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Problems and Prospects: Public Health Regulation of Dietary Supplements

Colin W. Binns,[1] Mi Kyung Lee,[2] and Andy H. Lee[1]

[1]School of Public Health, Curtin University, Perth, Western Australia 6845, Australia; email: c.binns@curtin.edu.au, andy.lee@curtin.edu.au

[2]School of Health Professions, Murdoch University, Perth, Western Australia 6150, Australia; email: m.k.lee@murdoch.edu.au

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Abstract

Dietary supplements are a global business worth more than US$100 billion annually. These supplements are taken by up to 50% of adults and perhaps one-third of children in economically advanced economies. Definitions of dietary supplements differ from country to country, and regulation is generally lax and often seems to be directed more toward promoting commerce than protecting public health. Supplements may directly cause toxic reactions or may interact with other supplements or pharmaceuticals. Some supplements are found to have been contaminated with heavy metals, and others do not contain the expected quantities of active ingredients. In general, supplements are not needed except in cases of established deficiencies, and excess of some nutrients can increase cancer rates. There are important public health reasons for taking some supplements, including folate and iodine in pregnancy. This review discusses the public health concerns associated with dietary supplements and suggests directions for further regulation.

INTRODUCTION

Food and good nutrition are the basis of human existence and good health; up to 50% of the burden of disease is attributable to food and nutrition (42, 126). Much of human culture is based around food and beliefs about its value to life. Some foods are served for special occasions, some foods mark transitions to new stages of life, some foods are for celebration, and still other foods are promoted for healing. In addition, staple foods provide the major proportion of our energy and the necessary macro- and micronutrients; all cultures use a variety of flavors and condiments to enhance our experience of food. Although usually classified as foods, these staple foods may also be sold as supplements, creating a definitional dilemma. For example, no Korean would consider a meal complete unless accompanied by kimchee, a fermented food that contains a probiotic (86). Turmeric is widely used as a food and as a dietary supplement. Thus the spectrum of what can be considered as a dietary supplement is wide and difficult to define.

The consumption of dietary supplements is increasing, and in most jurisdictions they are only loosely regulated, in contrast with pharmaceuticals. It is difficult to regulate products that are steeped in culture and are promoted by industry in a vacuum away from public health imperatives. Some supplements interact with each other and with prescription medications in ways that can adversely affect health. In this review, the range of products available, categories of complications, and existing controls are summarized from a representative range of countries. The options for future regulation and control of advertising are also discussed.

DEFINITION OF DIETARY SUPPLEMENTS

The US Food and Drug Administration (FDA) definition of a dietary supplement was included in the Dietary Supplement Health and Education Act (DSHEA) of 1994 (28). A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The DSHEA places dietary supplements, whatever their physical form, in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement.

The DSHEA defined "dietary ingredient" and "new dietary ingredient" as components of dietary supplements. In order for an ingredient of a dietary supplement to be considered a "dietary ingredient," it must be one or any combination of the following substances (28):

- a vitamin,
- a mineral,
- an herb or other botanical,
- an amino acid,
- a dietary substance for use by humans to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands), or
- a concentrate, metabolite, constituent, or extract.

A "new dietary ingredient" is one that meets the above definition for a "dietary ingredient" and was not sold in the United States in a dietary supplement before October 15, 1994 (116).

The European Union (EU) has given the following working definition: "As an addition to a normal diet, food business operators market food supplements, which are concentrated sources of nutrients (or other substances) with a nutritional or physiological effect. Such food supplements can be marketed in 'dose' form, such as pills, tablets, capsules, liquids in measured doses etc." (30). The main EU legislation is Directive 2002/46/EC related to food supplements containing vitamins and minerals. The European Food Safety Authority (EFSA) adds, "Supplements may be used to correct nutritional deficiencies or maintain an adequate intake of certain nutrients. However, in

some cases excessive intake of vitamins and minerals may be harmful or cause unwanted side effects; therefore, maximum levels are necessary to ensure their safe use in food supplements" (31).

The classification of dietary supplements into specific groups is made difficult by the large numbers of products involved, their varying content, and the range of actions and complications (130). Comparisons of consumption are difficult because definitions have changed over time, as in the National Health and Nutrition Examination Survey (NHANES) (130).

Dietary supplements may be found in many forms such as tablets, capsules, soft gels, gel caps, liquids, or powders. The NHANES questions on dietary supplements include the following description: "[S]upplements could be a capsule, tablet, pill, softgel, chew or gum, or other product containing one or more supplements" (59). They can also be manufactured into other forms, such as a snack bar or toothpaste to provide vitamin B_{12} to vegans (100).

The terms "supplement" or "supplementary food" or the alternate term "complementary food" are commonly used in infant feeding. Despite the risks of adding dietary supplements or ingredients to infant formula, as additions to formula are regulated separately, these are not discussed in this review (1). Specific dietary supplements are commonly used to treat severe malnutrition or specific nutritional deficiencies, especially in the developing world, and are regarded as special purpose foods. There are a number of examples of vitamins and minerals that could be considered either a supplement or a pharmaceutical. For example, if parental thiamine is used in acute vitamin B_1 deficiency (Wernicke's syndrome), it would be considered a pharmaceutical (40). Another food in its pure form that is not considered a supplement is refined sugar or sucrose, despite its impact on nutrition (95).

Probiotics have been consumed by humans since time immemorial, for example as fermented milks and yogurts (13). More than a century ago, Russian microbiologist Metchnikov used the word probiotics, from the Greek phrase "for life," to describe live microbial supplements designed to improve health. Working at the Pasteur Institute in Paris, he encouraged the use of fermented milk (lactobacilli) to promote health (41). The NIH Human Microbiome project has renewed interest in exploring the value of probiotics and the need for their regulation (54). Hoffman provides general principles for regulation, including "proportionality to risk, universal quality guidelines, and flexibility" (53). Although probiotics are considered a supplement in some jurisdictions, in most they are regulated as foods.

INCREASING USE OF DIETARY SUPPLEMENTS

The use of dietary supplements has increased worldwide. Two decades ago the annual value of dietary supplements used in the United States was US$12 billion (18). By 2015, the global market was US$109 billion and estimated to grow to US$180 billion by 2020, with the Asia-Pacific, Europe, and North America regional shares at 31%, 30%, and 25%, respectively (89). Another projection for the global market was US$278 billion by 2024 (45).

The range and composition of dietary supplements are almost endless, and even common multivitamins are packaged for specific groups by age, gender, physical conditions, and activity level. Nowak describes a general US supermarket that sells more than 500 different dietary supplements, and specialty stores sell significantly more (83). Although these numbers must overwhelm consumers, they represent only a small fraction of those available. One indication of the number of dietary supplements is from the US Office of Dietary Supplements: "The Dietary Supplement Label Database (DSLD) is a repository for all the information on the product label (composition, claims, manufacturer contact information, etc.) of dietary supplements. The database has data from more than 60,000 labels, and another 1,000 are added each month" (82, p. 7).

Data from the NHANES series showed that between 1980 and 2000 supplement use increased rapidly; however, between 1999 and 2012, use slowed. In 2012, ~52% of respondents reported regular supplement use (59). The types of supplement consumed have changed over time; multivitamin supplements decreased, fish oil supplements increased, and vitamin D increased fourfold (to 20%) (59). In a representative sample of older Americans (65–84 years) use of supplements has increased, particularly the use of multiple supplements (90); 36% of respondents regularly used five or more supplements or medications, and 15% of the combinations represented potentially harmful interactions. One elderly man was using in excess of 50 supplements simultaneously (102). Supplements are used by nearly one-third of children, and pediatric supplements often contain more than the recommended daily intake (RDI) (16, 67). Although a large proportion of the US population uses dietary supplements, fewer than 25% do so with the approval of their physician.

Several factors contribute to the increasing use of dietary supplements:

1. An aging baby boomer population, with concerns for wellness, fitness, and enhanced quality of life;
2. Increasing use of natural substances, while rejecting the so-called chemicals;
3. Increasing cost of drugs and a suspicion that drug companies have ignored "natural" products because their use could not be protected by patents (18);
4. A willingness to "try anything" in the search for a cure for a chronic disease (patients with chronic diseases often take more supplements than the general population) (34, 37, 46–48, 57, 75).

There is also increasing interest, particularly in emerging economies, of the "value" of tradition and acceptability of GRAS (generally recognized as safe) food supplements (18).

The marketing of dietary supplements has expanded in recent decades. Many thousands of products are advertised as being beneficial for health, disease prevention, or even enhancement of mental or physical performance. The increasing use of dietary supplements raises public health concerns about their efficacy and safety in both short and long terms. Monitoring and evaluating supplements are challenging because many of them contain multiple ingredients, change composition over time, or are used intermittently at doses difficult to measure (55). It may take a long time for the current systems of voluntary adverse event reporting to detect public health problems associated with inappropriate supplement use.

The risks of using dietary supplements include organ damage from inherent toxicity, interactions, or product contamination. Individuals who use supplements may also be more prone to forego potentially useful treatment for life-threatening diseases. Some individuals believe (falsely) that supplements have benefit comparable to a healthy diet and lifestyle. The USFDA estimates that some 50,000 adverse events occur annually that can be attributed to the use of dietary supplements. This is an underestimate, with perhaps only 1% being reported (120, 127). Some reports are substantiated by epidemiological studies and thorough reviews. Others are case reports with many papers along the spectrum between these extremes. Some are trivial, but others can be life-threatening, such as subarachnoid hemorrhage linked to Ginkgo biloba or liver failure requiring transplantation (113, 118). Most vitamins and minerals have a U-shaped dose-benefit curve, whereby the risk of damage is dose dependent (16). Vitamin A deficiency is a problem in parts of the developing world, but supplements with larger amounts cause complications.

Toxicity and complications from consuming dietary and herbal supplements are a common cause of hospital admissions, and Levy found that ~2% of hospitalizations may have been caused by adverse events associated with "dietary supplement–drug interactions" (63). Consumption of dietary and herbal supplements by hospital patients is common, and interactions are often missed by physicians (43). Herbal supplements are known to cause renal disease, and an analysis of NHANES

data found that 8% of US adults are taking at least one component that has a potential for causing renal disease (48). Many of these substances are found in supplements with "benign product names" that conceal their risk (48). Many publications on interactions come from Asia (29, 130).

Retrospective reporting can unnecessarily prolong complications. In 1989, there were more than 1,500 cases and 27 deaths from eosinophilia myalgia syndrome due to contaminated tryptophan in "muscle powders" (103). Millions of consumers took Hydroxycut products before these supplements were voluntarily recalled in 2009 (83). The FDA issued a consumer warning only after it had received 23 reports of serious health problems related to liver damage and a teenager had died. The DSHEA limits the FDA's ability to take swift or proactive measures (83, 113).

As the use of dietary supplements has increased, the number of liver injuries reported as complications of their use has also increased, and these complications are usually dose related (26, 79, 99). Commonly implicated agents include anabolic steroids used for body building, green tea extract, and multi-ingredient nutritional supplements. Navarro has identified three common types of liver injuries (80). Anabolic steroids cause prolonged jaundice due to cholestatic liver injury, usually self-limiting. Green tea extract and other single ingredient herbal products cause an acute hepatitis-like injury. The largest proportion of liver injury cases are due to multi-ingredient supplements, which may contain many ingredients, sometimes as many as 30–40, making it difficult or impossible to isolate the specific cause (80). Diagnosis is frequently complicated by the undeclared presence of synthetic chemicals or toxic herbs.

Risks

Contamination. In the 1980s, the USFDA advised consumers to limit their intake of calcium supplements because of the risk of lead contamination (15, 125). Contamination appears to have continued in recent years (92), which is of public health importance because osteoporosis becomes more prevalent as populations age. However, recommendations have moderated in recent years because the benefits of calcium supplementation for the prevention of fractures cannot be substantiated and may cause an increase in cardiovascular events among males (5, 60, 76, 93). With widespread lactase deficiency in Asia, it is difficult to meet calcium requirements through dairy products, and calcium supplements are increasingly being consumed (14, 106, 122, 132).

Increased rates of cancer reported in trials of micronutrient supplementation. Compared with trials of dietary intervention, it is easier to conduct trials on dietary supplements for disease prevention. The large SELECT trial ($n = 35{,}533$ men) of vitamin E and selenium and a combination thereof found no benefit in protecting against prostate cancer (64). A meta-analysis of 49 prospective cancer prevention trials ($n = 287{,}304$) concluded that there was a lack of evidence to support the use of dietary supplements as a primary method to prevent deaths from cardiovascular disease or cancer, and in some situations, cancer risk is even increased (96, 123). Also, vitamin A supplements in smokers increase the risk of lung cancer (107).

Substitution for regular treatment or nutrition programs. Supplements are no substitute for whole foods and healthy diets. The use of multivitamin supplements in nutrition programs for older Americans is a concern because of their potential use in nutrition programs to substitute for a diet that follows the Dietary Guidelines for Americans (69). Patients may not tell health professionals about their use of dietary supplements and herbal medicines, so there can be a risk of interactions or substitutions for prescribed medications or treatments (7). This risk is particularly relevant for patients with long-term diseases with a poor prognosis, such as cancer, as hope begins to wane.

Quality concerns. Many problems have been reported concerning the quality of dietary supplements. A study of multivitamin and mineral supplements demonstrated considerable differences between the amounts of various components listed on the labels and those found in the supplements themselves (6). An analysis of dietary supplements found that their content of vitamin D ranged from 8% to 177% of the declared label value (121). Active ingredients in iron and iodine supplements may vary (108). Ingredients may change owing to costs or availability. Fish oils are a commonly consumed dietary supplement and contain significant quantities of omega-3 long-chain polyunsaturated fatty acids. A New Zealand study showed that most of the contents of fish oil capsules were oxidized and were metabolically inactive by the time they were taken (3). When this result was challenged, the authors could not provide details of methods used to determine oxidation and potency, and oxidation of fish oil is a real concern (4, 81).

Unhealthy format. Dietary supplements have been marketed to children in the form of sweetened lozenges or candy. This practice is unhealthy and conveys an inappropriate nutrition education message (50).

Climate Change and Supplements

A growing issue for public health is climate change, which may affect the production and composition of crop-based supplements and may change the effect of heat on consumers using specific supplements (78). Creatine is a widely used dietary supplement for athletes and body builders and has become the most widely used dietary supplement used in military forces (51). It may be linked to deaths from heatstroke in hot environments (10, 65), although this result has been challenged (66).

Dietary Supplements in the Developing World

For vitamin and mineral supplements, their potential depends on whether the diet is deficient in that component (126). Dietary supplements have been widely used for the prevention and treatment of malnutrition in populations at significant risk for this condition. The supplements provided are usually high energy and protein-fortified with added vitamins and minerals. In Mali, for example, lipid-based dietary supplements improved the growth rates of children with moderate acute malnutrition (2). There are numerous other examples of supplements administered in the developing world, many of which date from the 1960s and 1970s and were successful in reducing severe malnutrition, particularly in emergency situations (44, 97, 98, 112). Multiple micronutrient powders (Sprinkles) have been successfully used to overcome deficiencies when trialed in children and pregnant women in Africa, Asia, and South America (19, 25, 85, 88). Improved food supply and a variety of nutritious foods would reduce any requirement for supplements in the developing world.

Dietary Supplements and Unethical Behavior

The temptation to gain fame and fortune by developing dietary supplements that would solve major nutritional problems has proven too much for some. One fraudulent episode stands out; a prominent nutrition scientist, the president of a national society and chair of a World Nutrition Congress, claimed that "nutritional supplementation can, for elderly people, protect against infection and greatly improve memory and ability to learn, and delay or even reverse dementia" (68). Other papers by Chandra have also been retracted, and yet his papers were still being cited in 2016 (124).

CURRENT REGULATION OF DIETARY SUPPLEMENTS

In this section, we review the regulation of dietary supplements by the major international and national bodies.

International Regulation (Codex Alimentarius International Food Regulations)

The Codex Alimentarius is a collection of standards, guidelines, and codes of practice adopted by the Codex Alimentarius Commission (CAC). The Commission is central to the Joint FAO/WHO Food Standards Program, established by the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) to protect consumer health, harmonize food standards, and promote fair practices in food trade. The Commission has 187 Member States and organizations (114, 128). In 2005, the Codex adopted the Guidelines for Vitamin and Mineral Food Supplements (35). These apply only to supplements that contain vitamins and/or minerals where these products are regulated as foods, and they address the composition of supplements, including their safety, purity, and bioavailability (36, 114).

United States

Legislation to control pharmaceuticals and to promote pure food did not come easily to the United States, and much has been written about the influence of Upton Sinclair whose novel *The Jungle* (published in 1906) documented the scandals in the Chicago meat industry (58). In 1906, the US Congress passed the Pure Food and Drug Act establishing the USFDA, which has been expanded to include dietary supplements. The sale of supplements is regulated under the ironically titled Dietary Supplements Health Education Act (DSHEA) of 1994. Under the DSHEA, supplement manufacturers do not need to demonstrate safety or efficacy; "rather, the DSHEA purposefully minimizes oversight by the FDA and focuses on the value of the industry for the US economy" (8, 16). Under the DSHEA, the FDA has the burden of proving that a particular dietary supplement is unsafe for consumer use before it can be taken off the market.

The current plans for the Office of Dietary Supplements (ODS) in the United States are detailed in their 2017–2020 triennium *Strengthening Knowledge and Understanding of Dietary Supplements* (82). The title suggests a very passive role in supplement regulation. The ODS budget has been reduced in recent years despite more than 50% of the American population using an increasing variety of dietary supplements. The ODS states that "the manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed and that the product label information is truthful and not misleading" (82, p. 1). No proof is required to demonstrate that the supplement is effective, but the ODS does provide information on the science of supplements (82). Accurate information on efficacy seems unlikely, given the sheer number of dietary supplements available. When the DSHEA was enacted in 1994, there were ~4,000 dietary supplements being marketed, increasing to 90,000 in 2014 (101). Despite the requirement to register new ingredients, even with the increase of 86,000 supplements on the market, only 170 notifications of new ingredients were received (101).

The effectiveness of the US approach is questioned by Cohen (22). "The USFDA initiates class I drug recalls when products have reasonable possibility of causing serious adverse health consequences or death. Recently, the FDA has used class I drug recalls to remove dietary supplements adulterated with pharmaceutical ingredients from US markets. Approximately half of all FDA class I drug recalls since 2004 have involved dietary supplements adulterated with banned pharmaceutical ingredients" (22, p. 1691). Harel et al. (49) provides more details of the FDA recalls. Cohen found that most of the banned supplements were still on sale six months after being

banned and that two-thirds still contained a pharmaceutical substance. However, when the FDA banned ephedra-containing supplements, the number of poisonings decreased (131).

Canada

Canada has a high prevalence of dietary supplement usage. For example, a recent review showed that 48% of Canadian women in the 65–69 age group regularly take vitamin D supplements (70). In Canada, dietary supplements are regulated by the Natural and Non-Prescription Health Products Directorate (NNHPD) of Health Canada (52). All products and their manufacturers must be licensed unless the products are made by health care practitioners who compound products on an individual basis for their patients or by retailers of natural health products (NHPs). Details must be provided on medicinal ingredients, source, dose, potency, nonmedicinal ingredients, and recommended use(s). The safety and efficacy of NHPs and their health claims must be supported by proper evidence so that consumers and Health Canada know that the products are indeed safe and effective. Evidence may include clinical trials data or references to published studies, journals, pharmacopoeias, and traditional resources. The type and amount of supporting evidence required depend on the proposed health claim of the product and its overall risks (52). However, given the large number of products registered and new applications processed each year, safety and efficacy rely on the manufacturer and not the agency (56). Under this system, 43,000 product licenses had been issued by 2011 (52).

European Union

The European Commission rules aim to ensure food supplement safety and proper labeling. In the EU, food supplements are regulated as foods, and the legislation focuses on vitamins and minerals used as ingredients of food supplements (30, 31). "There are EU-wide maximum and minimum levels set for each vitamin and mineral added to supplements. Companies wishing to market a substance not included in the permitted list need to submit an application to the European Commission" (31). The number of supplements regulated under this system is not reported because only main ingredients and their quantity are regulated. Many botanical products classified as dietary supplements in other countries are considered foods in the EU context. These products are typically labeled as natural foods, and health claims are often made about their value. The same products may be classified as foods or medicines depending on their use and place of sale.

The EFSA recognizes some of the problems in this approach: "While most of these products have a long history of use in Europe, some concerns exist about their safety and quality. These include the risk of chemical or microbiological contamination and the need to ensure that concentrations of bioactive agents are within safe limits" (32). Some botanicals are considered as traditional herbal medicinal plants and are used both in medicinal products and in food supplements. The European Medicines Agency is responsible for assessing the safety and efficacy of herbal preparations when they are used as medicines (32, 33).

Australia

The use of dietary supplements in Australia is at levels similar to those in other economically advanced countries (about 70% of the population), and the rate has been increasing in recent decades (11). Australian university students have a high level of usage; 69% of students consume vitamins and minerals, and 63% use other dietary supplements in combination with or instead of vitamins (12). In Australia, most dietary supplements are regulated under a category of complementary medicines, which includes vitamin, mineral, herbal, aromatherapy, and homeopathic

products, although some products may be regarded as foods for special purposes and regulated under the food authority (11, 38, 110, 111). Complementary medicines may be either listed or registered, depending on their ingredients and the claims made. The listed category is for low-risk ingredients, and manufacturers are required to compile evidence of safety and efficacy; however, this is not formally assessed. On average, 1,800 new products are listed each year.

China

China's long history of using dietary supplements and herbal medicines stretches back over many millennia, well before the development of Western medical sciences (105, 106). With rapid economic development, the quantity and variety of foods have expanded, nutritional deficiencies have declined, and an epidemic of chronic disease has emerged. In China, dietary supplements are regulated as health foods. The new Chinese Food Safety Law (enacted in 2015) includes 13 items related to health food regulation (27). The China Food and Drug Administration (CFDA) then implemented regulatory system changes, covering the registration and notification processes, creation of a health function claim catalog and an ingredient catalog for health foods, and labeling (20). Major changes include the following: a new notification system for products that use approved dietary ingredients from the health food ingredient catalog (domestic products), as well as vitamin and mineral products (imported products); and the establishment of the Provincial Food and Drug Administrations to oversee domestic health food product notification.

The health claim catalog and ingredient catalog for dietary supplements expand the scope of the regulations, enabling the CFDA to oversee both the end products and their ingredients. Producers with ingredients accepted in foods but not allowed in dietary supplements can apply for the addition of their ingredients to the catalog. To be legally sold in China, every dietary supplement must obtain a Health Food Approval Certificate from the CFDA, indicating that the Chinese government is now focused more on product safety and scientific evidence of functionality.

In Europe, Chinese medicine is very popular, and efforts are being made to provide adequate documentation of efficacy to aid registration (109, 129). The EU has funded a research program, Good Practice in Traditional Chinese Medicine Research, to inform best practice and harmonize research (117).

Japan

In Japan, sales of nutritional and dietary supplements were 1.19 trillion yen (US$11 billion) in 2015 (84). The Ministry of Health Labor and Welfare (MHLW) classifies foods into General Foods and Food with Health Claims (FHC); the latter (which includes dietary supplements) is managed by the Consumer Affairs Agency (24). FHC are further categorized into three subgroups (23, 74):

1. Foods with Nutrient Function Claims (FNFC): all food that is labeled with the nutrient function claims specified by the MHLW. Standards and specifications for indications of nutritional function have been established for 17 ingredients (12 vitamins and 5 minerals). These foods may be freely manufactured and distributed without any permission from the government, provided they meet the established standards and specifications (self-certification).
2. Foods for Specified Health Uses (FOSHU): foods containing dietary ingredients that have beneficial effects on the physiological functions of the human body to maintain and promote health and improve specific health-related conditions. These require individual approval and include conventional food forms as well as capsules and tablets (104).

3. Foods with Function Claims: a new category introduced in April 2015 of food products labeled with nutritional or health functions to enable consumers to make informed choices (24).

South Korea

Dietary supplements are included within the category of health functional foods (HFF) in South Korea, which is regulated by the Ministry of Food and Drug Safety (MFDS) under the HFF Act to ensure safety (94). Tablets, capsules, powders, granules, pastes, gels, jellies, and bars were covered in the Act, but this legislation was extended in 2008 to include conventional foods and other dietary supplements (72). In South Korea, individual ingredients must be approved by the KFDA (Korean Food and Drug Administration) to carry health claims, whereas in Japan, finished product approval is required. Nutrients, functional ingredients, raw materials, ingredients, and components are evaluated and approved by the KFDA, with ~360 approvals by 2016 (94). HFF products approved by the MFDS can use a limited number of health claims with the symbol "HFF." The health functional food market in South Korea was valued at US$10 billion in 2015 (61). Over the past 5 years, the average yearly growth of HFF production in South Korea has been 7.4% (62). Commonly used dietary supplements include ginseng, omega-3, glucosamine, cranberry, and saw palmetto, with red ginseng as the most popular (46.2%), followed by vitamins and minerals (13.8%) and probiotics (10.5%) (73).

FUTURE PUBLIC HEALTH REGULATION OF DIETARY SUPPLEMENTS

Most countries have relatively loose regulations, most often putting market access and industry profit above public health benefit. The EU and Japan have stricter regimes compared with other countries or international groups. In all cases, the challenges of assessing and controlling perhaps 100,000 products would overwhelm any system. The US$180 billion business, with its risk of complications and side effects, deserves tighter regulation and control of product labeling, warnings of side effects (banning if significant), and efficacy (if health claims are made).

Dietary supplements for specific life periods that are used on medical recommendation and part of clinical practice guidelines should be regulated separately. Examples include folate, iodine, iron, vitamin D, and vitamin K in pregnancy and neonates. In Australia, these recommendations are made by the National Health and Medical Research Council and are included in clinical guidelines.

Dietary supplements inhabit a no-man's-land between food and pharmaceuticals. It would simply not be possible to implement pharmaceutical-style regulations for dietary supplements. The prospect of undertaking or evaluating 100,000 randomized controlled trials is beyond imagination. In the food industry, safety measures include direct regulation, market-based incentive mechanisms, postmarket surveillance, and legal liability incentives (17), although enforcement levels vary between jurisdictions. Content of specific foods is generally tightly regulated, and foods cannot be marketed as such unless they strictly conform to compositional and purity standards, such as the Australian Food Standards (39). Nowak proposes that the US Congress enact more proactive legislation using the EU's Food Supplements Directive as a model (83). The Directive could also be used as a model by other countries and for the preparation of Codex regulations.

Dietary supplement regulation would include several minimum requirements:

1. A list of permitted substances, initially based on compounds already marketed safely. Where toxicity is documented, the product must be removed from all sales as rapidly as possible.

Improved surveillance of interactions and complications is required. The use of dietary supplements and complementary medicines should be recorded for all hospital admissions. The decision to initiate a review of a dietary supplement should be based on two criteria, including (*a*) severity and number of adverse events and (*b*) prevalence of usage.

2. A registration system for all products, with strict guidance on permitted compositional variation.
3. Implementation of a system of manufacturing plant inspections and licensing.
4. Use of the upper limits of nutrient reference values and RDIs for maximum content of minerals and vitamins.
5. More informative product labels with details of ingredients. It would seem evident that easy-to-comprehend, accurate, and comprehensive compositional labels are required. To that end, analyses should be undertaken by an accredited laboratory using standard methodology and within agreed tolerances. These tolerances are needed because many supplements are botanicals, which vary naturally in composition. Labeling for allergy prevention is required. Even with accurate labels, it would be impossible for the most experienced pharmacologist and epidemiologist to make informed choices about 50,000–100,000 or so products. Some products have up to 50 ingredients, which makes some products even more difficult to understand. For the lay person guidance should be provided by allowing only health claims that have been substantiated, even if determining effectiveness requires randomized controlled trials. [See the FDA website for examples (115).] However, extensive testing, evaluation of efficacy, and adequate substantiation of claims would be very costly.
6. Recommendations against off-label use.
7. Use of only cultivated products for commercial use. It is difficult to identify plants that are simply gathered from the forest (119).
8. Elimination of banned products, such as endangered animal species, from supplements. These bans must be enforced internationally and not just in some jurisdictions.
9. Adoption of standardized definitions and categories when conducting surveillance of use and of complications. Definitions must be consistent in registration and international trade, a process being undertaken by the Codex.
10. Enhancement of the International Regulations (Codex) in view of the current trade in dietary supplements. Many countries lack the expertise and resources to develop their own regulatory framework.
11. Improved regulation of dietary supplements sold online. The Internet is widely used to promote and sell many dietary supplements with no proven value. Supplements can be purchased over the Internet with little regulatory control. An international task force is required to mitigate this emerging issue.

CONCLUSION

The sale and consumption of dietary supplements represent a multibillion dollar enterprise industry as citizens pursue the goals of health, longevity, and quality of life (21). Unfortunately, as noted by more than one commentator, this practice usually results in expensive urine and little else (71, 77, 87). The exceptions are a small number of clinical indications for supplements such as folate, iodine, and iron during pregnancy and lactation. The best advice is to use dietary supplements only in specific cases of public health or medical need (e.g., iron, folic acid, or iodine deficiency). Eating a healthy diet based on fruits and vegetables and following the Dietary Guidelines for Americans are optimal strategies for leading a long and healthy life (9). Education programs to reduce supplement usage are warranted but are difficult in practice when facing a huge industry

whose massive profits would be threatened. But public health has had to cope with such challenges in the past.

The most advantageous public health option, as compared with using most dietary supplements on the market, with the exceptions noted above, is to eat a diet of nutritious foods that meets all macro- and micronutrient requirements. After modeling a series of diets, Raffensperger reached the following conclusion: "Starting with an expensive bad diet, a person wishing to get any remaining nutrients is more likely to spend less by eating additional carefully selected foods than by taking a supplement" (91, p. 52). This view is a good beginning for supplement education programs.

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AUTHOR CONTRIBUTIONS

The authors all contributed to the literature search for and the writing and editing of the manuscript.

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