for use of nutritional support statements and third-party literature became effective when the law was signed. The effective date for other labeling provisions and any FDA implementing regulations was after December 31, 1996.

## ***Historical Perspective to the Present***

The natural products industry grew out of the age-old knowledge that individuals can and should enhance their diets for better health. Naturopathic medicine evolved through centuries of people searching for the best natural healing systems, and established its roots in 19<sup>th</sup> century Europe, where many of its forerunners used therapies such as vegetarian diets, physical activity and relaxation techniques with their patients. It was in the early 20<sup>th</sup> century when naturopathy saw its early success in the United States, growing as quickly as the technological advances in medicine, including surgery and pharmaceuticals (Hale and Leamon).

Supporting this wave of growth were examples of significant advances in the treatment of deadly diseases using nutritional supplementation. The history of scurvy illuminates this point quite well. Scurvy was an often fatal wasting disease which primarily afflicted those on a cereal diet, such as sailors on long voyages. In the mid-18<sup>th</sup> century it was discovered that eating fresh fruit or vegetables could prevent scurvy – hence the description of British sailors as "limeys". But it wasn't until 1917 when it was ascertained that it was a deficiency of Vitamin C in the diet that resulted in this deadly disease. The same kinds of histories exist on diseases such as beri beri (lack of Vitamin B<sub>1</sub>) or rickets (lack of Vitamin D). Many scientists, as well as laymen, began to document the impact of natural products and dietary supplements in the treatment and prevention of these and other diseases of the time, passing along those traditions for future generations.

It was this rich and well-documented history of proven benefits that natural nutritional products were established as playing a key role in supporting human health. Beginning in the 1970s, worldwide population surveys began to uncover a consistent link between diet and health, driving a second wave of vitamin research. From these surveys,

researchers began to examine the information at the nutrient level, looking at minerals, vitamins and phytonutrients to determine which are most closely tied to specific diseases. Thanks to technology and new methods of research and manufacturing, use and knowledge of the benefits of vitamins, minerals and other nutrients has grown dramatically. In fact, many scientists and physicians now recognize the essential role of nutritional supplements and their relationship to health. A 1992 report in *Time* magazine reviewing recently published scientific research found that vitamins and minerals "play a much more complex role in assuring vitality and optimal health than previously thought. Vitamins, often in doses much higher than those usually recommended, may protect against a host of ills ranging from birth defects and cataracts to heart disease and cancer." The *Time* magazine report also established the key link between organic materials and vitamins, and the body's metabolic and regulatory systems, responsible for protecting cells, converting food to energy, and defending itself against disease (Toufexis).

Today, scientific research continues to document vitamin and mineral complexes' ability to prevent illness and alter some of the deleterious effects of the body's aging process. This scientific evidence, in large part, is driving the demand for and sales of dietary supplements. Surveys now estimate that more than half the U.S. population, or more than 100 million Americans, use dietary supplements such as vitamins, minerals and herbs as a safe and natural way to maintain good health and supplement inadequate diets (National Nutritional Foods Association). In fact, in 2002, Americans spent nearly \$19 billion on dietary supplements, while \$43 billion has been spent worldwide (Davidson).

### **U.S. Sales of Supplements, 2002**

	Sales in billions
Vitamins	\$6.2
Herbs	\$4.3
Meal Supplements	\$2.6
Specialty/Other	\$2.4
Sports Nutrition	\$1.8

Minerals	\$1.5
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Source: National Nutritional Foods Association

## ***Insufficient Nutrients in our Diet***

### **Genetic Necessity**

In 1985, Drs. Melvin Konner and Boyd Eaton reported that our nutritional needs have evolved over millions of years of natural selection and that these needs have not changed much since the Paleolithic era. Using anthropological information, their research determined that the levels of various vitamins and minerals in the human Paleolithic diet were much higher than they are today. Their conclusion was that we are currently eating foods that are out of balance, and that the “nutrient density” of our diet, a measure of the amount of vitamins and minerals, has gone down since the advent of food processing, even though our *requirements* for these nutrients for optimal health have remained constant with our evolutionary needs (Eaton and Konner). The difference between the two is termed a “nutrient gap”.

This nutrient gap can have adverse influences on the energy processes of the body that are necessary for all vital functions. Many nutritional researchers believe that we are now suffering from a different form of malnutrition as a consequence of these nutrient gaps. The malnutrition that is present in the United States is not that associated with frank deficiencies of vitamins or minerals resulting in conditions such as scurvy, beri beri, pellagra or rickets, but rather the malnutrition of “too much of too little” or overconsumptive undernutrition that results in increased risk of heart disease, hypertension, stroke, diabetes, osteoporosis, neurodegenerative diseases that result in memory impairment and dementia, and certain forms of cancer. Vitamin and mineral needs are genetically determined, and the proper intake level of nutrients is critical in establishing how well a person can abstract metabolic energy from their food (Eaton and Konner).

## Survey Data

Other discoveries with respect to the influence of diet on health are important and need to be explored more fully in modern medicine. Reports from the National Center for Health Statistics, the Centers for Disease Control and Prevention, and the Produce for Better Health Foundation now show that most American adults don't consume enough healthy foods such as fruits, vegetables, and grains to reach even their minimum recommended daily intake to assure proper health. In an exhaustive review of literature, Dr. Diane Hyson concluded that there was significant evidence linking the consumption of fruits and vegetables to health. Her research revealed that there is ample scientific to support a dietary goal of between 5-10 fruits and vegetables per day, and that this intake by individuals could have a major impact on the health of our nation (Hyson). It is Hyson's study that has become the cornerstone of the Produce for Better Health's 5-A-Day campaign. The following data provide detailed insight into how the American consumer is faring toward their fruit and vegetable consumption goals.

The statistics in Tables I and II were summarized by the Produce for A Better Health Foundation, using data from The Behavioral Risk Factor Surveillance System (BRFSS). These data are gathered via the world's largest telephone survey, established by the Centers for Disease Control and Prevention (CDC) for the purpose of tracking health risks of free-living U.S. residents. Data on nationwide fruit and vegetable intake for the years 1996, 1998, and 2000 are summarized below in Table I.

<b>Year</b>	<b>Never or &lt;1 a day</b>	<b>1 to &lt; 3 a day</b>	<b>3 to 5 a day</b>	<b>5+ times a day</b>
1996	3.6	32.3	40.4	23.6
1998	3.5	33.1	39.6	23.8
2000	3.8	34.1	38.7	23.1

*Source: Produce for Better Health Foundation; Centers for Disease Control and Prevention. 2000 BRFSS Summary Prevalence Report.*

According to Table I, more than 75% of U.S. residents failed to meet the minimum recommended 5 servings each day of fruits and vegetables. In addition to nationwide summary data, the BRFSS website provides a breakdown of demographic information on persons who achieve 5 fruits and vegetables each day. These data are provided in Table II below.

**Table II**  
*Demographic characteristics of persons consuming 5 or more servings of fruits and vegetables each day, Year 2000*

**Age**  
*Percentage of persons eating 5 or more servings per day of fruits and vegetables by age group*

<b>18-24</b>	<b>25-34</b>	<b>35-44</b>	<b>45-54</b>	<b>55-64</b>	<b>Over 65</b>
21.6%	19.1%	19.8%	21.8%	26.9%	31.7%

**Table II**  
*Demographic characteristics of persons consuming 5 or more servings of fruits and vegetables each day, Year 2000*

**Gender**  
*Percentage of persons eating 5 or more servings per day of fruits and vegetables by gender*

<b>Females</b>	<b>Males</b>
26.9%	18.9%

**Education**  
*Percentage of persons eating 5 or more servings per day of fruits and vegetables by education level*

<b>Non-HS grad</b>	<b>HS grad or GED</b>	<b>Some post-HS Ed</b>	<b>College Grad</b>
19.9%	19.6%	23.9%	27.8%

<b>Income</b>				
<i>Percentage of persons eating 5 or more servings per day of fruits and vegetables by yearly income level</i>				
<b>&lt;\$15,000</b>	<b>\$15,000- \$24,999</b>	<b>\$25,000- \$34,999</b>	<b>\$35,000- \$49,999</b>	<b>&gt;\$50,000</b>
22.4%	21.7%	21.5%	22.2%	24.2%

Source: Produce for Better Health Foundation; Centers for Disease Control and Prevention. 2000 BRFSS Summary Prevalence Report.

From these data, we can conclude the following:

- The number of individuals who eat less than 1 serving of fruits and vegetables per day has been growing since 1996;
- The number of individuals who consume greater than 5 servings per day is decreasing;
- Those individuals in lower income brackets are consuming less servings of fruits and vegetables per day than those in the higher income brackets;
- Persons with less education are consuming fewer servings than those with higher levels of education.

Overall, according to CDC data, the actual percentages of people who are consuming the recommended servings of fruits and vegetables for adequate nutrition are woefully low. On average, **only about 25% of Americans** are meeting the bare minimum in order to maintain baseline health.

These data are supported by a survey conducted by the USDA in their 1994-96 Continuing Survey of Food Intakes by Individuals (CSFII). This study is the most recent and most comprehensive evaluation of food intake in the U.S. In this study, food intakes of Americans are compared to recommendations in the U.S. Department of Agriculture's Food Guide Pyramid. They provide national probability estimates for the U.S. population based on food intakes reported by individuals 2 years of age and older on 2 nonconsecutive days. Once again we find that the average American diet fails to meet the minimum number of total vegetables and fruits per day.

**Mean Numbers of Pyramid Servings Consumed Per Day**

<b>Sex and Age in Years</b>	<b>Total Vegetable*</b>	<b>Total Fruit</b>
<b>Males</b>		
2-5	2.1	2.3
6-11	2.3	1.5
12-19	3.7	1.4
20-29	4.3	1.3
30-39	4.5	1.3
40-49	4.1	1.5
50-59	4.1	1.7
60-69	3.9	1.9
70 and over	3.4	2.1
20 and over	4.1	1.5
<b>Females</b>		
2-5	2.2	2.2
6-11	2.2	1.5
12-19	2.7	1.3
20-29	3.0	1.2
30-39	3.1	1.3
40-49	3.2	1.4
50-59	3.2	1.6
60-69	3.0	1.7
70 and over	2.8	1.8
20 and over	3.1	1.5
<b>All individuals 2 and older</b>	<b>3.3</b>	<b>1.5</b>

*\* Includes French fries and potato chips*

Source: USDA. Agricultural Research Service. Pyramid Servings Data for 1994-1996.

The Produce for Better Health Foundation (PBH) hired the NPD Group, a leading provider of market information to further examine the frequency of fruit and vegetable consumption habits of U.S. citizens. NPD has been tracking food consumption habits of roughly 5,000 individuals in 2000 households since 1980. Combining their 2002 results with the CSFII, they have concluded that:

- Fruit and vegetable consumption is declining.
- Americans are eating only about 4 servings of fruits and vegetables, *including French fries and potato chips*. Excluding these high-fat processed potato products, Americans are eating only about 3.6 servings of fruits and vegetables each day.
- Only 1 in 5 Americans meets the 5 A Day minimum requirement for fruits and vegetables.
- Only 13% of American families, 22% of single persons, 27% of ‘empty nesters’, and 39% of the elderly are eating the minimum recommended 5 servings per day of fruits and vegetables.
- Obesity levels are lowest among those who have high intakes of fruits and vegetables.
- 9 out of 10 teen girls (89%) and 96% of kids ages 2-12 do not eat 5 servings per day.
- The number of dishes in the average American dinner has declined, and the dish that’s being dropped is the side-dish, historically the place for seasonal or home-grown vegetables.
- Americans are eating more meals away from home, which translates into fewer opportunities for fruits and vegetables: nearly one in six dinner meals (16%) are obtained from a restaurant, up from 12% in 1985 (Produce for Better Health Foundation).

### **DRI Shortfalls**

In 1997, the new and improved Dietary Reference Intakes (DRIs) were unveiled, updating the 1940s-era Recommended Daily Allowances for vitamins and minerals, released by the United State Food and Nutrition Board. These DRIs are intended to be

met solely through diet, not through supplementation. However, the DRIs don't take into considerations the following facts:

- 1) Most people simply don't eat a well-balanced diet, and even if they do, the amount of processing that our food undergoes depletes an extraordinary amount of nutrients in the food we regularly consume. For example, when whole wheat grain is turned into white flour, between 29 and 95% of each key nutrient is lost in processing (Nutrition Consulting and Education Service).
- 2) At any given time, as much as one-third of the American population is dieting and taking in less than the normal 2000-3000 calories upon which the DRIs are based (Eades).
- 3) The DRIs are based on a set of criteria for the "average person" and does not consider individual needs.

### **The Phytonutrient Revolution**

The story of dietary insufficiency goes beyond the concern of suboptimal intake of vitamins and minerals alone. Over the past twenty years it has become increasingly well recognized that a diet composed of minimally processed plant foods contains thousands of important substances other than vitamins and minerals that influence health and protect us from the toxins in our environment. These substances are commonly called "phytonutrients" because they are derived exclusively from plants.

To be more specific, the food we eat is more than just the traditional vitamins, minerals, proteins, carbohydrates and fat. It is a smorgasbord of complex chemicals, phytonutrients, which have a wide variety of chemical properties and deliver many positive effects to our health. For example, tomatoes, peppers, pineapple strawberries, and carrots contain tens of thousands of phytochemicals, among them, p-coumaric acid and chlorogenic acid which stop the formation of cancer-causing substances. Many red, green, yellow, and orange fruits and vegetables are loaded with carotenoids, such as beta-

carotene and lycopene, which have been shown to reduce the accumulation of plaque in arteries (Beling). J.W. Fahey, et. al. at the Johns Hopkins School of Medicine identified a family of important phytonutrients in cruciferous vegetables, which include broccoli, cauliflower, cabbage and brussel spouts, called glucosinolates. These phytonutrients have been found to favorably influence the liver's ability to metabolize and excrete foreign chemicals (Fahey). Similarly, Drs. Herman Adlercreutz and Kenneth Setchell have discovered that soy contains a class of phytonutrients called isoflavones and flax phytonutrients called lignans that improve estrogen metabolism and action (Adlercreutz) (Setchell). In grapes a phytonutrient called resveratrol has been found to be a potentially important cancer prevention agent, and in garlic a variety of sulfur-containing phytonutrients have been found that help to control blood pressure and cholesterol levels. Beyond these few examples are the thousands of other phytonutrients in the bioflavonoid, carotenoid and polyphenol families that come from specific foods and have significant potential for beneficial influence on health.

Few of these phytonutrients are found in foods that are frequently consumed in our processed, shelf-stable diet. As our diets have become more processed and less reliant upon the consumption of minimally processed fruits, vegetables, grains and legumes, the consumption of health promoting phytonutrients has diminished and, according to Dr. Daniel T. Quigley, author of *The National Malnutrition*, "everyone who has in the past eaten processed sugar, white flour, or canned food has some deficiency... depending on the percentage of such deficient food in the diet (Quigley)." As a consequence, new categories of dietary supplements that are concentrates of these phytonutrients are being produced. Such concentrates of foods and spices have been safely used for many years by all cultures for their nutritional and health promoting value.

There has been some discussion as to whether or not phytonutrients supplements should be regulated as drugs. To do so, however, would call into question as to whether any food concentrate such as concentrated orange juice, table sugar, coffee, tea or hydrogenated oils should be classified as a drug. Vitamins, minerals and phytonutrients are not pharmaceuticals, but rather substances that humans evolved a need for over millions of years. Each individual possesses in their genetic inheritance needs for this complex array of nutrients that is unique. Nutritional supplements provide the opportunity to fill the gap between what is needed by the individual for optimal health

and what is available from their diet. As Dr. Edward Schneider, former Director of the National Institutes on Aging, pointed out in an article in the New England Journal of Medicine, as we age our nutritional needs change and the RDA's are not sufficient in defining what level of nutrients are needed to promote optimal health in an aging population (Schneider, et. al.).

### **Biochemical Individuality**

Further complicating this issue of low nutrient density diets is the recognition that we all have different nutrition needs to promote optimal health. In the 1950's, a Nobel Prize winning biochemist from the University of Texas, Dr. Roger Williams, proposed that people were much different one from another in their nutritional needs than had been assumed when the Recommended Dietary allowances (RDAs) were established (Williams). His pioneering work recently took on new meaning with the publication of the results of the Human Genome project. From these extraordinary discoveries came the recognition that humans have millions of variations of their genes called single nucleotide polymorphisms or SNP's. Many of these genetic variations are related to specific nutrient needs for promoting good health. The discovery of SNPs that affect individual nutrient needs led to the realization that nutritional requirements for one person may be very different than those for another person (Tolstoi).

This breakthrough in understanding of how genetic differences influence nutritional needs and how nutrients in turn influence genetic expression and cellular function has given birth to the new field called "nutrigenomics." Nutrigenomics is the study of how nutrients influence genetic expression and health. As an example, nutrigenomics research has shown that the need for folic acid can vary significantly if a person inherits a SNP (a genetic uniqueness) that affects the way they metabolize folic acid. This genetic uniqueness is carried by 10% - 30% of the population and has been associated with the increased risk to birth defects, heart disease, stroke, depression and dementia (Muller and Kersten). When the RDA/DRI's were formulated they did not take this type of genetic uniqueness into account. The standard diet that was assumed to provide adequate nutrient intake when the DRI's were formulated is insufficient to meet the needs of a large number

of people with SNPs (genetic uniqueness) that affect their nutrient requirements. The studies in the area of genetic uniqueness (SNPs) call into question the value of public health nutrition standards such as the RDA or DRI in defining nutrient needs for every individual.

It is clear from the previous information presented in this paper that Americans, overall, are falling short of the minimum requirements for vitamins, minerals, and other nutrients that are necessary for maintaining optimal health. Most worrisome are the negative effects from a low nutrient density diet combined with increased need for nutrients due to genetic uniqueness. The effects of these two factors are playing out with an increasing incidence of today's killer diseases type II diabetes, obesity, hypertension and cardiovascular disease. Proponents of dietary supplementation believe, for all the reasons listed above, that in order to protect against disease and aging, for many people diet may not be enough. Dietary supplements are beneficial for addressing the issue of genetic uniqueness in bringing the health status of many up to minimum standards.

### ***The Health Benefits of Dietary Supplements***

The previous sections of this document outline the various health roles that dietary supplements perform in our lives. At a minimum, dietary supplements can provide the nutritional support to help us in meeting the optimal levels of nutrients to ensure baseline health. Whether these levels are not being met due to dietary insufficiencies or as a result of genetic variation, many people are consuming dietary supplements to close the gap between their existing levels and the baseline levels of nutrient intake. History, as well as current studies which are outlined later in this document are also demonstrating the preventative role of dietary supplements, whether to defend against the past afflictions of scurvy, rickets and beri beri, or protection against today's more pressing problems of heart disease, osteoporosis, and neural tube defects. Current studies are now coming to light that document additional health benefits of dietary supplements.

Since Americans consume dietary supplements for many different reasons, we believe it is essential provide a comprehensive view of their proven, and growing, list of benefits.

## ***Safety of Dietary Supplements***

Are dietary supplements safe?

The risk of an adverse event, particularly a serious one, resulting from a dietary supplement taken within recommended dosages is extremely low. As will be seen later in this paper, very few Adverse Event Reports (AERs) are reported every year.

For the purpose of this paper, we will review the safety aspects of two distinct categories of dietary supplements: 1) vitamins and minerals; 2) herbal or botanical supplements; utilizing results from clinical trials, as well as data from the Poison Control Center. The FDA's Special Nutritional Adverse Event Monitoring System (AEMS) will not be referenced in this paper, due to serious questions that were raised by the FDA who stated that the system "was very limited and was provided in a manner that made it difficult for users to appropriately interpret the adverse events (USFDA)." Consequently, the FDA agreed to remove AEMS from its website.

### **Vitamins and Minerals**

#### ***Clinical Trials***

The Journal of the American Medical Association published study conducted in 1997 that was done to determine whether long-term vitamin E supplementation would enhance the immune response in healthy elderly subjects. In this clinical trial, subjects were provided with a level of Vitamin E greater than is currently recommended and, along with producing a favorable immune response outcome, there were no observed adverse effects associated with this higher level of supplementation (Meydani, et. al.).

In a July 2003 article in the *Annals of Internal Medicine*, "Routine Vitamin Supplementation To Prevent Cardiovascular Disease: A Summary of the Evidence for the U.S. Preventive Services Task Force," researchers state that "in most studies of

vitamin supplementation, adverse effects were not reported as might be expected in a pharmacologic trial (Morris, et. al.).” In another study published in 2001 by Kiely, et.al, food intake data and nutritional supplementation information was gathered for 1379 subjects. In addition to efficacy results, they also stated that “there appears to be little risk to supplement users of experiencing adverse side effects due to excessive intakes of micronutrients (Kiely, et. al.).”

Dr. John Hathcock, the Vice President for Scientific and International Affairs at the Council for Responsible Nutrition, developed a comprehensive document in April 2004 summarizing the safety of the most commonly consumed vitamins and minerals. In this document, he establishes the upper safe level of intake for dietary supplements, as well as identifying those ingredients that have potential adverse reactions beyond such levels. Overall, he discovered scant evidence demonstrating significant side effects due to vitamin and mineral intake, except in those cases of extremely high levels of consumption. In these cases, the most prevalent complaints were largely more of a nuisance, than of a genuine hazard. The only safety issues from his research where high dosages were involved included:

- Skin discoloration from beta-carotene supplementation, which is self-correcting with intake reduction;
- Strong interaction of Vitamin K for persons taking anticoagulant drugs;
- Diarrhea and related gastrointestinal adverse effects for persons taking very high intakes (over 2,000 mg per day) of Vitamin C;
- A flushing reaction to Niacin in its form as Nicotinic Acid;
- Mild to moderate (but easily reversible) diarrhea resulting from nonfood magnesium intakes at levels above 400 mg per day; Larger quantities of potassium as potassium chloride can produce gastrointestinal effects, especially on an empty stomach;
- Low frequency of mild gastrointestinal effects from Iron that are not pathological and are self-limiting due to consumer awareness (Hathcock).

One of the only available sources of data regarding vitamin and mineral safety is from the Poison Control Center TESS database. These data provide a single view of adverse

reactions, i.e., those incidents where an individual has reached the point of severe distress, without scientific or objective explanations behind the incidents. To this extent, the data are somewhat limited and incomplete. However, it is one data set that provides some insight into the safety of dietary supplements.

### ***Poison Control Center TESS Data***

The 2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS) (Watson, et. al.) tracks and summarizes calls made to poison control centers around the country for all types of potential poisonings, from adhesives and industrial cleaners to venomous insect bites. The report compiles exposures in the categories of vitamins and minerals, for herbal and botanical products, as well as for pharmaceutical products. The following summarizes the data for 2002.

Of the 64 reporting centers, 63 submitted data for the entire year, representing nearly 292 million people in 49 states, the District of Columbia and Puerto Rico; approximately 99.8% of the total population in these areas. Only North Dakota is not represented. A total of 2.38 million human poison exposures were reported by TESS in 2002.

The table below outlines the TESS data for Vitamins and Minerals for 2002.

<b><i>Vitamin and Mineral Exposures 2002</i></b>			
Number of Exposures	Total Number Of Adverse Outcomes	Number Of Deaths	Percentage of Deaths To Total Exposures
76,600	6,130	7	0.009%

Total number of adverse outcomes included all possible outcomes of exposure for those who called the Poison Control Center. These outcomes ranged from *minor effect*, which meant that the patient developed some signs or symptoms as a result of the exposure; to *major effect*, where the patient exhibited signs or symptoms as a result of the exposure

that were life-threatening or resulted in significant residual disability or disfigurement. For the vitamin/mineral category, only 133 of the 6,130 adverse outcomes were classified as having a *major effect*, approximately 2% of all adverse outcomes reported. This means that out of the 76,600 reports in this category, **0.17%, or less than two-tenths of 1%** of all exposures resulted in a serious health issue. The total number of deaths in this category included 4 deaths due to the mineral iron, 1 death from a multi-vitamin with iron overdose, 1 due to the mineral potassium, and 1 death from exposure to Vitamin E. Also notable was that over 17,000 of those who reported an exposure to a vitamin or mineral to the Poison Control Center *developed no signs or symptoms* as a result of the exposure whatsoever.

## **Herbal/Botanical Supplements**

The action of botanicals ranges from mild to powerful (potent). A botanical with mild action may have subtle effects. Chamomile and peppermint, both mild botanicals for example, are usually taken as teas to aid digestion and are generally considered safe for self-administration. Some mild botanicals may have to be taken for weeks or months before their full effects are achieved. For example, valerian may be effective as a sleep aid after 14 days of use but it is rarely effective after just one dose. In contrast a more powerful botanical produces a faster result. Kava, as one example, is reported to have an immediate and powerful action, reducing anxiety and improving muscle relaxation.

The most well-known powerful herb is Chinese Ma Huang or Ephedra. Ephedra is a special botanical that requires more discussion.

Ephedrine, the active alkaloid in *Ephedra sinica*, was first isolated from the Chinese herb Ephedra and characterized by a Japanese chemist, N.M. Nagai in 1887. Following a series of papers on the pharmacological properties of ephedrine published in 1924 by K.K. Chen and C.F. Schmidt of the Peking Union Medical College (Tyler), the Eli Lilly Company began marketing ephedrine to the West as a therapy for asthma, and a stimulant to the central nervous system (Griggs). Thus, Ephedra was the first Chinese herbal remedy to yield a synthetic active constituent, ephedrine, which was later widely used in traditional Western medicine (Tyler). In 1927, ephedrine was admitted as a standard

drug by the American Medical Association, and was synthesized in the laboratory. In the 1950's the pronounced side effects of ephedrine, namely increased blood pressure and heart palpitations, led the pharmaceutical companies to largely switch to pseudoephedrine, a close analog. The leaves and stems of *Ephedra sinica* contain many potentially active compounds but it is the protoalkaloids (ephedrine, pseudoephedrine, norpseudoephedrine) which have been isolated and used for their particular medical properties as asthma and cough medications (Chevallier).

Today, many over-the-counter cough suppressant, antiasthmatic and decongestant medications contain pseudoephedrine. Most Americans are probably familiar with brands names such as Dimetapp, Drixoral, Triaminic, and Sudafed which all contain pseudoephedrine salts (Zurich). Pseudoephedrine is often combined with antihistamines or codeine to further reduce nasal secretions and suppress cough (AVM). Generally these decongestants are ingested as tablets or cough syrups. Though most of the pharmaceutical industry switched to pseudoephedrine in the 1950s, ephedrine is still used in some antiasthmatic medications.

Controversy surrounding the botanical Ephedra has driven the issue of dietary supplement safety. Under the terms of the Dietary Supplement Health and Education Act (DSHEA), Ephedra the botanical had been allowed to be used as a dietary supplement, and ephedrine the synthetic drug derived from Ephedra is allowed to be used in pharmaceuticals. Ephedrine is not allowed for use as a dietary supplement since DSHEA prohibits OTC drugs to be sold as dietary supplements. From the FDA's request for information about Ephedra-associated health risks, the agency gathered and thoroughly reviewed all evidence on Ephedra's pharmacology: peer-reviewed scientific literature, adverse event reports, and tens of thousands of public comments. Some dietary supplements had been found to be adulterated with ephedrine and determined, based on this comprehensive review, to remove Ephedra from the marketplace. On February 6, 2004, the FDA acted under its power provided to it by DSHEA and issued its final ruling, prohibiting the sale of dietary supplements containing ephedrine alkaloids, or Ephedra, because of the potential for this herb to present an unreasonable risk of illness or injury (FDA).

Whether or not the adverse reactions attributed to Ephedra were caused by products adulterated with ephedrine is not clear. Even if the data are skewed by Ephedra adulterated with ephedrine, the incidence of adverse events is extremely low. A 2003 RAND report examined safety data on adverse events for Ephedra and ephedrine from clinical trials and case reports published in the literature, submitted to the FDA, and reported to Metabolife, a manufacturer of Ephedra-containing supplement products. Their conclusions were that the controlled trials studied relatively few people and in aggregate were insufficient to evaluate events with a risk of less than 1 per 1000. They also found that the majority of the case reports were insufficiently documented to make an informed judgment about the relationship between the use of ephedrine or Ephedra-containing dietary supplements and the adverse event in question (Shekelle, M.D., PhD., et. al.). The number of deaths reported in the TESS system for the botanical category including Ephedra products for 2002 was three; omitting Ephedra it was zero (Watson, et. al.).

Our interest, for the purpose of this paper, is to focus on the botanicals other than Ephedra, which represent the great majority of herbal products used by consumers in the U.S. today. Although there is no definitive list of toxic herbs vs. non-toxic botanicals and any product, whether natural or synthetic, may have toxic effects if taken to excess, the following chart provides examples of herbs in these two categories:

**Examples of Herbs**

<i>Common, Non-toxic Herbs</i>	<i>Common, Potentially Toxic Herbs</i>
<b>Feverfew</b>	<b>Belladonna</b>
<b>Chamomile</b>	<b>Chaparral</b>
<b>Echinacea</b>	<b>Coltsfoot</b>
<b>Milk Thistle</b>	<b>Comfrey</b>
<b>St. John's Wort</b>	<b>Ephedra (Ma Huang)</b>
<b>Ginkgo</b>	<b>Germander</b>

<b>Saw palmetto</b>	<b>Pennyroyal</b>
<b>Ginseng</b>	<b>Indian Snakeroot</b>
<b>Valerian</b>	<b>Yohimbe</b>
<b>Goldenseal</b>	<b>European Mistletoe</b>
<b>Ginger</b>	<b>Pokeroot</b>

*Source: O'Hara, et. al; Arch Fam Med 7 (1998): 523-536.*

- In general, Americans are turning to botanicals in greater numbers than ever before, the size of the market now reaching \$4.3 billion in 2002 (National Nutritional Foods Association). According to a survey published in early 1997 by Prevention magazine, approximately 60 million adult Americans – one-third of all adults – had used herbal supplements in 1996, spending an average of \$54 per person annually (American Botanical Council). Given these statistics, a review of safety for botanicals is extremely critical.

Dr. Stephen Straus of the National Center for Complementary and Alternative Medicine believes that herbal products present unique challenges to researchers as well as to medical professionals. Based on findings from early-phase trials, he feels that a few products are ready for larger trials and investigations and that further research is necessary and important due to the healing potential of these traditional products (Straus). Most scientists agree that the most effective way to demonstrate both the safety and the efficacy of both botanical and conventional remedies is through clinical trials.

### ***Clinical Trials***

Considerable attention has been paid to questioning the safety of botanical products sold as dietary supplements. There is a significant body of safety data from clinical reviews and trials associated with herbal supplements commonly taken by consumers. The following provides an overview of these trials for a few of the more commonly used botanicals taken by consumers.

St. John's wort extract, *Hypericum perforatum*, is a botanical that is used to treat depression. It has been approved as safe and effective by the German Commission E, a database that includes an assessment of the safety and efficacy of botanical products (American Botanical Council). A 1998 clinical research review on St. John's wort found 32 reports of side effects among a total of 3.8 million patients treated with St. John's wort extracts from 1991 to 1996 (Hippius). This represents an adverse events incidence of approximately one-one thousandth of a percent (0.001 percent), without a death or reported serious adverse illness. A meta-analysis of pooled data from 15 randomized, placebo controlled trials found a low incidence of side-effects with St. John's wort preparations that was actually lower than the incidence in the placebo groups. The percentage of patients reporting side effects from St. John's wort was 4.1%, versus 4.8% for placebo. Methodology of the trials was characterized as "reasonable to good (Linde, K. et. al.)." Another, more recent, review of St. John's wort clinical studies also found a low occurrence of side effects. A search of MEDLINE, EMBASE, PsychINFO and Cochrane Library databases identified 8 randomized double-blind trials of high methodological quality. Frequent laboratory monitoring of study subjects' blood chemistry, performed in 5 of the 8 trials, found no changes in complete blood count, liver function, or serum creatinine levels. This review concluded that "extracts of hypericum appear to be well-tolerated (Gaster and Holroyd)."

Ginkgo biloba is an extract that has been used extensively in European clinical trials. In Germany, ginkgo was ranked the #1 prescribed herb with sales reaching 280 million dollars in 1993. It is being used for a wide variety of ailments from senility, asthma and allergies, to tinnitus and fibromyalgia. It is also used as an anti-oxidant, to improve circulation, brain functions and memory. The seeds are said to possibly contain anti-cancer properties and are sedative and astringent. And it is safe. A review of adverse event reports associated with the use of ginkgo biloba extract (GBE) GBE from 1988 to 1998 stated that "tolerance was generally excellent (Defeudis)." A monograph published in the *Indian Journal of Hospital Pharmacy* notes that "few adverse effects have been reported with the use of GBE (Chavez and Chavez)." A review of GBE clinical trials published in the *Lancet* corroborates this conclusion, and states that "no serious side-

effects have been noted in any trial and, if present, side-effects were no different from those in patients treated with placebo (Keijnen and Knipchild).”

Echinacea is a native plant of the United States and many American Indian tribes have a history of using the herb for many problems ranging from the common cold to tooth problems. It is used in a variety of forms, including crude herb, teas, tinctures and solid extracts and is now one of the United States’ favorite herbs for its beneficial effects on the immune system. According to an assessment of the scientific evidence on herbal supplements published in *Alternative Therapies*, Echinacea has a favorable risk/benefit profile, based on a paucity of adverse effects (Barrett). Numerous clinical case reports record few adverse effects with the use of Echinacea, a finding that is corroborated by a large multi-centered clinical trial on 1,231 patients who took Echinacea lozenges three times a day for 4-6 weeks (Parnham). A review of clinical research on Echinacea examined data from five placebo-controlled, randomized studies with 134 subjects. Five different Echinacea preparations were used. No subjective side-effects were reported, and there were no effects of either Echinacea or placebo on blood pressure, heart rate or body temperature (Melchart et. al.). An open label trial on the use of Echinacea by more than 1000 patients found an extremely low incidence of adverse effects. Unpleasant taste was reported by 1.7 percent of subjects, while transient gastrointestinal upset was reported by 1.6 percent (Barrett, B. et. al).

The use of milk thistle seed, *Silybum marianum*, dates all the way back to the middle ages for removing obstructions from the liver to a preventative against all diseases. Today, milk thistle’s active property silymarin, is being studied for its ability of liver cells to regenerate through a vital bodily process known as protein synthesis. Milk thistle is also being used as a preventative herb, and may offer protection to the liver from alcohol and chemical abuse effects. It is widely used in Europe and is approved by the German Commission E, in both crude and extract forms. A recent meta-analysis of 14 randomized, placebo-controlled clinical trials on milk thistle found a low incidence of adverse effects that was “indistinguishable from placebo (Jacobs, et. al.)” A clinical trial review published by the Agency for Healthcare Research and Quality (AHRQ) also concluded that the incidence of adverse effects is “approximately equal in milk thistle and control groups (Anon., Evid Rep Technol Assess).” A review of 36 published papers on silymarin concluded that: “Silymarin has an excellent safety record and only rare

reports of gastrointestinal disturbances and allergic skin rashes have been published (Saller).” Drug monitoring studies on the use of silymarin on more than 3500 patients have found side-effects in 1% of patients, consisting mainly of mild gastrointestinal disturbances (Leng-Peschlow).

There are numerous other clinical studies that have been performed on the safety of botanical products. As with the previous research, results from these clinical studies reveal minimal safety concerns for those taking non-toxic, nutritive herbs.

***Poison Control Center TESS Data***

The following information summarizes TESS data on botanicals from the American Association of Poison Control Centers. This category represents several individual herbal ingredients, as well as multi-botanical formulations.

<b><i>Botanical Exposures 2002</i></b>			
Number of Exposures	Total Number Of Adverse Outcomes	Number Of Deaths	Percentage of Adverse Outcomes and Deaths To Total Exposures
15,187	5,312	3	35%

In this category, over 10,300 of the 15,000 or 69% of exposures that were reported by TESS involved Ephedra, either as a single exposure or as a multi-botanical blend. If Ephedra is removed from the data, the safety record for botanical dietary supplements is remarkably good. The following the safety tables reflect this change.

<b><i>Botanical Exposures, Excluding Ephedra products 2002</i></b>			
Number of Exposures	Total Number Of Adverse	Number Of	Percentage of Adverse Outcomes and Deaths

	Outcomes	Deaths	To Total Exposures
4,861	998	0	20%

The data now reveal that the total number of exposures from non-Ephedra botanical products is significantly smaller, less than 5,000 or only 35% of the total number of botanical exposures. The total number of *major effects* for these products is 40 or 0.82%, less than 1% of total exposures. Most important, the **number of deaths from non-Ephedra herbal supplements is zero.**

Given these statistics, and considering the extremely low incidence of adverse reactions, in particular fatal exposures, to herbal products, the relative safety of this category of dietary supplements is remarkably high.

We would like to make special mention of herbal or phytomedicine in Germany. In 1970 an estimated 52 percent of the general public in Germany used herbal remedies. That number had grown in 1993 to about 62 percent and to 65 percent in 1997. In fact, phytomedicines comprise about 30 percent of all “drugs” sold in German pharmacies (American Botanical Council). A key force behind mainstream acceptance of phytomedicine in Germany is the inclusion of coursework regarding herbal therapies in the medical and pharmacy school curricula. They do not perceive, as we do in the U.S., herbal therapies as alternative medicines, but rather part of so-called “traditional” medicine. Since 1993, all medical school students in Germany must successfully complete a portion of their board examinations in the area of phytotherapy as a precondition for practicing medicine. And, as one may expect, the high level of professional interest in herbs and phytomedicines in Germany has resulted in a considerable amount of scientific research. The Ministry of Health in Germany established the Commission E, a committee of doctors, pharmacists, scientists and herbalists to evaluate the safety, quality, and efficacy of herbs (Valli and Giardina). This commission approves new remedies and publishes monographs with recommendations on dose, indications, and contraindications.

Clearly, from the widespread study and usage of phytotherapies in Germany, as well as long-established, successful traditions of herbal therapies in countries like China and India, the safety of herbs is gaining ground.

### ***Safety of Prescription and Over-The-Counter Medications***

People commonly use dietary supplements as a natural way to ward off the negative potentialities of dietary deficiencies, or to boost their defenses against exposures that create free radicals in the body such as cigarette smoking and environmental toxins. There is a growing body of scientific evidence documenting the health benefits of dietary supplements for protection against the negative effects of a toxic environment.

Pharmaceuticals are typically taken once a person becomes unwell, and is suffering an injury, illness or disease. Some believe that dietary supplements should fall under the same legislative standards of approval as those for conventional drugs. Taking this thinking to the next step, we focus this section of our paper on the relative safety of conventional medicines and consider whether or not applying this logic to dietary supplements is appropriate, or if such standards necessarily result in safer products.

Pharmaceutical products come with instructions on proper usage. Individuals can choose to follow the instructions or not, regardless of whether they have acquired the product through prescription via a medical professional or off the shelf, as they can with OTC medications and with many dietary supplements. Earlier in this document, a thorough review of adverse events associated with dietary supplements was provided and it was determined that such reactions are rare, whether or not the consumer followed proper instructions. The key exception in the supplement category was Ephedra. Once Ephedra products are removed from the safety equation, adverse events from other dietary supplements are barely a blip on the radar screen. How do pharmaceutical products fare under the same type of scrutiny?

The standard way of discussing the safety of pharmaceutical products is through a review of adverse drug events (ADEs) or adverse drug reactions (ADRs). Reasons behind ADE's can be categorized in a number of ways. Some of the more common ones are listed below:

- ADE due to medical errors at any stage of the ordering, transcribing, dispensing, administering or monitoring of medication;
- ADE due to misuse by an individual, i.e. accidental overdosing;
- ADE due to intentional overdosing, i.e. recreation or attempted suicide;
- ADE due to allergic reaction to the medication;
- ADE due to interactions between multiple drugs.

This paper will touch on many of these ADE categories throughout this section. Most important to keep in mind, however, is that the purpose of this document is to determine whether or not the government standards of safety that exist for pharmaceuticals are effectively protecting people from their pharmacological effects and if it would be beneficial to impose drug regulatory standards on dietary supplements.

Pharmaceutical manufacturers are discovering new ways to treat more diseases and conditions. The FDA is now approving products at a record-setting pace, and the potential for adverse reactions continues to grow. Dr. Karen E. Lasser of Harvard Medical School, Boston, and her associates found that of 548 drugs approved by the FDA between 1975 and 1999, serious adverse drug reactions (ADRs) were noted in more than 10% of them *after* they had been publicly marketed (Lasser). With so many new drugs being introduced into the market, as many as a dozen medications are currently available for any one ailment, and it is difficult for pharmacists, doctors, or consumers to stay abreast of FDA warnings of potential risks (Stolberg).

In 1998, a study published in the *Journal of the American Medical Association (JAMA)* estimated that 106,000 people died from an adverse drug reaction, ranking ADRs between the 4<sup>th</sup> to 6<sup>th</sup> leading cause of death in the U.S (Lazarou). Summarizing studies from multiple medical journals and studies, McDonnell reports that ADRs occur in anywhere from 5-20% of all hospitalized patients, and that they cause between 3-28% of all hospital admissions (McDonnell).

One population that is currently at great risk of ADEs is the elderly. Harvard Medical School's associate professor of medicine, David Bates, states "Almost 40 percent of the elderly in this country take five or more different medicines a week, and what we found is that there are about 50 adverse drug events for every 1,000 people each year." In their study of 30,000 Medicare enrollees, researchers identified 1,523 adverse drug events, with 38 percent of these considered serious, life threatening or fatal (Harvard Gazette, 2003).

Side effects can also result in significant harm to individuals, but have even less visibility to the general population than adverse drug reactions. For example, new antipsychotic medications have side effects such as serious cases of Type I and Type II diabetes and hyperglycemia that have been reported in adults and some children (Goode). Statins, known for their ability to prevent deaths from heart attacks by lowering cholesterol, may cause rhabdomyolysis, a debilitating and deadly disorder if not detected in its early stages. In August 2001, Bayer voluntarily recalled cerivastatin, marketed as Baycol, after 31 people died from rhabdomyolysis caused by the drug. (Brody).

Finally, there is the problem of intentional abuse of prescription drugs. Abuse of prescription drugs is rising rapidly in the United States. Data released by the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2003 show that in 2001 almost three million youth aged 12 to 17 had used prescription medications non-medically in their lifetimes (SAMHSA). Commonly abused drugs included prescription pain relievers, stimulants, and tranquilizers. A prime example of prescription drug abuse is that of OxyContin. Since arriving on the market in 1996, OxyContin has become one of the most commonly prescribed narcotics for treating pain, whose effect is a euphoria that many drug experts say is equal to that produced by heroin (Janofsky). OxyContin became widely abused after people discovered ways to use it for this heroin-like high. But the high came at the cost of addiction, and in hundreds of cases it contributed to death (Ives). John Jenkins, M.D., Director of the FDA's Office of New Drugs warned that mixing pain relievers with other drugs or with alcohol can lead to death (Jenkins).

## Research Studies

There is a growing amount of research that has been done to suggest that adverse drug events in hospitals regularly occur, and result in substantial harm and death. We provide a summary of a just a few of these studies below:

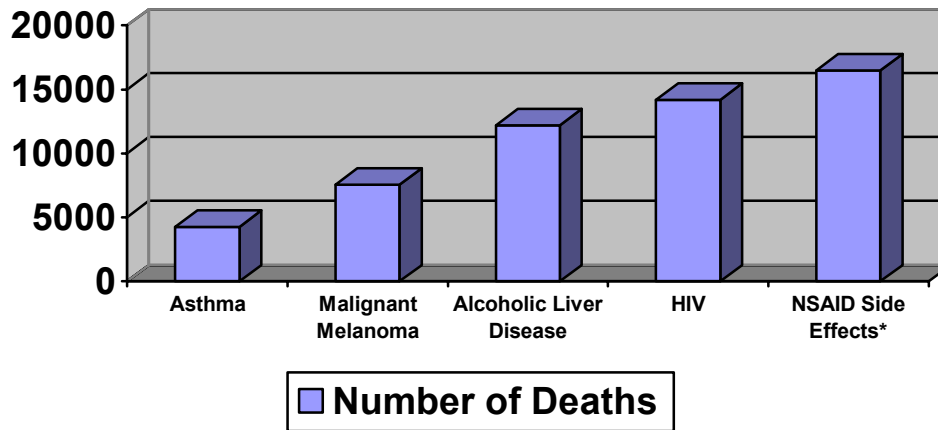
- Results of a study of over 4,000 adult admissions in two different hospitals over a 6-month period revealed 247 ADEs and 194 potential ADEs with 1% of resulting in death, 12% considered to be life-threatening, 30% serious and 57% significant. Of the life-threatening and serious ADEs, 42% were judged preventable. The conclusions reached in this study are that *adverse drug events are common and often preventable* (Bates and Cullen, et. al.).
- In the Harvard Medical Practice Study, 30,000 inpatient hospitalizations were intensively reviewed to ascertain the occurrence of adverse events at several New York state hospitals. This study concluded that at least 3.7% of all hospitalized patients developed a serious, disabling, and clinically important adverse event, of which nearly 20% were drug-related (Leape).
- A 1997 article in *JAMA* also studied mortality attributed to adverse drug events in hospitalized patients. Not only did those suffering from ADEs experience a significantly prolonged length of stay and increased economic burden, but, more frightening, an almost two-fold increased risk of death (Classen).
- In an exhaustive review of literature, it was found that the incidences of ADEs affected between nearly 1% and 6.5% of hospitalized patients, with nearly 57% of these events determined to be preventable. Researchers found that drug-related errors are the most common single cause of medical errors leading to over 7,000 deaths in the U.S. (von Laue, et. al.).

From this information, it is clear that conventional medications, when administered improperly – even under the watchful eye of medical professionals in hospitals – are powerful products that can result in injury and death.

But what about medications taken by individuals on a day-to-day basis to relieve symptoms from common maladies? Several important journal articles provide in-depth analysis of this problem.

- In a 2002 article in the *Archives of Internal Medicine*, researchers concluded that the use of NSAIDs other than aspirin (e.g. ibuprofen, naproxen), and acetaminophen was *significantly associated with increased risk of high blood pressure*. They believe that a substantial proportion of hypertension in the U.S., and the associated morbidity and mortality, may be due to the use of these medications (Curhan).
- Dr. Gurkirpal Singh, in a 1998 study submitted to the *American Journal of Medicine*, estimated that a minimum of 16,500 arthritis patients die each year for NSAID-related GI complications and approximately 107,000 patients are hospitalized due to NSAIDs (Singh and Wolfe). To put this in perspective, NSAIDs cause more than half as many deaths as prostate cancer, and almost as many deaths as asthma, cervical cancer, and malignant melanoma combined (National Center for Health Statistics).

## Number of Deaths in the United States, 2001



Source: National Center for Health Statistics; \* NSAID Side Effects data from Singh

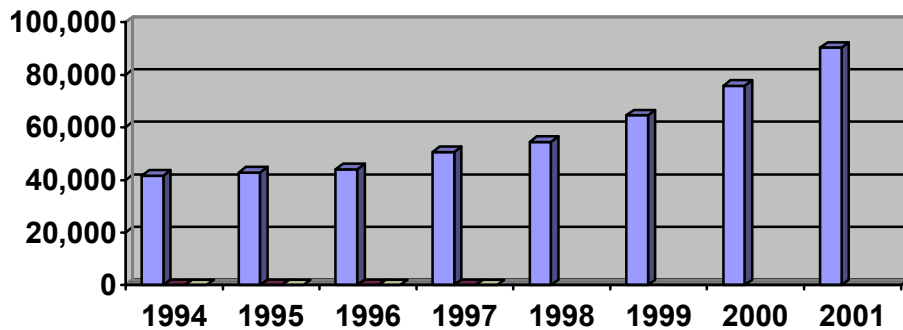
- In 2002, researchers studied whether or not the effects of OTC NSAIDs, presumably lower dosage than prescription NSAIDs, are safer than those prescribed by a health care practitioner. They discovered that users of OTC NSAIDs reported significantly more GI side effects than non-users, with the rate of self-reported GI symptoms (about 20%) among OTC NSAID users not substantially different from that reported by prescription NSAID users. They concluded that lower doses of OTC NSAIDs do not seem to lead to substantially lower rates of GI symptoms (Thomas).

### Drug Abuse Warning Network (DAWN), 2002

DAWN is an ongoing, national surveillance system that is operated by the Office of Applied Studies of the Substance Abuse and Mental Health Services Administration, under the auspices of the United States Department of Health and Human Services. This network collects data on drug-related visits to emergency departments from a national sample of hospitals, as well as compiling data on drug abuse deaths from participating medical examiners and coroners.

The following chart highlights the trends in narcotic analgesic related ED visits from 1994-2001.

**Trends in narcotic analgesic-related ED visits  
1994-2001**



Source: DAWN

As shown in the above chart, the incidence of emergency department (ED) visits related to narcotic analgesic abuse has more than doubled between 1994 and 2001. More revealing, however, are the statistics relative to the specific drugs involved. DAWN reports that ED visits due to oxycodone increased over 350% during this time, and that ED visits caused by hydrocodone increase by 131%. *Dependence* was the most frequently mentioned motive for narcotic analgesic abuse cases, followed by suicide and psychic effects.

### TESS Data

Once again, we turn our attention to the TESS report from the Poison Control Center, this time for pharmaceuticals. The following table highlights the exposures, adverse outcomes, and deaths reported by TESS for commonly used prescription and over-the-counter medications.

<i>Pharmaceutical and OTC Products 2002</i>				
Class of Medication	Number of	Total Number	Number Of	Percentage of Adverse Outcomes and

	Exposures	Of Adverse Outcomes	Deaths	Deaths To Total Exposures
Analgesics	256,843	66,472	659	26%
Antidepressants	99,860	45,772	318	46%
Cardiovascular Drugs	61,056	13,833	181	23%
Cold and Cough Medicines	100,612	19,603	22	19.5%
Gastrointestinal Preparations	53,165	5,367	16	10%
Sedatives/ Antipsychotics	111,001	59,889	364	54%
Antihistamines	69,107	17,010	71	25%
Muscle Relaxants	20,016	10,393	52	52%

From the data provided above, as well as deaths from other pharmaceuticals not listed, the total number of adverse outcomes for this category was over 300,000, or nearly 27% of all exposures. In the 2002 Poison Control Center data, nearly 1,900 people died from exposure to pharmaceutical drugs.

The following chart shows the categories with largest numbers of deaths, by ranking.

### **Total Deaths by Category Reported by the Poison Control Center**

<i>Overall Ranking</i>	<i>Category</i>	<i>Number of Deaths</i>
1	Analgesics	659

2	Sedative/hypnotics/psychotics	364
3	Antidepressants	318
5	Cardiovascular drugs	181
7	Antihistamines	71
9	Muscle Relaxants	52
15	Cough and cold preparations	22

### ***Relative Safety of Dietary Supplements vs. Prescription and OTC Drugs***

There are no comprehensive databases that include numbers of adverse events due to both dietary supplements and pharmaceuticals with the exception of the TESS report from the Poison Control Center. While the Poison Control Center data are less than ideal for such a comparison due to its inadequacies described earlier, it does compare apples to apples, across the same population and uses the same criteria for evaluating and categorizing exposures to these products. In the absence of any other objective data source, we can use TESS to gain some general understanding of how the two categories compare.

<b><i>Category</i></b>	<b><i>Number of Exposures</i></b>	<b><i>Adverse Outcomes</i></b>	<b><i>Number of Deaths</i></b>	<b><i>Percent of Adverse Outcomes and Deaths to total Exposures</i></b>

Pharmaceutical Drugs	1,132,631	301,524	1,877	27%
Vitamins, Minerals and Botanicals (excluding Ephedra products)	81,461	7,128	7	9%

As can be seen by the above table, exposures to dietary supplements were far less dangerous than exposures to pharmaceutical drugs in the reported 2002 TESS data. In fact, including dietary supplements with Ephedra products, *over 65 times as many people died from analgesics alone*, compared to the **total** category of dietary supplements. By comparison, nearly 5 times more people died due to exposures from household cleaning substances (32), over twice as many died from pesticide exposures (18), and nearly the same number perished from insect bites (6) as those who died from dietary supplements.

### ***Putting It All In Perspective***

We return once again to the question of dietary supplement safety. The previous research provides a compelling case on the comparative safety of dietary supplements versus pharmaceuticals. Yet, there is another perspective on this subject: the relative risk of mortality from taking dietary supplements, vs. the risk of other causes of death – especially people with diseases that could benefit from through the use of supplements.

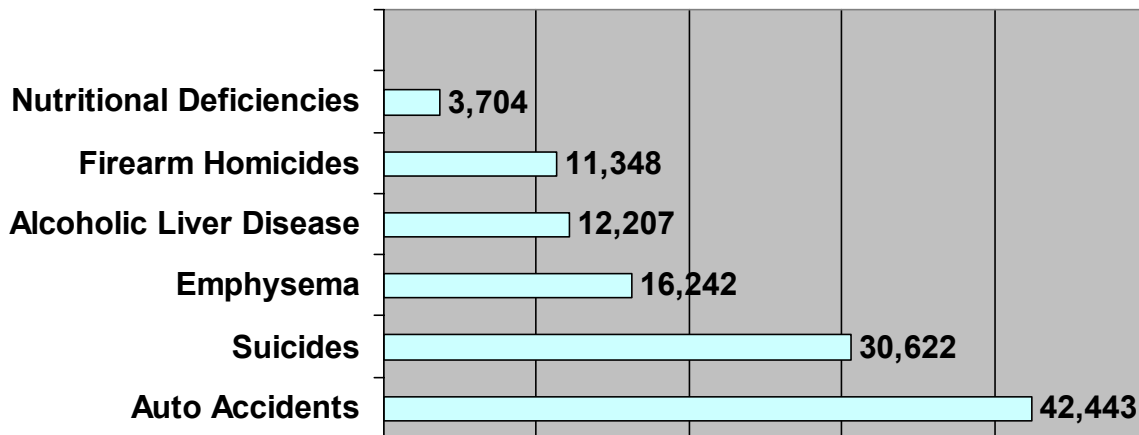
The number of deaths due to the ingestion of dietary supplements – or even for pharmaceutical products – is very difficult to obtain. The only accurate and consistent mortality data comes from National Vital Statistic Reports compiled from CDC data. As the lead federal agency for protecting the health and safety of people, CDC compiles statistical information working with partners throughout the health community collecting data from birth and death records, medical records, interview surveys, and through direct

physical exams and laboratory testing. Their published reports are comprehensive and extremely valuable, yet only provide a summary view of deaths due to all types of poisoning, which covers many different kinds of products, including dietary supplements and pharmaceuticals.

What stands out for us, however, is that relatively few journal articles, research studies, or even news media stories have been written to highlight side effects, adverse drug events, or even deaths from dietary supplements, with the exception of studies on the now-unavailable Ephedra products. Conversely, the data on the harmful effects of both prescription and OTC drugs was abundant. From the lack of such evidence, we can only conclude that the dearth of information on the hazards of dietary supplements speaks volumes about their safety.

The following information from the CDC's National Vital Statistics Reports for the year 2001 is shown below to provide some relative insight into what we are finding to be greater causes of harm to human life than the consumption of dietary supplements.

### Number of Deaths in the U.S 2001



*Source: National Center for Health Statistics*

Comparing the data from the CDC's National Vital Statistics Reports for 2001, to our data from articles cited earlier in the document brings to light a very different picture of

relative safety. These statistics tell a shocking story. While we realize that the data sources and timeframes differ, and that, for the most part, our numbers for adverse events is not exact, it does provide some framework for us to consider as we discuss overall threats to life and limb in the U.S.:

<i>Type of Incident</i>	<i>Number of Deaths</i>
Dietary Supplement Deaths	10
Fireworks	13
Shark injuries	18
Hornets, wasps and bees	46
Lightning	63
Bathtub Accidents	337
Foods	5,000
Firearm Homicides	11,348
NSAID-related Deaths	16,500
Auto Accidents	42,443
Deaths from Adverse Drug Reactions	106,000

*Sources: American Association of Poison Control Centers, CDC, Mead, Singh, Lazarou, Sims.*

If we take this information another step further, we can compare, too, the harmful effects of major disease to the risk of dietary supplement consumption. For example, results from the 1999-2000 National Health and Nutrition Examination Survey (NHANES) indicate that an estimated 64 percent of U.S. adults are either overweight or obese. It has been determined that by the National Institutes of Health that overweight and obese individuals are at increased risk for physical ailments such as:

- High blood pressure
- High blood cholesterol
- Type 2 (non-insulin dependent) diabetes
- Coronary heart disease
- Congestive heart failure

- Stroke
- Gallstones
- Gout
- Osteoarthritis
- Obstructive sleep apnea and respiratory problems
- Some types of cancer (such as endometrial, breast, prostate, and colon)
- Complications of pregnancy
- Poor female reproductive health (such as menstrual irregularities, infertility, irregular ovulation)
- Bladder control problems (such as stress incontinence)
- Psychological disorders (such as depression, eating disorders, distorted body image, and low self esteem) (National Center for Health Statistics).

Along with lifestyle changes, dietary supplementation has been successfully incorporated into long-term, effective weight-loss programs. Assessing the low potential for risk and high potential for benefit through the use of dietary supplements against the greater potential for disease and death due to overweight conditions seems worthy of much more study.

## **Efficacy of Dietary Supplements**

The data on the health benefits of using dietary supplements are becoming more widely available, driving medical professionals and researchers to take a look at these products in a new light.

Congress demonstrated its interest in the health benefits associated with dietary supplements in 1991 by pressuring the National Institutes of Health to increase its budget for studies of alternative medicines, setting aside \$2 million to establish an Office of Alternative Medicine (Stolberg). The establishment of this office was driven by the actions of Senator Tom Harkin after seeing amazing results for a friend of his, Representative Berkley Bedell of Iowa, who was successfully cured after utilizing an alternative approach to treat a bout with Lyme disease and prostate cancer. Today, the office is called the National Center for Complementary and Alternative Medicine, with a projected budget in 2004 of nearly \$118 million dollars and 76 full-time employees. NCCAM's primary responsibility is to conduct and support clinical research studies of entire systems of both traditional and indigenous medicine, including studies of botanicals that are used by the American public to treat many diseases, such as arthritis, cancer, and depression (National Center for Complementary and Alternative Medicine).

All of these forces have converged, and are now providing the momentum for researchers to begin trials and clinical studies in the areas of vitamins, minerals, and phytonutrients.

### ***Benefits of Dietary Supplements Highlighted in Popular Publications***

The popular press has begun to provide results of studies to the general public regarding the efficacy of dietary supplements. These articles have been key drivers for the growing numbers who are looking at less expensive, more natural alternatives to traditional medicines to treat common ailments.

In a May 13, 2004 article published in the *San Diego-Tribune* by Linda Johnson of the Associated Press, findings from two studies on the impact of B vitamins were reported, one conducted in Holland and the other in the U.S. The results not only support doctors' recommendations that people consume folic acid and other B vitamins to prevent severe birth defects and heart attacks, but ultimately conclude that these vitamins may also ward off broken bones from osteoporosis. Dr. Douglas P. Kiel, senior author of the U.S. study suggested that taking a standard multivitamin once a day would be beneficial in lowering people's levels of homocysteine, an amino acid already linked to an increased risk of heart attacks, strokes, Alzheimer's disease, and now osteoporosis-related fractures (Johnson).

World Health Agencies are now embracing an herb called artemisinin, a compound based on the Chinese herb known as qinghaosu, or sweet wormwood, which was isolated by Chinese military researchers in 1965 to treat malaria. Artemisinin has proven to be strikingly effective against malaria in poor countries, which causes about 300 million illnesses a year, and at least 1 million deaths. Because quinine derivatives are now evolving into resistant strains, the new Global Fund for AIDS, Tuberculosis and Malaria is providing grants to 11 countries to purchase this herbal extract, and is asking 34 others to switch from the older drugs to artemisinin (McNeil).

A new study of Vitamin E and its link to reducing bladder cancer, which kills about 12,500 Americans annually, was funded by the state of Texas. The study was based on questionnaires of the eating habits of about 1,000 Houston residents, and saw demonstrable reductions in the incidence of bladder cancer for those consuming higher quantities of Vitamin E, both from food sources as well as from dietary supplements. Both studies encouraged the proper intake of dietary sources of antioxidants from foods such as fruits, vegetables and nuts as a first line of defense (Haney). Unfortunately, as was revealed earlier in this document, relatively few individuals consume adequate amounts of foods to meet even the minimum requirements for these nutrients, bolstering the case for incorporating nutritional supplements into one's daily diet.

An article in the January 15, 2004 issue of the *Harvard Gazette* describes exciting results from a study done by researchers at the Harvard School of Public Health, utilizing

surveys from more than 185,000 women from the Brigham and Women's-based Nurses' Health Study, and Nurses' Health Study II. Their results revealed that women taking a vitamin D supplement of 400 IU per day or more had a reduced risk for developing multiple sclerosis. They also discovered that there was *no reduction in risk associated with vitamin D intake through food alone* (Harvard Gazette).

Barbara Saffir, in an article published in the *Washington Post*, reports that the military is now testing nutrient supplements in the form of lozenges and transdermal patches, as part of a Defense Department plan to use naturally occurring nutrients to increase stamina and alertness. They are studying caffeine for its stimulant capabilities, as well as compounds from echinacea and from turmeric spice plants which possess anti-inflammatory qualities and have fewer side effects than NSAIDs (Saffir). The use of turmeric has been demonstrated to have significant antioxidant and anti-inflammatory effects in both laboratory and actual human clinical studies (Vukovic).

Officials at the National Institute of Neurological Disorders and Stroke reported on some very promising research linking a naturally occurring antioxidant, coenzyme Q10 (CoQ10), to combat Parkinson's disease. They found that those people who were taking the highest daily dose of CoQ10, compared to those on placebo or lower doses, had less decline in motor and mental functions, and showed great benefit in their day-to-day activities, such as dressing, bathing, and eating. Currently, people with Parkinson's take prescription drugs at a cost of about \$2,000 yearly and while these medications control some of the symptoms, they do not slow the neurological damage done by the disease (Packer-Tursman).

Results from a study published in the May 1998 *Harvard Gazette* revealed that HIV-positive pregnant women in Tanzania who were given vitamin supplements showed a 40 percent reduction in fetal deaths, low birth weight, and severe pre-term births. They also discovered that the immune status of the mothers was significantly improved by taking daily doses of multivitamins, as was seen by significant increases in blood cells called lymphocytes which bolster the immune system against infection (Harvard Gazette).

## ***Benefits of Dietary Supplements Highlighted in Clinical Trials***

The following pages highlight a number of clinical trials that have been conducted in an attempt to determine the efficacy of dietary supplements. The actual number of clinical trials on dietary supplements has grown to be quite large. This section highlights the major findings from several of these studies, and provides references at the end of this paper for those wishing to obtain greater detail on this research.

<b><i>Name of Study</i></b>	<b><i>Objective</i></b>	<b><i>Results</i></b>
Vitamin C and Risk of Coronary Heart Disease in Women (Osganian, et. al.)	To examine the relation between vitamin C intake and risk of coronary heart disease (CHD) in women.	Researchers observed a modest significant inverse association between total intake of vitamin C and risk of CHD, concluding that users of <i>vitamin C supplements</i> appear to be at lower risk for CHD.

<b><i>Name of Study</i></b>	<b><i>Objective</i></b>	<b><i>Results</i></b>
Vitamin E Supplementation and In Vivo Immune Response in Healthy Elderly Subjects (Meydani, et. al.)	To determine whether long-term vitamin E supplementation enhances in vivo, clinically relevant measures of cell-mediated immunity in healthy elderly subjects.	<ul style="list-style-type: none"> <li>• A level of vitamin E greater than currently recommended enhances certain clinically relevant in vivo indexes of T-cell-mediated function in healthy elderly adults.</li> <li>• No adverse effects</li> </ul>

		were observed with vitamin E supplementation.
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<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
Effects of Selenium Supplementation for Cancer Prevention in Patients with Carcinoma of the Skin (Clark, et. al.)	To determine whether a nutritional supplementation will decrease the incidence of cancer.	Supplemental selenium may reduce the incidence of, and mortality from, carcinomas of several sites.

<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
Prospective Study of Calcium, Potassium, and Magnesium Intake and Risk of Stroke in Women (Iso, et. al.)	To study the intakes of these minerals in relation to risk of stroke.	Low calcium intake, and perhaps low potassium intake, may contribute to increased risk of ischemic stroke in middle-aged American women.

<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
Effect of a Multivitamin and mineral Supplement on Infection and Quality of	To determine the effect of a daily multivitamin and mineral supplement on	<ul style="list-style-type: none"> <li>• Participants with type 2 diabetes taking multivitamin and</li> </ul>

Life (Barringer, et. al.)	infection and well-being.	<p>mineral supplements reported fewer days absent from work than participants taking a placebo;</p> <ul style="list-style-type: none"> <li>• Multivitamin and mineral supplements appear to reduce infections in people with type 2 diabetes mellitus, a group at risk for micronutrient deficiency.</li> </ul>
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<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women (Feskanich, et. al.)	To assess relations between postmenopausal hip fracture risk and calcium, vitamin D and milk consumption.	<ul style="list-style-type: none"> <li>• Women consuming more than 1250 mg of vitamin D from food plus supplements had a 37% lower risk of hip fracture than those consuming less than 350 mg;</li> <li>• Neither milk nor a high-calcium diet appears to reduce risk; <i>researchers recommend supplement use or dark fish</i></li> </ul>

		consumption.
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<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
Summary of a systematic review on oral nutritional supplement use in the community (Stratton).	To determine the value of oral nutritional supplements (ONS) in patients with different diseases, using a review of 84 trials.	<ul style="list-style-type: none"> <li>• ONS produce demonstrable clinical and functional benefits, with the nature and extent of these benefits varying with the underlying chronic condition.</li> </ul>

<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
The Influence of Folate and Multivitamin Use on the Familial Risk of Colon Cancer in Women (Fuchs, et. al.)	To estimate the relative risk of colon cancer according to a history of colorectal cancer in a first-degree relative and categories of folate, methionine (an essential amino acid), and alcohol intake in women.	<ul style="list-style-type: none"> <li>• The influence of family history was markedly diminished by use of multivitamins containing folic acid. High levels of dietary methionine also reduced the effect of family history.</li> </ul>

<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
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<p>St. John's Wort for Depression (Gaster and Holroyd)</p>	<p>Eight randomized, controlled, double-blind trials were reviewed on the pharmacology, cost, regulation, and safety of St. John's Wort in its use for depression.</p>	<ul style="list-style-type: none"> <li>• St. John's wort is more effective than placebo in the treatment of mild to moderate depression, having an increased response rate of 23-55% higher than those taking placebo;</li> <li>• Rates of side effects for those taking St. John's wort were low.</li> </ul>
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<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
<p>The effect of low-dose potassium supplementation on blood pressure in apparently healthy volunteers (Naismith and Braschi)</p>	<p>To evaluate the effect on blood pressure of a low-dose potassium supplementation for an extended period.</p>	<ul style="list-style-type: none"> <li>• After 6 weeks of supplementation, mean arterial pressure, systolic and diastolic blood pressure were all reduced;</li> <li>• A daily dietary supplement of potassium, equivalent to the content of five portions of fresh fruits and vegetables, induced a substantial reduction in mean arterial pressure.</li> </ul>

<i>Name of Study</i>	<i>Objective</i>	<i>Results</i>
Calcium Intake and Risk of Colon Cancer in Women and Men (Wu, et. al.)	To examine the association between calcium intake and colon cancer risk.	Higher calcium intake is associated with a reduced risk of distal colon cancer in both men and women.

Given the evidence from the above clinical studies as well as from thousands of others not listed, it is evident that dietary supplements offer significant health benefits to a large percentage of the population. The huge growth in the dietary supplement industry is understandable given the continuous flow of research documenting the health benefits of dietary supplements. Supplements are considered an integral part of a healthy lifestyle by the millions of Americans who use them. Overall, they have a safety record that is comparable to that of any food category and superior to that of drugs. There is no doubt that as long as they continue to be effective, low-cost, and safe alternatives, millions will derive health benefits from dietary supplements.

## Costs

Costs encompass many things, from the actual dollar outlay to the potential for emotional or physical costs associated with an adverse event. We will explore several of these components in this section.

### ***Dietary Supplements – Costs vs. Benefits***

The cost/benefit profile of dietary supplements is one of the factors that drives an individual's decision to purchase dietary supplements. One of the biggest challenges has been *quantifying* the actual cost effectiveness of dietary supplements. Researchers estimate that by increasing our intake of vitamins and minerals, we would significantly reduce health care costs. At this time, however, the actual dollar estimate of the potential benefits associated with dietary supplementation has not been determined.

A November 2003 article compared the dollar outlay for two popular pharmaceuticals, Ambien and Prozac®, to their supplement counterparts. Two dietary supplements that consumers often use instead of Ambien for promoting sound sleep are valerian and melatonin. The author determined that valerian costs an average of \$0.15 per tablet and melatonin \$0.12, both **less than 10%** of the cost of a single Ambien tablet. Prozac® is prescribed by physicians to treat depression. In the world of dietary supplements, St. John's wort and kava-kava are useful for maintaining a positive mood. A recommended daily intake of St. John's wort costs about \$0.22, and a single capsule of kava-kava averages \$0.24, roughly **one-quarter the cost** of the least expensive source of generic fluoxetine. The article concludes that “for health issues where dietary supplements are useful, the daily cost often runs from 10% to 25% of pharmaceutical alternatives (Snow).” Given earlier data which outlined the potential efficacy, and lack of risks in taking dietary supplements, in general we can conclude that the cost/benefit ratio of using these dietary supplements is very favorable.

The single most important scientific study of the cost effectiveness of daily multivitamins for older adults was prepared by Dr. Al Dobson, et. el. of The Lewin Group, Inc. They

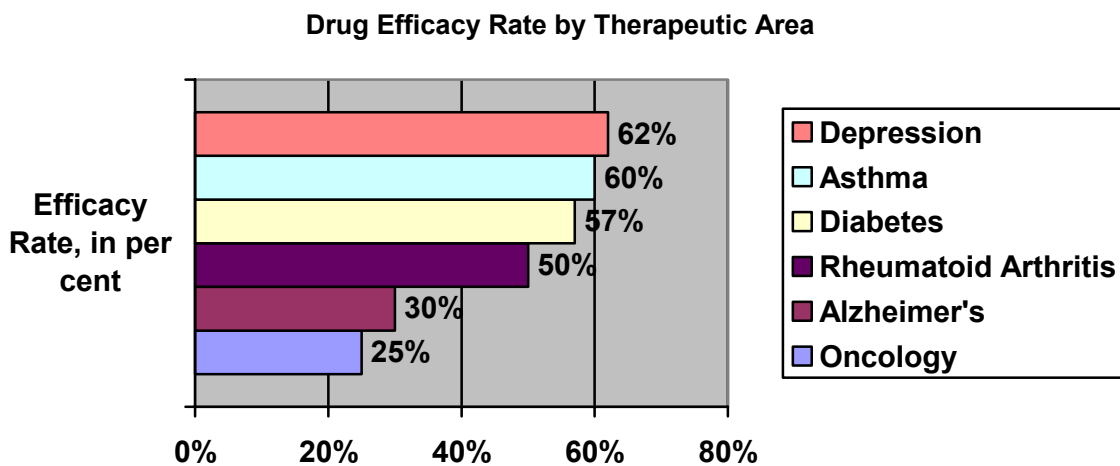
were commissioned by Wyeth Consumer Healthcare to attempt to establish some of the economic impacts of daily vitamin use by older adults. In an exhaustive literature review, researchers concluded that a daily multivitamin for the elderly is potentially associated with significant health benefits, and is nearly risk free. Specifically, they found that through providing older adults with a daily multivitamin, the potential savings over a five year period resulting from a reduction in the relative risk of coronary artery disease and improved immune functioning was approximately \$1.6 billion. In these estimates, The Lewin Group looked at costs savings as a result of the following factors:

- Avoidance of hospitalization for fatal and nonfatal heart attacks
- Avoidance of hospitalizations, nursing home stays, and home health services for infection

The study concluded that, from the perspective of a “payer” of health insurance, such as Medicare, or other health care service, encouraging older adults to use a daily multivitamin could be very cost effective. Generally speaking, seniors are at high risk for nutrient deficiencies, due to the fact that they consume more drugs than any other age group, their difficulties with nutrient absorption, and poor teeth. This, combined with extensive literature that demonstrates efficacy of vitamins is evidence enough that, in the elderly population, the benefits of taking multivitamins far outweigh the costs (Dobson, et. al.).

## Pharmaceuticals – Costs vs. Benefits

In a December 2003 article in *The Independent Digital*, science editor Steve Connor reports that a senior executive from drug giant GlaxoSmithKline (GSK) claimed “fewer than half of the patients prescribed some of the most expensive drugs actually derived any benefit from them.” In fact, many pharmaceutical products are ineffective in patients, often due to genetic susceptibilities to different medications (Connor). The following table is an example of the drug efficacy rate, from some of the more commonly used prescription drugs:



Source: Conner

For every equation on benefits, there is an important cost element to consider. Since their efficacy is less than ideal, we would expect that the overall costs of taking pharmaceuticals would be justified.

## Costs of Purchasing Prescription Drugs

Prescription drug expenditures continue to climb at a greater rate than other key expenses in the health care system, such as physician and clinical services, contributing greatly to the overall increases in healthcare expenditures in the U.S.

Between 1998 and 2000, prices for prescription drugs rose more than 3 times the inflation rate (AARP, Washington State Labor Council). In fact, it is expected that drug expenditures will continue to outpace all other medical service sectors over the next 10 years. The latest estimates for prescription drug spending are pointing to nearly \$460 billion by the year 2012, or a total of 17% of all personal health care spending. The overall average prescription price in 2000 was double that in 1990, from \$22.06 to \$45.79 (Kaiser Family Foundation, KFF).

For aging and low-income populations, these data are even more sobering. Consider these facts:

- Average annual growth for prescription drugs in the Medicaid program was **six times greater** than growth in acute health care from 1995-1998 (KFF);
- Seniors typically spend double the amount for prescription drugs than all other consumers, and nearly 3 times as much of their overall household spending as that of other consumers. The average out-of-pocket expense to all Medicare beneficiaries in 2002 was \$860 (AARP);
- It is estimated that overall spending on prescription drugs by and for Medicare beneficiaries will triple within the next 7 years, to nearly \$230 billion dollars (KFF);

What the data are telling us is quite simple: more people are taking more expensive medicines for a greater number of conditions than ever before. The financial costs to consumers show no signs of slowing any time soon.

## **Costs Associated with Adverse Drug Events**

The exact toll of adverse drug events on individuals is difficult to quantify, in part because there are so many elements to consider. How can we begin to estimate the cost of a preventable death? For those who do not survive, the emotional cost to their surviving families and friends is inestimable. Patients who experience a long hospital stay or disability as a result of these errors suffer greatly in both physical and psychological discomfort. Attempting to estimate the ripple effect from lost work or lost education from school attendance is futile at best. Some estimates put the figure at somewhere between \$17 and \$29 billion per year, including the expense of additional care caused by ADEs, as well as lost income and household productivity and disability. One-half of these costs can be attributed to healthcare (Institute of Medicine).

A study published in the *Journal of the American Medical Association* by Classen, et. al. attempted to quantify the attributable lengths of stay, extra costs, and potential for increased risk of death for those suffering from an adverse drug event while hospitalized. In this article, researchers effectively outline costs associated with length of stay, as well as mortality data, which gives some insight into actual costs that are assumed by individuals. Extrapolating this data to the U.S. overall, hospital costs alone could reach \$4.2 billion, and the national excess hospital length of stay attributed to ADEs would exceed 1.5 million days.

### **Attributable Costs for Various Types of Adverse Drug Events**

<b>Type of ADE</b>	<b>Attributable Cost</b>	<b>Attributable Length of Stay (days)</b>
Diarrhea	\$4631	4.4
Fever	\$9022	5.49
Renal Failure	\$1371	4.5
Bleeding	\$6702	4.89
Cardiac arrhythmia	\$4410	3.93

Source: Classen, et.al.

The conclusions reached in this study were that an ADE is associated with a significantly prolonged length of stay, increased economic burden, and nearly a 2-fold increased risk of death (Classen, et. al.).

Costs of ADEs *causing* admission are significantly higher. A study comparing the overall data between ADEs occurring after hospitalization with those causing admission revealed the following (Senst, et. al.):

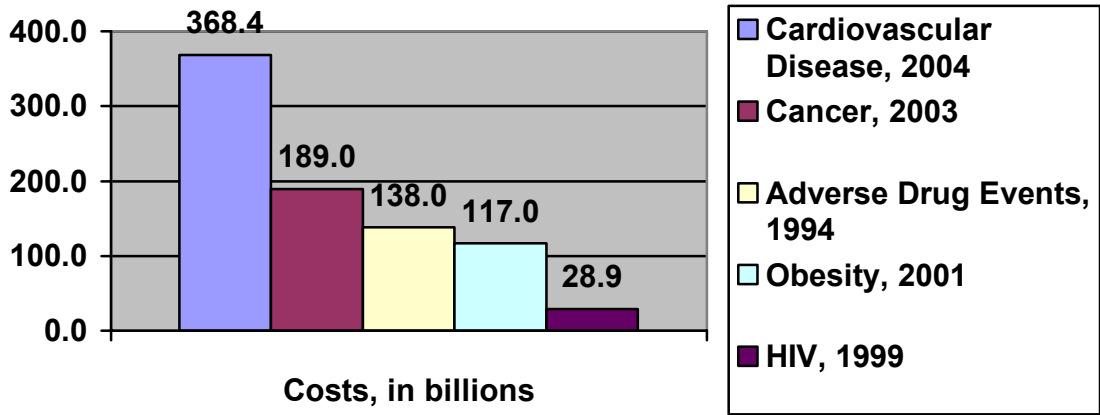
<b>Variable</b>	<b>ADEs Occurring After Hospitalization</b>	<b>ADEs Causing Hospital Admission</b>
Average Increase in Length of Stay	1.2 Days	10.5 Days
Average Increase in Cost Per Patient	\$2,162	\$6,685
Annualized Cost at UNMHSC*	\$1.7 Million	\$4.9 Million

\* University of New Mexico Health Sciences Center

*Source: Senst, et. al.*

Johnson and Bootman conducted a drug-related morbidity and mortality study in the ambulatory setting since most other studies had focused primarily on increased costs of ADE's in terms of hospital expenses. Their methodology incorporated estimating total direct costs of "drug misadventures" or misuse of prescription medications, which included costs such as outpatient physician visits, return visits to the pharmacy, emergency room visits, and additional treatment of new medical problems – along with hospitalization expenses and those for long-term care facilities. Their estimates of the costs associated with drug-related morbidity and mortality ranged from \$30.1 billion for the more conservative end of the range of negative therapeutic outcomes to \$136.8 billion in a worst-case scenario. These costs do not include the societal costs associated with adverse drug events, such as the impact of lost productivity. However, they attempted to apply a ratio from previous studies to estimate total costs including the societal costs and believed the overall costs of ADE's to range from \$138 to \$182 billion per year. The researchers go on to compare the overall costs of mortality and morbidity of adverse drug events to other major societal diseases, and conclude their study by stating that drug-related morbidity and mortality should be considered one of the leading diseases, in terms of resources consumed.

### Direct and Indirect Costs of Morbidity and Mortality



Source: American Heart Association, National Institute of Diabetes and Digestive and Kidney Diseases

Clearly, adding up all the various ADE effects associated with the use of pharmaceuticals, the potential costs to both individuals and to our society are significant.

## **Benefits and Risks of Dietary Supplements**

The word “risk” sounds alarming. However, in the context of dietary supplements it is an important component to explore, especially due to the vast numbers of Americans who are opting to consume these products as a natural alternative for health promotion. To assess the actual benefit/risk profile of dietary supplements, we need to look at two key measures of risk: frequency and severity. Assessing frequency means to ask: If I take a dietary supplement, what are the chances that I'll get a good result or a bad result? Evaluating severity is asking: If I get a bad result, how bad will it really be? Catastrophic or merely a nuisance?

To correctly evaluate the risk of taking dietary supplements, we must assess both the frequency and severity elements, along with the potential benefit that may flow from the action. Wrapped around the entire benefit/risk profile is the component of cost which plays a key part in the overall analysis. If taking a dietary supplement has a high probability of working, and the potential negative consequences are mild, then the only question is: "Is the reward good enough to make it worth the cost?" However, if the chances of success on any one try are small, and the consequences or costs of failure are severe, then the overall benefit/risk profile is in question.

### **Review of the benefit/risk profile for dietary supplements.**

To start our analysis, we will review the benefits of taking dietary supplements:

- To meet baseline RDI requirements for maintaining good health;
- To supplement diet which may be inadequate due to overconsumption of processed foods;
- To compensate for genetic variability, individual needs relative to one's ability to metabolize nutrients;
- To protect against the nutrient deficiencies common in diseases such as heart disease, birth defects, osteoporosis, and cancer, among others;
- The numerous clinical trials which have demonstrated the efficacy of taking dietary supplements for health promotion.

Below we review the frequency component of risk:

- Clinical trials reveal a minimum of adverse events associated with vitamin and mineral supplementation;
- The Poison Control Center reporting system (TESS) showed that less than two-tenths of 1% (0.2%) of all exposures to vitamins and minerals resulting in a serious health issue.

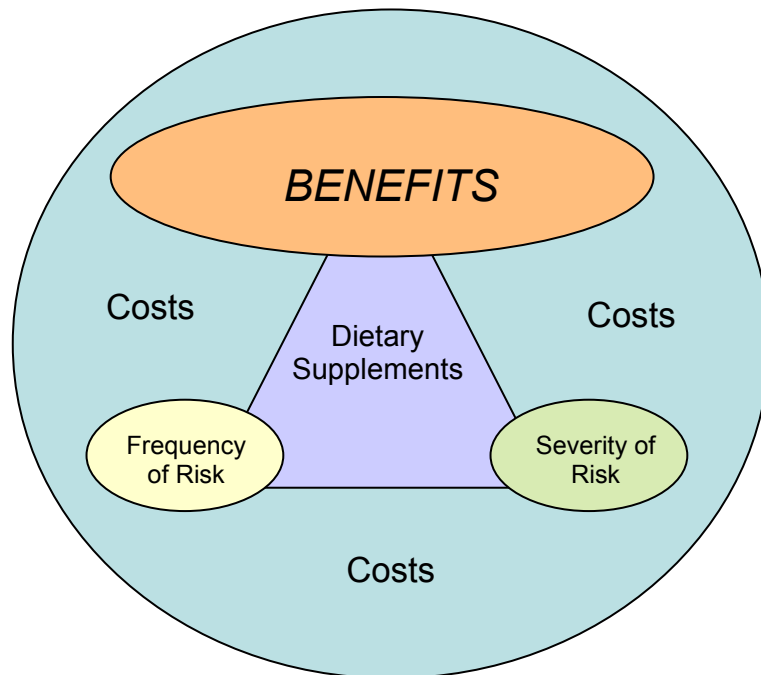
Issues of severity include:

- The adverse events reported from clinical trials for vitamins, minerals and herbs are generally regarded as more of a nuisance to individuals, as opposed to being catastrophic, and most are easily remedied by lowering intake levels.
- TESS showed that only 2% of all reported adverse outcomes were reported as having a major effect in the vitamin and mineral category, and less than 1% in the botanical category. There were only 7 deaths out of nearly 81,500 reported adverse event exposures overall due to vitamins, minerals, and botanicals. All 7 deaths were caused by overdoses; Ephedra (3), Iron(4).
- Accurate frequency of use data for dietary supplements are difficult to obtain. But, it is generally accepted that approximately 100 million U.S. residents are regular consumers of dietary supplements. If these 100 million consumers took only two dietary supplements per year, the incidence of adverse events (TESS 81,500) is extremely low 0.04% and the incidence of death is even more rare at 0.0035%.

The cost component is the final piece of the benefit/risk profile associated with dietary supplement usage. For our analysis, there are several cost considerations involved. These include:

1. Estimates by researchers that increasing our intake of vitamins and minerals would significantly reduce health care costs;

2. Cost savings for older adults as a result of taking a daily multivitamin can be seen in the avoidance of hospitalization for fatal and nonfatal heart attacks, and for nursing home stays and home health services for infection;
3. Lack of major adverse outcomes from dietary supplements translates into minimal costs for hospital stays, lost work or school, physician and emergency room visits.



In our final analysis, because of the significant benefit of taking dietary supplements, the relatively low frequency and severity of risk, and the overall cost savings, the perception that dietary supplements, in general, are dangerous is clearly not supported by the facts. One could not say the same thing regarding fireworks which are responsible for 13 deaths per year, since they provide little benefit other than entertainment value. Nor could a case be made for the benefit/risk profile of bathtubs which kill 337 every year when a safer alternative, “the shower”, could be used instead. The massive number of deaths associated with pharmaceutical drugs, over 106,000 per year, raises serious questions about their benefit/risk relationship.

The need for applying pharmaceutical regulatory standards and associated regulatory expenses to dietary supplements does not seem to be justified when comparing the relative risks and costs of drugs to those of dietary supplements. It is curious that dietary

supplements have become such a hot political issue when other more serious risk/benefit issues creating greater morbidity, mortality and costs to the public are being ignored.

Considering the fact that over 100 million Americans are regular consumers of dietary supplements, they stand out as very safe when compared to other risk factors with which they are faced.

## Medical Bias and Research Tactics

There are numerous aspects of bias with regard to health care and the negative views which commonly impact dietary supplement acceptance. A critical split between conventional and alternative approaches to health originates in the training delivered in medical school. For example, most traditional medical students in the United States study disease, rather than health, and therefore spend much of their time learning about pharmaceutical drugs to treat disease. Health practitioners from alternative disciplines focus a majority of their studies on health, specifically the promotion of health through natural approaches, utilizing nutrition and dietary supplementation when diet is not enough. The lack of training in the conventional medical environment creates significant biases and problems for today's proponents of dietary supplements.

Dr. Victor Sierpina, an Associate Professor of Family Medicine at the University of Texas, tells the story of this unfortunate gap in the knowledge, skills and ability to communicate with patients who are now turning to complementary and alternative (CAM) therapies (Sierpina). According to Sierpina, the problem for today's health care practitioners begins with the lack of systemized education in CAM therapies that they should be receiving during medical training. When the physician is confronted by the patient regarding alternative approaches to health care, he or she is placed in the situation of either recommending an unfamiliar therapy or of rejecting the therapy out of hand. Often times, the physician takes on a dismissive attitude toward alternative therapies, simply out of lack of confidence or knowledge. As a result, health care professionals take a less than holistic view of medicine and patients miss key opportunities to not only gain important insight from an experienced professional, but also to gain benefits and reduce both risks and costs for treatment.

Articles and publications that reinforce this attitude abound. This "publisher bias" can be seen in magazines and journals which are peer-sponsored and reviewed, and, as a result, lead to questionable conclusions. For example, in a survey that was performed and reported in the March 26, 2001 issue of the *Archives of Internal Medicine*, researchers concluded that consumers have a mixed opinion regarding the use and benefits of dietary supplements (Blendon, R.J., et. al.). However, in a follow-up analysis of this study, it

was clear that the survey questions provided to respondents in this study were framed in a way to predispose and bias their answers (Snow). The analysis of the article found the following biases:

- Vitamins and minerals were removed from the category of dietary supplements, which removed almost one-third of their respondents from the category of *regular user*, affecting results and invalidating researcher's conclusions.
- Supplements were consistently labeled “mostly untested and unregulated products.”
- Vague terms and yes/no questions were often used in the survey, which confused respondents and prevented them from providing more exact responses.
- Leading questions were used, which ultimately let the authors of the survey get the responses they were originally seeking. Snow says this section of the journal article “resembles jokes about ‘when did you stop beating your wife?’” and, unfortunately, didn't allow for more in-depth answers from respondents.

Since the *Archives of Internal Medicine* is published by the American Medical Association, the results published in their journals drop into the laps of medical professionals, potentially alienating them from considering CAM therapies, and driving them to continue rejecting complementary approaches to health.

Another type of publisher bias involves the strong ties between clinical researchers and pharmaceutical companies. In fact, according to an article written by Dr. Marcia Angell in the *New England Journal of Medicine*, “researchers serve as consultants to companies whose products they are studying, join advisory boards and speakers' bureaus, enter into patent and royalty arrangements, agree to be the listed authors of articles ghostwritten by interested companies, promote drugs and devices at company-sponsored symposiums, and allow themselves to be plied with expensive gifts and trips to luxurious settings. Many also have equity interest in the companies (Angell).” The problems with this kind of partnerships are many.

One obvious concern is that these ties will bias the type of research that is done, as well as what ultimately may be reported. Dr. Thomas Bodenheimer cites a number of instances, demonstrating considerable evidence that researchers with ties to drug

companies are indeed more likely to report results that are favorable to the products of those companies than researchers without such ties (Bodenheimer). Medical students become used to receiving gifts and favors from drug companies, who use their influence to impact continuing training programs, and learn that “for every problem, there is a pill; and a drug company representative to explain it (Angell).”

A study published in the *Journal of the American Medical Association* reviewed data from 37 peer-reviewed studies published between 1980 and 2000 and found that 25% of biomedical researchers at universities had commercial ties "serious enough to raise questions of financial conflict" and in many cases, "enough to skew their research." Using these results, the study estimates that industry-sponsored research is 3.6 times more likely to have results favorable to the company that funded the research. About two-thirds of the universities studied had equity in companies whose research they were supposed to monitor; 27 universities had equity in 10 or more companies. Drug industry funds have become the "lifeblood" of biomedical research accounting for 62% of U.S. expenditures on prescription drug research in 2000. The authors concluded that financial ties between academic researchers and universities and pharmaceutical companies are “pervasive and may impact the research process (Bekelman, et. al.).”

The *San Diego Union-Tribune* published a story on May 14, 2004 regarding Pfizer’s recent settlement for \$430 million, surrounding its epilepsy drug, Neurontin. By law, pharmaceutical companies are not allowed to promote drugs for nonapproved purposes. Pfizer had been charged with encouraging doctors to prescribe Neurontin to patients with bipolar disorder, even though a study had shown that the medicine was no better than a placebo in treating the disorder. In fact, 90% of Neurontin’s sales continue to be for ailments for which the drug is not an approved treatment, including Lou Gehrig’s disease, attention deficit disorder, restless leg syndrome and drug and alcohol withdrawal seizures. More disturbing, however, are the behaviors of physicians, who were flown to Hawaii, the 1996 Olympic Games, and were treated to expensive dinners at which unapproved uses of Neurontin were discussed. According to internal company documents, doctors who attended these dinners wrote 70 percent more prescriptions for the drug than those who did not attend (Harris).

The underlying biases in the world of conventional medicine are important components to consider in any discussion of the safety and efficacy of health care. These biases not only undermine the solid research efforts and quality care that should be undertaken, but also detract from and create hostility toward complementary and proven, effective methods of treatment. Our nation's health should be approached in a patient-centered manner, considering the needs and desires of each individual without the influences of biases that have permeated clinical studies, our institutions of education, or have resulted from the emotional ranting by the media.

It would be shameful if our nation entrusts its healthcare to those whose key interest in their work is to obtain funding for a clinical trial or a trip to Disneyworld, versus patient-centered health. In the end, it will be the patient who pays dearly for this bias.

## Conclusion

We believe that we have addressed our original purpose for developing this paper as outlined in our introduction:

- 1) We have provided objective data supporting the conclusion that dietary supplements provide significant health benefit with very little risk.
- 2) The most current information on the safety and efficacy of dietary supplements has been reviewed and summarized;
- 3) A comparison of the relative safety of dietary supplements compared to risks of other hazards facing the American public has been provided;
- 4) We have alerted readers of this paper to the existing bias regarding the safety of dietary supplements that is not supported by fact;
- 5) We have alerted readers of this paper to more serious health issues which are negatively affecting millions of Americans;
- 6) We have provided objective, science-based data which can be used in creating appropriate public policy for regulating dietary supplements.

The results of scientific studies continue to be published, driving more demand by American consumers for high-quality, cost effective and safe dietary supplements. These studies are gaining greater acceptance in the traditional medical community, and health care professionals are beginning to develop the confidence and knowledge to recommend dietary supplements to complement the services that they are already providing to their patients.

It is critical that dietary supplements continue to be accessible and cost effective to meet the demands of our developing and aging populations. The basic nutritional foundations of supplements are essential for life, and have great application and low risk for the prevention of the ravages of illness that people are facing each day. Diet has not been sufficient to prevent the deficiencies that cause disease. Supplements can be a powerful ally in this battle.

The picture is clear:

- Dietary supplements are safe: over 100 million Americans are purchasing and consuming dietary supplements without significant numbers of adverse events, making the risk/benefit profile of supplements very favorable.
- The ingredients of many dietary supplements are critical to the basic, healthy functioning of each human being and furthermore are proven to provide additional important health benefits, such as folic acid to reduce the risk of having a baby with a neural tube birth defect, high calcium intake to slow the rate of bone loss and help protect against fractures, and taking vitamins E and C on a regular basis to protect against heart disease, cancer and cataracts.
- If dietary supplement companies introduce harmful dietary supplements to the market, the FDA currently has full regulatory authority under DSHEA, the existing law applicable to dietary supplements, to remove harmful dietary supplements from the market, if necessary. DSHEA needs to be enforced.
- The current cost of dietary supplements makes it possible for the majority of people, of all ages, to have access to and reap the health benefits of dietary supplements.
- Attempting to over-regulate dietary supplements unnecessarily could limit access to effective, inexpensive and safe products the average American can use to maintain good health and reduce health care costs.

The DSHEA regulations are working. Attempting to over-regulate dietary supplements due to the adverse effects of Ephedra, could limit access to effective, inexpensive and safe products the average American can use to pursue their personal health goals. Limiting availability of these products could deepen our nation's health care crisis beyond what we currently experience. We must not limit options, nor increase costs for consumers to purchase dietary supplements by "fixing" legislation that isn't broken.

Why not focus on enforcement of regulations already in place? Regulations that address the dire problems of morbidity and mortality associated with adverse drug reactions would benefit many more Americans. Our nation's state of health – and the associated economic impact – will benefit from a prudent course of action. We depend on our government representatives to make the right decisions for the 100+ million consumers who rely on dietary supplements today, and for the growing numbers of those who are turning to dietary supplements to support their health in the future.

## References

AARP. *Medicare and Prescription Drugs*. Accessed 3 Jun 2004  
<[http://research.aarp.org/health/dd77\\_rx.html](http://research.aarp.org/health/dd77_rx.html)>.

AVM. "Pseudoephedrine." Accessed 16 Oct 1997  
<<http://www.avm.com.au/agtm/drugprofiles/pseudoephedrine.html>>.

Adlercreutz, Herman, et. al. "Inhibition of Human Aromatase By Mammalian Lignans and Isoflavonoid Phytoestrogens." *J Steroid Biochem Molec Biol.* 44:2 (1993): 147-153.

American Botanical Council. "The Complete German E Commission Monographs." American Botanical Council: 1999 <[www.herbalgram.org](http://www.herbalgram.org)>

American Botanical Council. "Common Herbs."  
[http://www.herbalgram.org/default.asp?c=common\\_herbs](http://www.herbalgram.org/default.asp?c=common_herbs)>.

American Heart Association. *Economic Costs of Cardiovascular Disease*. Accessed 4 May 2004 <<http://www.americanheart.org/downloadable/heart/>>.

Anderson, James W., M.D., et. al. "Meta-analysis of the Effects of Soy Protein Intake on Serum Lipids." *The New England Journal of Medicine* 333 (5) (1995): 276-82.

Angell, Marcia. M.D. "Is Academic Medicine For Sale?" *The New England Journal of Medicine* 342 (2000): 1516-1518.

Anon. "Milk thistle: effects on liver disease and cirrhosis and clinical adverse effects." *Evid Rep Technol Assess* 21 (2000): 1-3.

Barrett, B., et. al. "Assessing the risks and benefits of herbal medicine: an overview of scientific evidence." *Alternative Therapies* 5:4 (1999): 40-9.

Barrett, B, et al. "Echinacea for upper respiratory infection." *Journal of Family Practice* 48:8 (1999): 628-34.

Barringer, Thomas A., M.D., et. al. "Effect of a Multivitamin and Mineral Supplement on Infection and Quality of Life." *Annals of Internal Medicine* 138 (2003) 365-372.

Bates, David W., M.D., MSc, Cullen, David J. M.D., et. al. "Incidence of Adverse Drug Events and potential Adverse Drug Events." *JAMA* 274 (1995): 29-34.

Bates, David W., M.D., MSc, Spell, Nathan, M.D., et. al. "The Costs of Adverse Drug Events in Hospitalized Patients." *JAMA* 277 (1997): 307-311.

- Beckelman, et. al. "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systemic Review." *JAMA* (2003).
- Beling, Stephanie M.D. *Power Foods*. New York: HarperCollins, 1997.
- Blendon, R.J., et. al. "Americans views on the use and regulation of dietary supplements." *Archives of Internal Medicine* 2001 Mar 26;161(6):805-10.
- Blumenthal, M. and King, P. "The Agony of the Ecstasy." *HerbalGram* 37 (1997): 20-49.
- Blumenthal, M, et al. [Eds.] *The Complete German Commission E Monographs* Austin: American Botanical Council, 1998.
- Bodenheimer, Thomas, M.D. "Uneasy Alliance – Clinical Investigators and the Pharmaceutical Industry." *The New England Journal of Medicine* 342 (2000):1539-1544.
- Boodman, Sandra G. "Painful Choices; Consumers Face a Baffling Wall of Choices – and a Surprising Number of Serious Risks – When They seek Relief From Minor Pains and Illnesses in the Drug Aisle." *The Washington Post*. 11 Feb 2003 (F01): Final Edition.
- Brody, Jane E. "Personal Health; Statins: Miracles for Some, Menace for a Few." *New York Times on the Web*. 10 Dec 2002. Accessed 5 May 2004. <<http://www.nytimes.com/>>.
- Brooks, P.M., et. al., *Journal of Rheumatology* 9: 3 (1982).
- Burkholder, Rebecca. *Statement of the National Consumers League Before the Food and Drug Administration Nonprescription Drugs Advisory Committee*. 20 Sep 2002. Accessed 3 Jun 2004. <<http://www.ismp.org/>>.
- Centers for Disease Control and Prevention. *2000 BRFSS Summary Prevalence Report*. <<http://www.cdc.gov/brfss/pdf/2000prvrpt.pdf>>.
- Centers for Disease Control and Prevention. *National Ambulatory Medical Care Survey: 2001 Summary*. Accessed 3 Jun 2004 <<http://www.cdc.gov/nchs/data/ad/ad337.pdf>>
- Centers for Disease Control and Prevention. *National Center for Health Statistics, Fast Stats, Therapeutic Drug Use*. Accessed 3 Jun 2004 <<http://www.cdc.gov/nchs/fastats/drugs.htm>>.
- Centers for Medicare and Medicaid Services. CMS Press Release Archives, 1997-2004. <<http://www.cms.hhs.gov/media/>>.
- Chavez, M.L. and P.I. Chavez. "Ginkgo (part 2): clinical efficacy, dosage and adverse effects." *Indian Journal of Hospital Pharmacy* 33:9 (1998): 1076-95.

Chevallier, Andrew. *The Encyclopedia of Medicinal Plants*. New York: DK Publishing Inc., 1996.

Clark, Larry C., PhD, et. al. "Effects of Selenium Supplementation for Cancer Prevention in Patients With Carcinoma of the Skin." *Journal of the American Medical Association* 276:24 (1996): 1957-63.

Classen, David C., M.D., et. al. "Adverse Drug Events in Hospitalized Patients." *JAMA* 277:4 (1997): 301-306.

Connor, Steve. "Glaxo chief: Our drugs do not work on most patients." *The Independent Digital* 08 Dec 2003.  
<[http://news.independent.co.uk/world/science\\_technology/story.jsp?story=471139](http://news.independent.co.uk/world/science_technology/story.jsp?story=471139)>

Council for Responsible Nutrition. *The Dietary Supplement Pyramid*. Accessed 27 Aug 2004. <[http://www.crnusa.org/about\\_pyramid.html](http://www.crnusa.org/about_pyramid.html)>.

Curhan, Gary C., et. al. "Frequency of Analgesic Use and Risk of Hypertension in Younger Women." *Archives of Internal Medicine*. 162 (2002) 2204-8.

Davidson, Michael H., M.D. and Chris T. Geohas, M.D. "Efficacy of Over-the-counter Nutritional Supplements." *Current Atherosclerosis Reports* 2003: 5:15-21.

DAWN. *Emergency Department Trends from DAWN: Final Estimates 1994-2001*. Accessed 5 May 2004.  
<[http://dawninfo.samhsa.gov/pubs\\_94\\_02/edpubs/2001final/default.asp](http://dawninfo.samhsa.gov/pubs_94_02/edpubs/2001final/default.asp)>.

Defeudis, F.V. *Ginkgo biloba extract (Egb761): Pharmacological activities and clinical applications*. Paris: Elsevier 1991.

Department of Health. "Study Shows Children are Not Eating Enough Fruits and Vegetables." 01 Jun 2000; ref number 200/0320 Accessed 7 Jun 2004  
<<http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/>>.

Dingle, J.T., *European Journal of Rheumatology and Inflammation*. 16: 47 (1996).

Dobson, Al, Ph.D., et. al. "A Study of the Cost Effects of Daily Multivitamins for Older Adults." January, 14, 2004. Prepared by The Lewin Group for Wyeth Consumer Healthcare.

Eades, Mary Dan M.D. *The Doctor's Complete Guide to Vitamins and Minerals*. Princeton: Dell Publishing, 2000.

Eaton, S.B. and Konner, M. "Paleolithic Nutrition. A consideration of its nature and current implications." *New England Journal of Medicine*. 312(5) 1985: 283-9.

Einbinder, Jonathan, M.D., MPH, and Kenneth Scully, MS. "Using a Clinical Data Repository to Estimate the Frequency and Costs of Adverse Drug Events." *AMIA Annual Symposium*. (2001): 154-8.

- FDA. *Dietary Supplement Health and Safety Education Act of 1994*. Center for Food Safety and Applied Nutrition, December 1, 1995. <<http://vm.cfsan.fda.gov/~dms/dietsupp.html>>.
- FDA. *FDA Determines Cholestin to be an Unapproved Drug*. May 20, 1998. Accessed 3 Jun 2004 <<http://www.fda.gov/bbs/topics/ANSWERS/ANS00871.html>>.
- FDA. *FDA Issues Regulation Prohibiting Sale of Dietary Supplements Containing Ephedrine Alkaloids and Reiterates Its Advice That Consumers Stop Using These Products*. 6 Feb 2004. Accessed 3 Jun 2004. <<http://www.cfsan.fda.gov/~lrd/fpephed6.html>>.
- FDA. *The Food Label*. May 1999. Accessed 3 Jun 2004 <<http://www.ific.org/nutrition/functional/index.cfm>>.
- Fahey, J.W., et. al. "The Chemical Diversity and Distribution of Glucosinolates and Isothiocyanates Among Plants." *Phytochemistry*. 56 (2001): 5-51.
- Feskanich, Diane, et. al. "Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women." *American Journal of Clinical Nutrition* 77 (2003): 504-11.
- Fletcher R.H. and Fairfield K.M. "Vitamins for chronic disease prevention in adults: clinical applications." *Journal of the American Medical Association*. 287(23) (2002): 3127-9.
- Food and Nutrition Information Center at the National Agricultural Library. <<http://www.nal.usda.gov/fnic/>>.
- Fuchs, Charles S., et. al. "The Influence of Folate and Multivitamin Use on the Familial Risk of Colon Cancer in Women." *Cancer Epidemiology, Biomarkers & Prevention* 11 (2002): 227-234.
- Gaster, Barak, M.D. and John Holroyd, M.D. "St. John's Wort for Depression." *Archives of Internal Medicine* 160 (2000): 152-156.
- Goode, Erica. "Leading Drugs for Psychosis Come Under New Scrutiny." *New York Times on the Web*. 20 May 2003. Accessed 5 May 2004. <<http://www.nytimes.com/>>.
- Griggs, Barbara. *Green Pharmacy: A History of Herbal Medicine*. New York: The Viking Press, 1982.
- Grodstein, Francine, et. al. "High-dose antioxidant supplements and cognitive function in community-dwelling elderly women." *American Journal of Clinical Nutrition* 77 (2003): 975-84.
- Cohen, Michael. *Institute for Safe Medication Practices*. Accessed 3 Jun 2004. <<http://www.ismp.org/>>.

HHS News. *U.S. Department of Health and Human Services*. "FDA Proposes Safety Measures for Ephedrine Dietary Supplement." June 2, 1997. Accessed 3 Jun 2004 <<http://www.cfsan.fda.gov/>>.

Hale, Susie, N.D., L.P.C. and Krista M. Leamon, N.D. "The History of Naturopathy." Clayton College of Natural Health, NH101: 2003.

Haney, Daniel Q. "Study: Vitamin E May Cut Cancer Risk." *San Diego Union-Tribune* 29 Mar. 2004, sec. A:10

Harris, Gardiner. "Pfizer Settles Neurontin Case for \$430 Million." *The San Diego Union Tribune*. 14 May 2004, sec. C:1

Harvard Gazette. "Medication Mistakes by Elderly Avoidable." *Harvard Gazette*. 13 Mar 2003. Accessed 5 May 2004.

Harvard Gazette. "High Intake of Vitamin D Is Linked To Reduced Risk of M.S." *Harvard Gazette*. 15 Jan 2004. Accessed 5 May 2004.

Harvard Gazette. "Vitamins Reduce Fetal Deaths, Improve Immune Status of Pregnant Women with HIV." *Harvard Gazette*. 21 May 1998. Accessed 5 May 2004.

Hathcock, John N., Ph.D. "Safety of Vitamin and Mineral Supplements." International Alliance of Dietary/Food Supplement Associations: Apr 2004.

Hermansen,, Kjeld, M.D., DMSc, et.al. "Effects of Soy and Other Natural Products on LDL:HDL ratio and Other Lipid Parameters: A Literature Review." *Advances In Therapy* 20:1 (Jan/Feb 2003): 50-78.

"High intake of vitamin D is linked to reduced risk of MS." *Harvard Gazette*. 15 Jan 2004. Accessed 5 May 2004.

Hippius, H. "St. John's wort (*Hypericum perforatum*)—an herbal antidepressant." *Current Medical Research and Opinion* 14:3 (1998): 171-84.

Hyson, Diane, PhD., M.S., R.D. "The Health Benefits of Fruits and Vegetables." Produce For Better Health Foundation, 2002 <<http://www.5aday.com/html/>>.

Institute of Food Technologists. Accessed 4 Jun 2004 <<http://www.ift.org/cms/>>.

Institute of Medicine, "To Err is Human: Building a Safer Health System." November 1999 <[www.iom.edu](http://www.iom.edu)>.

Iso, Hiroyasu, M.D., et. al. "Prospective Study of Calcium, Potassium, and Magnesium Intake and Risk of Stroke in Women." *Stroke* 2 Jun 1999. <<http://stroke.ahajournals.org/>>

Ives, Nat. "The Media Business: Advertising; The Maker of Oxycontin, a Painkiller That Is Addictive, Sponsors a Campaign on Drug Abuse." *New York Times on the Web*. 4 Sep 2003. Accessed 5 May 2004. <<http://www.nytimes.com/>>.

- Jacobs, B.P., et. al. "Milk thistle for the treatment of liver disease: a systematic review and meta-analysis." *American Journal of Medicine* 113:6 (2002): 506-15.
- Janofsky, Michael. "Drug Fighters Turn to Rising Tide of Prescription Drug Abuse." *New York Times on the Web*. 18 Mar 2004. Accessed 5 May 2004 <<http://www.nytimes.com/>>.
- Jenkins, John, M.D. "FDA, SAMHSA join to educate public on dangers of Rx drug abuse." Center for Drug Evaluation and Research. *News Along the Pike*. 21 Feb 2003. Accessed 7 Jun 2004 <<http://www.fda.gov/cder/pike/JanFeb2003.htm>>.
- Jensen, Bernard. *Dr. Jensen's Guide to Better Bowel Care*. New York: Avery, 1999.
- Johnson, Jeffrey A., and Lyle Bootman, PhD. "Drug Related Morbidity and Mortality." *Archives of Internal Medicine*. 155 (1995): 1949-1956.
- Johnson, Linda. "B Vitamins Found to Ward Off Fractures from Osteoporosis." *San Diego Union-Tribune* 13 May 2004, sec. A:10.
- Johnston, B. 1997. "One-Third of Nation's Adults Use Herbal Remedies: Market Estimated at \$3.24 Billion." *HerbalGram* 40: 49
- Kaiser Family Foundation. *Prescription Drugs*. Accessed 3 Jun 2004 <<http://www.kff.org/rxdrugs/index.cfm>>
- Kiely, M. et. al. "The efficacy and safety of nutritional supplement use in a representative sample of adults in the North/South Ireland Food Consumption Survey." *Public Health Nutrition*. 4(5)A 2001: 1089-1097.
- Kleijnen J., and P. Knipschild. "Ginkgo biloba." *Lancet* 340:8828 (1992): 1136-39.
- Lasser, K.E., et. al. "Timing of New Black Box Warnings and Withdrawals from Prescription Medications." *JAMA*. 287(17) May (2002): 2215-2220.
- Lazarou, Jason, M.Sc., et. al. "Incidence of Adverse Drug Reactions in Hospitalized Patients." *JAMA* 279:15 (1998): 1200-1205.
- Leape, Lucian L., M.D., et. al. "The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study." *New England Journal of Medicine*. 324 (1991): 377-384.
- Leng-Peschlow, E. "Properties and medical use of flavonolignans (Silymarin) from *Silybum marianum*." *Phytotherapy Res* 10 (1996): S25-S-26.
- Linde K, Ramirez G, et. al. "St. John's wort for depression—and overview and meta-analysis of randomized clinical trials." *British Medical Journal*, 313:7052 (1996): 253-58.

Lukaczer, Dan, N.D., et. al. "A Randomized, Controlled Prospective Trial Comparing a Soy Protein and Phytosterol Functional Food and a Low-Glycemic-Index Diet (LGID) with the AHA Step 1 Dietary Program." Functional Medicine Research Center, Gig Harbor, Washington. 2004.

McDonnell, Patrick J. and Michael R. Jacobs. "Hospital Admissions Resulting from Preventable Adverse Drug Reactions." *The Annals of Pharmacotherapy* 36 (2002) 1331 – 1336.

McNeil, Donald G. Jr. "Herbal Drug Widely Embraced in Treating Resistant Malaria." *New York Times on the Web* 10 May 2004.

Mead, P.S., Slutsker, L., Dietz, et al. "Food-related illness and death in the United States." *Emerging Infectious Diseases*. 5(5) (1999): 607-25.

Medem, Inc. "Good Food That's Good For You." American Medical Association. Accessed 9 Jun 2004. <<http://www.medem.com/search/article>>.

MedicineNet.com. "Medications." Accessed 5 May 2004 <<http://www.medicinenet.com/medications/article.htm>>.

Melchart, D., et. al. "Results of five randomized studies on the immunomodulatory activity of preparations of Echinacea." *Journal of Alternative and Complementary Medicine* 1:2 (1995): 145-60.

Meydani, S.N., et. al. "Vitamin E Supplementation and In Vivo Immune Response in Healthy Elderly Subjects." *Journal of the American Medical Association* 277:17 (1997): 1380-6.

Miller, Robert Keith, et. al. *The Writer's Harbrace Handbook*. Orlando: Harcourt, Inc., 2001.

Morris, Cynthia D., PhD, et. al. "Routine Vitamin Supplementation To Prevent Cardiovascular Disease." *Annals of Internal Medicine*. 139 (2003): 67

Muller, Michael and Sander Kersten. "Nutrigenomics: Goals and Strategies." *Nature Reviews/Genetics*. 4 (2003): 315-322.

Murray, Michael, N.D. and Joseph Pizzorno, N.D. *Encyclopedia of Natural Medicine*. Revised 2<sup>nd</sup> ed. Rocklin, CA: Prima Publishing, 1998.

Naismith, Donald J. and Alessandro Braschi. "The effect of low-dose potassium supplementation on blood pressure in apparently healthy volunteers." *British Journal of Nutrition* 90 (2003): 53-60.

National Association of Chain Drug Stores. *Industry Facts and Resources*. Accessed 3 Jun 2004. <[http://www.nacds.org/user-assets/PDF\\_files/Pharmacy\\_Sales.pdf](http://www.nacds.org/user-assets/PDF_files/Pharmacy_Sales.pdf)>.

National Cancer Institute. Eat 5 to 9 a Day for Better Health. Accessed 21 Sep 2004. <http://5aday.gov/9aday/>>.

- National Center for Complementary and Alternative Medicine. *About NCCAM*. Accessed 5 May 2004 <<http://altmed.od.nih.gov/about/ataglance/index.htm>>.
- National Center for Health Statistics. *Deaths: Final Data for 2001*. Accessed 5 May 2004. <<http://www.cdc.gov/nchs/about/major/dvs/mortdata.htm>>.
- National Consumer's League. "Medication Errors: Protect Yourself." Accessed 5 May 2004. <<http://www.sosrx.org/mederrors.htm>>.
- National Council for Patient Information and Education. "The Other Drug Problem. Statistics on Medicine Use and Compliance." Accessed 3 Jun 2004 <<http://www.ismp.org/>>.
- National Institute of Diabetes and Digestive and Kidney Diseases. *Statistics Related to Overweight and Obesity*. Accessed 4 May 2004 <<http://www.niddk.nih.gov/health/nutrit/pubs>>.
- National Institute for Health Care Management. *Prescription Drug Expenditures in 2001: Another Year of Escalating Costs*. Rev 6 May 2002 <[www.nihcm.org](http://www.nihcm.org)>.
- National Institutes of Health. Office of Dietary Supplements, IBIDS Database. Accessed 5 May 2004 <<http://dietary-supplements.info.nih.gov/>>.
- National Nutritional Foods Association. *Media and News, Industry Facts*. Retrieved May 17, 2004 from the World Wide Web: <<http://www.nnfa.org/news/industry>>.
- Newman, M.N., and Ling, R.S.M., *Lancet* 2: 11 (1985).
- Office of the Surgeon General. <[www.surgeongeneral.gov/library/reports](http://www.surgeongeneral.gov/library/reports)>.
- O'Hara M., et. al. "A Review of 12 Commonly Used Medicinal Herbs." *Arch Fam Med* 7 (1998): 523-6
- Ornish, Dean, M.D., et. al. "Intensive Lifestyle Changes for Reversal of Coronary Heart Disease." *Journal of the American Medical Association* 280:23 (1998): 2001-7.
- Osganian, Stavroula K., M.D., et. al. "Vitamin C and Risk of Coronary Heart Disease in Women." *Journal of the American College of Cardiology* 42.2 (2003): 246-252
- Packer-Tursman, Judy. "Pill 'Very Promising'; CoQ10 May Arrest Parkinson's Disease." *Washington Post on the Web* 22 Oct. 2002. F: 01.
- Parnham, M.J. "Benefit-risk assessment of the squeezed sap of the purple coneflower (*Echinacea purpurea*) for long-term oral immunostimulation." *Phytomedicine* 3:1 (1996): 95-102.
- Produce for Better Health Foundation. *State of the Plate Study*. October 2002. Accessed 8 Jun 2004 <<http://www.5aday.com/html/research/consumptionstats.php#highlights>>.

Public Citizen. "America's Other Drug Problem: A Briefing Book on the Rx Drug Debate." Apr 2003. Accessed 5 May 2004.

<<http://www.citizen.org/congress/reform/rxfacts/>>.

Quigley, D.T., M.D. The National Malnutrition. 1952. The Lee Foundation For Nutritional Research. Accessed 3 May 2004

<<http://www.soilandhealth.org/02/0203cat/020309quigley>>.

SAMHSA. *2001 National Household Survey on Drug Abuse*. Accessed 3 Jun 2004

<<http://oas.samhsa.gov/nhsda/2k1nhsda/vol1/toc.htm>>.

Saffir, Barbara J. "New Nutrient Supplements Could Help Troops Stay Alert." *Washington Post on the Web*. 23 Jun. 2003. A: 19.

Saller, R., et. al. "The use of silymarin in the treatment of liver diseases." *Drugs* 61:14 (2001): 2035-63.

Schneider, Edward L., M.D., et. al. "Recommended Dietary Allowances and the Health of the Elderly." *The New England Journal of Medicine*. 314:3 (1986): 157-60.

Senst, Bonnie L., et. al. "Practical Approach to Determining Costs and Frequency of Adverse Drug Events in a Health Care Network." *American Journal of Health-System Pharmacists* 58 (2001): 1126-1132.

Setchell, K. "Discovery and potential clinical importance of mammalian lignans." *Flaxseed in Human Nutrition*. Champaign: AOCS Press, 1995, pp. 82-97.

Shekelle, Paul, M.D., PhD., et. al. "Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects." *Southern California Evidence-Based Practice Center RAND; AHRQ Publication No. 03-E022, Feb 03*.

Sierpina, Victor S. M.D. "Meeting the Challenge of Integrating CAM into Medical Education." *University of Texas Medical Branch: Alternative and Integrated Health Care Program*. Accessed 11 May 2004.

<<http://atc.utmb.edu/altmed/Vs%20CAM%20Education%20View%20FINAL.htm>>.

Sims, Amy C. "Shark Deaths Dwarfed by Other Dangers." *Fox News*. Saturday, July 13, 2002. <<http://www.foxnews.com>>

Singh, G. "Recent considerations in nonsteroidal anti-inflammatory drug gastropathy." *American Journal of Medicine*. 105:1B (1998): 31S-38S.

Snow, Wyn. "FDA Strangling Consumer Health." *SupplementQuality.com* 6 Nov 2003. Accessed 9 Jun 2004.

<[http://www.supplementquality.com/news/skyrocketing\\_drug\\_costs.html#controls](http://www.supplementquality.com/news/skyrocketing_drug_costs.html#controls)>.

Snow, Wyn. "Supplement Study in AMA Journal Shows Bias and Misunderstanding." *SupplementQuality.com*. 12 Aug 2001. Accessed 9 Jun 2004

<[http://www.supplementquality.com/editorials/archives\\_biased.html#clueless](http://www.supplementquality.com/editorials/archives_biased.html#clueless)>.

- Soeken, Karen L., PhD. "Selected CAM Therapies for Arthritis-Related Pain: The Evidence From Systematic Reviews." *Clinical Journal of Pain* 20:1 (2004): 13-18.
- Stolberg, Sheryl Gay. "Folk Cures On Trial: A Special Report; Alternative Care Gains a Foothold." *New York Times on the Web*. 31 Jan. 2000.
- Stolberg, Sheryl Gay. "The Boom in Medications Brings Rise in Fatal Risks." *New York Times on the Web*. 3 Jun 1999.
- Stratton, Rebecca J. "Summary of a systematic review on oral nutritional supplement use in the community." *Proceedings of the Nutrition society* (2000) 59: 469-476
- Straus, Stephen E., M.D. "Herbal Medicines – What's in the Bottle?" *New England Journal of Medicine* 347:25 (2002): 1997-1998.
- Thomas, Joseph III Ph.D., et. al. "Over the Counter Nonsteroidal Anti-Inflammatory Drugs and Risk of Gastrointestinal Symptoms." *The American Journal of Gastroenterology*. 97 (2002): 2215-9.
- Tolstoi, Linda G. "The Clinical Significance of the Human Genome Project in Single Gene Defects: Gene-Nutrient Interactions." *Nutrition Today*. 31 – 1 Jan/Feb (2000): 22-28.
- Toufexis, Anastasia. "The New Scoop on Vitamins." *Time Magazine* 6 Apr. 1992.
- Tyler, Varro E. *Herbs of Choice: The Therapeutic Use of Phytomedicinals*. New York: Pharmaceutical Products Press, 1994.
- Tufts. "Multivitamins and Public Health: Exploring the Evidence." Results of conference co-sponsored by Friedman School of Nutrition Science and Policy at Tufts University and UCLA Center for Human Nutrition. 1 Oct 2003.
- USDA. Agricultural Research Service. *Pyramid Servings Data for 1994-1996* <<http://www.barc.usda.gov/bhnrc/foodsurvey>>.
- USFDA. Center for Food Safety and Applied Nutrition. *AEMS Removal Letter* Accessed 5 May 2004 <<http://vm.cfsan.fda.gov/~dms/aems.html>>.
- Valli, Georgianne, M.D., and Elsa-Grace V. Giardina, M.D. F.A.C.C. "Benefits, Adverse Effects and Drug Interactions of Herbal Therapies With Cardiovascular Effects." *Journal of the American College of Cardiology* 39:7 2002.
- van Blitterswijk, Wim J, et. al. "Glucosamine and chondroitin sulfate supplementation to treat symptomatic disc degeneration: Biochemical rationale and case report." *BMC Complementary and Alternative Medicine* 2003. 3:2 <<http://www.biomedcentral.com/1472-6882/3/2>>
- von Laue, Nicoletta C., et. al. "The epidemiology of preventable adverse drug events: A review of the literature." *The Middle European Journal of Medicine*. 115/12 (2003): 407-415.

“Vitamin Cocktail Cuts Cancer Deaths.” *BBC News on the Web*. 08 Apr. 2004.

“Vitamins Reduce Fetal Deaths, Improve Immune Status of Pregnant Women with HIV.” *Harvard Gazette on the Web*. 21 May 1998.

Vukovic, Laurel. “Turmeric.” *Delicious Living*. May 2004: 28-30.

Washington State Labor Council. Prescription Drug Costs. Accessed 3 Jun 2004. <<http://www.wslc.org/legis/prescrip.htm>>.

Watson, William A., PharmD, et. al. “2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System.” *American Journal of Emergency Medicine*. 21:5 (2003): 353-410. Accessed 5 May 2004. <<http://www.aapcc.org/>>.

Web MD. Accessed 5 May 2004 <<http://www.webmd.com/>>.

Williams, Roger, PhD. “The Concept of Genetotropic Disease.” *The Lancet*. 1 (6599). (1950): 287-289.

Wolfe, M. Michael, M.D., et. al. “Gastrointestinal Toxicity in Nonsteroidal Anti-Inflammatory Drugs.” *New England Journal of Medicine*. 17 Jun (1999): 1888-1899.

Wood, Alastair J.J., M.D. “Herbal Remedies.” *New England Journal of Medicine*. 347; 25. (2002): 2046 - 2056.

Wu, Kana, et. al. “Calcium Intake and Risk of Colon Cancer in Women and Men.” *Journal of the National Cancer Institute* 94 (2002): 437-46.

Zurich, Daniel B. *Physician's Desk Reference*. New Jersey: Medical Economic Company, Inc., 1993.