

REPORTS OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

The following reports, 1–7, were presented by Lee R. Morisy, MD, Chair:

1. CSAPH SUNSET REVIEW OF 2002 HOUSE POLICIES

Reference committee hearing: see report of [Reference Committee E](#).

HOUSE ACTION: RECOMMENDATIONS ADOPTED AND REMAINDER OF REPORT FILED

At its 1984 Interim Meeting, the House of Delegates (HOD) established a sunset mechanism for House policies (Policy G-600.110, AMA Policy Database). Under this mechanism, a policy established by the House ceases to be viable after 10 years unless action is taken by the House to retain it.

The objective of the sunset mechanism is to help ensure that the AMA Policy Database is current, coherent, and relevant. By eliminating outmoded, duplicative, and inconsistent policies, the sunset mechanism contributes to the ability of the AMA to communicate and promote its policy positions. It also contributes to the efficiency and effectiveness of House of Delegates deliberations.

At its 2002 Annual Meeting, the House modified Policy G-600.110 to change the process through which the policy sunset review is conducted. The process now includes the following steps:

- In the spring of each year, the House policies that are subject to review under the policy sunset mechanism are identified.
- Using the areas of expertise of the AMA Councils as a guide, the staffs of the AMA Councils determine which policies should be reviewed by which Councils.
- For the Annual Meeting of the House, each Council develops a separate policy sunset report that recommends how each policy assigned to it should be handled. For each policy it reviews, a Council may recommend one of the following actions: (a) retain the policy; (b) rescind the policy; or (c) retain part of the policy. A justification must be provided for the recommended action on each policy.
- The Speakers assign the policy sunset reports for consideration by the appropriate reference committees.

Although the policy sunset review mechanism may not be used to change the meaning of AMA policies, minor editorial changes can be accomplished through the sunset review process.

In this report, the Council on Science and Public Health (CSAPH) presents its recommendations on the disposition of the House policies from 2002 that were assigned to it. The CSAPH's recommendations on policies are presented in the Appendix to this report.

RECOMMENDATION

The Council on Science and Public Health recommends that the House of Delegates policies that are listed in the Appendix to this report be acted upon in the manner indicated in the Appendix and the remainder of this report be filed.

APPENDIX - Recommended Actions on 2002 House Policies

Policy Number	Title	Recommended Action and Rationale
H-60.942	Childhood Asthma: Emerging Patterns and Prospects for Novel Therapies	Rescind. Superseded by Policy H-160.932.
H-60.943	Bullying Behaviors Among Children and Adolescents	Retain. Still relevant.
H-85.960	Certification of Cause of Death	Retain. Still relevant.
H-85.961	Accuracy, Importance, and Application of Data from the US Vital Statistics System	Retain in part. Rescind (1) accomplished. Retain (2) as it is still relevant.

Policy Number	Title	Recommended Action and Rationale
H-120.950	Change DEA Procedures in Partial Filling of Schedule II Prescriptions	Retain. Still problematic.
H-120.973	DEA, Diagnosis and ICD-9-CM Codes on Prescriptions	Retain in part to read as follows: Note: (2) is superseded by Policies H-100.972 and H-100.982. Our AMA, in order to protect patient confidentiality and to minimize administrative burdens on physicians opposes, will (1) work to eliminate requirements by pharmacies, prescription services, and insurance plans to include such information as ICD-9-CM codes, DEA numbers, and diagnoses on prescriptions; and (2) inform physicians of their rights to withhold DEA numbers from prescriptions that do not legally require them. (Sub. Res. 518-A-93; Reaffirmation A-97; Reaffirmed by Sub. Res 205-A-98; Reaffirmed: Res. 523-A-00; Amended: Res. 527-A-02)
H-160.926	Sharpening the Focus on Men's Health	Rescind. Already accomplished.
H-210.991	The Education of Physicians in Home Health Care	Retain policy. Still relevant. Change terminology to read: Home Care rather than Home Health Care as indicated, including Title.
H-250.988	Low Cost Drugs to Poor Countries During Times of Pandemic Health Crises	Retain. Still a global issue.
H-370.971	Increasing Organ Donation	Retain. Still relevant.
H-370.977	The Inclusion of Advance Directives Concerning Organ Donation in Living Wills	Rescind. Accomplished.
H-370.981	Organ Procurement Legislation	Rescind. Accomplished.
H-370.983	Tissue and Organ Donation	Reaffirm pending policy consolidation report.
H-370.984	Organ Donation Education	Reaffirm pending policy consolidation report.
H-370.986	Donor Tissues and Organs for Transplantation	Reaffirm pending policy consolidation report.
H-370.990	Transplantable Organs as a National Resource	Reaffirm pending policy consolidation report.
H-370.995	Organ Donor Recruitment	Reaffirm pending policy consolidation report.
H-370.996	Organ Donor Recruitment	Reaffirm pending policy consolidation report.
H-370.998	Organ Donation and Honoring Organ Donor Wishes	Reaffirm pending policy consolidation report.
H-410.960	Quality Patient Care Measures	Retain. Remains an important philosophical stand.
H-440.889	Smallpox: A Scientific Update	Retain. Still relevant.
H-440.921	Drug-Resistant Streptococcus Pneumococcal <u>Pneumonia Vaccination</u>	Retain in part to read with Change in Title as follows: Pneumococcal Vaccination - Our AMA encourages state medical societies to urge their members physicians to expand their use of <u>23-valent pneumococcal vaccine per current ACIP recommendations, for those at increased risk of serious pneumococcal infection age two and over, and for all persons age 65 and over, in light of the accelerating rise in frequency of multiple resistant strains to penicillin and related drugs.</u> (Res. 512, A-94; Reaffirmed: Res. 515. I-01; Reaffirmed: Res. 520, A-02)
H-470.963	Boxing Injuries <u>Safety</u>	Retain in part with Change in Title to read as follows: Boxing Safety - <u>While the AMA recognizes that boxing is a violent sport associated with brain and eye injuries, we recommend it is the policy of the AMA that: (1) until such time as boxing is banned in this country, the following preventive strategies should be pursued to reduce such brain and eye injuries in boxers: (1) Relevant regulatory bodies are encouraged to: (a) require the use of ideally, head blows should be prohibited. Otherwise, our AMA should encourage universal use of protective gear such as headgear, and thumbless, impact absorbing gloves. (b) the World Boxing Council, World Boxing Association, and</u>

Policy Number	Title	Recommended Action and Rationale
		<p>other regulatory bodies should develop and enforce objective brain injury risk assessment tools to exclude individual at-risk boxers from sparring or fighting, including APOE24 screening, neuroimaging, clinical neurological assessment, neurophysiological assessment, and indices of cumulative brain injury. (be) the World Boxing Council, World Boxing Association, and other regulatory bodies should develop and enforce standard criteria for referees, ringside officials, and ringside physicians to halt sparring or boxing bouts when a boxer has experienced concussive or subconcussive blows that place him or her at imminent risk of more serious injury. (cd) the World Boxing Council, World Boxing Association, and other regulatory bodies should encourage implementation of measures advocated by the World Medical Boxing Congress designed to reduce the incidence of brain and eye injuries. (de) the World Boxing Council, World Boxing Association, and other regulatory bodies should require initial and repeat eye examinations for amateur and professional boxers and mandate suspensions from sparring or boxing for specific ocular pathology according to recommendations of the American Academy of Ophthalmology. (2) Our AMA promotes the concept that the professional responsibility of the physician who serves in a medical capacity at a boxing contest is to protect the health and safety of the contestants. The desire of spectators, promoters of the event, or even injured athletes that they not be removed from the contest should not be controlling. The physician's judgment should be governed only by medical considerations. (CSA Rep. 3, A-99; Reaffirmed: Res. 412, A-02) (CSA Rep. 3-A-99; Reaffirmed: Res. 412-A-02)</p>
H-480.964	Alternative Medicine	<p>Retain in part. Retain (2) and (3). Amend (1) to read as follows: Policy of the AMA is: (1) There is little evidence to confirm the safety or efficacy of most alternative therapies. Much of the information currently known about these therapies makes it clear that many have not been shown to be efficacious. Well designed, stringently controlled research should be done to evaluate the efficacy of alternative therapies.</p>
H-525.984	Breast Implants	<p>Retain in part to read as follows: Our AMA: (1) supports the FDA's request that women be fully informed about the risks and benefits associated with breast implants and that once fully informed the patient should have the right to choose; (2) urges physicians to recognize and address the considerable public anxiety concerning the safety of breast implants. This anxiety is not warranted based on current scientific evidence; based on current scientific knowledge, supports the continued practice of breast augmentation or reconstruction with implants when indicated. and (4) urges the FDA and its Commissioner, David A. Kessler, MD, to adopt, endorse, and promulgate the recommendation of its advisory panel, thus allowing silicone gel filled breast implants to remain on the market pending further studies. (CSA Rep. M-I-91; Modified: Sunset Report, I-01; Reaffirmed Res. 727-I-02)</p>
H-525.993	Mammography Screening in Asymptomatic Women Forty Years and Older	<p>Decision pending disposition of CSAPH Report on Screening Mammography expected at A-12.</p>

2. LABELING OF BIOENGINEERED FOODS (RESOLUTIONS 508-A-11 AND 509-A-11)

Reference committee hearing: see report of [Reference Committee E](#).

**HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS
IN LIEU OF RESOLUTIONS 508-A-11 AND 509-A-11 AND
REMAINDER OF REPORT FILED**
See Policy [H-480.958](#)

INTRODUCTION

Resolution 508-A-11, introduced by the Illinois Delegation, asked that our American Medical Association (AMA) study the impact of food containing genetically engineered ingredients and take further action based on the results of the study. Resolution 509-A-11, introduced by the Indiana Delegation, asked that our AMA study the impact of mandated labeling of food containing genetically engineered ingredients and take further action based on the results of the study. Both resolutions were referred.

In a 2000 report, the Council on Scientific Affairs reviewed in depth the technology used to produce transgenic crops, as well as issues relevant to the use of bioengineered ingredients in food, including the regulatory framework, human health effects, and potential environmental impacts.¹ The Council believes that the information in its 2000 report is still current and valid, and therefore will not revisit many of those issues in this report. Rather, it will focus on the issue raised in Resolution 509-A-11, that of labeling foods containing bioengineered ingredients.

METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2000 and 2012 using the search terms “genetically modified food,” “genetically engineered food,” and “bioengineered food,” combined with the terms “health,” “safety,” and “labeling.” To capture other reports, news articles and press releases, Google searches were conducted using the same search terms. Additional articles were identified by manual review of the captured literature citations.

BACKGROUND

Genetic modification of plants has occurred for centuries, as farmers seek to improve yields, disease resistance, and agronomic qualities.^{1,2} Genetic modification by conventional breeding techniques such as crossbreeding, selection, and hybridization can be a lengthy process requiring many generations. Examples of common foods produced through conventional genetic modification include nectarines (which are genetically modified peaches) and tangelos (genetic hybrid of tangerine and grapefruit).³ Late in the 20th century, genetic modification techniques advanced to the molecular level with transgenic technology. Transgenic technology involves the introduction of an advantageous genetic trait into a plant or animal via the direct transfer of a gene or other construct conferring expression of that trait. Examples of the current use of transgenic technology are the production of corn varieties resistant to certain insects, and soybeans resistant to common herbicides.

Food crops produced through transgenic technology are often referred to as “GMOs” (genetically modified organisms). Since plants that are genetically enhanced through conventional breeding techniques can also be considered genetically modified, the Food and Drug Administration (FDA) uses the terms “bioengineered” or “genetically engineered” to refer to transgenically-produced plants. For clarity and consistency with FDA regulatory documentation, this report uses the term “bioengineered” to refer to foods produced through transgenic technologies.

To date, more than 80 transgenic crops have undergone regulatory clearance in the US; however, only about a dozen are currently marketed for human consumption.^{4,5} The most common transgenic crops in the US are soybeans, corn, sugar beets, and cotton (for cottonseed oil). Each of these crops makes up approximately 90% of the total amount planted each year.⁶ Transgenic varieties of rapeseed (for canola oil), papaya, and squash are also common in the US food supply. It is estimated that approximately 70% of processed foods sold in US grocery stores contain ingredients derived from transgenic crops.⁷

Approval of the first transgenically-produced animal intended for human consumption has been under consideration by the FDA for several years.⁸ The animal is an Atlantic salmon containing a growth hormone gene from the Chinook salmon and a gene from the ocean pout that activates the transgenic growth hormone gene year round. As a result, the salmon grows to market size in 16-18 months rather than 3 years.

Intense debate has surrounded bioengineered foods, with critics arguing that safety data are lacking and the potential human health effects of consuming bioengineered foods have not been fully explored. Several groups have called for mandatory labeling of foods containing bioengineered ingredients so that consumers are able to avoid such foods if desired. In this report, the potential adverse health effects of bioengineered foods are reviewed and implications for labeling are addressed. More detailed descriptions of transgenic crop production methods and traits, environmental concerns, and potential benefit for global food production can be found in the Council's 2000 report.¹

AMA POLICY ADDRESSING LABELING OF BIOENGINEERED FOODS

AMA Policy H-480.958 "Genetically Modified Crops and Foods" (AMA Policy Database; see Appendix) is broad, covering the belief that regulatory oversight of bioengineered foods should be science-based and involve systematic safety assessments, supporting research into environmental consequences, and encouraging unbiased information and education of consumers. With regard to labeling, the policy states that "as of December 2009, there is no scientific justification for special labeling of genetically modified foods, as a class, and that voluntary labeling is without value unless it is accompanied by focused consumer education."

POTENTIAL HUMAN HEALTH EFFECTS OF BIOENGINEERED FOODS

Bioengineered foods have been consumed for close to 20 years, and during that time, no overt consequences on human health have been reported and/or substantiated in the peer-reviewed literature.^{1,9,10} However, a small potential for adverse events exists. These potential events are centered around horizontal gene transfer, allergenicity, and toxicity.

Horizontal gene transfer

Horizontal gene transfer (HGT) is the process by which an organism transfers genetic material to another organism other than its offspring and which is followed by integration and expression of the genetic material.¹¹ This process is common among bacteria and other prokaryotes.¹² Speculation that HGT could occur between ingested bioengineered food and enteric bacteria present in the human mouth, stomach, and gut has been expressed. Of special concern are bioengineered foods made from transgenic plants that express antibiotic-resistance markers (ARMs), which are employed during the development of the transgenic plant to select for those that have incorporated the transgene.¹³ When humans ingest food derived from plants that express an ARM, it is theoretically possible that the ARM could be taken up and stably integrated into enteric bacteria through HGT, resulting in bacteria that are resistant to specific antibiotics. This situation has never been reported, although studies point to its possibility. The *epsps* transgene, which confers resistance to a common herbicide, survives intact through the small intestine of humans when bioengineered food made with Roundup Ready soybeans (resistant to the herbicide glyphosate, commonly called Roundup®) is consumed.¹⁴ Also, M13 bacteriophage DNA has been shown to survive transiently in the gastrointestinal tract of mice and is able to enter the bloodstream.¹⁵ However, these studies demonstrate only the ability of certain DNA molecules to resist degradation by salivary and gastric enzymes; no studies to date have demonstrated the ability of the DNA molecules to become stably integrated into the bacterial genome by HGT.¹⁶

Some consumers have reported concerns that consumption of bioengineered foods means that humans will ingest the "foreign" DNA present in transgenes.¹¹ A DNA sequence of particular concern is the cauliflower mosaic virus 35S promoter, commonly used to direct expression of plant transgenes. This promoter is efficient and functional in a variety of organisms, and it has been suggested that it might lead to inappropriate overexpression of genes in species into which it is transferred and promote HGT, or recombine with dormant endogenous viruses present in humans, leading to new infectious viruses.¹⁷ However, almost all genomes of human endogenous retroviruses contain lethal mutations that prevent replication and production of viral particles.¹¹ Also, the cauliflower mosaic virus is present naturally in approximately 10% of cabbages and cauliflowers, and so is regularly ingested by humans. No adverse consequences from the consumption of this virus have been reported.¹¹

Several factors limit the possibility of HGT of plant transgenes into enteric bacteria.¹³ First, depending on the type of food, DNA is broken down during food processing. Second, if it survives food processing, it is then subjected to degradation enzymes in the saliva and gastrointestinal tract when consumed. Third, if DNA were to be taken up by enteric bacteria, it would be subjected to bacterial restriction enzymes that cleave foreign DNA. Further, for stable integration and expression to occur, the DNA fragment would have to be homologous to bacterial DNA (to allow for recombination), and would have to be inserted near the proper regulatory sequences that drive expression. The combination of these barriers results in a nearly impossible chance for stable integration. Nonetheless, in an effort to avoid any chance of enteric bacteria becoming antibiotic resistant, selection methods that do not confer such resistance have been developed and are now commonly used.^{18,19} AMA Policy H-480.958 supports these alternative selection methods.

It should be noted that all foods, even those that are not bioengineered, contain varying amounts of DNA, both from the ingredients themselves and from microorganisms present in the food. To the extent that HGT, although unlikely, could potentially occur, bacteria present in non-bioengineered foods have as much potential to carry out HGT as bacteria present in bioengineered food.²

Toxicity

A serious concern voiced by consumers and others is whether the protein products of transgenes themselves might be toxic to humans, or whether those proteins may induce unintended effects on plant metabolism that could lead to upregulated expression of toxins. This concern was heightened with the publication of a 1999 study reporting negative effects in the gastrointestinal tract of rats fed with potatoes expressing a lectin transgene conferring insecticide activity.²⁰ However, the experimental design of this study is widely regarded as flawed, with subsequent studies unable to reproduce the findings.¹¹ Further studies using the same transgene found that observed differences in blood biochemistry, hematology, immunological parameters, and organ weights were not adverse, and likely to be caused by increased water uptake in the rats consuming food containing the lectin transgene.²¹ The potential toxicity of lectins has been widely documented, and for that reason, no transgenic plants carrying lectin genes have been commercialized.

Other studies have examined potential toxicity of transgenic crops. In one, mice fed Roundup Ready soybeans had modifications in the nuclei of hepatocytes, suggesting that bioengineered soybeans are able to modify the metabolic activities of hepatocytes.²² In another, results suggested that bioengineered soybeans can influence the function of pancreatic acinar cells in mice.²³ However, these studies too have been criticized as being tainted by important flaws.¹¹ In contrast, other groups have demonstrated that neither Roundup Ready soybeans nor Bt corn (expressing a transgene that acts as an insecticide) have any negative effects in mice.^{24,25} The same is true for several other transgenic varieties of soybeans and corn fed to rats.²⁵⁻³⁰ Relevant for humans, the processing of bioengineered foods intended for consumption leads to a complete loss of functional activity for most transgenic proteins.³¹

Before bioengineered foods reach the market, producers perform safety assessments to evaluate potential toxicity. The safety assessments are based on the concept of “substantial equivalence,” which involves a thorough comparison of the new transgenic crop with its conventionally bred counterpart that is generally accepted as safe based on a history of human consumption.^{1,32,33} If the transgenic crop possesses similar levels and variations of critical nutrients and toxicants as its conventional counterpart, it is considered to be substantially equivalent; the presence of novel DNA or protein does not itself qualify as a difference.¹ Any defined differences subject the transgenic crop to additional testing.^{1,32} Newer profiling techniques that aim to increase the probability of detecting toxicants and unintended effects are increasingly being employed.^{2,11}

Allergenicity

The transgene expressed by transgenic crops has the potential to encode a protein that is allergenic to humans. Potential allergenicity problems have occurred in two documented cases. In both, pre- and post-market safety procedures effectively halted exposure.¹¹ The first case involves a transgenic soybean intended for use in animal feed; the soybeans were engineered to express a methionine-rich protein from the Brazil nut. Pre-market testing verified that the transgenic protein was able to bind to Immunoglobulin E (IgE) from people allergic to Brazil nuts, an indication that the protein is an allergen. As a consequence, and even though it was only intended for animal feed, the transgenic soybean variety was never commercialized.³⁴ The second case involved a variety of corn engineered to express Cry9C, an insecticidal protein. The corn was approved for use as an animal feed, but not for human

consumption because upon pre-market testing, Cry9C showed some attributes associated with an allergen.¹¹ Traces of the transgenic corn were detected in some human food products, and after publication of the contamination, some consumers reported adverse effects. However, extended evaluations made by independent institutions could detect no direct implication of Cry9C in the incidents.^{35,36} This variety of corn is no longer commercialized.

To date, no evidence has supported an increased degree of allergenicity of bioengineered foods compared to their non-bioengineered counterparts.^{9-11,37} This is due in part to the safety assessments to which bioengineered foods are subjected prior to marketing.³³ Thorough pre-market evaluation is considered to be the most effective tool to protect the public. Current safety assessments are based on a “weight-of-evidence” approach, where each food product is evaluated on a case-by-case basis using a number of elements.^{38,39} These elements are:

- Source of the transgene: Does the gene encoding the new protein come from a commonly allergenic source such as a food (e.g., peanut, hazelnut, eggs, or milk), respiratory allergen (e.g., pollen or dust mite), or contact allergen (latex)?
- Protein sequence: How closely does the sequence of the newly introduced protein match that of a known allergen?
- IgE-testing: Does the protein encoded by the transgene bind IgE-antibodies from people known to be allergic to the source of the transgene?
- Stability testing: Is the expressed protein highly resistant to digestion by pepsin?
- Abundance: Is the protein abundant and stable in the food?

For each bioengineered food product, the results of these elements are aggregated and interpreted to determine potential allergenicity.³⁸ It should be noted that absolute avoidance of all risk is not achievable. Thus the safety assessments that have been developed focus on avoiding risks that are predictable and likely to cause common allergic reactions. Research to examine more effective methods of allergenicity assessment is ongoing.^{9,40,41}

LABELING OF BIOENGINEERED FOODS

FDA labeling policy

The FDA regulates food labeling using an approach designed to provide consumers with information relative to health, nutrition, and safety. The Federal Food and Drug Cosmetic Act (FD&C Act) lays out the FDA’s science-based labeling policy; all foods, whether or not they are derived from transgenic crops or animals, are subject to the policy.^{42,43} The FDA has the authority to initiate regulatory action if a product fails to meet the requirements of the FD&C Act.³

Three key provisions in the FDA’s labeling policy pertain to the issue of labeling bioengineered foods. First, the law requires that all food labels include a name that accurately describes the basic nature of the food.^{3,43} Regarding bioengineered foods, name changes are only appropriate when the food is significantly different from its traditional counterpart, such that the common or usual name no longer adequately describes the new food. Changes to the name of the product are not appropriate if the resulting bioengineered food is not materially different from its traditional counterpart (i.e., unless the bioengineered food differs in nutritional quality, taste, etc.).

Second, significant differences in food arising from production processes must be disclosed in labeling.^{3,43} Thus, if the transgenic production method materially changes a food’s nutritional profile or results in a safety concern, this must be disclosed on the label. For example, if a bioengineered food were to contain a commonly recognized allergen not present in its non-bioengineered counterpart, the presence of the allergen must be stated on the label. Under this provision, the FDA cannot require labeling based solely on differences in the production process if the resulting products are not materially different or do not pose a safety risk. While the definition of a “material difference” is not specified in the FD&C Act, precedent guides the FDA in its interpretation of the term.³ Generally, the FDA has limited the scope of the materiality concept to information about the attributes of the food itself. The fact that a food or any of its ingredients were produced using transgenic methods is not considered material, and therefore does not constitute information that must be disclosed in labeling. The FDA therefore has neither a scientific nor a legal basis to require such labeling.^{3,42}

Third, the FDA allows voluntary labeling about production methods as long as the labeling is not false or misleading.³ In 2001, the FDA released a Draft Guidance for Industry to provide information to manufacturers

wishing to use informative statements about whether foods contain bioengineered ingredients.⁴⁴ Examples of acceptable statements for foods that do not contain bioengineered ingredients are: “This product does not contain ingredients that were produced using biotechnology” or “This oil is made from soybeans that were not genetically engineered.” The FDA discourages the use of acronyms such as “GMO-free” since some consumers may not know what the acronym stands for, and since “genetically modified” can refer to conventional techniques to alter genotype.

The FDA believes that its current labeling policies, combined with pre-market safety assessments, are sufficient to ensure the safety of bioengineered foods.³ Before marketing foods with bioengineered ingredients, companies voluntarily notify the FDA, leading to a two-part consultation process between the agency and the company that initially involves discussions of relevant safety issues and subsequently the company’s submission of a safety assessment report containing test data on the food in question.⁴⁵ The FDA has considered making the pre-market notification process mandatory, but has stated that it does not believe such a rule is needed since the voluntary process has fully protected the public.^{46,47} To date, all manufacturers of bioengineered foods intended for marketing have engaged in the voluntary notification process.⁷

Although the approval procedures for transgenic animals intended for human consumption are different than those for transgenic plants, the same labeling principles apply. Thus, if bioengineered food produced from a transgenic animal is materially different from its non-bioengineered counterpart in its nutritional or safety profile, it must be labeled as such. As in the case of bioengineered foods produced from transgenic plants, the FDA does not consider the methods used to develop the animal as “material.”⁴⁸

Consumer perspectives on labeling

Fears that bioengineered foods pose a safety threat to consumers, as well as a “right to know” what is being consumed and to be afforded the choice to avoid bioengineered foods, are the basis for arguments that bioengineered foods should be labeled as such.⁴² Several surveys have attempted to characterize consumers’ wishes with regard to labeling bioengineered foods. In surveys asking whether consumers are satisfied with US food labeling policies, only 18% report that information is missing; among this group, only 3% report that information about bioengineering should be included in the label.⁴⁹ However, when direct questions about labeling of bioengineered food are asked of consumers, such as whether they support mandatory or voluntary labeling policies, the overwhelming majority favor mandatory labeling policies.^{7,50-52}

Consumer groups have been outspoken in their support of a mandatory labeling policy for bioengineered foods.^{53,54} A petition calling for mandatory labeling was submitted to the FDA by the Center for Food Safety in the fall of 2011 and more than 400 organizations have expressed their support for the “Just Label It” campaign.^{55,56} The FDA responded in the spring of 2012, saying that it had not yet made a decision on the petition and would continue to consider it. Others have criticized the FDA’s approval and labeling policies as inadequate in the face of advancing plant and animal transgenic technologies and have called for reform.^{57,58} Additionally, more than a dozen states and the US House and Senate have considered legislation focused on mandatory labeling of bioengineered plants and animals. Only Alaska has passed a law, requiring that bioengineered salmon be labeled (bioengineered salmon are not currently marketed).

Mandatory labeling of foods would involve significant costs, especially the costs of testing for the presence of bioengineered ingredients, segregating the crops, and monitoring for truthfulness of labeling and enforcement of the regulations that exist.^{59,60} These costs would likely be passed to the consumer; it is estimated that mandatory labeling would increase the average household’s annual grocery bill by \$140-\$200 per year.^{7,50} Surveys of US consumers reveal that while some are willing to pay a premium for foods that do not contain bioengineered ingredients, the majority of consumers are not willing to pay for increases commensurate with the costs of mandatory labeling policies.^{50,61,62}

Regarding consumers’ “right to know” argument, courts have found that consumer curiosity alone is not enough to require special labeling.^{63,64} The reasoning behind these rulings is that 1) special labeling places an unfair financial burden on industries that would have to investigate, document, and label the “level” of bioengineering in their product; 2) it may mislead consumers into thinking that bioengineered foods are less safe than their conventional counterparts; 3) it places a burden on the FDA itself, which would have to divert resources away from safety-based

labeling to address consumer curiosity; and 4) it places no end on the information consumers could request manufacturers to disclose.

In Europe, all food with bioengineered ingredients must be labeled as such. Several other countries have also adopted mandatory labeling policies.^{59,65} Examination of these policies reveals that mandatory labeling fails to result in consumer choice because stores have chosen not to sell foods with bioengineered ingredients, rather than be seen as supportive of bioengineered foods. In countries that have adopted mandatory labeling, it is often difficult, if not impossible, to find food items bearing such labels.⁶⁶ This is considered to be unfair to those who prefer to buy presumably lower-cost bioengineered foods.⁶⁶

Consumers wishing to avoid bioengineered foods can purchase foods that are certified USDA Organic. This labeling term indicates that no bioengineered ingredients were used in the food.

CONCLUSION

Despite strong consumer interest in mandatory labeling of bioengineered foods, the FDA's science-based labeling policies do not support special labeling without evidence of material differences between bioengineered foods and their traditional counterparts. The Council supports this science-based approach, and believes that thorough pre-market safety assessment and the FDA's requirement that any material difference between bioengineered foods and their traditional counterparts be disclosed in labeling, are effective in ensuring the safety of bioengineered food. To better detect potential harms of bioengineered foods, the Council believes that pre-market safety assessment should shift from a voluntary notification process to a mandatory requirement. The Council understands that some consumers may wish to choose foods that do not contain bioengineered ingredients, and notes that consumers may do so by purchasing food products that are labeled USDA Organic.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolutions 508-A-11 and 509-A-11, and the remainder of the report be filed:

That Policy H-480.958 "Genetically Modified Crops and Foods" be amended by insertion and deletion as follows:

Bioengineered (Genetically ~~Modified~~ Engineered) Crops and Foods

(1) Our AMA recognizes the continuing validity of the three major conclusions contained in the 1987 National Academy of Sciences white paper "Introduction of Recombinant DNA-Engineered Organisms into the Environment." [The three major conclusions are: (a) There is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms; (b) The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods; (c) Assessment of the risk of introducing rDNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced.]

(2) That federal regulatory oversight of agricultural biotechnology should continue to be science-based and guided by the characteristics of the plant or animal, its intended use, and the environment into which it is to be introduced, not by the method used to produce it, in order to facilitate comprehensive, efficient regulatory review of new ~~genetically modified~~ bioengineered crops and foods.

(3) Our AMA believes that as of ~~December 2009~~ June 2012, there is no scientific justification for special labeling of ~~genetically modified~~ bioengineered foods, as a class, and that voluntary labeling is without value unless it is accompanied by focused consumer education.

(4) Our AMA supports ~~efforts for the~~ mandatory pre-market systematic safety assessments of ~~genetically modified~~ bioengineered foods and encourages: (a) development and validation of additional techniques for the detection and/or assessment of unintended effects; (b) continued use of methods to detect substantive changes in nutrient or toxicant levels in ~~genetically modified~~ bioengineered foods as part of a substantial equivalence

evaluation; (c) development and use of alternative transformation technologies to avoid utilization of antibiotic resistance markers that code for clinically relevant antibiotics, where feasible; and (d) that priority should be given to basic research in food allergenicity to support the development of improved methods for identifying potential allergens. The FDA is urged to remain alert to new data on the health consequences of bioengineered foods and update its regulatory policies accordingly.

(5) Our AMA supports continued research into the potential consequences to the environment of ~~genetically modified~~ bioengineered crops including the: (a) assessment of the impacts of pest-protected crops on nontarget organisms compared to impacts of standard agricultural methods, through rigorous field evaluations; (b) assessment of gene flow and its potential consequences including key factors that regulate weed populations; rates at which pest resistance genes from the crop would be likely to spread among weed and wild populations; and the impact of novel resistance traits on weed abundance; (c) implementation of resistance management practices and continued monitoring of their effectiveness; ~~and~~ (d) development of monitoring programs to assess ecological impacts of pest-protected crops that may not be apparent from the results of field tests; and assessment of the agricultural impact of bioengineered foods, including the impact on farmers.

(6) Our AMA recognizes the many potential benefits offered by ~~genetically modified~~ bioengineered crops and foods, does not support a moratorium on planting ~~genetically modified~~ bioengineered crops, and encourages ongoing research developments in food biotechnology.

(7) Our AMA ~~recognizes that the~~ urges government, industry, consumer advocacy groups and the scientific and medical communities ~~have a responsibility~~ to educate the public and improve the availability of unbiased information and research activities on ~~genetically modified~~ bioengineered foods ~~and of research activities.~~

APPENDIX - AMA Policy on Bioengineered Foods

H-480.958 Genetically Modified Crops and Foods

(1) Our AMA recognizes the continuing validity of the three major conclusions contained in the 1987 National Academy of Sciences white paper "Introduction of Recombinant DNA-Engineered Organisms into the Environment." [The three major conclusions are: (a) There is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms; (b) The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods; (c) Assessment of the risk of introducing rDNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced.] (2) That federal regulatory oversight of agricultural biotechnology should continue to be science-based and guided by the characteristics of the plant, its intended use, and the environment into which it is to be introduced, not by the method used to produce it, in order to facilitate comprehensive, efficient regulatory review of new genetically modified crops and foods. (3) Our AMA believes that as of December 2009, there is no scientific justification for special labeling of genetically modified foods, as a class, and that voluntary labeling is without value unless it is accompanied by focused consumer education. (4) Our AMA supports efforts for the systematic safety assessment of genetically modified foods and encourages: (a) development and validation of additional techniques for the detection and/or assessment of unintended effects; (b) continued use of methods to detect substantive changes in nutrient or toxicant levels in genetically modified foods as part of a substantial equivalence evaluation; (c) development and use of alternative transformation technologies to avoid utilization of antibiotic resistance markers that code for clinically relevant antibiotics, where feasible; and (d) that priority should be given to basic research in food allergenicity to support the development of improved methods for identifying potential allergens. (5) Our AMA supports continued research into the potential consequences to the environment of genetically modified crops including the: (a) assessment of the impacts of pest-protected crops on nontarget organisms compared to impacts of standard agricultural methods, through rigorous field evaluations; (b) assessment of gene flow and its potential consequences including key factors that regulate weed populations; rates at which pest resistance genes from the crop would be likely to spread among weed and wild populations; and the impact of novel resistance traits on weed abundance; (c) implementation of resistance management practices and continued monitoring of their effectiveness; and (d) development of monitoring programs to assess ecological impacts of pest-protected crops that may not be apparent from the results of field tests. (6) Our AMA recognizes the many potential benefits offered by genetically modified crops and foods, not support a moratorium on planting genetically modified crops, and encourage ongoing research developments in food biotechnology. (7) Our AMA recognizes that the government, industry, and the scientific and medical communities have a responsibility to educate the public and improve the availability of unbiased information on genetically modified crops and of research activities. (CSA Rep. 10, I-00; Modified: CSAPH Rep. 1, A-10)

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3. SAFETY OF BOTTLED WATER (RESOLUTION 420-A-11)

Reference committee hearing: see report of [Reference Committee D](#).

**HOUSE ACTION: RECOMMENDATIONS ADOPTED
IN LIEU OF RESOLUTION 420-A-11 AND
REMAINDER OF REPORT FILED**

See Policy [D-440.999](#)

Resolution 420-A-11 "Public Health Concerns with Safety of Bottled Water," introduced by the American Association of Public Health Physicians and referred to the Board of Trustees, asks:

That in order to protect the public from further dental caries and gum disease, our American Medical Association publicly call for immediate action on the part of the bottled water industry to bring up the level of fluoride in their water to the same level as required in the community where bottles are filled and that information be placed on the label along with the original source of water in plain English, and

The AMA Board ask its Council on Science and Public Health for a timely study of various public health concerns that arise from bottled water and recommendations to make bottled water safer and consumers better informed with report back at the A-2012 meeting of the AMA House of Delegates.

Current AMA policy supports federal regulation and appropriate labeling of the chemical content of commercially bottled water, as well as partnership with the American Dental Association to promote the availability of fluoridated bottled water to consumers (Policy D-440.999, AMA Policy Database). AMA Policy also supports a comprehensive program of fluoridation of all public water supplies that are fluoride-deficient based on current standards (Policy H-440.972).

METHODS

English-language reports were selected from a PubMed search of the literature from 1995 to March 2012 using the MeSH terms “drinking water,” “fresh water,” “water supply,” or “water pollutants,” combined with the terms “analysis,” “standards,” “chemistry,” “toxicity,” “government regulation,” “maximum allowable concentration,” “consumer satisfaction/attitude,” “disease outbreaks,” and “environmental exposure.” A similar search was conducted using the MeSH terms “fluorides or fluoridation/analysis,” combined with “dental caries,” and “epidemiology,” “etiology,” “prevention and control” and the text term “bottled water.” Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the US Environmental Protection Agency (EPA), US Food and Drug Administration (FDA), General Accountability Office (GAO), National Resources Defense Council, Environmental Working Group, International Bottled Water Association, Beverage Marketing Corporation, and the Drinking Water Research Foundation.

BACKGROUND

The per capita consumption of bottled water in the United States more than doubled from 13.4 gallons per person in 1997 to 29.3 gallons per person in 2007.¹ With the onset of the economic recession, domestic bottled water consumption declined in 2008 and 2009 but resumed its growth in 2010 reaching a new high of 8.75 billion gallons in 2010.² The top three bottled water companies in the United States are Nestle Waters North America, Coca-Cola, and PepsiCo.² More than 95% of bottled water consumed in the US is noncarbonated, and the majority of plastic bottles used for bottled water are constructed from the resin polyethylene terephthalate (PET or PETE), which also is used in the packaging of other food products and cosmetics.^{1,2} Individuals who have largely replaced municipal tap water with bottled water for consumption believe that bottled water is safer and healthier than tap water; taste preference and convenience also play a role in consumer’s decisions to forgo reliance on tap water.³⁻⁹

With the surge in bottled water consumption, the regulatory framework for manufacturing and the quality and safety of bottled water have been scrutinized. Questions also have been raised about labeling and whether consumers are adequately informed about the source and treatment of bottled water. Environmental issues related to energy consumption, recycling, and groundwater extraction also exist. These issues were recently examined in a report commissioned by the General Accounting Office.¹ Finally, as more consumers turn to bottled water and parents substitute bottled water for tap water for their children, the beneficial effects of drinking fluoridated tap water in reducing tooth decay may be lost.

REGULATION OF WATER FOR CONSUMPTION

In the United States, bottled water is regulated by the Food and Drug Administration (FDA) as a food under the Federal Food, Drug, and Cosmetic Act (FFDCA).¹⁰⁻¹² The Environmental Protection Agency (EPA) regulates tap water, also referred to as municipal water or public drinking water, under the Safe Drinking Water Act.¹³ Because the increase in bottled water consumption has been fueled by perceptions that bottled water is safer and healthier than tap water, some attention has been devoted to how both sources are regulated, as well as their relative quality and safety requirements.

Tap Water

In the US about 30% of all people get their tap water from ground water sources, and about 70% of people get their tap water from surface water sources. More than 97 percent of the nation’s 157,000 public water systems serve fewer than 10,000 people, and more than 80 percent of these systems serve fewer than 500 people.¹⁴

The Safe Drinking Water Act establishes national regulations to control the level of contaminants (known or anticipated to occur) in drinking water; standards reflect maximum contaminant levels. When it is not economically or technically feasible to set a maximum contaminant level, the EPA creates a required “treatment technique” which specifies how the water should be treated to remove contaminants (e.g., viruses, bacteria, protozoa, certain chemicals). The EPA also requires that public water systems provide annual drinking water quality reports to consumers.

States can assume primary enforcement responsibility for public water systems if they adopt regulations that are at least as stringent as the EPA's primary drinking water regulations. In so doing, states must: (1) establish statutory or regulatory enforcement authority to compel compliance with national quality standards; (2) maintain an inventory of public water systems operating in the state; (3) have a systematic program for conducting sanitary surveys of public water systems; and (4) establish a certification program for laboratories that conduct analytical measurements for annual consumer reports. Although such states are responsible for inspecting their public water systems, they do so under regional EPA oversight subject to (at least) annual review.

Bottled Water

The FDA regulates bottled water that is sold in interstate commerce as a packaged food product. Bottled water packaged and sold within the same state is not covered by these regulations and must be regulated at the state level. For bottled water sold in interstate commerce, FDA applies the same statutory and regulatory provisions applicable to all packaged food and beverage products. The general requirements for food labeling include ingredient and nutrition information, as well as product name, name and address of manufacturer, packer, or distributor and the net contents.¹⁵ Some states require additional information regarding the water source and treatments applied to the bottled water. Regulations specific to bottled water under 21 CFR address definitions, identity standards, quality standards, and good manufacturing practices.¹⁰⁻¹²

Definitions and identity standards. Bottled water is "water that is intended for human consumption and that is sealed in bottles or other containers with no added ingredients except that it may optionally contain safe and suitable antimicrobial agents." Fluoride may be optionally added (see below) within the limitations established in 165.110(b)(4)(ii). In addition to the terms "bottled water" and "drinking water," several other identity designations are allowed on the label based on the water source and process (see Table). The FDA's definition of bottled water exempts many types of bottled water (i.e., carbonated water, seltzer water, soda water, or tonic water) from federal regulations.

Quality standards. Federal regulations (21 CFR § 165) create quality standards that establish limits for chemical, microbiological, physical, and radioactive substances for the finished bottle water product. FDA's quality standards for bottled water must be "no less stringent" than EPA's corresponding maximum contaminant level for tap water.¹⁶ These regulations establish enforceable quantifiable limits for 91 microbiological, physical, chemical, and radiological substances. For a list of such contaminants see 21 CFR § 165(110);¹⁷ for side-by-side comparisons with the maximum contaminant levels for tap water see the GAO report or a publication offered by the Drinking Water Research Foundation.^{1,18} If the EPA changes or establishes a new maximum contaminant level, the FDA is obligated to follow suit within 180 days or publish its rationale for not doing so. If the FDA fails to do so, then the EPA regulation becomes applicable to the quality standards for bottled water.

Good manufacturing practices (GMP). GMPs address protection of the water source from contamination, sanitation at the bottling facility, manufacturing production and process controls, and sampling and testing requirements for contaminants. States or localities are responsible for approving sources of water.

The FDA inspects domestic bottling plants for filling, capping, sealing, washing, and sanitizing operations; verifies use of approved water sources; checks labels for compliance; and also requires the bottlers to test their source and bottled water periodically. According to the GAO, the FDA has increasingly contracted with state agencies to conduct inspections; states now conduct about 70% of all inspections, but state-based agreements to obtain analytical results may be lacking.¹

Many states have enacted their own laws and regulations addressing bottled water through state environmental, food, or agricultural agencies, some of which (e.g., California) are more stringent than federal regulations. However, in contrast to the federal regulatory authority embedded in the Safe Water Drinking Act, which establishes regional EPA oversight of state-based activities, the FDA lacks similar statutory authority to ensure state compliance with national quality standards. According to the GAO, most but not all states require use of a certified laboratory for microbiological tests on bottled water, but approximately 40% of states do not require that bottled water quality tests or violations be reported.¹

Imported Bottled Water

FDA oversight of imported bottled water was described in the GAO Report as “limited” but is accomplished according to the same protocol that governs food imports. That process involves review of scheduled imports, transmission of information to the US Customs and Border Protection database, and electronic screening of these entries for terrorism and serious health risk-related concerns. Electronic review either allows the import to proceed or flags the product for inspection. More than 95% of bottled water and 99% of spring or mineral water imports escape any further review.¹ Since 2004, only one import alert has been issued for bottled water.¹

Industry Driven Standards

In addition to federal and state regulations and requirements for bottled water, industry standards have been established by the International Bottled Water Association (IBWA).¹⁹ The IBWA Code of Practice is a set of self-regulating industry standards. The Code of Practice establishes a comprehensive set of standards for bottler members that address product quality, GMPs and operational requirements, source water monitoring, finished product monitoring, and labeling. Some of the IBWA’s water quality standards are more stringent than federal requirements.

According to IBWA, its membership includes about 80 percent of the bottled water manufacturers in the United States, although two of the largest manufacturers (Coca-Cola and PepsiCo) are not members. To be a member, IBWA requires bottled water facilities to undergo an annual plant inspection, conducted by an independent third-party organization. Conforming to the technical and regulatory requirements of the Code may be a “valuable tool for the company’s promotional activities.”¹ The Code also establishes standards to ensure a secure facility. Such security standards are not required by FDA for bottled water facilities, but the agency has published guidance on this topic.²⁰

REGULATORY DIFFERENCES THAT IMPACT BOTTLED WATER

FDA’s quality standards are identical to the EPA’s maximum contaminant levels in most instances. The EPA has standards in place for various treatment techniques to eliminate certain infectious agents (i.e., viruses, *Cryptosporidium*, *Giardia*, *Legionella*), certain organic chemicals, and asbestos; the FDA has not adopted these standards but has issued an explanation for not doing so. For example, FDA has not set a standard of quality for bottled water for the infectious organisms noted above because they are only found in surface water or groundwater sources under the direct influence of surface water. Bottled water groundwater sources are not permitted to be under the direct influence of surface water (i.e., in contact with the atmosphere).¹¹

The FDA, on the other hand, has quality standards that are more stringent than EPA for lead, copper, nickel, and total phenols. With the FDA’s final rule requiring bottled water manufacturers to test weekly for coliform organisms at both the source and in finished products (except for bottled water derived from municipal sources), any bottled water containing *E. coli* now is considered misbranded, and water sources containing *E. coli* are not considered to be safe.²¹ The FDA also recently adopted a final rule on a quality standard for di(2-ethylhexyl)phthalate (DEHP) that adopts the EPA maximum contaminant level.²² The lack of a DEHP standard and a zero tolerance policy for *E. coli* had been the source of ongoing criticism.

Safety and Quality of Bottled Water

A comprehensive analysis of federal and state regulations affecting bottled water and random chemical analyses of bottled water samples by the National Resources Defense Council in 1999 raised some concerns about regulatory gaps, as well as contaminants (including bacteria) that might appear in bottled water.²³ However, the majority of samples tested were of high quality and the “levels of synthetic organic and inorganic chemicals of concern (which were tested) were either below detection limits or well below all applicable standards.”^{23,24} Similar concerns also were raised by the Environmental Working Group which analyzed contaminants in 10 major bottled water brands.²⁵ Also attention has been devoted to possible leaching of substances, including phthalates, endocrine disruptors, antimony from plastic resins used to construct the containers for bottled water, and arsenic concentrations in spring water.²⁶⁻³¹ Bottlers are not required to test water after storage, nor are they required to list the bottling dates for their water. Other independent studies, some from Europe, generally found that bottled water samples were safe and free of serious contamination.³²⁻³⁷

Despite these types of periodic analyses, the Drinking Water Research Foundation claims that “according to FDA records, over the past 20 years, there have been only 6 Class I recalls of bottled water; 5 for extreme levels of arsenic in imported product from one foreign company and 1 for misbranding of isopropyl alcohol as purified water.” In addition there have been approximately 50-60 Class II and Class III recalls.”¹⁸ Class II recalls imply that an adverse effect is temporary or medically reversible and Class III recalls imply that exposure is not likely to cause adverse health effects. Accordingly, the FDA places a low priority on enforcement and compliance activities with respect to the bottled water industry. In contrast, 36 disease outbreaks associated with public drinking water (including 3 deaths) were reported to the CDC in 2007-2008, mostly from bacterial, viral, or parasitic contamination.³⁸ Approximately 60% of these involved contamination in the source water, treatment facility, or distribution system. Additionally, the EPA recorded more than 11,000 violations of maximum contaminant levels involving more than 5,000 public water systems in 2010.¹⁸ When comparing these relative values, it is important to keep in mind that the EPA requires mandatory reporting when a maximum contaminant level is breached, and testing is much more frequent. Also, a publicly available database of ongoing water quality reports for bottled water companies is not available. Finally, the number of contamination events is a vanishingly small percentage of annual exposures given that municipal water supplies directly serve more than 280 million individuals accessing more than 80 million residential customer connections.³⁹

Environmental Concerns

Using customers in the city of Los Angeles as the destination, the average energy cost of creating and transporting 1 L of bottled water is 1000-2000 fold higher than tap water.⁴⁰ The plastic container for most bottled water is PETE, which also is commonly used to package other food products, cosmetics, and house-hold cleaners. The majority of such plastic bottles appear to be discarded rather than recycled, but overall they represent a small fraction of the total discarded US solid municipal waste (<1%). PETE is relatively inert, but the recycling rate of such plastic bottles needs to be improved. Some companies have voluntarily changed the composition and shape of their bottles to require the use of less plastic. The GAO concluded that “groundwater extraction for bottled water is small relative to groundwater withdrawals for other uses, but can have noticeable local impacts, leading some states to enact new or amended requirements for extracting groundwater for bottled water.”^{1,41,42}

FLUORIDATION OF WATER

Water fluoridation is a community-based intervention that optimizes the level of fluoride in drinking water, resulting in preeruptive and posteruptive protection of the teeth.⁴³ The United States Department of Health and Human Services has a pending recommendation for the optimal level of fluoride in tap water at 0.7 ppm (1 ppm = 1 mg/L). This concentration effectively reduces tooth decay while minimizing the occurrence of dental fluorosis. More than two-thirds of US communities are served by public water systems that are optimally fluoridated. The EPA’s maximum contaminant level for fluoride is 4 mg/L (4 ppm); any community water supply that exceeds 2 mg/L is required to alert consumers. Earlier studies revealed that water fluoridation reduces the amount of cavities in baby teeth as much as 60% and cavities in adult permanent teeth by 35%.^{44,45} Currently, community water fluoridation reduces dental carries 20-40% even with the availability of other fluoride sources such as topical fluoride or fluoride-supplemented toothpaste.^{44,46}

All ground and surface water in the US contains some naturally occurring fluoride. The FDA requires that the fluoride content of bottled water be identified only if fluoride is added to the water during processing. Bottled water quality standards allows for a range of fluoride concentrations (1.4 to 2.4 mg/L) depending on average annual maximum temperature at locations where the bottled water is sold. Variability in air temperature is deemed important for overall fluoride exposure because people who live in warm climates tend to drink more water (and thus more fluoride) than those who live in cold climates. Imports are limited to a maximum of 1.4 mg/L. Bottled water that contains added fluoride is limited to a range of 0.8 to 1.7 mg/L, with imports restricted to the lower limit of this range. Ninety to ninety-seven percent of bottled water that has been randomly tested contains less than optimal amounts of fluoride for prevention of tooth decay, although some mineral waters have sufficient fluoride concentrations, and some may exceed optimal levels.⁴⁷⁻⁵⁰ Most consumers are not knowledgeable about fluoride in drinking water.⁵¹

While it is intuitive that drinking bottled water to the exclusion of tap water would increase caries incidence, few clinical investigations have been conducted to directly evaluate this hypothesis. In a secondary analysis of participants in the Iowa Fluoride Study, bottled water users had significantly lower fluoride intake, but no significant

differences were found in either permanent tooth caries or primary second molar caries.⁵² The power of this study was limited by the fact that only 10% of the participants drank bottled water. An Australian study found a significant positive relationship between deciduous caries experience and consumption of bottled water only for children with 100% lifetime availability of fluoridated water; the effect of consumption of nonpublic water on permanent caries experience was not significant.⁵³

American Dental Association Policy

In order to ensure optimal fluoride intake, the American Dental Association (ADA) urges its members to educate their patients regarding the level of fluoride in bottled water and inquire about their patients' primary and secondary water source as part of the health history.⁵⁴ The ADA also supports the labeling of bottled water with the fluoride concentration of the product and has guidelines for its acceptance in place for applying its Seal of Acceptance to bottled water products with fluoride concentrations in the optimal range for prevention of tooth decay.⁵⁴

American Academy of Pediatrics

In their policy statement regarding "preventive oral health interventions for pediatricians," the AAP notes that secondary preventive strategies are "hierarchical and (currently) consist of dietary counseling, oral hygiene instruction, and judicious administration of fluoride modalities."⁵⁵ AAP policy is silent on the issue of bottled water and caries prevention.

DISCUSSION

Public drinking water and bottled water are both regulated extensively. The FFDCA requires the FDA to regulate bottled water as a food, as opposed to public drinking water subject to the Safe Water Drinking Act. Because bottled water has had a relatively good safety record over the years, bottled water facilities are generally assigned a low priority for inspection. Resource constraints and the lack of statutory authority to mandate use of certified laboratories or require the reporting of quality violations also contribute to this practice. In fact, the quality standards for bottled water are as stringent as those for tap water. Where the EPA requires the use treatment techniques, the FDA has explained why these are not necessary for bottled water.

The oversight and safety of public drinking water in the US is of such high quality that in the vast majority of cases little medical need exists for the public to choose bottled water over public drinking water other than convenience and social habit. The advantages of most municipal drinking water sources include fluoridation to reduce dental caries and a lack of environmental pollution from plastic beverage containers. Additionally, although most data suggest that bottled water is generally no healthier or safer than most tap water, consumers are paying 1000-2000 times the cost of tap water to obtain bottled water, which in many cases is simply municipal water that has been subject to additional treatment. Consumers also could benefit from a more transparent reporting of bottled water quality reports that are available in an easily accessible format.

Little is known about the effects of temperature and storage on the potential leaching of substances from the plastic resins used to construct water bottles; more information should be developed regarding potential changes in contaminant levels at the point of consumption. With lessons learned from dietary exposure to bisphenol A, the FDA should be cognizant of how plastic resins and packaging can contaminate beverages with chemicals.

Because the majority of commercial bottled water is low in fluoride, a potential exists for an increase in dental caries in children and adolescents. By initiating communication with parents and educating them about appropriate preventive strategies including dietary counseling and fluoride sources, health care and dental providers may be able to better evaluate the adequacy of children's fluoride exposure and decide whether fluoride supplementation is necessary. To assist in this process, the fluoride content of bottled water should be clearly labeled. Currently there is a lack of evidence that reliance on bottled water, in and of itself, increases tooth decay.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolution 420-A-11:

That D-440.999, Chemical Analysis Report of Public and Commercial Water, be amended by insertion and deletion to read as follows:

Our AMA: (1) requests the appropriate federal agency to require analysis and appropriate labeling of the chemical content, including fluoride, of commercially bottled water, as well as of the water supplies of cities or towns; (2) ~~will work with the American Dental Association to promote the availability of fluoridated, commercially bottled water to consumers.~~ urges the FDA to require that annual water quality reports from bottled water manufacturers be publicly accessible in a readily available format; and (3) urges the FDA to evaluate bottled water for changes in quality after typical storage conditions.

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Table. Identity Definition of Bottled Water^a

Name	Definition/Nomenclature
Artesian/Artesian well water	Water from a well tapping a confined aquifer in which the water level stands at some height above the top of the aquifer.
Mineral water	Water containing not less than 250 parts per million (ppm) total dissolved solids (TDS), coming from a source tapped at one or more bore holes or springs, originating from a geologically and physically protected underground water source.
Purified water	Water that has been produced by distillation, deionization, or reverse osmosis. This water is intended to be essentially free of chemicals (<10 parts/billion) and may also be free of microbes if treated by distillation or reverse osmosis. Alternatively, the terms "deionized," "distilled," or "reverse osmosis water" or drinking water may be used on the label.
Sparkling bottled water	Water that, after treatment and possible replacement of carbon dioxide, contains the same amount of carbon dioxide from the source that it had at emergence from the source.
Spring water	Water derived from an underground formation from which water flows naturally to the surface of the earth.
Well water	Water from a hole bored, drilled, or otherwise constructed in the ground which taps the water of an aquifer.
Sterile or Sterilized water	Water that meets the requirements under "Sterility Tests" in the United States Pharmacopeia (free of all microbes).

Ground water	Water from a subsurface saturated zone that is under a pressure equal to or greater than atmospheric pressure but not under the influence of surface water (open to the atmosphere).
<p>“When bottled water comes from a community water system, except when it has been treated to meet the definitions “purified water” or “sterilized water” and is labeled as such, the label shall state “from a community water system” or, alternatively, “from a municipal source” as appropriate, on the principal display panel or panels.</p>	

4. LIGHT POLLUTION: ADVERSE HEALTH EFFECTS OF NIGHTTIME LIGHTING

Reference committee hearing: see report of [Reference Committee D](#).

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS AND REMAINDER OF REPORT FILED

See Policies [H-135.932](#) and [H-135.937](#)

INTRODUCTION

Current AMA Policy H-135.937 (AMA Policy Database) advocates for light pollution control and reduced glare from (electric) artificial light sources to both protect public safety and conserve energy. Lighting the night has become a necessity in many areas of the world to enhance commerce, promote social activity, and enhance public safety. However, an emerging consensus has come to acknowledge the effects of widespread nighttime artificial lighting, including the: 1) impact of artificial lighting on human health, primarily through disruption of circadian biological rhythms or sleep; 2) intersection of ocular physiology, vehicle headlamps, nighttime lighting schemes, and harmful glare; 3) energy cost of wasted and unnecessary electric light; and 4) impact of novel light at night on wildlife and vegetation. In addition to these health and environmental effects, an esthetic deficit is apparent with the progressive loss of the starry night sky and interference with astronomical observations. With the assistance of experts in the field, this report evaluates the effects of pervasive nighttime lighting on human health and performance. Concerns related to energy cost, effects on wildlife and vegetation, and esthetics are also briefly noted.

METHODS

English-language reports in humans were selected from a PubMed search of the literature from 1995 to March 2012 using the MeSH terms “circadian/biological clocks/rhythm,” “chronobiology/disorders,” “photoperiod,” “light/lighting” “sleep,” “work schedule,” or “adaptation,” combined with the terms “physiology,” “melatonin,” “adverse effects/toxicity,” “pathophysiology,” “neoplasm,” “epidemiology/etiology,” “mental disorders,” “energy metabolism,” and “gene expression.” Additional articles were identified by manual review of the references cited in these publications; others were supplied by experts in the field who contributed to this report (see Acknowledgement).

LIGHT AND HUMAN PHYSIOLOGY

The solar cycle of light and dark provides the essential basis for life on Earth. Adaptation to the solar cycle has resulted in fundamental molecular and genetic endogenous processes in virtually all life forms that are aligned with an approximately 24-hour period (circadian biological rhythm). The circadian genetic clock mechanism is intimately involved in many, if not most, facets of cellular and organismal function.¹ Although the circadian system spontaneously generates near-24-hour rhythms, this master clock must be reset daily by the light-dark cycle to maintain proper temporal alignment with the environment. In humans and other mammals, this daily entrainment is achieved primarily by novel photoreceptors that project directly to the site of the circadian clock (suprachiasmatic nuclei (SCN) of the hypothalamus).²⁻⁵ The tandem development of an endogenous rhythm sensitive to light presumably evolved to allow for precise 24-hour regulation of rest and activity, and for adapting to seasonal changes in night-length, while maintaining the advantages of an underlying physiology that anticipates day and night. Understanding the molecular and physiological basis of endogenous rhythms, how light information is communicated, and the health implications of disruptions to this system are topics of intensive study.

ELECTRIC LIGHTING AND HUMAN HEALTH

Biological adaptation to the sun has evolved over billions of years. The power to artificially override the natural cycle of light and dark is a recent event and represents a man-made self-experiment on the effects of exposure to

increasingly bright light during the night as human societies acquire technology and expand industry. At the same time, increasing numbers of people work inside buildings under electric lighting both night and day. Artificial lighting is substantially dimmer than sunlight and provides a very different spectral irradiance. Sunlight is strong at all visible wavelengths, peaking in the yellow region, whereas electric lighting has either extreme characteristic wavelength peaks (fluorescent) or exhibits a monotonic increase in irradiance as wavelength lengthens (incandescent). In contrast to outdoor lighting conditions, much of the modern world now lives and works in relatively dim light throughout the day in isolation from the sun, with often poor contrast between night and day, even for those who live and work in sunny environments.⁶

Extensive nighttime lighting is required for contemporary society and commerce. Therefore, it is imperative to evaluate the unintended adverse health consequences of electric lighting practices in the human environment, and determine their physiological bases so that effective interventions can be developed to mitigate harmful effects of suboptimal light exposure. For example, engineers have already developed less disruptive night lighting technologies, and continued progress in this area is anticipated. That such technologies exist, however, does not guarantee that they will be purchased, installed and properly implemented. The medical community and public can take the lead on advocating a healthier environment, as illustrated by recent changes in public smoking policies worldwide. As the research on the biology of circadian rhythms has advanced, the range of potential disease connections due to disrupted circadian rhythms and sleep has expanded.

Biological Impact of Light on Human Physiology

Light is the most powerful stimulus for regulating human circadian rhythms and is the major environmental time cue for synchronizing the circadian clock. In addition to resetting the circadian pacemaker, light also stimulates additional neuroendocrine and neurobehavioral responses, including suppression of melatonin release from the pineal gland, directly alerting the brain, and improving alertness and performance.⁷⁻⁹ Melatonin is one of the most studied biomarkers of the human physiological response to light.¹⁰ This substance is the biochemical correlate of darkness and is only produced at night, regardless of whether an organism is day-active (diurnal) or night-active (nocturnal). Conceptually, melatonin provides an internal representation of the environmental photoperiod, specifically night-length. The synthesis and timing of melatonin production requires an afferent signal from the SCN. Ablation of this pathway, which occurs in some patients from upper cervical spinal damage, completely abolishes melatonin production. Certain other circadian rhythms (e.g., cortisol, body temperature, sleep-wake cycles) do not depend on this pathway and persist if the SCN pathway is damaged.

Light is not required to generate circadian rhythms or pineal melatonin production. In the absence of a light-dark cycle (e.g., totally blind individuals), the circadian pacemaker generates rhythms close to, but not exactly a 24-hour periodicity, reflecting the timing of processes under SCN control.² However, as previously noted, the timing of SCN rhythms and consequently the rhythms controlled by the circadian clock are affected by light, and require daily exposure to the light-dark cycle to be synchronized with the 24-hour day.

When light information fails to reach the SCN to synchronize the clock and its outputs, the pacemaker reverts to its endogenous non-24-hour period (range 23.7-25.0 h). Consequently, the timing of physiology and behavior that is controlled by the circadian system, for example the sleep-wake cycle, alertness and performance patterns, the core body temperature rhythm, and melatonin and cortisol production, becomes desynchronized from the 24-hour day.² The resultant clinical disorder is termed “non-24-hour sleep-wake disorder” and is characterized by alternating episodes of restful sleep, followed by poor night-time sleep and excessive day-time napping, as the non-24-hour circadian pacemaker cycles in and out of phase with the 24-hour social day.¹¹ Another effect of light exposure at night is the immediate suppression of melatonin production. Under natural conditions, organisms would never be exposed to light during the night in substantial amounts and would not experience melatonin suppression. Electric light, however, efficiently suppresses melatonin at intensities commonly experienced in the home at night.¹²

Measures of Illumination

Luminous flux is the measure of the perceived power of light. The lumen is the standard international unit of luminous flux, a measure of the total “amount” of visible light emitted by a source, while illumination is a measure of how much luminous flux is spread over a given area (intensity of illumination). One lux is equal to one lumen/m². Luminous flux measurements take into account the fact that the human eye and visual system is more sensitive to some wavelengths than others. The peak luminosity function is in the green spectral region; white light sources

produce far fewer lumens. To provide some perspective, the illuminance associated with a full moon is less than 1 lux, versus 50 lux for a typically incandescent lit family room, 80 lux in a narrower hallway, 325-500 lux for office lighting, 1,000 lux for an overcast day, and 32,000-130,000 lux for direct sunlight.

Initially it was thought that bright light of at least 2,500-20,000 lux was needed to suppress nighttime melatonin secretion or phase shift the melatonin rhythm (as in jet lag) in humans.¹³⁻¹⁵ It is now established that when exposure of the human eye is carefully controlled, illuminance as low as 5-17 lux of monochromatic green light or 100 lux of broadband white light can significantly suppress melatonin in normal human volunteers.^{12,16-18} Similarly, circadian phase shifts of the melatonin rhythm can be evoked with an illuminance of 5 lux of monochromatic blue light or <100 lux of white fluorescent light, however, exposure to red light is not disruptive.^{18,19} Typical lighting in bedrooms in the evening after dusk (but before bedtime) can also suppress melatonin and delay its nocturnal surge.¹² Acute enhancement of both subjective and objective measures of alertness can be evoked with as little as 5 lux of monochromatic blue light.²⁰ Dose-response curves for melatonin suppression by night-time light exposure to fluorescent light show that ~100 lux of light induces 50% of the maximal response observed with 1,000-10,000 lux of light.^{18,21}

Ocular Physiology Mediating Photic Effects

Factors that alter the amount and spectral quality of light reaching the retina include gaze behavior relative to a light source, age (of the ocular lens), and pupillary dilation. Once a light stimulus reaches the retina, physiology within the retina and within the nervous system determines the capacity of the stimulus to evoke circadian, neuroendocrine or neurobehavioral responses. This physiology includes: 1) the sensitivity of the operative photopigments and photoreceptors; 2) location of these photoreceptors within the retina; 3) the ability of the nervous system to integrate photic stimuli spatially and temporally; and, 4) the state of photoreceptor adaptation.

In particular, both short and long-term photoreceptor adaptation can significantly modify the biological and behavioral responses to light and acutely suppress melatonin in humans.²² For example, a full week of daytime exposure to bright light (by daylight and/or indoor light boxes at ~ 5,000 lux) or a three-day period of exposure to moderate indoor lighting (200 lux) reduces an individual's sensitivity to light suppression of nighttime melatonin compared with exposure to dim indoor lighting (0.5 lux); similar dim light conditions also enhance circadian phase shifting.²³⁻²⁵ Two hours of exposure to 18 lux of white incandescent light versus full dark exposure in a single evening modifies the sensitivity of an individual for light-induced melatonin suppression later that same night.²⁶ Hence, photoreceptor adaptation, like the other ocular and neural elements noted above, can significantly modify the biological and behavioral responses to light.¹⁶

In general, photobiological responses to light are not all-or-none phenomena. In the case of acutely suppressing high nighttime levels of melatonin or phase-shifting the entire melatonin rhythm, light works in a dose-response fashion. Once threshold is exceeded, increasing irradiances of light elicit increasing acute plasma melatonin suppression or longer-term phase-shifts of the melatonin rhythm in healthy individuals.^{16,18,27} All humans, however, are not equally sensitive to light; significant individual differences exist in sensitivity to light for both neuroendocrine and circadian regulation.^{16,18} For a detailed description of the molecular and cellular basis for how photoreceptive input regulates circadian and neuroendocrine system function, see the Addendum.

HUMAN CONCERNS-DISABILITY AND DISCOMFORT GLARE

Glare from nighttime lighting can create hazards ranging from discomfort to frank visual disability. Disability glare has been fairly well-defined based on the physiology of the human eye and behavior of light as it enters the ocular media. Discomfort glare is less well-defined and more subjective as it is not based on a physical response per se but rather a psychological response. Accordingly, the respective bases of (and research into) these two responses are fundamentally different.

Disability Glare

Disability glare is unwanted and poorly directed light that temporarily blinds, causes poor vision by decreasing contrast, and creates an unsafe viewing condition, especially at night, by limiting the ability of the person to see. There are natural causes of disability glare, such as solar glare at sunset on a dirty windshield which can be lessened by cleaning the windshield. Unfortunately, nighttime glare while driving is not easily remedied. It is caused by the

misapplication of luminaires that comprise the lighting design which are generally overly bright and unshielded, and/or sources of poorly directed light that enters the eye and scatters among ocular structures resulting in diminished contrast and impeded vision. Such effects dramatically worsen as the human eye ages, contributing to poor night vision and difficulty in driving at night for older drivers.

Disability glare is caused by light scatter from ocular media.²⁸ As light enters the eye, it collides with cornea, lens, and vitreous humor, scattering photons and casting a veil of light across the retina²⁹⁻³¹ (see Figure 1). The veil of light reduces the contrast of the object that the driver is trying to see, having the same effect as increasing the background luminance of the object. This veiling light is represented by the term veiling luminance. Veiling luminance is directly related to the illuminance of the light source and inversely related to the square of the angle of eccentricity of the light source with an age dependent multiplier across the entire equation.²⁸ This means that the disability from a light source is lessened the farther the source is from the line of sight.^a

Accordingly, proper design techniques and consideration for the glare caused by lighting systems need to be considered. One of the primary difficulties, especially for roadways, is that the lighting is not governed by a single jurisdiction. Roadway lighting may be designed properly and provide a low level of glare; however lighting can emanate from adjacent properties, spilling out into the roadway thus affecting the driver and overall performance and suitability of a lighting system. Control over all environmental sources of nighttime lighting is therefore critical for the overall control of disability glare.

Discomfort Glare

Discomfort glare is less well defined but emanates from a glare source that causes the observer to feel uncomfortable. The definition of discomfort is not precise, and some research has shown that a person's response to a glare source is based more on his/her emotional state than on the light source itself. Discomfort glare may be based primarily on the observer's light adaptation level, the size, number, luminance and location of the light sources in the scene.³²

Both overhead roadway lighting and opposing headlamps are involved with discomfort glare in the driver. A numerical rating scale based on the dynamic nature of glare in simulations is available to measure the discomfort level experienced by drivers (Appendix).³³ The overall impact of discomfort glare on fatigue and driver safety remains an issue.

Lighting and Glare. Both discomfort and disability glare have specific impacts on the user in the nighttime environment. Research has shown that both of these glare effects occur simultaneously. Research also shows that the effects of the glare are cumulative, meaning that the glare from two light sources is the sum of the glare from the individual light sources. As a result, every light source within the field of view has an impact on the comfort and visual capability of the driver.

Overhead lighting

For overhead roadway lighting, design standards include a methodology for controlling the disability glare through a ratio of the eye adaptation luminance to the veiling luminance caused by the light source. As the veiling luminance is related to the illuminance the light source produces at the eye, a roadway luminaire that directs light horizontally has a much greater effect on the driver than a light source that cuts off the horizontal light. A trend towards flat glass luminaires, which provide a cut off of light at horizontal angles, provides a lower level of both disability and discomfort glare.

Decorative luminaires (e.g., acorn or drop lens) have a high level of horizontal light and typically are used in areas where pedestrians are the primary roadway users. The horizontal light in this situation is useful for facial recognition of a pedestrian, but it limits the driver's ability to perceive other objects in the roadway. As a result, many cities are designing and installing two lighting systems, one for the pedestrian and one for the roadway.

^a As an example, high mast lighting systems where the roadway lighting is over 100 feet in the air have significantly less glare than traditional systems, which are typically located 30–50 feet in the air. Because of the inverse squared relationship, a high mast system reduces glare by 75% compared with a traditional system.

Luminaires employing solid state technologies and light-emitting diodes (LED) provide light from an array of small sources rather than a single large source. These designs either rely on each small source to provide a component of the light distribution, or the components of the lighting array provide individual luminating fields of the light distribution. In the first instance, the arrays are typically flat and have an optic to provide the light distribution; if a single LED fails, the others still provide the light distribution. In the second method, the components of the array are aimed to different areas of the beam distribution. This approach typically results in light aimed at the driver and pedestrians causing a higher glare impact. The other issue with the multiple sources used in LED luminaires is that each of the sources typically has a very high luminance itself as the source is very small and very bright; in the absence of sufficient diffusion, they cause significant glare. Accordingly, solid state lighting systems typically have a higher glare impact than traditional sources.

The final issue with glare from overhead lighting is the cyclic nature of the impact. As drivers course along a roadway, they pass from one luminaire to another. The glare experience increases as they approach the luminaire and then diminishes as they pass beyond. While typically not an issue for disability glare, this repetitive process can cause discomfort and fatigue.³⁴

Opposing vehicle headlamps

Vehicle headlamps are aimed at the opposing driver eye level resulting in very high ocular illuminance and significant disability glare. The impact of opposing headlamps on the ability of the oncoming driver to observe beyond the headlamps is significant. For example, the visibility of a pedestrian standing behind a vehicle can be reduced by as much as 50%.³⁵

In order to minimize the glare impact, headlamps are designed with lower left side light intensity than the right side. This reduces the glare to an opposing vehicle but does not eliminate it. New technologies such as turning headlamps and headlamps that hide part of the headlamp beam when a vehicle passes are possible solutions for this issue. With the advent of high intensity discharge Xenon headlamps and LED-based technologies, the glare issue has become more serious. While the intensity towards a driver is limited, the small but brighter source generates a much higher impression of glare than traditional technologies. These “blue” headlamp sources have a higher complaint rate for glare than for any other light source.

Effects of Lighting Design on Traffic Accidents

Adult, and especially elderly drivers, experience increased glare sensitivity, and elderly drivers may not be able to sufficiently fulfill the criteria for night driving ability because of contrast and glare sensitivity.³⁶ Prospective studies indicate that reduction in the useful field of view, visual field loss, and glare sensitivity increase crash risk in older drivers.^{37,38} Crash risk begins to increase around age 50 years of age and continues to increase with aging.³⁹ No studies have explicitly compared traffic accident rates under different highway lighting conditions.

HEALTH EFFECTS OF DISRUPTED CIRCADIAN RHYTHMS

Epidemiological studies are a critical component of the evidence base required to assess whether or not light exposure at night affects disease risk, including cancer. These studies, however, are necessarily observational and can rarely provide mechanistic understanding of the associations observed. Carefully designed and controlled basic laboratory studies in experimental animal models have the potential to provide the empiric support for a causal nexus between light exposure at night and biological/health effects and to help establish plausible mechanisms. One area of considerable study on the possible effects of nighttime light exposure involves cancer.

CANCER

Light at Night, Melatonin and Circadian Influences on Carcinogenesis

Experimental Evidence. The majority of earlier studies in experimental models of either spontaneous or chemically-induced mammary carcinogenesis in mice and rats demonstrated an accelerated onset of mammary tumor development accompanied by increased tumor incidence and number in animals exposed to constant bright fluorescent light during the night as compared with control animals maintained on a strict 12 hours light/12 hours dark cycle.⁴⁰⁻⁵¹

More recent work has focused on the ability of light at night to promote the growth progression and metabolism in human breast cancer xenografts. Nocturnal melatonin suppresses the growth of both estrogen receptor negative (ER-) and estrogen receptor positive (ER+) human breast cancer xenografts; the essential polyunsaturated fatty acid, linoleic acid is necessary for the growth of such (ER-) tumors, and its metabolism can be used as a biomarker of cellular growth.⁵²⁻⁵⁵ Exposure of rats with such cancer xenografts to increasing intensities of white, fluorescent polychromatic light during the 12 hour dark phase of each daily cycle results in a dose-dependent suppression of peak nocturnal serum melatonin levels and a corresponding marked increase in tumor metabolism of linoleic acid and the rate of tumor growth. Exposure to even the very dimmest intensity of light during the night (0.2 lux) suppressed the nocturnal peak of circulating melatonin by 65% and was associated with marked stimulation in the rates of tumor growth and linoleic acid metabolic activity. In this model, measurable effects on xenograft growth and linoleic acid metabolism were apparent with 15% suppression in nocturnal melatonin levels.

The ability of light exposure at night to stimulate tumor growth (including dim exposures) has been replicated in rat hepatoma models.^{54,56-58} The reverse also is true; gradually restoring circulating melatonin by reducing initial exposure to light at night (24.5 lux) is accompanied by a marked reduction in tumor growth and linoleic acid metabolic activity to baseline rates in the breast cancer and hepatoma models.⁵⁹

The important role of melatonin as a nocturnal anticancer signal is further supported by the growth responses of human breast cancer xenografts perfused with human whole blood collected from young, healthy premenopausal female subjects exposed to complete darkness at night (e.g., high melatonin), compared with xenografts that were perfused with blood collected from the same subjects during the daytime (e.g., low melatonin).⁵⁴ The growth of xenografts perfused with blood collected during the dark was markedly reduced. Addition of a physiological nocturnal concentration of melatonin to blood collected from light-treated subjects restored the tumor inhibitory activity to a level comparable to that observed in the melatonin-rich blood collected at night during total darkness. Moreover, the addition of a melatonin receptor antagonist to the blood collected during darkness (i.e., high melatonin) eliminated the ability of the blood to inhibit the growth and metabolic activity of perfused tumors. Some evidence also exists that circadian disruption by chronic phase advancement (e.g., simulating jet lag) may increase cancer growth in laboratory animals.^{60,61}

Potential Anticancer Mechanisms of Melatonin

The preponderance of experimental evidence supports the hypothesis that under the conditions of complete darkness, high circulating levels of melatonin during the night not only provide a potent circadian anticancer signal to established cancer cells but help protect normal cells from the initiation of the carcinogenic process in the first place.^{62,63} It has been postulated that disruption in the phasing/timing of the central circadian pacemaker in the SCN, in general, and the suppression of circadian nocturnal production of melatonin, in particular, by light at night, may be an important biological explanation for the observed epidemiological associations of cancer risk and surrogates for nocturnal light exposure (such as night shift work, blindness, reported hours of sleep, etc.) (see below).⁶⁴

Melatonin exerts several cellular effects that may be relevant in this regard. It exhibits antiproliferative and antioxidant properties, modulates both cellular and humoral responses, and regulates epigenetic responses.⁶⁵⁻⁶⁷ Melatonin also may play a role in cancer cell apoptosis and in inhibiting tumor angiogenesis.^{68,69}

Human Studies

While the experimental evidence from rodent cancer models links disruption of circadian rhythms and circulating melatonin concentrations (inversely) with progression of disease, the human evidence is indirect and based on epidemiological studies. Breast cancer has received the most study.

The hypothesis that the increasing use of electricity to light the night might be related to the high breast cancer risk in the industrialized world, and the increasing incidence and mortality in the developing world was first articulated in 1987.⁷⁰ Potential pathways include suppression of the normal nocturnal rise in circulating melatonin and circadian gene function.^{54,71,72} Conceptually, this theory would predict that non-day shift work would raise risk, blind women would be at lower risk, reported sleep duration (as a surrogate for hours of dark) would be inversely associated with risk, and population nighttime light level would co-distribute with breast cancer incidence worldwide.^{72,73} Only the first hypothesis has been systematically evaluated. Based on studies of non-day shift occupation and cancer (mostly breast cancer) published through 2007, the International Agency for Research on Cancer (IARC) concluded “shift-

work that involves circadian disruption is *probably carcinogenic* to humans” (Recommendation Level 2A).⁷⁴ A detailed review of the individual studies supporting this conclusion is available.⁷⁵

Since the IARC evaluation was conducted, several new studies of breast cancer and nighttime light have been published with mixed results.⁷⁶⁻⁷⁹ Two found no significant association between shift work and risk of breast cancer.^{76,77} A large case-control study of nurses in Norway⁷⁸ found a significantly elevated risk in subjects with a history of regularly working five or more consecutive nights between days off, and another found that as the type of shift (e.g., evening, night, rotating) became more disruptive, the risk increased.^{79,80} In the Nurses Health Study cohort, increased urinary excretion of melatonin metabolites also was associated with a lower risk of breast cancer.⁸¹ Each of these studies has strengths and limitations common to epidemiology, particularly in exposure assessment and appropriate comparison groups (e.g., no woman in the modern world is unexposed to light-at-night, but quantifying that exposure is difficult).

Although shiftwork represents the most extreme example of exposure to light at night and circadian disruption, perturbation of circadian rhythms and the melatonin signal is also experienced by non- shift workers with a normal sleep/wake-cycle.¹² Anyone exposing themselves to light after dusk or before dawn is overriding the natural light-dark exposure pattern as noted in the earlier discussion on measures of illumination.

After lights out for bedtime, it is not yet clear whether the ambient background light from weak sources in the bedroom or outside light coming through the window could influence the circadian system; a brief exposure at these levels may not have a detectable impact in a laboratory setting, although long-term chronic exposure might. Four case-control studies have now reported an association of some aspect of nighttime light level in the bedroom with breast cancer risk.⁸²⁻⁸⁵ The elevated risk estimate was statistically significant in two of them.^{83,85} As case-control designs, in addition to the limitation of recall error, there is also the potentially significant limitation of recall bias.

Despite the difficulty of gathering reliable information on bedroom light level at night, the possibility that even a very low luminance over a long period of time might have an impact is important. The lower limit of light intensity that could, over a long time period, affect the circadian system is not established. In the modern world few people sleep in total darkness. When eyelids are shut during sleep, only very bright light can penetrate to lower melatonin and only in some individuals.⁸⁶ Frequent awakenings with low level light exposure in the bedroom and certain nighttime activities (e.g., bathroom visits) may disrupt the circadian system, but any related health effects are unknown.⁸⁷

Other Cancers

Light-at-night and circadian disruptions have been suggested to play a role in other cancers including endometrial, ovarian, prostate, colorectal, and non-Hodgkins lymphoma but evidence comparable to that obtained for breast cancer has not yet been developed.⁸⁸ On the other hand, engaging in night shift work may protect against skin cancer and cutaneous melanoma.⁸⁹

Other Diseases

Obesity, Diabetes, and Metabolic Syndrome. The modern world has an epidemic of obesity and diabetes that may be influenced by lack of sleep, lack of dark, and/or circadian disruption.⁹⁰ Non-day shift workers have a higher incidence of diabetes and obesity.⁹¹ Epidemiological studies also show associations of reported sleep duration and risk of obesity and diabetes.⁹² Circadian disruption may be a common mechanism for these outcomes and potential links between the circadian rhythm and metabolism.⁹³⁻⁹⁵

Other Disorders. Although in the early stage of development, emerging evidence suggests that other chronic conditions also may be exacerbated by light at night exposure and ongoing disruption of circadian rhythms, including depression and mood disorders, gastrointestinal and digestive problems, and reproductive functions.⁸⁸

DARK VERSUS SLEEP

The circadian rhythm and sleep are intimately related but not the same thing. Adequate daily sleep is required for maintenance of cognitive function and for a vast array of other capabilities that are only partially understood. Sleep is not required to synchronize the endogenous circadian rhythm, whereas a stable 24-hour light-dark cycle is

required. The epidemiological and laboratory research on sleep and health cannot entirely separate effects of sleep duration from duration of exposure to dark, because the sleep-wake cycle partitions light-dark exposure to the SCN and pineal gland.⁹⁶ The distinction is important because a requirement for a daily and lengthy period of dark to maintain optimal circadian health has different implications than a requirement that one must be asleep during this entire period of dark; many individuals normally experience a wakeful episode in the middle of a dark night.⁸⁷

Light during the night will disrupt circadian function as well as sleep, and the health consequences of short sleep and of chronic circadian disruption are being intensively investigated.⁹⁷ A growing number of observational and clinical studies on sleep and metabolism suggest short sleep periods have substantial harmful effects on health; however, it is not yet clear that sleep and dark have been entirely disentangled in these studies.^{97,98} For example, in one study, sleep duration (verified by polysomnography) was associated with morning blood levels of leptin, a hormone that plays a key role in energy expenditure and appetite.⁹⁹ However, the duration of typical sleep reported by each subject was more strongly associated with leptin concentrations. Mean verified sleep was 6.2 hours, whereas mean reported sleep was 7.2 hours. Reported “sleep duration” probably reflects the time from when a person turns out their light for bed and falls asleep and when they get up in the morning (i.e., actual hours of dark exposure). An important question is to determine what portion of the health effects of dark disruption is due to sleep disruption and what portion is due directly to circadian impact of electric light intrusion on the dark of night.

Media use at night (i.e., televisions, computer monitors, cell phone screens) negatively affects the sleep patterns of children and adolescents and suppresses melatonin concentrations.¹⁰⁰⁻¹⁰² The American Academy of Pediatrics recommends removing televisions and computers from bedrooms to assist in limiting total “screen time” on a daily basis.¹⁰¹ This action also may help in improving sleep patterns.

ENERGY COST

Electric lighting accounts for about 19% of electricity consumption worldwide and costs about \$360 billion.¹⁰³ Much of the light that is produced is wasted, for example, by radiating light into space away from the task or environment intended to be illuminated. Estimates of how much is wasted vary; one estimate from the International Dark-Sky Association is 30% in the United States.¹⁰⁴ Such a percentage worldwide would account for an annual cost of about \$100 billion.

ENVIRONMENTAL ISSUES

Although not directly under the purview of human health and disease, the following considerations are indirectly related to human well-being.

Esthetics

The Milky Way is no longer visible to the majority of people in the modern world. As societies have increasingly used electricity to light the night, it has become difficult to see more than a few of the innumerable stars from Earth's surface.¹⁰⁵ This has been carefully documented in a cover story by National Geographic Magazine in November 2008, which includes extensive visual documentation on its website.¹⁰⁶ Though the major impact of electric light at night is in major metropolitan areas, even the once pristine nights of the US National Parks are beginning to be degraded, more rapidly in the East but also in parks in the West as well.¹⁰⁷

Impact on Wildlife

Life on the planet has evolved to accommodate the 24-hour solar cycle of light and dark. Human imposition of light at night and disruption of the natural dark-light cycle represents a dramatic change to the environment.¹⁰⁸ Study of the effects of light at night on animal and plant life is in the early stages, but the entire spectrum of life, including animal, plant, insect, and aquatic species, may be affected.

About 30% of all vertebrate species and 60% of invertebrate species on Earth are nocturnal and depend on dark for foraging and mating.¹⁰⁸ Documented wildlife destruction by light at night has been evident in bird species, which fly into lit buildings at night in enormous numbers when migrating, and in the disruption of migration and breeding cycles in amphibians.¹⁰⁸⁻¹¹¹ The most studied case in reptiles involves sea turtle hatchlings on the coast of Florida, which historically have scurried from their nest directly to the ocean. With increased development along the coast,

and attendant increased electric lighting at night, these hatchlings become confused and often migrate away from shore to the lights. Hundreds of thousands of hatchlings are believed to have been lost as a result of this stray electric lighting at night in Florida.¹⁰⁹ Furthermore, many billions of insects are lost to electric light annually, which reduces food availability for other species in addition to unnecessarily reducing living biomass. It is concerning that light at night also may be vector attractant for diseases such as malaria.¹¹²

The circadian biology of plants is as robust as animals, and the impact of light at night on plant life may also be considerable due to the role of light in photosynthesis and the fact that many plants are pollinated at night.^{113,114}

POLICY AND PUBLIC HEALTH IMPLICATIONS OF LIGHT AT NIGHT

Some responses to public health concerns associated with light-at-night exposures are readily apparent, such as developing and implementing technologies to reduce glare from vehicle headlamps and roadway lighting schemes, and developing lighting technologies at home and at work that minimize circadian disruption, while maintaining visual efficiency and aesthetics. Additionally, clinical studies support efforts to reduce child and adolescent night-time exposure from exogenous light derived from various media sources, especially in the bedroom environment. Recommendations to use dim lighting in residences at night raise issues for elderly patients. The American Geriatrics Society recommends ensuring well lit pathways within households to reduce the incidence of falls in elderly patients.¹¹⁵

Individuals who are subject to shift work experience disrupted circadian rhythms, fatigue, and cognitive dysfunction. Many industries, including hospitals, require a 24-hour workforce. The American College of Occupational and Environmental Medicine has established guidelines to address fatigue risk management in the workplace.¹¹⁶ In healthcare workers, such as nurses who experience rapidly rotating shifts, brief morning light exposure improves subjective symptoms and performance.¹¹⁷ The judicious use of bright light and/or melatonin supplements can improve adaptation to permanent, long-term night work.¹¹⁸

SUMMARY AND CONCLUSIONS

The natural 24-hour cycle of light and dark helps maintain precise alignment of circadian biological rhythms, the general activation of the central nervous system and various biological and cellular processes, and entrainment of melatonin release from the pineal gland. Pervasive use of nighttime lighting disrupts these endogenous processes and creates potentially harmful health effects and/or hazardous situations with varying degrees of harm. The latter includes the generation of glare from roadway, property, and other artificial lighting sources that can create unsafe driving conditions, especially for older drivers. Current AMA policy advocates that all future outdoor lighting be of energy efficient designs to reduce energy use and waste. Future streetlights should incorporate fully shielded or similar non-glare design to improve the safety of our roadways for all, but especially vision impaired and older drivers.

More direct health effects of nighttime lighting may be attributable to disruption of the sleep-wake cycle and suppression of melatonin release. Even low intensity nighttime light has the capability of suppressing melatonin release. In various laboratory models of cancer, melatonin serves as a circulating anticancer signal and suppresses tumor growth. Limited epidemiological studies support the hypothesis that nighttime lighting and/or repetitive disruption of circadian rhythms increases cancer risk; most attention in this arena has been devoted to breast cancer. The quality and duration of sleep and/or period of darkness affect many biological processes that are currently under investigation. Further information is required to evaluate the relative role of sleep versus the period of darkness in certain diseases or on mediators of certain chronic diseases or conditions including obesity. Due to the nearly ubiquitous exposure to light at inappropriate times relative to endogenous circadian rhythms, a need exists for further multidisciplinary research on occupational and environmental exposure to light-at-night, the risk of cancer, and exacerbation of chronic diseases.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of the report be filed:

That our American Medical Association:

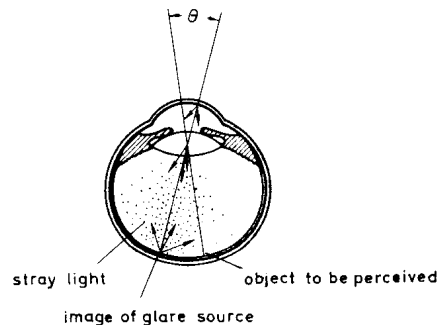
1. Supports the need for developing and implementing technologies to reduce glare from vehicle headlamps and roadway lighting schemes, and developing lighting technologies at home and at work that minimize circadian disruption, while maintaining visual efficiency.
2. Recognizes that exposure to excessive light at night, including extended use of various electronic media, can disrupt sleep or exacerbate sleep disorders, especially in children and adolescents. This effect can be minimized by using dim red lighting in the nighttime bedroom environment.
3. Supports the need for further multidisciplinary research on the risks and benefits of occupational and environmental exposure to light-at-night.
4. That work environments operating in a 24/7 hour fashion have an employee fatigue risk management plan in place.
5. That Policy H-135.937 be reaffirmed.

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APPENDIX

Figure 1. Stray light in the ocular media



DeBoer Scale

DeBoer Numerical Rating	Glare Intensity
1	Unbearable
3	Disturbing
5	Just Admissible
7	Satisfactory
9	Unnoticeable

Molecular and Cellular Basis for Photoreceptive Regulation of Circadian and Neuroendocrine System Function

In the past decade, there has been an upheaval in the understanding of photoreceptive input to the human circadian and neuroendocrine systems. A study on healthy human subjects confirmed that the three-cone system that mediates human vision during the daytime is not the primary photoreceptor system that transduces light stimuli for acute melatonin suppression.¹¹⁹ That discovery was rapidly followed by the elucidation of two action spectra in healthy human subjects that identified 446-477 nm as the most potent wavelength region for melatonin suppression.^{3,4} To date, ten published action spectra have examined neuroendocrine, circadian, and neurobehavioral responses in humans, monkeys, and rodents. The action spectra demonstrate peak sensitivities in the blue region of the visible spectrum, with calculated peak photosensitivities ranging from 459 nm to 484 nm.¹²⁰⁻¹²² Further, a set of studies has confirmed that shorter wavelength, monochromatic light is more potent than equal photon

densities of longer wavelength light for evoking circadian phase shifts, suppressing melatonin, enhancing subjective and objective correlates of alertness, increasing heart rate, increasing body temperature, and inducing expression of the circadian clock gene *Per2* in humans.^{19,20,123-126}

Studies using both animal and human models are clarifying the neuroanatomy and neurophysiology of the photosensory system that provides input for circadian, neuroendocrine, and neurobehavioral regulation. A recently discovered photopigment, named melanopsin, has been localized both in the retinas of rodents and humans.¹²⁷ More specifically, melanopsin is found in a subtype of intrinsically photoreceptive retinal ganglion cells (ipRGCs).^{128,129} These light sensitive ganglion cells project to nuclei and regions of the central nervous system that mediate the biological and behavioral effects of light.^{130,131} Although ipRGCs provide the strongest input for regulation of biology and behavior, studies on genetically manipulated rodents, normal monkeys, and humans demonstrate that the visual rod and cone photoreceptors integrate into this physiology.^{5,132-134} Continued advances in understanding the physiology of this phototransduction will undoubtedly yield further insights into potential health impacts of electric lighting.

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5. TAXES ON BEVERAGES WITH ADDED SWEETENERS (RESOLUTION 417-A-11)

Reference committee hearing: see report of [Reference Committee D](#).

**HOUSE ACTION: RECOMMENDATIONS ADOPTED
IN LIEU OF RESOLUTIONS 417-A-11 AND 407 AND
REMAINDER OF REPORT FILED**
See Policy [H-150.933](#)

INTRODUCTION

Resolution 417-A-11, "Taxes on Beverages with Added Sweeteners," introduced by the Oklahoma Delegation at the 2011 American Medical Association (AMA) Annual Meeting and referred to the Board of Trustees, asks:

That our AMA: (1) support the adoption of a state tax on sugar-sweetened soft drinks with a substantial portion of the revenue from these taxes to be earmarked for the prevention and treatment of obesity; (2) work for and encourage all levels of the Federation and other interested groups to pass a tax on sugar sweetened beverages at the municipal and state levels; and, (3) work with its national partners and Federation members on developing and implementing a national strategy to pass municipal and state taxes on sugar sweetened beverages.

Two reports by the Board of Trustees previously addressed this issue at the 2006 Annual and Interim Meetings. Both reports recommended that the AMA support adoption of small local, state, and federal taxes on soft drinks sweetened with caloric sugars, with a substantial portion of the revenue from these taxes being earmarked for the prevention and treatment of obesity, as well as public health and medical programs that serve vulnerable populations. However, these recommendations were not adopted.

This report examines literature that has emerged in the last six years, as well as some earlier studies, to determine if limiting consumption of beverages with added sweeteners is likely to improve health outcomes; and, if so, whether taxation of sweetened beverages would be an effective public health strategy to help reduce consumption.

CURRENT AMA POLICY RELATED TO TAXES AND BEVERAGES WITH ADDED SWEETENERS

Current AMA policy does not directly address taxes on food or beverages, other than alcohol. However, several AMA policies support public health efforts to promote the consumption of naturally nutritious beverages and to discourage consumption of added sweeteners and of beverages high in calories and naturally low in other nutrients, particularly as obesity reduction strategies (Appendix). AMA policies also support taxes as a public health strategy to discourage consumption of alcohol and tobacco products and to use the resultant funds for health education, disease treatment, and counter-advertising efforts.

METHODS

English language reports were selected from searches of the PubMed, Google Scholar, and Cochrane Library databases from 2001 to March 2012 using the search terms “sugar sweetened beverages,” “soda,” “sugar,” “artificial sweeteners,” “health effects,” “obesity,” “diabetes,” “taxes,” and “taxing.” Additional articles were identified by manual review of the reference lists of pertinent publications. Websites managed by federal agencies and applicable professional and advocacy organizations also were reviewed for relevant information.

BACKGROUND

Taxation of sugar-sweetened beverages (SSBs) has become an increasingly popular proposal to help reduce the prevalence of obesity and related conditions in the United States. Academic research into the relationships between SSBs and obesity and related health outcomes, as well as the potential health impact of SSB taxes, has increased substantially since 2006 when the Board of Trustees last examined the issue. However, opinions on this issue within academic and larger public spheres remain divided.

Supporters of SSB taxes cite the success of tobacco and alcohol taxes in reducing rates of smoking and alcohol consumption, particularly in concert with other public health measures such as smoking bans, educational campaigns, and tougher alcohol-impaired driving laws. Opponents of SSB taxes are generally skeptical that SSBs should be singled out among the many factors that contribute to obesity and related conditions, such as overconsumption of other foods and lack of physical activity, and/or they believe that such taxes will have little impact on total calorie consumption. These issues are discussed in more detail below.

DEFINITIONS AND CONSUMPTION PATTERNS

The terms “added sweeteners” and “added sugars” are generally used interchangeably to refer to all sugars and syrups added to foods and beverages during processing, preparation, or at the table.^{1,2} Although these terms could refer to both caloric and non-caloric sweeteners, they generally refer only to caloric sweeteners, such as sugar (sucrose), high fructose corn syrup, honey, and fruit juice concentrates, all of which provide 4 kcal per gram (g). Non-caloric sweeteners approved for use in the US include the artificial sweeteners acesulfame potassium, aspartame, neotame, saccharin, and sucralose, and the natural sweetener rebaudioside A (a highly purified extract from the stevia plant). These non-nutritive sweeteners do not contain any calories, except for aspartame, which has 4 kcal/g. Due to their intense sweetness, very small quantities are needed, making the amount of energy actually consumed even from aspartame negligible.³

SSBs generally refer to all non-alcoholic beverages that contain any amount of added caloric sweeteners, excluding 100% fruit and vegetable juices, infant formulas, and dietary aids for medical conditions, although some studies also exclude sweetened milk and milk substitutes.

Added caloric sweeteners in the US food supply increased 27% since 1966, from 113 pounds per person annually to 143 pounds per person annually in 2005.⁴ Increased consumption of soft drinks and fruit drinks contributed to more than half of this increase in added sugar intake.⁵ Consumption of added sugars has decreased since then, in both adults and children, due primarily to decreased SSB consumption.^{6,7} Nevertheless, consumption of added sugars continues to exceed recommended limits, averaging 77 grams per day (18 tsp); sodas, fruit drinks, and sports drinks remain the largest contributors to added sugar intakes.⁶ Half of Americans over age 2 consume SSBs on any given day, not including sweetened teas or flavored milks, with average intakes of 175 kcal/d for males and 94 kcal/d for females.⁸ Intakes are highest among adolescents (12 to 19 years of age) and young adults (20 to 39 years of age), with 70% of boys and 60% of girls aged 2 to 19 years consuming SSBs on any given day.⁸ The percentage of daily calories from SSBs is highest among Non-Hispanic Blacks (9%) and among lower-income individuals (8-9% in children and adults with incomes below 130% of the poverty line).⁸

The percentage of Americans consuming non-caloric sweeteners has increased from 3% in 1965 to 15% in 2004.⁹ Beverages are the most widely consumed source of non-caloric sweeteners, with 11% of Americans consuming non-calorically sweetened (diet) beverages in 2004.⁹ Per capita intake of diet beverages was 129 g per day in 2004, although intake among consumers of diet beverages was 752 g daily.⁹ Daily intakes of diet beverages range from 27 mL/d in children 2 to 6 years of age to 290 mL/d in adults aged 40 to 59.¹⁰

HEALTH EFFECTS OF CALORICALLY SWEETENED BEVERAGES

The 2010 Dietary Guidelines for Americans,¹ the American Heart Association (AHA)² and the AMA (Policy D-150.981, AMA Policy Database) recommend that consumers limit the amount of added caloric sweeteners in their diet. The recommended USDA food patterns for a standard 2,000 kcal/d diet limit intake of solid fats and added sugars, combined, to 258 kcal/d (13% of calories).¹ The AHA divides this “discretionary calorie” allowance in half (assuming no discretionary calories from alcohol consumption), and recommends that most women consume no more than 100 kcal/d (6 tsp) and men no more than 150 kcal/d (9 tsp) of added sugars.²

A single 12 oz serving of most SSBs easily meets or exceeds the AHA limits, with roughly 130- 150 kcal and 34-38g (8 to 9 tsp) of added sugar,^{2,11} leaving no room in the diet for added sugars from other foods, such as sweetened yogurt, breakfast cereal, or even spaghetti sauce. SSB consumption often crowds out consumption of other foods and beverages rich in micronutrients, such as skim milk and whole fruit, and minimizes consumers’ ability to meet the rest of their daily nutrient requirements without exceeding their calorie needs. SSB consumption has been inversely associated with consumption of milk, calcium, fruit, and dietary fiber, and with overall dietary quality.¹² Reducing intake of SSBs, which comprise nearly half (46%) of Americans’ added sugar intake, is a simple way to reduce intake of added sugars without compromising the nutrient adequacy of a person’s overall diet.¹ Thus, the Dietary Guidelines and MyPlate explicitly advise the public to “drink water instead of sugar drinks.”^{1,13}

SSB consumption has been strongly and consistently associated with higher total calorie consumption in cross-sectional, longitudinal, and experimental studies.¹² Experimental trials have found that people generally do not compensate for calories from beverages as well as they do from foods.¹² This means that after drinking a calorie-containing beverage, people eat nearly as many calories at a subsequent meal as when they do not consume any liquid calories beforehand.^{12,14} In contrast, after eating a snack of solid food, people generally eat less at their subsequent meal, so that their total energy intake for the day remains relatively constant, even when they consume food, such as jelly beans, that contains as many added sugars and calories as an SSB.¹⁵ In several studies, people actually consumed *more* calories at a subsequent meal after consuming SSBs than after consuming no calories.^{12,15} In other words, daily calorie intakes increased from both the additional calories from the SSBs as well as from additional calories consumed at subsequent meals. This suggests that SSBs reduce feelings of satiety, increase hunger, and/or acclimate individuals to prefer sweeter and generally more calorie-dense foods.¹²

Research in animal models suggests that simple sugars, particularly fructose, may be responsible for decreased satiety signals, inducing symptoms of “habituation” and possibly addiction signals similar to those observed with alcohol.¹⁶ However, evidence of addiction in humans remains anecdotal.^{16,17} Furthermore, a recent meta-analysis reported that fructose per se, independent of excess calories, does not appear to be the primary contributor to weight gain.¹⁸ The lack of energy compensation after SSB consumption may have more to do with its liquid form than its fructose content. A recent randomized trial in humans found that consumption of liquids, or *perceived* liquids, resulted in more rapid gastric-emptying and orocecal transit times compared to semi-solid foods (gelatin cubes), as well as lower insulin and glucagon-like peptide 1 (GLP-1) release and less ghrelin suppression.¹⁹ As GLP-1 promotes satiety and ghrelin increases hunger and appetite, it was unsurprising that individuals then consumed more calories at subsequent meals after consuming a liquid, or a perceived liquid, than after consuming a solid or a perceived solid.¹⁹ It appears that the human body and mind find liquids less satiating than solid foods, even if they contain the same amounts of sugars and calories.

Intake of SSBs has been strongly and consistently associated with increased body weight and a number of related cardiometabolic conditions in cross-sectional, longitudinal, and long-term experimental studies,^{5,12,14,20} particularly in those studies not funded by the beverage industry.²⁰ SSBs have been associated with increased blood pressure;^{2,21,22} triglyceride levels; total cholesterol; and liver, visceral and skeletal muscle fat.²³ SSBs also have been associated with decreased HDL cholesterol,² as well as markers of inflammation^{2,14,24} and oxidative stress,^{2,14} dental caries, and kidney stones.¹² SSB consumption also is related to increased risk for type 2 diabetes^{14,25} and coronary heart disease (CHD),^{14,24} with increased body weight explaining only part of the excess risk.¹⁴

HEALTH EFFECTS OF NON-CALORICALLY SWEETENED BEVERAGES

Efforts to discourage consumption of SSBs may result in increased consumption of diet beverages as a comparable substitute beverage. Relatively short-term randomized trials (less than 3 months) find modest benefits of artificial sweetener use on weight loss, prevention of weight gain, blood pressure, and inflammatory markers.^{26,27,28} A recent

6-month intervention trial also reported a modest benefit of replacing 2 servings/d of SSBs with 2 servings of diet beverages, resulting in an average weight loss of 2 kg over 6 months (a serving was equal to 12–16 oz).²⁹ Another recent 6-month intervention trial observed a slight increase in weight among those randomized to 1L/d (approximately 34 oz) of regular soft-drinks (or semi-skim milk) compared to those randomized to diet soft drinks or water, although the results were not statistically significant.²³ These modest benefits may add up to greater weight loss, or at least weight maintenance, over time, particularly at the population-level.²⁹

Despite the negligible calorie content of diet beverages and the intervention trials noted above, several, although not all, large cross-sectional and prospective observational studies find direct associations between consumption of artificial sweeteners and body weight.^{30,31} It has been suggested that those struggling to control or reduce their weight may be more likely to consume diet beverages.³² Consumers of diet beverages also may believe the lack of calories allows them to consume more calories from other foods.²⁰ In addition, regular consumption of intensely sweet artificial sweeteners may foster a preference for sweet tastes²⁰ and make less sweet, but healthier foods such as fruits, vegetables, and legumes less appealing.³³ Some have suggested that by disassociating sweetness from calories, artificial sweetener consumption may alter normal hormonal and neurobehavioral pathways that control hunger and satiety.³³ Evidence in animal models finds that artificially sweetened foods and beverages lead to increased food intake, weight gain, body fat, and reduced calorie compensation compared to foods and beverages containing glucose.³⁴ However, direct evidence in humans is lacking.

Prospective follow-up studies have linked artificial sweeteners to increased risks of metabolic syndrome, type 2 diabetes,^{35,36,37} and vascular events (stroke, myocardial infarction, or vascular death).³² In some studies, the associations were observed only with diet beverages, but not SSBs,^{32,35} although others found SSBs, but not diet beverages, increased the risk of CHD^{24,38} and diabetes.²⁵ Adding to the lack of clarity was an observation that diet, non-cola carbonated beverages, but not diet colas, were associated with increased risk for CHD equal to that for SSBs.²⁴

If potentially harmful effects of diet beverages exist, children may be particularly susceptible due to their smaller body size and relatively high intake of beverages.³¹ Like SSBs, diet beverages may displace nutrient-rich milk and 100% juice at mealtimes.³¹ It has been suggested that diet beverages may not even protect against dental caries when consumed in acidic beverages such as sodas.³⁹ Concern also exists that the potentially adverse metabolic and behavioral effects (e.g., habituation to sweet cravings) of artificial sweeteners have not been adequately studied in children and adolescents, as such effects may persist into adulthood.³¹ Other ingredients in diet beverages, including caffeine and artificial colors, also have raised potential health concerns, particularly in children, although the evidence remains inconclusive.⁴⁰

Not all public health advocates recommend taxing diet beverages, since they are calorie-free and the long-term adverse health effects of regular consumption are not as well established as for SSBs.²⁰ Nevertheless, neither artificial sweeteners nor diet beverages are explicitly recommended by the 2010 Dietary Guidelines for Americans, even as a means of reducing added sugar intake.¹ As in SSBs, the water in diet beverages contributes to hydration, although non-caloric sweeteners are not required nutrients and do not appear to confer any known health benefits in and of themselves; their only apparent benefit, at present, is as a short-term aid to weight loss or weight maintenance.

POTENTIAL HEALTH EFFECTS OF TAX STRATEGIES

As of July 1, 2011, sugar-sweetened sodas were taxed in 35 states (40 taxed sugar-sweetened sodas sold in vending machines).⁴¹ In 14 states, sodas were taxed at a higher rate than other foods. The other 21 states did not tax food, but did not consider soda a food.⁴¹ Most of the SSB taxes were in the form of sales taxes, although seven states also imposed other types of taxes and fees.^{42, 43} At an average rate of 5.2% (maximum 7%),⁴¹ these taxes appear to have had minimal impact on rates of overweight and obesity.^{44,45,46} Currently, these soda taxes do not include other SSBs, but some include diet sodas. In most cases, the taxes are not intended to influence consumption patterns or fund health related programs.⁴⁷

The minimal impact of existing soda taxes on obesity rates is unsurprising. Sales taxes are generally paid after the purchase decision has been made⁴⁸ and are easily minimized through purchases of larger containers, cheaper brands, other SSBs, or by ordering beverages in restaurants offering free refills.²⁰ In addition, studies indicate that small price increases (< 10%) are unlikely to impact consumer behavior.^{44, 49}

Therefore, a larger excise tax of a penny per ounce on sodas and other SSBs has been increasingly proposed as a more effective public health strategy to reduce the prevalence of obesity and related health conditions.^{20,46,50} The penny per ounce tax represents roughly a 15-25% increase in price and would include taxes on syrups and powders equivalent to one cent per ounce.⁴⁶ Taxing per ounce, rather than per bottle or glass, ensures that the tax is applied equally to beverages of different sizes. Excise taxes, which tax beverage producers and wholesalers, are preferred because they are generally passed on directly to consumers and reflected in the shelf price.²⁰

A penny per ounce SSB excise tax is estimated to decrease SSB consumption by 10-25%,^{20,46} depending on how much consumers actually change their purchases in response to the tax (price elasticity), and which beverages or foods they consume instead (compensation).⁴⁶ On average, soft drink prices are relatively elastic,⁵¹ particularly among youth, and low-income and obese individuals.⁵² Less established is the extent to which consumers will substitute other high calorie foods and beverages for SSBs; analyses have assumed calorie compensations ranging from 0% to 100%.^{46,53}

Decreased SSB consumption is expected to result in modest reductions in calorie intake, body weight, and disease outcomes.²⁰ Most population-level estimates range from no impact on total calories and body weight to as high as 37 fewer kcal/d in adults and 43 fewer kcal/d in children, resulting in annual weight losses up to 4 pounds in adults and 4.5 lbs in children.^{46,54} Overall, a penny per ounce SSB tax could reduce the prevalence of overweight and obesity by 5% in children and adults.⁵⁴ These seemingly small reductions could have a larger impact on health outcomes and medical cost savings at a population-level. A recent analysis determined that a penny per ounce tax would decrease SSB consumption by 15% and diabetes incidence by 2.6%, and prevent 95,000 coronary heart events, 8,000 strokes, and 26,000 premature deaths over the next ten years. It would also reduce medical costs by \$17 billion over ten years.⁴⁶ Since the greatest impact on consumption and body weight is expected in younger adults, even greater health and cost savings are likely longer-term.⁴⁶

Most SSBs have relatively high profit margins, so many manufacturers could, in theory, absorb the cost of an excise tax without passing it on, at least in full, to consumers. Therefore, effective tax proposals would have to clearly specify that the tax be passed on to consumers.⁵⁰ Nevertheless, some suspect that special sales and coupon offers would minimize the impact of the tax on final purchase prices.⁴⁹

Other concerns are that taxing SSBs will drive consumers to other beverages and foods with equally high, or even higher, calorie content, such as 100% fruit juice and whole milk; however, 100% compensation seems unlikely.^{55, 56} Currently, 100% fruit juices and unsweetened milk cost as much or more than most SSBs, particularly in restaurants and vending machines, and their price will not decrease simply because SSBs are taxed. Equal calorie substitution with foods is also unlikely, as they tend to be more satiating than liquid SSBs. As an added benefit, even some skeptics of SSB taxes point out that decreased SSB consumption may in turn decrease demand for foods often consumed with SSBs, such as salty snacks.⁵⁶

The high sugar and calorie content of 100% fruit juices remains a concern,⁴⁹ although most SSB tax proposals exempt them from tax.^{20, 46, 50} The US Dietary Guidelines count 100% fruit and vegetable juices as servings of fruits and vegetables and not as added sugars.¹ Furthermore, increased consumption of micronutrient-rich 100% juices and milk would likely improve other health outcomes,⁵³ including diabetes and heart disease, even if calorie intakes and BMI did not decrease, since only part of the association between SSBs and these diseases is due to body weight.^{20,46} Nevertheless, continued consumer education about adequate serving sizes, even of healthy foods, is warranted, and the impact of SSB taxes is likely to be enhanced if the revenues were channeled toward obesity prevention and health promotion efforts.⁵³

The literature remains divided on whether to tax sweetened milk/milk substitutes and diet beverages. Milk provides protein and several vitamins and minerals, yet intake of milk and milk products is below recommended levels.¹ Sweetened milk contains about 2-6 tsp of added sugars per 8 oz serving, which is less than most SSBs, but still a significant amount, especially if Americans meet their 2-3 daily servings of dairy with sweetened milk products. Just as water with added sweeteners (SSBs) is not a necessary component of the diet, sweetened versions of milk are not necessary. A tax on all beverages with added sweeteners would emphasize that the tax is on the added sweetener, not the water or milk. As for diet beverages, most analyses of the health benefits of SSB taxes have excluded diet beverages. Even if SSBs alone, and not diet beverages, were to be taxed, some analyses find that diet beverage purchases also would decrease.⁵⁴ Given the potential for diet beverages to influence taste preferences and their possible associations with adverse health outcomes, particularly in children, it is possible that even greater

improvements in long-term health outcomes would be observed by decreased consumption of both SSBs and diet beverages.

FINANCIAL AND POLITICAL CONSIDERATIONS

Public support for SSB taxes varies by year and survey design,²⁰ but overall, roughly one-third to one-half of consumers support SSB taxes.^{20, 57} More than 2/3 support SSB taxes if the revenues will be used for obesity prevention and health promotion.²⁰ Nevertheless, at least 15 states discussed SSB tax proposals to help curb obesity rates in 2011, but none passed.⁴⁶

The beverage industry has spent tens of millions of dollars to successfully block and repeal SSB taxes in recent years.⁵⁶ The industry provides jobs in many communities, both directly in their processing facilities, and indirectly through distributors and retailers.⁵⁶ In recent years, even the paper and trucking industries lobbied against SSB taxes, and many proposals were defeated or even repealed after beverage companies threatened to move their operations out of state.^{20, 58} The potential loss of jobs is a concern, but it is unknown how extensively a penny per ounce tax would decrease industry profits. It is possible that sales of unsweetened waters and teas could replace those lost by SSBs.

The beverage industry also funds the development of educational resources by a number of prominent medical and health professional organizations, as well as K-12 educational and sports programs in schools. Critics contest that these activities are merely another form of marketing. Industry efforts to encourage greater consumption of highly palatable and affordable SSBs easily exceed both private and public educational efforts to limit SSB consumption.⁴² In 2010 alone, beverage companies spent \$948 million to market SSBs in all measured media.⁵⁹ While beverage companies argue for the need for greater consumer education and “personal responsibility,”²⁰ their excessive advertising budgets suggest that it takes substantial effort to override people’s sense of personal responsibility and desire to eat right and be healthy.

It is argued that SSB taxes would disproportionately burden low-income individuals for whom food costs represent a greater proportion of their income.⁵⁵ However, as discussed above, SSBs are not a necessary part of the diet, and tap water is a lower cost and healthier substitute that is readily available in most households and restaurants. Many argue that an SSB tax could disproportionately *benefit* low-income individuals, who currently consume more SSBs than higher income individuals.⁴² Because they are more price sensitive, low-income individuals could reap greater long-term benefits with reduced rates of chronic diseases that currently burden low income groups disproportionately.⁶⁰

The US spends \$174 billion a year to treat diabetes and at least \$147 billion (9% of US health care expenditures) on health problems related to overweight and obesity.⁴⁶ A nationwide penny per ounce tax on SSBs is estimated to generate roughly \$13-15 billion in its first year,^{20, 47} and taxing both SSBs and diet beverages would generate close to \$20 billion annually.^{47, 61} These revenues are predicted to have an even larger impact on population health and medical costs if they were used for obesity prevention or other health promotion.⁴² While tap water is the cheapest beverage, many schools and other public places do not have easily accessible, fully functioning water fountains or faucets. Therefore, using tax revenues to improve access to public water supplies would likely improve public support for SSB taxes, as well as health outcomes.

Just as tobacco taxes have not eliminated heart disease or lung cancer, SSB taxes are not expected to eliminate obesity or diabetes.²⁰ Other efforts must be made to educate and empower people to choose healthier foods. Such efforts, supported at least in part by the revenue from SSB taxes, could have a greater impact on health outcomes than any direct effect of SSB taxes on consumption habits, even at existing tax rates.⁶²

AREAS REQUIRING FURTHER RESEARCH

More research is needed about the potential for both caloric and non-caloric sweeteners to induce symptoms of habituation and addiction. Research also is needed on the potential long-term effects, whether beneficial or adverse, of regular consumption of artificial sweeteners, particularly in children and adolescents.^{31, 33} Research should compare SSBs to both diet beverages and unsweetened water and should be funded by non-industry sources to reduce the potential for real or perceived bias.

Long-term data is needed on the influence of other environmental and personal behavioral factors, beyond price, on food and beverage purchase behaviors.⁶³ In the event that higher taxes on SSBs and diet beverages are enacted, it will be important to conduct rigorous evaluations over several years to evaluate the reasons behind their success or failure.⁵⁰

SUMMARY AND CONCLUSION

It is interesting to note that in 1942 the AMA Council on Food and Nutrition issued an opinion⁶⁴ which stated in part:

Some restriction of the consumption of sugar may be desirable from the standpoint of public health. The consumption of sugar and of other relatively pure carbohydrates has become so great during recent years that it represents a serious obstacle to the improved nutrition of the general public.

From the health point of view it is desirable especially to have restriction of such use of sugar as is represented by consumption of sweetened carbonated beverages...

Nothing has happened in the intervening 70 years to change this view. The Dietary Guidelines for Americans, as well as the AMA, recommend limiting intake of added sweeteners in order to reduce the risk of obesity and other chronic diseases. Reducing intake of SSBs, which comprise nearly half (46%) of Americans' added sugar intake, is a simple way to reduce intake of added sugars without compromising the nutrient adequacy of the overall diet.¹ In addition, liquid calories have been shown to be less satiating than those from solid foods, and most people compensate poorly for the added calories from SSBs. SSB consumption has been strongly and consistently associated with increased body weight, as well as a number of related cardiometabolic conditions including type 2 diabetes and coronary heart disease. Limiting consumption of SSBs is likely to improve health outcomes.

While non-caloric (diet) beverages do not directly contribute to added sugar intakes, they do not appear to confer any known health benefits in and of themselves, although they may assist in short-term weight loss efforts in adults. Some recent studies suggest that high and chronic consumption of diet beverages may increase risk of metabolic syndrome, type 2 diabetes, and vascular events, although other studies do not. Concern also exists that diet beverages may displace more healthful beverages such as milk in children, and may alter taste preferences and energy regulation. More long-term studies are warranted, particularly in children and adolescents, in order to confirm the potential health benefits or harms of regular diet beverage consumption.

Current research models predict that increased taxes on SSBs would result in modest reductions in calorie intake and body weight, resulting in only a 5% reduction in the prevalence of overweight and obesity in children and adults. These small reductions have been predicted to reduce medical costs by \$17 billion over ten years. However, greater health benefits would accrue if SSB tax revenues were used primarily for programs to prevent and/or treat obesity and related conditions, such as educational campaigns and improved access to potable drinking water, particularly in schools and communities disproportionately affected by obesity and related conditions. The tax revenues also could fund research into the population health outcomes that may result from the taxes. The Council recognizes that a wide array of efforts are necessary to reduce SSB consumption and improve overall dietary habits and public health; SSB taxes are one means by which local, state, or federal governments may choose to finance these efforts.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted in lieu of Resolution 417-A-11 and the remainder of this report be filed:

1. Our American Medical Association (AMA) recognizes the complexity of factors contributing to the obesity epidemic and the need for a multifaceted approach to reduce the prevalence of obesity and improve public health. A key component of such a multifaceted approach is improved consumer education on the adverse health effects of excessive consumption of beverages containing added sweeteners. Taxes on beverages with added sweeteners are one means by which consumer education campaigns and other obesity-related programs could be financed in a stepwise approach to addressing the obesity epidemic.

2. Where taxes on beverages with added sweeteners are implemented, the revenue should be used primarily for programs to prevent and/or treat obesity and related conditions, such as educational ad campaigns and improved access to potable drinking water, particularly in schools and communities disproportionately effected by obesity and related conditions, as well as on research into population health outcomes that may be affected by such taxes.
3. That our AMA advocate for continued research into the potentially adverse effects of long-term consumption of non-caloric sweeteners in beverages, particularly in children and adolescents.

APPENDIX - Current AMA Policies Relevant to the Issue of Taxing Beverages to Improve Public Health

H-150.937 Reducing the Price Disparity Between Calorie-Dense, Nutrition-Poor Foods and Nutrition-Dense Foods

Our AMA supports: (1) efforts to decrease the price gap between calorie-dense, nutrition-poor foods and naturally nutrition-dense foods to improve health in economically disadvantaged populations by encouraging the expansion, through increased funds and increased enrollment, of existing programs that seek to improve nutrition and reduce obesity, such as the Farmer's Market Nutrition Program as a part of the Women, Infants, and Children program; and (2) the novel application of the Farmer's Market Nutrition Program to existing programs such as the Supplemental Nutrition Assistance Program (SNAP), and apply program models that incentivize the consumption of naturally nutrition-dense foods in wider food distribution venues than solely farmer's markets as part of the Women, Infants, and Children program. (Res. 414, A-10)

D-150.981 The Health Effects of High Fructose Syrup

Our AMA: (1) recognizes that at the present time, insufficient evidence exists to specifically restrict use of high fructose corn syrup (HFCS) or other fructose-containing sweeteners in the food supply or to require the use of warning labels on products containing HFCS; (2) encourages independent research (including epidemiological studies) on the health effects of HFCS and other sweeteners, and evaluation of the mechanism of action and relationship between fructose dose and response; and (3) in concert with the Dietary Guidelines for Americans, recommends that consumers limit the amount of added caloric sweeteners in their diet. (CSAPH Rep. 3, A-08)

D-150.978 Sustainable Food

Our AMA: (1) supports practices and policies in medical schools, hospitals, and other health care facilities that support and model a healthy and ecologically sustainable food system, which provides food and beverages of naturally high nutritional quality; (2) encourages the development of a healthier food system through the US Farm Bill and other federal legislation; and (3) will consider working with other health care and public health organizations to educate the health care community and the public about the importance of healthy and ecologically sustainable food systems. (CSAPH Rep. 8, A-09; Reaffirmed in lieu of Res. 411, A-11)

D-150.987 Addition of Alternatives to Soft Drinks in Schools

Our AMA will seek to promote the consumption and availability of nutritious beverages as a healthy alternative to high-calorie, low nutritional-content beverages (such as carbonated sodas and sugar-added juices) in schools. (Res. 413, A-05; Reaffirmation A-07)

H-150.960 Improving Nutritional Value of Snack Foods Available in Primary and Secondary Schools

The AMA supports the position that primary and secondary schools should replace foods in vending machines and snack bars, which are of low nutritional value and are high in fat, salt and/or sugar, with healthier food choices which contribute to the nutritional needs of the students. (Res. 405, A-94; Reaffirmation A-04; Reaffirmed in lieu of Res. 407, A-04; Reaffirmed: CSA Rep. 6, A-04; Reaffirmation A-07)

H-150.944 Combating Obesity and Health Disparities

Our AMA supports efforts to: (1) reduce health disparities by basing food assistance programs on the health needs of their constituents; (2) provide vegetables, fruits, legumes, grains, vegetarian foods, and healthful nondairy beverages in school lunches and food assistance programs; and (3) ensure that federal subsidies encourage the consumption of products low in fat and cholesterol. (Res. 413, A-07)

D-150.989 Healthy Food in Hospitals

Our AMA will urge: (1) component medical societies, member physicians and other appropriate local groups to encourage palatable, health-promoting foods in hospitals and other health care facilities and oppose the sale of unhealthy food with inadequate nutritional value or excessive caloric content as part of a comprehensive effort to reduce obesity; and (2) health care facilities that contract with outside food vendors to select vendors that share their commitment to the health of their patients and community. (Res. 420, A-05)

D-440.954 Addressing Obesity

Our AMA will: (1) assume a leadership role in collaborating with other interested organizations, including national medical specialty societies, the American Public Health Association, the Center for Science in the Public Interest, and the AMA Alliance,

to discuss ways to finance a comprehensive national program for the study, prevention, and treatment of obesity, as well as public health and medical programs that serve vulnerable populations; (2) encourage state medical societies to collaborate with interested state and local organizations to discuss ways to finance a comprehensive program for the study, prevention, and treatment of obesity, as well as public health and medical programs that serve vulnerable populations; and (3) continue to monitor and support state and national policies and regulations that encourage healthy lifestyles and promote obesity prevention. (BOT Rep. 11, I-06)

H-440.902 Obesity as a Major Health Concern

The AMA: (1) recognizes obesity in children and adults as a major public health problem; (2) will study the medical, psychological and socioeconomic issues associated with obesity, including reimbursement for evaluation and management of obese patients; (3) will work with other professional medical organizations, and other public and private organizations to develop evidence-based recommendations regarding education, prevention, and treatment of obesity; (4) recognizes that racial and ethnic disparities exist in the prevalence of obesity and diet-related diseases such as coronary heart disease, cancer, stroke, and diabetes and recommends that physicians use culturally responsive care to improve the treatment and management of obesity and diet-related diseases in minority populations; and (5) supports the use of cultural and socioeconomic considerations in all nutritional and dietary research and guidelines in order to treat overweight and obese patients. (Res. 423, A-98; Reaffirmed and Appended: BOT Rep. 6, A-04; Reaffirmation A-10)

H-150.953 Obesity as a Major Public Health Program

Our AMA will: (1) urge physicians as well as managed care organizations and other third party payers to recognize obesity as a complex disorder involving appetite regulation and energy metabolism that is associated with a variety of comorbid conditions; (2) work with appropriate federal agencies, medical specialty societies, and public health organizations to educate physicians about the prevention and management of overweight and obesity in children and adults, including education in basic principles and practices of physical activity and nutrition counseling; such training should be included in undergraduate and graduate medical education and through accredited continuing medical education programs; (3) urge federal support of research to determine: (a) the causes and mechanisms of overweight and obesity, including biological, social, and epidemiological influences on weight gain, weight loss, and weight maintenance; (b) the long-term safety and efficacy of voluntary weight maintenance and weight loss practices and therapies, including surgery; (c) effective interventions to prevent obesity in children and adults; and (d) the effectiveness of weight loss counseling by physicians; (4) encourage national efforts to educate the public about the health risks of being overweight and obese and provide information about how to achieve and maintain a preferred healthy weight; (5) urge physicians to assess their patients for overweight and obesity during routine medical examinations and discuss with at-risk patients the health consequences of further weight gain; if treatment is indicated, physicians should encourage and facilitate weight maintenance or reduction efforts in their patients or refer them to a physician with special interest and expertise in the clinical management of obesity; (6) urge all physicians and patients to maintain a desired weight and prevent inappropriate weight gain; (7) encourage physicians to become knowledgeable of community resources and referral services that can assist with the management of overweight and obese patients; and (8) urge the appropriate federal agencies to work with organized medicine and the health insurance industry to develop coding and payment mechanisms for the evaluation and management of obesity. (CSA Rep. 6, A-99; Reaffirmation A-09; Reaffirmed: CSAPH Rep. 1, A-09; Reaffirmation A-10; Reaffirmation I-10)

H-495.987 Tobacco Taxes

(1) Our AMA will work for and encourages all levels of the Federation and other interested groups to support efforts, including education and legislation, to pass increased federal, state, and local excise taxes on tobacco in order to discourage tobacco use. (2) An increase in federal, state, and local excise taxes for tobacco should include provisions to make substantial funds available that would be allocated to health care needs and health education, and for the treatment of those who have already been afflicted by tobacco-caused illness, including nicotine dependence, and to support counter-advertising efforts. (3) Our AMA continues to support legislation to reduce or eliminate the tax deduction presently allowed for the advertisement and promotion of tobacco products; and advocates that the added tax revenues obtained as a result of reducing or eliminating the tobacco advertising/promotion tax deduction be utilized by the federal government for expansion of health care services, health promotion and health education. (CSA Rep. 3, A-04; Modified: BOT Rep. 8, A-05; Reaffirmed: BOT Rep. 8, A-08)

H-30.939 Increasing Taxes on Alcoholic Beverages

It is AMA policy that federal, state, and local tax rates on alcoholic beverages be based on the grams of ethanol present in the beverage, not on the fluid volume of beverages such as beer, wine, and distilled spirits. (Res. 438, A-05)

D-30.995 Increasing Taxes on Alcoholic Beverages

Our AMA will: (1) support increases in federal taxes on beer, wine, and liquor, with a substantial portion of the new revenues to be earmarked to the prevention of alcohol abuse and drunk driving, treatment of persons with alcohol dependence or at-risk drinking patterns, and public health and medical programs that serve vulnerable populations; (2) encourage state and local medical societies to support increases in state and local taxes on beer, wine, and liquor, with a substantial portion of the new revenues to be earmarked to the purposes noted above; (3) support, to the extent possible, state and local efforts to increase taxes on beer, wine, and liquor; (4) collaborate with other national organizations with an interest in this subject, including national medical specialty societies, the American Public Health Association, the Center for Science in the Public Interest, Mothers Against Drunk Driving, and the AMA Alliance; and (5) when state legislative efforts to increase alcohol taxes are stymied,

encourage state medical societies to give consideration to the use of ballot initiatives in the 24 states that allow such initiatives. (Res. 438, A-05)

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6. SCREENING MAMMOGRAPHY (RESOLUTION 509-A-10, RESOLVE 1)

Reference committee hearing: see report of [Reference Committee E](#).

**HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS
IN LIEU OF RESOLVE 1 OF RESOLUTION 509-A-10 AND
REMAINDER OF REPORT FILED**

See Policy [H-525.993](#)

INTRODUCTION

Resolution 509-A-10, introduced by the Illinois Delegation, asked that our American Medical Association (AMA): (1) recommend that physicians and patients continue to follow the guidelines of the American Cancer Society regarding screening mammography and patient breast self-examination; and (2) encourage government panels and task forces dealing with specific disease entities to have representation by physicians with expertise in those diseases. Resolve 1 was referred for decision; Resolve 2 was adopted.

The Board of Trustees considered Resolve 1 and referred it to the Council on Science and Public Health, asking for a report back on the issue of screening mammography, especially with regard to screening women ages 40-49 years. Accordingly, this report will highlight current screening mammography guidelines, explore the established benefits and harms of mammography, review the process by which the United States Preventive Services Task Force (USPSTF) developed its updated recommendations on screening mammography, and update the AMA's current policy recommendations.

METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2000 and 2012 using the search terms "screening mammography," and "mammography AND USPSTF," and "mammography AND 40." To capture reports that may not have been indexed on PubMed, as well as news articles and press releases, periodic Google searches were conducted using the search terms "mammography," "mammography AND USPSTF," and "mammography AND 40." Additional articles were identified by review of the literature citations in articles found in the PubMed and Google searches. Specific information on the USPSTF was obtained from its website.

BACKGROUND

From 2002-2009, the USPSTF recommendations on breast cancer screening supported routine screening mammography, with or without a clinical breast exam, every 1-2 years for women age 40 years and older.¹ These recommendations were similar to the recommendations of several other medical professional societies and cancer advocacy groups, including the American Cancer Society (ACS), American College of Radiology (ACR), American Congress of Obstetricians and Gynecologists (ACOG), and the National Comprehensive Cancer Network (NCCN).

In November 2009, the USPSTF updated its guidelines on screening for breast cancer.² These guidelines recommend against routine screening mammography in women aged 40-49 years, and recommend biennial screening mammography in women aged 50-74 years.² The USPSTF concluded that the evidence was insufficient to recommend for or against routine screening mammography in women older than age 74 years.² In December 2009,

the USPSTF updated the language of its recommendation regarding women under age 50 years to clarify its original and continued intent. That recommendation now states: “The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient’s values regarding specific benefits and harms.”²

The USPSTF also updated recommendations on clinical breast examination (CBE), self-breast examination (SBE), digital mammography, and magnetic resonance imaging (MRI), however this report will focus on the recommendations for screening mammography.

RELEVANT AMA POLICY

AMA policy strongly supports mammography screening for the early detection of breast cancer (see Appendix I). Policy H-55.993 [Early Detection of Breast Cancer, AMA Policy Database] encourages recognition of mammography as an effective screening technique and additionally encourages education and awareness about breast self-examination. Policies H-55.984 [Screening and Treatment for Breast and Cervical Cancer], H-55.985 [Screening and Education Programs for Breast and Cervical Cancer Risk Reduction], and D-525.998 [Mammography Screening for Breast Cancer] support funding for screening programs, including for low-income women; H-55.985 additionally encourages educational programs to inform women about screening.

With regard to recommendations directly addressing screening mammography in women between the ages of 40-49 years, AMA policy is the following:

H-525.993 Mammography Screening in Asymptomatic Women Forty Years and Older

1. Our AMA strongly endorses the positions of the American College of Obstetrics and Gynecology, the American Cancer Society, and the American College of Radiology that all women have screening mammography as per current guidelines. 2. Our AMA favors participation in and support of the efforts of the professional, voluntary, and government organizations to educate physicians and the public regarding the value of screening mammography in reducing breast cancer mortality. 3. Our AMA advocates remaining alert to new epidemiological findings regarding age-specific breast cancer mortality reduction following mammography screening. 4. Based on recent summary data our AMA recommends annual screening mammograms and continuation of clinical breast examinations in asymptomatic women 40 years and older. 5. Our AMA encourages the periodic reconsideration of these recommendations as more epidemiological data become available. 6. Our AMA supports seeking common recommendations with other organizations. 7. Our AMA reiterates its longstanding position that all medical care decisions should occur only after thoughtful deliberation between patients and physicians. (CSA Rep. F, A-88; Reaffirmed: Res. 506, A-94; Amended: CSA Rep. 16, A-99; Appended: Res. 120, A-02)

The original iteration of this policy was adopted in 1988, based on the recommendations in Council on Scientific Affairs Report F-A-88.³ The report recommended supporting annual screening mammography in women age 50 and older, and mammography screening every 1-2 years in women aged 40-49 years.³ The policy was updated in 1999 by CSA Report 16-A-99, which recommended supporting annual screening mammography in asymptomatic women age 40 years and older.⁴ In 2002, with the adoption of Resolution 120-A-02, the policy was further amended to endorse the screening guidelines of ACOG, ACS, and ACR.

CURRENT MAMMOGRAPHY SCREENING GUIDELINES

Many organizations have developed or endorsed guidelines regarding screening mammography. The Table below summarizes the recommendations of several groups in this country, as well as those from the Canadian Task Force for Preventive Health Care⁵ and Britain’s National Health Service.⁶

The USPSTF recommends routine screening mammography beginning at age 50 years and continuing biennially through age 74 years; the American Academy of Family Physicians (AAFP) endorses the recommendations of the USPSTF.^{2,7} For women aged 40-49 years, the USPSTF (with AAFP endorsing) and the American College of Physicians (ACP) recommend individual patient assessment for breast cancer risk, along with patient education about the benefits and limitations of mammography, as the basis for a decision to screen.^{2,7,8}

ACOG, ACR, ACS, and NCCN recommend annual routine screening mammography beginning at age 40 years.⁹⁻¹² ACOG, ACS, and NCCN include in their guidelines a recommendation to discuss with women the predictive value of mammography and its limitations.^{9,11,12} ACOG states that based on individual risk, biennial screening may be appropriate for some women.⁹ ACOG, ACR, ACS, and NCCN guidelines do not specify an age at which screening should end. While NCCN states that the appropriate upper age limit has not yet been determined,¹² ACR recommends continuation until life expectancy reaches less than five to seven years,¹⁰ and ACS recommends continuation as long as the patient is in good health.¹¹ ACOG notes that women 75 years or older should, in consultation with their physicians, decide whether or not to continue mammographic screening.⁹

Organization (year recommendation updated)	Age at which <u>routine</u> screening should begin	Frequency	Age at which <u>routine</u> screening should end
AAFP (2009) ^a	50	Biennial	75
ACOG (2011)	40 (with discussion ^c)	Annual (Biennial may be appropriate for some)	Not specified
ACR/SBI ^b (2010)	40	Annual	Life expectancy <5-7 years
ACS (2003)	40 (with discussion ^c)	Annual	As long as patient is in good health
NCCN (2011)	40 (with discussion ^c)	Annual	Not yet established
USPSTF (2009)	50	Biennial	75
CTFPHC (2011)	50	Triennial	75
NHS (2011)	50 (expanding to 47)	Triennial	70 (expanding to 73)

Table: Screening mammography recommendations of several groups. Abbreviations are as follows: AAFP: American Academy of Family Physicians; ACOG: American Congress of Obstetricians and Gynecologists; ACR: American College of Radiology; SBI: Society of Breast Imaging; ACS: American Cancer Society; NCCN: National Comprehensive Cancer Network; USPSTF: United States Preventive Services Task Force; CTFPHC: Canadian Task Force for Preventive Health Care; NHS: National Health Service (Britain)

- The AAFP endorses the USPSTF's recommendations
- ACR and SBI have joint recommendations.
- Recommendation includes the discussion of the predictive value and limitations of mammography.

A survey of the International Breast Cancer Screening Network shows that 5 of 19 member countries recommend screening beginning at age 40 years, with most screening biennially.¹³ The recommendations of the different countries are, by and large, based on the same data, but reflect a difference of opinion in data interpretation.¹³

It is important to note that the guidelines discussed in this report are for routine screening mammography, i.e., mammography for women who are at average risk for breast cancer. They are not appropriate for women at increased risk due to underlying genetic mutations (such as *BRCA1* or *BRCA2*), family history, previous chest radiation, or other risk factors; guidelines for women at increased risk are substantially different.^{11,12}

BENEFITS AND HARMS OF SCREENING MAMMOGRAPHY

Breast cancer is the most common cancer in women in the US, with more than 200,000 women receiving a diagnosis of invasive breast cancer each year and nearly 40,000 dying.¹⁴ The average woman's lifetime risk of developing breast cancer is 1 in 8, or 12%,¹⁴ however factors such as age, family or personal history of cancer, dense breasts, and previous exposure to chest radiography can increase risks.¹⁵ In the US, digital mammography has rapidly replaced the older method of film mammography.¹⁶ Though mammography is the most reliable breast cancer screening tool for the general population, it carries potential harm along with its benefits. Recommendations regarding screening frequency and age of initiation are based on the balance of benefits and harms.

Benefits of screening mammography

Mortality reduction. There is wide agreement that screening mammography leads to a reduction in breast cancer mortality,¹⁷ although disagreements exist about how to calculate such reductions. Randomized controlled trials (RCTs) have estimated the reduction in mortality across all age groups to be approximately 15-30%,¹⁸⁻²² while observational and modeling studies have estimated mortality reduction across all age groups to be higher, with a

range of 30% to more than 40%.²³⁻²⁶ In RCTs, mortality reduction is based on the number of women invited to screen, rather than those who have actually undergone screening in the trial. This “number invited to screen” includes those women who are part of the screening arm of the trial but who decline screening. Those who fit into this category and who also die of breast cancer will be counted in the larger number of women in the screening arm that died of breast cancer.²⁶ Based on this method, noncompliance to the screening protocol potentially underestimates the mortality reduction derived from screening.²⁶ Similarly, women who are assigned to the control, non-screening arm sometimes seek mammography on their own, skewing the potential mortality reduction downward.²⁶

There have been few RCTs designed to determine mortality reduction from mammography screening in specific age groups; estimates have been derived from subanalyses of trials designed for other outcomes. Pooled data from RCT subanalyses show mortality reduction from mammography screening to be greatest in women aged 60-69 years (approximately 32%).¹⁸ For women aged 39-49 years and 50-59 years, pooled data show mortality reduction to be 15% and 14%, respectively.^{18,21,27-32} Although these values appear to indicate a similar mortality reduction for both of these age groups, it should be noted that estimated reductions are based on *relative* risk (risk of breast cancer mortality in women of a particular age group who undergo mammography versus those in the same age group who do not undergo mammography). Because a woman’s risk for breast cancer increases sharply with age, *absolute* mortality risk reduction (reduction in the overall risk of breast cancer mortality) from screening is greater for women aged 50-59 years than that for women aged 40-49 years.^{2,18} Mortality reduction estimates for women age 70 years and older are lacking because of insufficient data.¹⁸

Subanalyses of trials designed to estimate benefit across larger age groups, as well as more recent retrospective studies, have shown benefits for women aged 40-49 years who undergo screening mammography.^{21,26,30} Between 40-49 years of age, tumors detected by mammography are smaller with less nodal metastasis (compared to those tumors detected without mammography), and 5-year and disease-free survival are improved.³³ Additionally, a 2010 study showed that mammography in women younger than age 50 years with a family history of breast cancer increases cancer detection, reduces risk of advanced stage disease, and is associated with lower mortality and higher 10-year survival from invasive cancer.³⁴

Based on analyses of breast cancer mortality reduction before and after the implementation of screening programs, some argue that the observed reduction is only partially due to screening, with the rest due to improved therapy and management of breast cancer disease and to changes in staging techniques.^{25,35,36} However, this is refuted by others. In regions without formal screening but with access to improved treatments, the mortality rate did not decrease until screening was introduced.^{37,38}

It is possible that the mortality reduction associated with screening mammography could be greater. Only approximately 65% of women age 40 years or older report having undergone screening mammography within the last two years.³⁹ Increasing adherence to recommendations could potentially increase the number of women in whom cancer is detected early, leading to greater mortality reduction.^{2,39}

Harms of screening mammography

Although there is broad agreement that screening mammography reduces mortality from breast cancer, it is not a perfect tool. Along with the intended early detection of invasive breast cancer, mammography carries with it potential harms, such as false-positive results, overdiagnosis, and exposure to radiation.

False-positive results. A false positive is defined as an abnormal screening mammography result that does not end in a diagnosis of invasive carcinoma or ductal carcinoma *in situ* (DCIS) within one year of the screening examination.⁴⁰ The reported specificity of mammography is 94-97%.^{20,41} In other words, 94-97% of mammograms correctly rule out the presence of disease in disease-free individuals. Though this specificity appears to be high, it must be considered in the context of the number of mammograms performed. More than 33 million screening mammograms are performed in the US each year.⁴² Taking into account the annual incidence of breast cancer (approximately 124 cases per 100,000 women),⁴³ the reported specificity implies that every year, approximately 1-2 million women receive an abnormal mammography result that will turn out not to be breast cancer. Many of these women will undergo further imaging and invasive procedures.⁴⁴

A 2011 study, designed to address limitations in previous estimates of false-positive rates,⁴⁵⁻⁴⁸ found that after 10 years of annual screening, the probability of receiving a recall (recommendation for immediate follow-up imaging) is 61.3%; this probability drops to 41.6% for 10 years of biennial screening.⁴⁴ These estimates are similar whether screening begins at age 40 or 50 years. Older studies report that false-positive mammograms occur in 21-49% of all women after 10 mammography examinations, and in up to 56% for women aged 40-49 years.¹⁸ The probability of a false-positive biopsy recommendation (recommendation for biopsy, fine-needle aspiration, or surgical consult after imaging work-up) is 7-9% after 10 years of annual screening and 4-6% after 10 years of biennial screening.⁴⁴ While biennial screening appears to decrease the probability of a false-positive mammography result, it may be associated with an increase in the probability of a late-stage cancer diagnosis.⁴⁴

Many women who have been recalled for further screening become distressed, and some report persistent anxiety despite eventual negative results.^{18,49} Others report only transient anxiety.^{18,37} False-positive results appear to affect breast cancer-specific distress, anxiety, apprehension, and perceived risk rather than general depression and anxiety.^{18,50}

False-positive results can also affect adherence to screening recommendations. In a 2011 study, women who received a false-positive result were less likely to return for routine screening compared with women who received negative results.⁵¹ However, reattendance improved with the number of completed screening participations, suggesting that abnormal results in younger women (who have completed relatively few screens) are more likely to negatively impact reattendance than in women who have undergone several routine screens.⁵¹

Variation in screening mammography specificity has been noted among physicians and facilities. For example, recall rates are lower and specificity rates higher among radiologists who have more years of experience interpreting mammograms.^{52,53} Higher specificity is seen at facilities that offer screening mammography alone (versus those that offer both screening and diagnostic mammography), have a breast-imaging specialist interpreting mammograms, and conduct audit reviews two or more times each year.⁵⁴ AMA policy (H-525.985 Safety and Performance Standards for Mammography; see Appendix I) supports high quality standards of performance for those administering and interpreting mammograms, including “evidence of appropriate training and competence for professionals.”

Overdiagnosis. Overdiagnosis is the detection of cancer that would not have clinically surfaced in a person’s lifetime, usually because of lack of progressive potential.²⁴ Overdiagnosis is easily confused with false-positive results, i.e., a positive screening result that is subsequently determined not to be cancer. In contrast, an overdiagnosis represents a case in which the pathological criteria for cancer has been fulfilled.⁵⁵ Stable disease including some DCIS, indolent cancers, and slow-growing tumors are thought to be most commonly overdiagnosed by mammography.^{55,56} Some reports have concluded that a small percentage of mammography-detected cancers may spontaneously regress, although others have criticized this assertion.⁵⁶⁻⁵⁸

Evidence for overdiagnosis comes from RCTs designed to demonstrate the benefit of mammography. In these trials, women are randomly assigned to screening mammography and non-screening mammography arms; since the assignments are random, the number of breast cancers that develop over time should be the same in each group.⁵⁹ In the group receiving screening mammography, the number of women receiving breast cancer diagnoses will initially be higher than in the non-screening group, since the mammograms will detect tumors too small to be detected otherwise. With time, as the small tumors in women in the non-screening group grow and become detectable, the number of breast cancer diagnoses should become similar to those in the screening group. However, some trials have shown that breast cancer diagnoses in the screening group are persistently higher, even after many years. This persistent difference represents overdiagnosis.⁵⁹

Quantification of overdiagnosis is difficult; it is not ethically possible to set up prospective clinical trials to determine which cancers will remain indolent if left untreated.⁶⁰ Therefore, the proportion of mammography-detected breast cancers that are estimated to be overdiagnoses is widely variable, ranging between 1-30%; estimates are derived from screening programs in several countries that are statistically difficult to combine.¹⁸ Observational and modeling studies have attempted to narrow the range. For example, a 2012 study used data from different geographic regions in Norway, where screening mammography began at staggered times over a nine-year period.⁶¹ By comparing breast cancer incidence in regions with a screening program to incidence in regions that had yet not implemented screening, the study estimated that 15-25% of mammography-detected breast cancers were overdiagnoses.⁶¹ Within different age groups, modeling studies have shown only small differences in the rate of

overdiagnosis.²¹ In general, the risk for overdiagnosis increases with age, likely because in older age groups, rates of competing causes of mortality increase.²⁴ The difficulty in accurately estimating rates of overdiagnosis has led to arguments that the estimates are artificially high, and are complicated by follow-up times, lead-time, and changes in breast cancer incidence over several years.⁶²

Overdiagnosis is regarded by some as the most serious harm associated with mammography;⁵⁹ at the time of diagnosis, clinicians cannot know who has been overdiagnosed, so all are treated for potentially lethal cancer.^{55,56} These patients will not benefit from treatment and almost certainly will be harmed.⁵⁵

A perceived benefit of mammography screening is that it reduces the need for mastectomies and increases the potential for breast-conserving treatment.⁶³ However, a 31% increase in breast surgery and 20% increase in mastectomy for women exposed to screening has been reported.¹⁹ A 2011 Norwegian study corroborated these findings, and concluded that overdiagnosis is likely to have contributed to the increases in surgical intervention.^{63,64} Other studies have reported no increase in the rate of mastectomy.^{65,66}

Radiation exposure. Little evidence exists to suggest that low-dose radiation exposure from mammography is a significant risk.¹⁸ Widely-ranging cumulative radiation doses of 0.3-43.4 Gy are thought to significantly increase the risk for breast cancer;⁶⁷ the average dose for a bilateral, two-view mammogram is 7 mGy or less,^{68,69} and for women aged 40-49 years, annual mammography screening for 10 years (with potential additional imaging) exposes the individual to approximately 60 mGy.⁶⁷ The number of radiation-induced breast cancer deaths associated with biennial screening between the ages of 50-74 years has been modeled at 1.6 per 100,000 women screened. This model also predicts that extending the biennial screening period to women between the ages of 40-74 years results in 3.7 radiation-induced breast cancer deaths per 100,000 women.⁶⁹ These rates are considered negligible, with screening benefits far outweighing the risk of radiation exposure.^{18,69} For comparison, the ratio of breast cancer deaths prevented by mammography to the number of deaths induced by radiation exposure is 684:1 for women aged 50-74 years, and 349:1 for women aged 40-74 years.⁶⁹

Special consideration of the effects of radiation exposure should be given to women who have previously undergone diagnostic chest radiographs or had therapeutic radiation for other cancers. These women are at increased risk for cancer since cumulative radiation exposure is increased.⁷⁰

THE USPSTF AND ITS RECOMMENDATIONS FOR SCREENING MAMMOGRAPHY

Background

The mission of the USPSTF is to review the scientific evidence for clinical preventive services and to develop evidence-based recommendations for primary care physicians as well as the broader health care community.⁷¹ Congress codified the USPSTF as an independent body in 1998. Though the Agency for Healthcare Research and Quality (AHRQ) is mandated to convene the USPSTF, its sole role is to support the USPSTF by providing meeting space, organizing conference calls, managing contracts for systematic reviews, and providing staffing.⁷¹ No individual at AHRQ has a vote in the recommendations, or otherwise influences the priorities or decisions of the USPSTF.⁷¹

The USPSTF comprises 16 members who serve terms of 4-6 years; members are appointed by the AHRQ director based on recommendations developed by the USPSTF Chair and Vice-Chair following a public nomination process.⁷¹ Members are experts in primary care and preventive health-related disciplines, and collectively possess expertise in evidence-based clinical research, screening, clinical epidemiology, behavioral science, health services research, outcomes and effectiveness in clinical preventive medicine, and decision modeling.⁷¹ The USPSTF does not deliberately seek out task force members who are experts on specific topics; experts bring substantial knowledge regarding guideline development processes but also may retain inherent biases.^{72,73} It is sometimes difficult for experts to fairly assess and critique studies that they or their colleagues have conducted, contradict beliefs entrenched since training, and recommend against services that may benefit themselves or their specialties.⁷² Also, many experts in specific topic areas lack training in epidemiology and biostatistics.⁷² The USPSTF is considered unique in that it convenes primary care providers and scientists with skills in objectively critiquing studies without preconceived views or a stake in the outcome.⁷²

The USPSTF follows a detailed protocol for guideline development.⁷⁴ For each topic under consideration, an AHRQ evidence-based practice center conducts a systematic review of the evidence, which enables a subcommittee of the USPSTF to develop estimates of the magnitude and certainty of benefits and harms. These estimates are extensively reviewed by the full USPSTF in order to reach consensus and vote on recommendations. Cost and cost-effectiveness are not considered in the guideline development process.⁷¹ A full explanation of the USPSTF's evidence grading and subsequent recommendation system is published on the USPSTF website.⁷⁴

Subspecialist experts in the disease at hand, as well as partner organizations, are asked to review and comment on USPSTF work at three points in the recommendation development process: 1. the initial analytic framework and key questions that drive the systematic review; 2. the systematic review itself; and 3. the draft recommendation statement. USPSTF partner organizations that are also members of the AMA Federation of Medicine are AAFP, ACOG, ACP, the American College of Preventive Medicine (ACPM), the American Academy of Pediatrics, and the American Osteopathic Association.

Recommendations for screening mammography

Plans for the update of the 2002 USPSTF recommendations on screening mammography began in late 2006. In 2007, the USPSTF commissioned two reviews: a targeted systematic evidence review of the benefits and harms of screening⁷⁵ and a decision analysis based on modeling techniques that compared the expected health outcomes of starting and ending mammography at different ages and using annual and biennial screening strategies.²⁴ The systematic review excluded studies other than RCTs and systematic reviews or those without breast cancer mortality as an outcome.^{18,75} The systematic review included analyses of evidence regarding CBE, SBE, digital mammography, and MRI, but this section will focus on the evidence analyzed to develop recommendations on screening mammography.

In its 2009 update, the USPSTF recommended against routine screening mammography for women aged 40-49 years, and instead recommended an individualized decision to screen during this time period. This recommendation is partially based on findings in the commissioned systematic review.¹⁸ The systematic review was carried out by the Oregon Evidence-based Practice Center, funded by AHRQ. Prior to its finalization, the draft report was reviewed by 15 experts not affiliated with the USPSTF. These reviewers included one oncologist, an expert in modeling, two radiologists, one breast surgeon, and three physician/epidemiologists.⁷⁶ The names of the reviewers are included in the full systematic review available on the National Library of Medicine website.⁷⁵

Mortality reduction was considered an important outcome in the formation of the recommendations.² The systematic review estimated the mortality reduction for women aged 39-49 years, 50-59 years, and 60-69 years to be 15%, 14%, and 32% respectively.¹⁸ These estimates are similar to those established in the USPSTF's 2002 systematic review, but include new data from an update of a previously completed trial,³⁰ and another clinical trial completed after 2002.^{2,20,31} Since these mortality reduction estimates are based on relative risk, the USPSTF considered calculations of the number needed to invite for screening to prevent one death from breast cancer, which more clearly explains mortality reduction.² The "number needed to screen" calculation is based on absolute risk, so it takes into account the background risk for breast cancer.^{77,78} This number can more clearly reflect the benefit of mammography in each age group since it includes the increasing absolute risk of breast cancer with advancing age. The number needed to invite for screening (to prevent one death) is 1904 for women aged 40-49 years, 1339 for women aged 50-59 years, and 377 for women aged 60-69 years.²

In addition to the mortality reduction benefit associated with mammography, the USPSTF considered harms. In some studies, the probability of receiving a false-positive mammography result is slightly higher in women aged 40-49 years.¹⁸ A false-positive mammography result often leads to additional imaging, and after several years participating in a screening program, nearly 10% of women receive a false-positive biopsy recommendation.⁴⁴ Though the range of reported overdiagnosis is large, between 1-30%, and therefore difficult to estimate precisely, it is a risk that many agree is serious, since it leads to treatment that may not be necessary.¹⁸ Radiation exposure was not considered to be a serious risk of screening mammography, except for the small percentage of the population previously exposed to chest radiography and therapeutic radiation.⁷⁰

The USPSTF-commissioned decision analysis compared the expected health outcomes of starting and ending mammography at different ages and using annual and biennial screening strategies.²⁴ For the screening models compared, biennial screening retains 70-99% of the reduction in mortality that occurs with annual screening,

depending on the age range for screening.²⁴ The models predict that beginning screening at age 40 years yields an additional 3% mortality benefit compared with beginning screening at age 50 years.²⁴ This additional mortality benefit is the same with either annual or biennial screening beginning at age 40 years.²⁴ Extending screening to age 79 years yields an additional 8% or 7% mortality benefit compared with screening programs ending at age 69 years, for annual and biennial screening, respectively.²⁴ If the two strategies are compared, these data indicate that greater mortality reduction could be achieved by continuing screening past age 69 years rather than by initiating it at age 40 years. However, if life-years gained is considered, models show that initiating screening in younger women rather than extending screening in older women results in more benefit; this is not surprising since younger women have longer life expectancies than older women. Annual screening between the 29 year period comprising ages 40-69 years yields a median of 33 life-years gained per 1000 women screened, whereas annual screening between the 29 year period comprising ages 50-79 years yields a median of 24 life-years gained per 1000 women screened.²⁴ Biennial screening with these parameters yielded 25 and 23.5 life-years gained in the two groups, respectively.

The decision analysis also compared the harms associated with different screening models. Annual screening between ages 40-69 years yields 2,250 false positive results for every 1000 women screened over the 29 year period, almost twice as many as that of a biennial screening period.²⁴ Consequently, many more women who are screened annually will undergo biopsy compared with those who are screened biennially.²⁴ The models also predict an increase in the risk of overdiagnosis as age increases. Overall, initiating screening at age 40 years (compared to age 50 years) had a smaller effect on overdiagnosis than extending screening beyond age 69 years.²⁴ Overdiagnosis risk was smaller with biennial screening, but by less than half.²⁴

The USPSTF studied the balance of benefits and harms of mammography, as well as the results of the systematic review and the decision analysis study, to develop its final recommendations. It concluded that compared with initiating screening at age 50 years, screening mammography provides a small benefit when performed annually in women aged 40-49 years, but is more likely to be accompanied by false-positives and overdiagnosis, resulting in a smaller net benefit.^{2,71} The ages at which the balance of benefits and harms becomes acceptable to individuals and society are not clearly resolved by available evidence.¹⁹ Because of the small net benefit, the USPSTF concluded that mammography in women aged 40-49 years should not be automatic, but should instead be initiated as a result of an individual decision based on the woman's specific clinical situation, preferences, and values regarding the potential benefits and harms.^{2,71}

REACTION TO USPSTF RECOMMENDATIONS

The 2009 USPSTF screening mammography recommendations were met with opposition by several medical specialty societies, public advocacy groups and individuals in the medical community. ACR stated that the USPSTF recommendations were "ill-advised" and would result in "countless unnecessary breast cancer deaths each year."^{79,80} ACOG, ACS, the Radiological Society of North America, the Society of Breast Imaging, the American Society of Breast Disease, and other groups also publicly stated opposition to the recommendations.⁸⁰⁻⁸⁴ Most reiterated support of guidelines that recommend routine screening mammography beginning at age 40 years. Several publications addressing perceived flaws in the interpretation of data by the USPSTF have appeared in peer-reviewed journals.^{23,26,38,85-88}

Among the criticisms of the USPSTF process was reliance on only RCTs in the evidence review, with the exclusion of additional observational studies showing higher mortality benefit and reduced numbers needed to screen.⁷⁹ Several studies, including some RCTs, did not meet the USPSTF's strict inclusion criteria; others received only a grade of "fair" for their shortcomings.^{74,75} Another criticism was the use of the "number needed to invite for screening" value, rather than the number actually screened.²⁶ The USPSTF reported that the level of participation in the trials was high, and that data from trials with lower participation rates was graded as lower quality.^{71,74,75} The USPSTF also reported that the use of only participating women, rather than those who were merely invited to screen, yielded only a slightly higher benefit.⁷¹

In contrast to the opposition, several organizations, including those representing primary care physicians and public health providers, expressed public support for the 2009 USPSTF recommendations. In a letter to members of Congress, 11 health care organizations, including the AAFP, ACP, and ACPM defended the recommendations.⁸⁹ The AAFP also joined with four of its affiliate groups to urge the Secretary of the Department of Health and Human Services to reject calls to remove the USPSTF recommendations from the AHRQ website.⁹⁰ Advocacy groups,

including the National Breast Cancer Coalition, Breast Cancer Action, and the National Women's Health Network also publicly supported the USPSTF recommendations.⁹¹⁻⁹³

Media coverage of the USPSTF recommendations was often controversy-oriented.⁹⁴⁻⁹⁷ A recent study reported that more than half of media reports about the recommendations took an unsupportive stance; nearly 70% of reports included the belief that "delayed screening leads to more breast cancer and related deaths" or concern over "cost and government rationing of health care."⁹⁸ Seventeen percent of the reports took a supportive stance, based on beliefs that "the recommendations were based on science" and that there is "potential harm in mammography."⁹⁸ Not surprisingly, laywomen who had, or currently have, breast cancer were angered by the recommendations, strongly believing that mammography saved their lives.⁹⁹ The opinions of women who have not experienced breast cancer also were strongly influenced by media coverage, with women who had viewed commentary that was critical of the USPSTF guidelines more likely to overestimate individual risk for breast cancer and feel uncomfortable about delaying mammography until age 50 years, compared to those who viewed commentary that supported the USPSTF guidelines.¹⁰⁰

At the time that the recommendations were released, the country was deeply involved in the debate about health care reform. Since the USPSTF is convened by a government agency (AHRQ), several media outlets and others expressed serious concern that the recommendations would be binding in government health care policy. Several journal publications expressed the opinion that USPSTF is an "opponent of screening" and that its recommendations were intended to restrict patient access to mammography.^{26,38,86} Others joined in suggesting that the recommendations would directly affect costs and insurance coverage for breast cancer screening, and calls were made for Congress to intervene. In response, in early December 2009, the Senate passed 2 amendments to its proposed health care reform legislation: one requiring the federal government to effectively ignore the new recommendations, and the other guaranteeing no-cost breast screening for women in their 40s. These provisions were signed into law in 2010 as part of the Affordable Care Act.

INDIVIDUAL AND RISK-BASED SCREENING

The USPSTF is not the first group recommending an individualized, risk-based approach to mammography screening in women aged 40-49 years,⁸ but the attention paid to the mammography recommendation has highlighted consideration of that approach. Individualized screening refers to screening mammography at an age and frequency decided upon by both physician and patient, based on the physician's assessment of patient clinical factors that influence breast cancer risk and the patient's values regarding the balance of benefits and harms of screening mammography.

Data suggest that women themselves want to be involved in the decision to initiate screening mammography, and often request specific information prior to their first mammogram, including information about benefits and harms.¹⁰¹ Women acknowledge anxiety about false positives, but show little awareness of overdiagnosis.¹⁰² Physicians have an ethical obligation to educate women with balanced information appropriate to the desire expressed by each patient for such information.¹⁰² Model physician-patient dialogue and patient decision aids have been developed as resources to support the shared decision-making underlying the individualized screening approach.¹⁰³⁻¹⁰⁵

Some argue that the individualized risk-based screening approach will fall short in effectively detecting early cancer. A large percentage of cancers are diagnosed in women with no apparent risk factors, suggesting that relying on the identification of personal or family risk factors to indicate the need for mammography will miss many cancers that could have been detected by mammography.^{106,107} Also, randomized data are lacking to support a risk-based approach between the ages of 40-49 years since no RCTs have stratified participants by risk.¹⁰⁶ However, there are hints that a risk based approach may be effective. In a recent single arm (non-controlled) study, women ages 40-50 years at intermediate risk for breast cancer (those with at least one first-degree relative with breast cancer) who were screened annually had smaller tumors that were less likely to be node-positive when compared to control groups from other studies.³⁴ Additionally, a meta-analysis and systematic review examining several risk factors found that breast cancer in a first-degree relative and extremely dense breasts were associated with increased risk in women ages 40-49 years.¹⁰⁸ An accompanying modeling study found that for women with either one of those two risk factors, biennial screening mammography beginning at the age of 40 years has the same balance of benefits and harms as that for biennial screening mammography beginning at age 50 years in women without those risk factors.¹⁰⁹

The individualized approach relies heavily on the identification of red flags in a patient's family history, yet many patients do not receive adequate familial cancer risk assessment in the primary care setting.¹¹⁰⁻¹¹³ Further, a patient's family history will change over time as family members' health status changes. Clinically relevant family history changes substantially during early and middle adulthood (between the ages of 30-50 years), particularly for breast cancer.¹¹⁰ If a patient's family history is not updated adequately during those years, risk factors that would indicate a need for more intensive screening will be missed.¹¹⁰ Some physicians also do not follow recommendations for referral of women for high-risk cancer genetic counseling, suggesting that estimation of breast cancer risk by these physicians is faulty.¹¹⁴ This behavior may reflect a misunderstanding of what constitutes "high risk," since definitions are variable.^{2,8,115,116}

GUIDELINE REFORM

The controversy stemming from the 2009 USPSTF recommendations has brought attention to the process of guideline development. ARHQ's National Guideline Clearinghouse contains close to 2,700 clinical practice guidelines, and the number of groups issuing guidelines has proliferated, along with substantially different development methodologies.¹¹⁷ The Clearinghouse was originally created by AHRQ in partnership with the AMA and the American Association of Health Plans (now America's Health Insurance Plans). With the growth in the number of guidelines being developed, physicians, consumer groups, and other stakeholders have expressed concern about the quality of the processes used to develop guidelines, and the resulting questionable validity of many guidelines.^{117,118} Concerns stem from limitations in the scientific evidence base, a lack of transparency in the methodologies used by guideline-developing groups, conflict of interest among guideline-developing group members and funders, and uncertainty regarding how to reconcile conflicting guidelines.¹¹⁷ Additionally, significant variability in the recommendations of guidelines can lead to confusion and frustration on the part of health care providers and patients.¹¹⁹

Specific to mammography guidelines, a recent study suggests that guideline development reform is needed. The study assessed the quality of guidelines that provide recommendations on mammography screening in asymptomatic women aged 40-49 years, and concluded that both the evidence reviews underlying the guidelines, as well as the guidelines themselves, were of vastly different quality.¹¹⁹ Based on quality assessment instruments, the study assigned an overall assessment for use in clinical practice to each of the guidelines. Of the 11 guidelines studied, only three received "strongly recommend" or "recommend" assessments.¹¹⁹ The remaining guidelines were found to have deficiencies in their development processes, and were given "unsure" or "would not recommend" assessments.¹¹⁹

In response to concerns that the guideline development process is widely variable, thus leading to guidelines that are variable in quality, the Institute of Medicine (IOM) recently undertook a project to define standards for guideline development.¹¹⁷ The standards, released in Spring 2011, promote the development of unbiased, valid, and trustworthy guidelines that incorporate a grading system for characterizing the quality of evidence and strength of clinical recommendations.¹¹⁹ Standards are focused on establishing transparency, managing conflicts of interest, composition of the development group, systematic review use, evidence strength, articulation of recommendations, external review, and updating.¹¹⁷ The ACS recently announced that it plans to change its guideline development process to more closely follow the standards recommended by the IOM.¹²⁰

CONCLUSIONS

Mammography is a proven method for detecting breast tumors, with demonstrated reductions in mortality for women who undergo regular screening. The potential for harm exists, which underlies differences in recommendations regarding the frequency and age at which to begin and end screening. Groups developing guidelines have placed different emphasis on these harms, resulting in varied conclusions about whether benefits outweigh the harms, and whether that balance changes in different age groups. The USPSTF carefully considered the balance of harms and benefits while studying this issue, commissioning a systematic evidence review and a modeling study to inform its recommendations. It has endured criticism from those who disagree with its recommendations but has stood by them. The USPSTF and others, some of whom disagree with the USPSTF recommendations, have stated that this issue is a case in which qualified and competent physicians and researchers can review and interpret the same evidence but come to different conclusions.^{76,84}

The Council is respectful of the time, expertise, and thought that guideline-developing groups, many of whom are represented in the AMA House of Delegates (HOD), have devoted to the topic of mammography screening. Importantly, all are working toward one goal, to optimize the health outcomes for those with breast cancer and to minimize harms to those without. Previous consideration of this subject in the context of Resolution 509-A-10 revealed deep disagreements within the HOD, but the Council notes that agreements exist as well: that mammography is the best existing tool for the routine detection of breast cancer and that it has its shortcomings. The Council also strongly believes that every woman age 40 years or older who wants a screening mammogram and whose physician recommends one should receive one, regardless of her insurance coverage status.

AMA POLICY CONSIDERATIONS

The Council has given much thought to the mammography screening policies of the AMA. Most remain valid and important, even in light of the recent controversy following the USPSTF recommendations. Mammography screening guidelines themselves regularly undergo review and update processes, and the Council believes that it is appropriate for AMA policies referencing such guidelines to be reviewed and updated as well. Indeed the very policy under consideration, Policy H-525.993 [Mammography Screening in Asymptomatic Women Forty Years and Older], encourages periodic review of its recommendations. There are several parts to this policy, which the Council addresses in turn below.

Part 1 of H-525.993 states: “Our AMA strongly endorses the positions of the American College of Obstetrics and Gynecology, the American Cancer Society, and the American College of Radiology that all women have screening mammography as per current guidelines.” Given the role of the AMA in representing hundreds of different medical societies, the Council does not believe it is appropriate to single out support for the guidelines of particular societies. This is not a comment on the content of such guidelines, rather it reflects the equity of all members of the HOD and respect for their professional expertise.

Part 2 of H-525.993 states: “Our AMA favors participation in and support of the efforts of the professional, voluntary, and government organizations to educate physicians and the public regarding the value of screening mammography in reducing breast cancer mortality.” The Council strongly supports educating physicians and the public about mammography, including its value and its limitations.

Part 3 of H-525.993 states: “Our AMA advocates remaining alert to new epidemiological findings regarding age-specific breast cancer mortality reduction following mammography screening.” The Council agrees.

Part 4 of H-525.993 states: “Based on recent summary data our AMA recommends annual screening mammograms and continuation of clinical breast examinations in asymptomatic women 40 years and older.” The Council recognizes the difficulty faced by guideline-making groups when balancing the proven and quantifiable mortality reduction of screening mammography with the nearly impossible task of quantifying harms, including overdiagnosis and anxiety/mental anguish associated with false-positives. Not having undergone the rigorous processes of guideline-making groups (and not equipped to do so), the Council cannot in good faith recommend a frequency and specific age at which screening mammography should begin, nor does it believe that the AMA, representing the divergent views of many guideline-making groups who are also members of the HOD, should do so. However, the Council strongly supports the autonomy of physicians and their responsibility to care for patients in a manner in which they believe is appropriate; this includes beginning annual mammography at age 40 years when it is believed to be clinically appropriate. Support for clinical breast examination is included in a separate policy, H-525.985 [Safety and Performance Standards for Mammography].

Part 5 of H-525.993 states: “Our AMA encourages the periodic reconsideration of these recommendations as more epidemiological data become available.” The Council agrees.

Part 6 of H-525.993 states “Our AMA supports seeking common recommendations with other organizations.” The Council is aware that differing recommendations can cause confusion and frustration for physicians and patients, and therefore believes that common recommendations are in the best interest of the clinical practice and patients. The Council cites as a best practice the “Consensus Points on Screening Mammography,” (see Appendix II) jointly developed by the ACP and ACR to assist physicians and patients in their discussions of mammography.¹²¹ For common recommendations to retain value, it is important that they be based on an approach that is unbiased, valid, and trustworthy.

Part 7 of H-525.993 states: “Our AMA reiterates its longstanding position that all medical care decisions should occur only after thoughtful deliberation between patients and physicians.” The Council strongly agrees and notes that this is the foundation of recommendations that advocate an individualized approach to screening mammography between the ages of 40-49. Specific to the USPSTF, AMA policy H-410.967 [Guide to Clinical Preventive Services] states that the USPSTF guidelines “...should not take the place of clinical judgment and the need for individualizing care with patients; physicians should weigh the utility of individual recommendations within the context of their scope of practice and the situation presented by each clinical encounter.”

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolve 1, Resolution 509-A-10, and the remainder of the report be filed:

That Policy H-525.993 “Mammography Screening in Asymptomatic Women Forty Years and Older” be amended by insertion and deletion as follows:

H-525.993, Screening Mammography ~~Screening in Asymptomatic Women Forty Years and Older~~

~~1. Our AMA;~~

~~strongly endorses the positions of the American College of Obstetrics and Gynecology, the American Cancer Society, and the American College of Radiology that all women have screening mammography as per current guidelines.~~

~~a. recognizes the mortality reduction benefit of screening mammography and supports its use as a tool to detect breast cancer.~~

~~b. recognizes that as with all medical screening procedures there are small, but not inconsequential associated risks including false positive and false negative results and overdiagnosis.~~

~~c. 2. Our AMA favors participation in and support of the efforts of the professional, voluntary, and government organizations to educate physicians and the public regarding the value of screening mammography in reducing breast cancer mortality, as well as its limitations.~~

~~3. Our AMA d. advocates remaining alert to new epidemiological findings regarding age-specific breast cancer mortality reduction following screening mammography screening.~~

~~4. Based on recent summary data our AMA recommends annual screening mammograms and continuation of clinical breast examinations in asymptomatic women 40 years and older.~~

~~5. Our AMA encourages the periodic reconsideration of these recommendations as more epidemiological data become available.~~

~~6. Our AMA e. believes that beginning at the age of 40 years, all women should be eligible for screening mammography.~~

~~f. encourages physicians to regularly discuss with their individual patients the benefits and risks of screening mammography, and whether screening is appropriate for each clinical situation given that the balance of benefits and risks will be viewed differently by each patient.~~

~~g. encourages physicians to inquire about and update each patient's family history to detect red flags for hereditary cancer and to consider other risk factors for breast cancer so that recommendations for screening will be appropriate.~~

~~h. supports insurance coverage for screening mammography.~~

~~i. supports seeking common recommendations with other organizations, informed and respectful dialogue as guideline-making groups address the similarities and differences among their respective recommendations, and adherence to standards that ensure guidelines are unbiased, valid and trustworthy.~~

~~7. Our AMA j. reiterates its longstanding position that all medical care decisions should occur only after thoughtful deliberation between patients and physicians.~~

APPENDIX I - Relevant AMA Policies on Screening Mammography

H-55.993 Early Detection of Breast Cancer

(1) The AMA supports public education efforts to help women recognize their important role in breast self-examination and to encourage them to report immediately to their physicians any changes that they notice. (2) The AMA encourages physicians to educate their patients in the process of breast cancer detection, emphasizing the technique of self-examination of their breasts. (3) Physicians requesting mammographic examinations should refer their patients to radiologists who use properly functioning equipment that provides the best image resolution at the lowest level of radiation exposure. (4) Physicians are encouraged to recognize the importance of mammography as an effective screening device to detect early breast cancer. (5) The AMA

encourages pharmaceutical companies to include in the packaging of their contraceptives, and all female hygiene products, materials which promote the package and correct techniques of breast self-examination, and which stress the importance of physician breast examinations and appropriate use of screening mammography. (CSA Rep. A, I-83; Reaffirmed: CLRPD Rep. 1, I-93; Res. 501, I-95; Reaffirmed and Modified: CSA Rep. 8, A-05)

H-55.984 Screening and Treatment for Breast and Cervical Cancer

The AMA: (1) supports increased funding for comprehensive programs to screen low income women for breast and cervical cancer and to assure access to definitive treatment; and (2) encourages state and local medical societies to monitor local public health screening programs to assure that they are linked to treatment resources in the public or private sector. (Res. 411, A-92; Reaffirmed: CSA Rep. 8, A-03)

H-55.985 Screening and Education Programs for Breast and Cervical Cancer Risk Reduction

Our AMA supports (1) programs to screen all women for breast and cervical cancer and that government funded programs be available for low income women and (2) the development of public information and educational programs with the goal of informing all women about routine cancer screening in order to reduce their risk of dying from cancer. (Res. 418, I-91; Reaffirmed: Sunset Report, I-01; Reaffirmed: CSAPH Rep. 1, A-11)

D-525.998 Mammography Screening for Breast Cancer

In order to assure timely access to breast cancer screening for all women, our AMA shall advocate for legislation that ensures adequate funding for mammography services. (Res. 120, A-02)

H-525.993 Mammography Screening in Asymptomatic Women Forty Years and Older

1. Our AMA strongly endorses the positions of the American College of Obstetrics and Gynecology, the American Cancer Society, and the American College of Radiology that all women have screening mammography as per current guidelines. 2. Our AMA favors participation in and support of the efforts of the professional, voluntary, and government organizations to educate physicians and the public regarding the value of screening mammography in reducing breast cancer mortality. 3. Our AMA advocates remaining alert to new epidemiological findings regarding age-specific breast cancer mortality reduction following mammography screening. 4. Based on recent summary data our AMA recommends annual screening mammograms and continuation of clinical breast examinations in asymptomatic women 40 years and older. 5. Our AMA encourages the periodic reconsideration of these recommendations as more epidemiological data become available. 6. Our AMA supports seeking common recommendations with other organizations. 7. Our AMA reiterates its longstanding position that all medical care decisions should occur only after thoughtful deliberation between patients and physicians. (CSA Rep. F, A-88; Reaffirmed: Res. 506, A-94; Amended: CSA Rep. 16, A-99; Appended: Res. 120, A-02)

H-525.985 Safety and Performance Standards for Mammography

Our AMA actively encourages the development of new activities, and supports the coordination of ongoing activities, to ensure the following: (1) that the techniques used in performing mammograms and in interpreting mammograms meet high quality standards of performance, including evidence of appropriate training and competence for professionals carrying out these tasks; (2) that the equipment used in mammography is specifically designed and dedicated. The performance of mammography imaging systems is assessed on a regular basis by trained professionals; (3) that the American College of Radiology Breast Imaging Reporting and Database System is widely used throughout the United States and that mammography outcome data in this database are used to regularly assess the effectiveness of mammography screening and diagnostic services as they are provided for women in the United States; and (4) regular breast physical examination by a physician and regular breast self-examination should be performed in addition to screening mammography. (BOT Rep. JJ, A-91; Reaffirmed: Sunset Report, I-01; Reaffirmed: CSAPH Rep. 1, A-11)

APPENDIX II - ACP-ACR Consensus Points on Screening Mammography

1. Screening mammography has been shown to decrease the number of deaths from breast cancer in women ages 40-74.
2. The benefits and harms associated with screening vary by age, and women will view these benefits and harms differently. Thus, all women should discuss the benefits and harms of breast cancer screening with their primary care provider.
3. Breast cancer incidence increases steadily with age. There is no abrupt change in incidence at age 50. Additionally, the outcomes of screening (recall rates, biopsy recommendation rates, and cancer detection rates) also change steadily with increasing age, without any sudden change at the age of 50.
4. Younger women have a lower risk of breast cancer but more potential years of life saved by detection and successful treatment.
5. Since women over the age of 74 were not included in the randomized, controlled trials, there is no proof that screening saves lives in older women. Decisions about screening in this age group should be individualized and made between a woman and her primary care provider.

6. The majority of breast cancers occur in women without major risk factors.
7. There are false positive screening studies at all ages that result in women being recalled for additional evaluation that ultimately shows no evidence of cancer. With increasing age, there is a gradual decrease in the percentage of false positives as the incidence of breast cancer increases.
8. It is important to note that mammography does not find all cancers, and some cancers that are detected may not be found early enough to result in a cure. If a woman discovers a lump, even after having had a negative mammogram, she should bring it to her doctor's attention. If a clinician remains concerned about a clinically evident finding, even after a negative mammogram, the finding should be evaluated further.
9. The primary benefit of screening mammography is a reduction in mortality from breast cancer.
10. The potential harms associated with screening mammography include:
 - a. Transient discomfort from the study
 - b. Recall for a false positive mammogram resulting in anxiety and inconvenience; the majority of these are resolved by additional mammographic views and/or ultrasound
 - c. The need for biopsy of a lesion that is ultimately proven to be benign
 - d. Treatment of a cancer that would not have become clinically significant. At present, we are unable to distinguish cancers that have lethal potential from those that do not, whether or not they are clinically evident or detected by screening mammography. Consequently, all women being evaluated for breast cancer, no matter how it was detected, should be informed that it is possible they may undergo treatment for a cancer that might not have lethal potential.
11. Third-party payers should cover screening mammography for all women ages 40 and above who elect to be screened.

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7. DRUG SHORTAGES UPDATE

Reference committee hearing: see report of [Reference Committee E](#).

HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS IN LIEU OF RESOLUTIONS 509, 510, 524 AND 525 AND REMAINDER OF REPORT FILED

See Policy [H-100.956](#)

Council on Science and Public Health Report 2-I-11 reviewed the historical involvement of the American Medical Association (AMA) in the drug shortage issue, examined recent trends on drug shortages, the explanations for such shortages, and potential solutions that have been advanced to help address this critical problem.¹ The report recommended that the AMA support a suite of 21 recommendations to address the drug shortage issue emanating from a 2010 drug shortages summit convened by the American Society of Health System Pharmacists (ASHP), American Society of Anesthesiologists, American Society of Clinical Oncologists, and the Institute for Safe Medication Practices.² In addition, the House of Delegates directed CSAPH (Policy H-100.956, AMA Policy Database) to report back at the 2012 Annual Meeting on efforts to mitigate drug shortages, including the evaluation

of potential economic and regulatory factors that may contribute to drug shortages, especially with respect to oncology drugs.

Because existing drug shortages created a public health emergency and legislative action may not take place until Congress considers the Prescription Drug Users Fee Act Reauthorization (PDUFA) later this year, the Administration issued an executive order on October 31, 2011 that instructed the FDA to increase staff in its drug shortage program office, expand efforts to speed review of drug applications and approve replacement manufacturing sites, investigate and penalize price gouging for products in short supply, and urge manufacturers to voluntarily notify the agency of impending shortages.³ The Administration also released two new reports on the underlying causes of shortages and the FDA's role in preventing them.^{4,5} Subsequently, both the General Accountability Office (GAO) and IMS released reports analyzing drug shortages.^{6,7} These various analyses reinforced the findings of CSAPH Report 2-I-11 on the general causes of drug shortages, citing manufacturing problems, business decisions, disruption in the supply of active ingredients, unexpected increases in demand, industry consolidation, unstable supply chains, manufacturing capacity constraints, and lean inventory systems as primary contributing variables.^{4,7}

Accordingly, this report reviews our current understanding of drug shortages and various regulatory initiatives and legislative proposals intended to prevent or mitigate drug shortages; most of the latter are part of the ongoing legislative process related to passage of PDUFA. The AMA has been extensively involved in this process. At the time of this writing, PDUFA negotiations remained ongoing. For further information on current federal regulations, comprehensive sources of information on existing drug shortages, and the general causes of drug shortages, see CSAPH Report 2-I-11.

CURRENT DRUG SHORTAGE INFORMATION

As of May 23, 2012, the Drug Shortages Management Resource Center maintained by ASHP identified 226 existing drug shortages.⁸ The Food and Drug Administration drug shortages website identified 122 existing shortages of "medically necessary drugs."⁹ Existing and new drug shortages continue to be problematic. Manufacturing issues and the discontinuation or suspension of production are the most commonly cited reasons, followed by increased demand.⁸ Manufacturing problems may result from temporary shut down in order to maintain or upgrade a production line or the entire facility, or may be related to temporary manufacturing suspension of a specific drug to evaluate or resolve a manufacturing problem.

In April 2011, the ASA re-surveyed its members on drug shortages.¹⁰ More than 90% of respondents reported they are currently experiencing a shortage of at least one anesthesia drug. Virtually all respondents (>98%) reported they have experienced a shortage of at least one anesthesia drug in the last year, most commonly propofol (89%), succinylcholine (80%), and thiopental (60%). Because respondents had to use alternative drugs or change procedures in some way, nearly half of their patients reportedly experienced less optimal outcomes (e.g., post-operative nausea and vomiting) and longer operating room or recovery times. Additionally, some surgical cases were postponed or even cancelled.

On a positive note, the FDA reported that 42 new shortages of medically necessary drugs had been reported through April 2012 compared with 90 at the same time last year.¹¹ This reduction has been attributed to more extensive early notification of potential problems by manufacturers and expedited solutions (see below).

ANALYSES OF THE DRUG SHORTAGE PROBLEM

Four new reviews and comprehensive analyses of drug shortages have been released since the previous Council report was drafted. The Office of Science and Data Policy within the Assistant Secretary for Planning and Evaluation (ASPE) conducted an analysis of the underlying factors leading to periods of shortages in the prescriptions drug market, particularly those that have contributed to the current shortages in the areas of sterile injectable oncology drugs.⁵ A companion report from the FDA reviewed the agency's approach to medical product shortages.⁴ The GAO reviewed trends in drug shortages, described FDA's response, and evaluated the FDA's ability to protect public health; a detailed analysis of 15 selected drug shortages of anti-infective, oncologic, and anesthesia drugs was included in the GAO report.⁶ The IMS Institute for Healthcare Informatics also examined in some detail factors associated with products experiencing shortages, suppliers, and volume volatility.⁷ Although these reports took somewhat different approaches, several important facts and realities emerged. The next five sections are based

on the findings in these reports. Specific findings and conclusions vary somewhat depending on the time period studied.

Overview of Demand Issues

As medically necessary products, few or no substitutes are available to physicians and hospitals that can buffer shifts in consumption over time. Services for consumers in the prescription drug market are accomplished through health insurance contracts that pre-establish payment rates and both consumers and hospital/physician demand for prescription medication are not very responsive to the average wholesale price paid to manufacturers for the drug. Thus, sterile injectable products used for acute, medically necessary indications are characterized by very low price responsiveness on the demand (and supply) side. This condition increases the likelihood of a shortage in the presence of demand changes that are not anticipated by manufacturers.

Overview of Supply Issues

On the supply side, production line processes for sterile injectables are complex. Generic companies operate a limited number of facilities each containing multiple production lines. However, cytotoxic oncologic drugs (and certain antibiotics) require specific equipment and regulatory approvals limited to that class. These special containment controls can limit a manufacturer's transfer of production of these drugs to other lines. Furthermore, these drugs have a limited shelf life so that holding excess inventory can be very expensive. Therefore, manufacturers of these products cannot respond simply to supply chain disruptions.

Purchasing and Pricing

Most sterile injectable drugs are purchased by hospitals (and in some cases physicians) through group purchasing organizations (GPOs), which negotiate prices with manufacturers. Drug delivery is accomplished by wholesalers who purchase inventory at the wholesale acquisition price with manufacturers issuing a "chargeback" if the acquisition price exceeds the GPO's negotiated price. Hospitals also may source their products outside of this structure. GPO contracts typically have price adjustment clauses as well as "failure to supply" penalties. The latter usually do not apply when the product is not available, are otherwise of limited duration, and have been characterized by "erosion" of their impact.⁵ Pricing flexibility by suppliers may be constrained by long-term purchase contracts, although in many cases companies have multiple contracts staggered throughout the year, which provides some ability to adjust pricing to market conditions.⁵

The Medicare Prescription Drug, Improvement, and Modernization Act, enacted in 2003, substantially reduced payment rates for chemotherapy drugs administered on an outpatient basis starting in January 2005. Currently, in Medicare, injectable drugs are covered under Part B, which pays physicians the average sale price (ASP) plus 6% to cover the cost of administering the drugs. Increases are limited to maximum of 6% every six months. Although some proposals have suggested that this formula contributes to drug shortages, no consensus exists that raising the ASP formula (or changing the metric to use average wholesale prices instead) would lessen drug shortages because of other complexities in the drug distribution chain. Reimbursement cost, whatever it may be, is not the price that is paid to the manufacturers. A disconnect exists between money paid to purchasers, GPOs, and manufacturers. The HHS report concluded that increased production capacity for generic sterile injectable drugs is the single most important solution to the drug shortage crisis while maintaining that payments to manufacturers are not the primary problem.⁵

Some Relevant Drug Shortage Findings⁴⁻⁷

- The number of drug shortages has increased each year from 2006-2011, and sterile injectables make up a disproportionate share of the drugs in shortage. Impacted patients therefore are mostly acute care and/or cancer patients being treated in hospitals and in out-patient facilities.
- About half of the sterile injectable market is branded and half is generic, but the latter fraction is increasing. Overall, current shortages (~75-80%) of sterile injectables are concentrated in the generics industry.
- Two-thirds of drugs on the shortage list are used in oncology, infectious diseases, cardiovascular diseases, pain management, and central nervous system disorders. Half were marketed before 1990 but 25% have been introduced since 2000; 6.5% were controlled substances. For the oncology products, an estimated 550,000 cancer patients may be affected annually.

- Overall (brand and generic) production of sterile injectables has increased. From 2006-2011, the supply of sterile injectable oncology drugs increased 14% overall and 20% within Medicare, but generic volume increased disproportionately by 30%.
- Drugs that were in short supply sometime in 2008 or beyond experienced a declining volume of sales from 2006-2008; those that were not in short supply experienced an increase (11%) in sales volume over the entire period. Similarly, drugs that eventually experienced a shortage demonstrated a mean 27% drop in price, while prices of drugs that did not develop a shortage were steady or slightly increased.
- More than 80% of the market for generic sterile injectables is supported by seven manufacturers in the US; for oncologic products, typically 3 or fewer companies comprise the market and more than 50% of the drugs have two or fewer suppliers.
- During 2006-2011, the number of new generic manufacturer-drug combinations in the sterile injectable market increased every year, outnumbering the number of exits from the market.
- After remaining relatively constant from 2000-2007 (varying between 62 to 79 annually except for 2003), the overall number of new generic injectable approvals surged in 2008 (135) and 2009 (103), creating a much larger portfolio of possible drugs for manufacturing sites.
- Among drug shortages occurring from 2009 through June 2011, 59% involved more than one manufacturer.

In summary, the volume of injectable chemotherapy drugs used has increased and the number of products available for generic manufacturing has increased dramatically. The process itself remains complex and subject to Good Manufacturing Practice regulations, precluding early entry into the marketplace, and financial incentives are lacking for investing in excess capacity. Contrary to some belief, consolidation of manufacturing among sterile injectable companies has not occurred, but current capacity is limited. A limited ability to benefit from failure-to-supply clauses and low price elasticity prompts manufacturers to limit reserve inventory.

Supplies and Volume of Sales over Time

Based on their proprietary drug supply chain data, IMS examined the problem of drug shortages (168 drugs) on the FDA list as of October 7, 2011 including supplies and volume and sales of these drugs over time.⁷ The overall supply of drugs experiencing shortages has increased or been stable over the past five years, but not in a uniform fashion. In aggregate, injectable volume has grown 4% over the past five years for drugs on the FDA shortage list, and dollar sales have trended upward. Although the supply has been stable, the contribution of individual suppliers may change from month-to-month. A “high volatility with unusually sharp swings in supply” has been especially pronounced in the past year.⁷ A segment of the drugs on the shortage list exhibits declining sales in 2010-2011 compared with the base period of 2006-2009; a smaller percentage is stable; and about 20% are experiencing growing volume sales (over 3-fold since 2006). For those in the declining category, monthly supply has fallen an average of 47% over the five-year period. The average annual price per standard unit varies significantly across these three segments but not in a consistent way.

Although a number of firms produce sterile injectables (~80), the production of any given molecule is commonly concentrated among a very small number of manufacturers. The top three generic injectable manufacturers account for 71% of the market by volume and most sterile injectables have one manufacturer that produces at least 90% of the drug; 60% of sterile injectables in 2010 were virtually sole sourced (90% or more of market share by one manufacturer). Two-thirds of the drugs in short supply are produced by three or fewer companies. Fifty-six products were provided by sole source manufacturers and 51% of products with shortages have two or fewer suppliers. Only 1% of products have two of the top producers accounting for less than 50% market share by volume. Substantial market concentration increases the vulnerability of the supply system to shortages, and the number of companies supplying these products has fluctuated over the last five years. Several current oncology shortages can be traced to just three cytotoxic lines operated by two separate manufacturers.⁷

The IMS report recommended that FDA create an early warning system for drug shortages that would include systematic risk identification, continuous long-term demand forecasting, creation of a supply volatility index as signal for problems, and comprehensive predictive modeling.⁷

STAKEHOLDER RESPONSES

Food and Drug Administration

On December 19, 2011, the FDA issued an interim final rule modifying the definitions of “discontinuance” and “sole manufacturer” {§ 314.81(b)(3)(iii)}.¹² Under Section 506C of the FD&C Act, a sole manufacturer of a prescription drug product that is “life-supporting, life sustaining, or intended for use in the prevention of a debilitating disease or condition” is required by statute to notify the Agency of a discontinuance of that drug product at least six months prior to discontinuing manufacture of the product. The interim final rule modifies the term “discontinuance” and clarifies the term “sole manufacturer” with respect to notification of discontinuance requirements. The broader reporting resulting from these changes will enable FDA to improve its collection and distribution of drug shortage information to physician and patient organizations and to work with manufacturers and other stakeholders to respond to potential drug shortages.

Under this interim final rule, the FDA is now defining “discontinuance” to “include both permanent and temporary interruptions in the manufacturing of a drug product, if the interruption could lead to a disruption in supply of the product.” For example, delays in acquiring active pharmaceutical ingredients (APIs) or inactive ingredients that lead to an interruption in manufacturing or a suspension in production for maintenance or other routine services that exceeds expected durations would trigger a “discontinuance” reporting requirement under the new definition. These types of temporary discontinuances must be reported only if the discontinuance reasonably could be expected to lead to a disruption in supply of the product. A planned maintenance period would not necessarily be reported to the FDA if it is not expected to impact production and does not exceed scheduled down-time.

“Sole manufacturers” now include any companies who are the “only entity currently manufacturing a drug product of a specific strength, dosage form, or route of administration for sale in the United States, whether the product is manufactured by the applicant or for the applicant under contract with one or more different entities.” A manufacturer will be considered a “sole manufacturer even if other manufacturers hold an approved new drug application (NDA) or abbreviated new drug application (ANDA) for the same product, if the other applicants are no longer manufacturing (or have never manufactured) the product for sale in the United States.” The definition of sole manufacturer is linked to the specific strength, dosage form, and route of administration, because these characteristics may be critical for the targeted needs of particular patients. Manufacturers are responsible for determining whether their particular situation falls within the mandatory reporting requirement.

Guidance for Industry

The FDA subsequently published a Guidance for Industry in February 2012 reflecting the above amendments to the implementing regulations of the interim final rule.¹³ This document provides: (1) guidance to industry on requirements for mandatory notification to the FDA of discontinuances; (2) additional explanation of the voluntary notification processes; and, (3) advice on advance planning strategies that might be considered to prevent or mitigate product shortages.

FDA Actions to Mitigate or Prevent Drug Shortages

The FDA’s response to drug shortages is managed by the Drug Shortage Program within the Center for Drug Evaluation and Research. The FDA can take certain actions to help alleviate or prevent a shortage from occurring in the first place. Analysis of the Agency’s response to 127 shortages of medically necessary drugs that occurred in 2010-2011 revealed that the FDA asked other companies to boost production (31%), exercised regulatory discretion (28%), expedited review of other sources (26%), and occasionally exercised discretion on importation, or a sole source manufacturer to boost production.⁷

The FDA may exercise regulatory discretion to allow the continued marketing of a product with labeling errors for misbranded products or quality issues, assuming an interim solution to the quality problem (e.g., filtering of impurities or particulates) can be identified. In some cases, the FDA may work to accomplish importation of drugs that are approved for use in foreign countries, but not the US. Two recent examples of regulatory discretion assisted in relieving two high profile drug shortages. The FDA approved the temporary importation of an unapproved liposomal doxorubicin drug product, and expedited the approval of a new manufacturer for preservative-free methotrexate and convinced other manufacturers to increase the supply of this product as well.

For these strategies to work, there must be enhanced communication between FDA and manufacturers, and the industry must give early notice of potential problems. FDA Commissioner Margaret Hamburg, MD recently revealed that since President Obama's October 31, 2011 directive, the FDA had prevented 128 new drug shortages, prompted by a six-fold increase in voluntary reports from manufacturers.¹¹ Shortages were prevented by expediting the review of new manufacturing sites, new suppliers and specification changes, exercising regulatory flexibility and discretion, and asking other firms to ramp up production. According to the GAO analysis, the FDA was able to mitigate 90% of potential shortages that it learned about in advance in the first half of 2011.⁶

In addition to increased staffing, improved communication, voluntary reporting, and expedited action, the FDA has proposed implementing and maintaining a database that can analyze the characteristics of drug shortages. The GAO report noted that the Agency needs to implement a systematic approach to managing its complex workload and to maintain data in a manner that enhances its ability to understand trends in shortages and the effectiveness of interventions related to preventing or mitigating the effects of shortages.⁶

Generic Manufacturers

Several generic manufacturers of sterile injectables (e.g., APP Pharmaceuticals, Hospira, Bedford Laboratories, Teva) are building new plants and expanding facilities to help them better respond when manufacturing lines are shut down.¹⁴

The Generic Pharmaceutical Association (GPhA) also announced a proposal, known as the Accelerated Recovery Initiative (ARI) to address sterile injectable drug shortages, although not all prominent generic drug manufacturers have endorsed the plan.¹⁵ It would involve voluntary communication between an independent third party and stakeholders involved in the manufacturing and distribution of generic injectable medications currently in shortage and be designed to use real-time supply and distribution information to give stakeholders, especially manufacturers, wholesalers, distributors, GPOs and the FDA a clear picture of current conditions and a plan to expand the production and supply of critical drugs in short supply. Specific elements of this initiative include:

- Use of an independent third party to gather current and future supply information from stakeholders for products identified as meeting the critical criteria;
- That information be used to determine current and potential supply gaps, with a focus on those products where a shortage is expected to last longer than 90 days; and
- A high-level dedicated drug shortage management team be formed within the FDA with the ability to quickly respond to critical shortages and work with the current drug shortage staff.

Implementation of this voluntary initiative would require Federal Trade Commission and HHS approval. In April 2012, GPhA selected IMS Health to act as the proposed independent third party to collect production and release schedule information in a voluntary manner from manufacturers and work with industry and FDA to mitigate shortages.

LEGISLATIVE APPROACHES

The Council on Legislation (COL) recommended to the Board of Trustees (BOT) that our AMA support the "Preserving Access to Life-Saving Medications Act," a bipartisan bill (H.R. 2245) to reduce shortages of drugs and biologics introduced by Representatives Diana DeGette (D-CO) and Tom Rooney (R-FL). H.R. 2245 would establish an early warning system to help prevent sudden shortages of medication by requiring manufacturers of all prescriptions, including drugs and biologics, to notify FDA of any discontinuance or interruption in the product of a drug at least six months in advance, or in the event of unforeseen or unplanned circumstances, as soon as possible. Also, the bill would require the FDA to develop criteria for drugs vulnerable to a shortage. Thereafter, the AMA expressed support for a nearly identical Senate bill, S. 296, "Preserving Access to Life-Saving Medications Act" after concerns with that bill were addressed by the sponsor, Senator Amy Kloubacher (D-MN).

More recently, the COL recommended that the BOT not support H.R. 3839, the "Drug Shortage Prevention Act," introduced by John Carney (D-DE) and Larry Bucshon (R-IN) until AMA concerns and questions about a key provision were resolved. This provision directs the FDA to provide advance notice to wholesale distributors prior to informing the public that there is a shortage without any specific obligation on the part of distributors to prevent hoarding or gray market stratagems.

None of these bills address possible changes to reimbursement or other financial incentives that have been mentioned in some quarters as contributing factors. Payment reforms have generally not been viewed as a key solution. Other economic incentives being discussed include tax credits for research and development or creating manufacturing redundancy.

Both the House and Senate are actively engaged in drafting legislative proposals related to drug shortages as part of the PDUFA authorizations. On the House side, many provisions of the Carney and DeGette bills have been incorporated into legislative drafts that are being widely circulated, lacking controversial provisions including the requirement that the FDA provide wholesale distributors advance notice of actual shortages prior to public disclosure. The AMA strongly supports the efforts of the Senate to address the crisis of drug shortages and met with the Senate Health, Education, Labor, and Pensions (HELP) Committee majority staff to underscore the concern of AMA members and to emphasize our support for the requirement that manufacturers provide the FDA advance notice of anticipated or actual shortages. The Senate PDUFA bill (S. 3187) as amended provides that manufacturers of drugs that are: life-supporting; life-sustaining; intended for use in the prevention of a debilitating disease or condition; a sterile injectable product; or used in emergency medical care or during surgery, shall notify the FDA of permanent discontinuation or temporary interruption in manufacturing 6 months in advance or as soon as practicable. The Secretary also may include biological and biosimilar manufacturers in the reporting requirement through rule-making. The foregoing is a vast improvement over the status quo and the AMA believes that most prescription drugs would meet one of these criteria.^{15,16} The current version does not include any enforcement authority, such as civil monetary penalties, but it does direct the FDA to report when manufacturers fail to report as required by law. It also creates positive incentives for reporting because manufacturers will be eligible for expedited consideration.

The S. 3187 section on drug shortages also would authorize the Secretary of HHS to expedite facility inspections and review of supplements and applications that could help mitigate or prevent a “shortage,” as defined in this title. It also would require the Secretary to establish a task force to enhance the Secretary’s response to shortages and create a strategic plan to address stated aspects of shortages. The AMA is particularly supportive of provisions that require the FDA to consult and collaborate with impacted stakeholders. In addition, the AMA supports the preparation of a report studying market factors contributing to drug shortages and stockpiling.^{15,16}

DISCUSSION

Several solutions and approaches for addressing the drug shortage problem have been recently advanced by the FDA, GAO, IMS, and HHS (see Table). Just-in-time manufacturing and inventory practices leave little margin for error. The “current class-wide shortages in the sterile injectable drug industry appear to be a consequence of a substantial expansion in the scope and volume of products produced by the industry that has occurred over a short period of time without a corresponding expansion in manufacturing capacity.”⁵ However, lower profits available for the manufacture of generic drugs have led to lower levels of redundancy in manufacturing for these products.

The structure of the sterile injectable market, the recent expansion in volume and scope, and the consequent very high level of capacity utilization, means that small disruptions to supply – such as may occur because of quality problems – and which might otherwise be absorbed through diversion of capacity, can lead to cascading and persistent shortages. Quality problems are linked with a majority (more than 50%) of sterile injectable shortages.

The most robust solution is to expedite review of new manufacturing capacity and expand supply and maintenance of product quality in sectors with high capacity utilization. More extensive and complete analysis is required on the potential economic causes of drug shortages and what would constitute appropriate and effective incentives. In the meantime, based on the demonstrated success of early notification, FDA and the industry should continue to work on collaborative solutions to individual shortage problems until legislative solutions emerge.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of the report be filed.

That Policy H-100.956 National Drug Shortages be amended by insertion and deletion to read as follows:

1. Our AMA supports the recommendations of the 2010 Drug Shortage Summit convened by the American Society of Health System Pharmacists, American Society of Anesthesiologists, American Society of Clinical ~~Oncologists~~ Oncology and the Institute for Safe Medication Practices and work in a collaborative fashion with these and other stakeholders to implement these recommendations in an urgent fashion.
2. Our AMA supports ~~drug shortage legislation such as H.R. 2245 and S. 296 that would require~~ requiring all manufacturers of Food and Drug Administration approved drugs, including those who share the market with others FDA approved drugs with recognized off-label uses, to notify give the FDA agency advance notice (at least 6 months prior or otherwise as soon as practicable) of any anticipated voluntary or involuntary, permanent or temporary, discontinuance, interruption, or adjustment in of the manufacture of a drug that may result in a shortage or marketing of such a product.
3. ~~Our AMA will express appreciation to the President of the United States for issuing an Executive Order intended to assist in mitigating ongoing drug shortages.~~ Our AMA supports authorizing the Secretary of Health and Human Services to expedite facility inspections, and the review of manufacturing changes, drug applications and supplements that would help mitigate or prevent a drug shortage.
4. ~~Our AMA supports the creation of a task force to enhance the HHS Secretary's response to preventing and mitigating drug shortages and to create a strategic plan to: (a) enhance interagency coordination; (b) address drug shortage possibilities when initiating regulatory actions (including the removal of unapproved drug products from the market); (c) communicate with stakeholders; and (d) consider the impact of drug shortages on research and clinical trials.~~
- 4.
5. ~~Our AMA will advocate that the U.S. Food and Drug Administration and/or Congress require drug manufacturers to establish a plan for continuity of supply of vital and life-sustaining medications and vaccines to avoid production shortages whenever possible. This plan should include establishing the necessary resiliency and redundancy in manufacturing capability to minimize disruptions of supplies in foreseeable circumstances including the possibility of a disaster affecting a plant.~~
5. ~~The Council on Science and Public Health will report back at the 2012 Annual Meeting on efforts to mitigate drug shortages, including the evaluation of potential economic and regulatory factors that may contribute to drug shortages, especially with respect to oncologic drugs.~~
6. ~~Our AMA publicly declares the problem of unsafe and unverifiable medicines and medicine shortages a national public health emergency.~~ The Council on Science and Public Health will continue to evaluate the drug shortage issue and report back on progress made in addressing drug shortages at the 2012 Interim Meeting of the House of Delegates.
7. ~~Our AMA urges the development of a comprehensive independent report on the root causes of drug shortages. Such an analysis should consider federal actions, the number of manufacturers, economic factors, including federal reimbursement practices, as well as contracting practices by market participants on competition, access to drugs, and pricing.~~
8. ~~Our AMA urges that procedures be put in place: (1) for the FDA to monitor the availability of Schedule II controlled substances; (2) for the FDA to identify the existence of a shortage that is caused or exacerbated by existing production quotas; and, (3) for expedited DEA review of requests to increase aggregate and individual production quotas for such substances.~~
9. ~~Our AMA urges regulatory relief designed to improve the availability of prescription drugs by ensuring that such products are not removed from the market due to compliance issues unless such removal is clearly required for significant and obvious safety reasons.~~
10. ~~Our AMA urges Congress to amend the 2003 Medicare Modernization Act to allow for more reasonable payment rates for prescription drugs.~~

Table. Recent Recommendations to Address Drug Shortages

<i>IMS Recommendations</i>	
Risk Identification	Systematically identify the high-risk sectors of the generics market. Identify all the low-cost, technically challenging and critical medicines – whether or not they are currently on shortage lists.
Demand Forecasting:	Continuously forecast the long-term demand for low-cost, technically challenging and critical medicines. Adjust forecasts based on such factors as demand trends, new medications, changes in clinical guidelines, practice patterns, care delivery changes and needs of clinical trials.
Volatility Index	A quantitative measure to systematically track and report month-to-month changes in the volume of drugs supplied to hospitals, clinics and retail pharmacies.
Predictive Modeling:	With the wealth of data available, predictive modeling techniques could be applied to anticipate shortages or supply disruptions for critically important medications at the national and regional levels. As data accumulate and measures are improved, the model can tightly focus interventions on those specific parts of the market and supply chain genuinely needing attention.
<i>GAO Recommendations</i>	
Drug Shortage Program	Assess the resources allocated to the Drug Shortage Program to determine whether reallocation is needed to improve the agency's response to drug shortages.
Informatics	Develop an information system that will enable the Drug Shortage Program to manage its daily workload in a systematic manner, track data about drug shortages—including their causes and FDA's response—and share information across FDA offices regarding drugs that are in short supply.
Strategic Planning	Ensure that FDA's strategic plan articulates goals and priorities for maintaining the availability of all medically necessary drugs—including generic drugs.
Performance Metrics	Develop results-oriented performance metrics to assess and quantify the implementation of the agency's goals and FDA's response to drug shortages.
<i>FDA Recommendations</i>	
Manufacturer Communication	Write a letter to drug manufacturers reminding them of their current legal obligations to notify FDA in advance of the discontinuation of certain drugs and urging them to voluntarily notify FDA of other potential disruptions to the supply of drugs that are not currently required, as soon as they become aware of them.
Guidance	Develop guidance and regulations that clarify and enhance the information on potential drug shortages that is submitted by industry.
Staffing	Provide additional staffing resources for FDA's efforts to prevent and mitigate shortages.
Legislation	Support legislation that requires early notification by manufacturers for drug shortages and provides new authority to FDA to enforce these requirements.
Informatics	Implement and maintain a database that can analyze the characteristics of drug shortages.
Preventing Shortages	Identify factors that contribute to success or failure in preventing drug shortages and continue exploring new approaches to preventing drug shortages under existing authorities.
Quality	Identify the quality issues in manufacturing practices that have contributed to severe drug shortages and develop approaches to addressing them.
Manufacturing Redundancy	Encourage product manufacturers to develop and maintain a plan for back up manufacturing and sources of Active Pharmaceutical Ingredients and other essential product components.
Early Warning	Explore development of a sentinel reporting network (e.g., major healthcare systems, wholesalers, physician specialty societies) to facilitate early warning of drug shortages.
Wholesalers	Encourage wholesalers to develop and publicize their procedures for distributing medical products in shortage.
Public Notification	Continue to maximize public disclosure of information regarding medical product shortages in FDA's possession, within the bounds of what must remain confidential.
Communication	Continue improving communication between FDA's field investigators and the Center for Drug Evaluation and Research's Office of Compliance and Drug Shortage Program staff.
Website	Improve the Drug Shortage Program's web site as a communications tool for health-care providers and other members of the public.
Probability Forecasting	Explore the feasibility of developing a model based on available data on drug shortages, manufacturer characteristics, and market factors with the goal of assessing the probability of future shortages.

ASPE Recommendations	
Regulatory Responses	Policymakers must balance the short-run benefits of tailoring regulatory responses to specific situations against the risk of strategic behavior and consequent reductions in competition in the long run.
Expedited Review	Steps that both expedite expansion of supply and maintain product quality in sectors with high capacity utilization could reduce the risk of shortages not only in the current situation, but in the future as well. To facilitate this, FDA can expedite review of new manufacturing capacity in this area and we understand that FDA is committed to doing this.
Purchase Agreements	Private organizations that purchase drugs and vaccines (including GPOs and insurers), can help to alleviate future shortages by strengthening the failure-to-supply requirements in their contracts in exchange for increases in price. Such contract changes are likely to lead manufacturers to invest in extra capacity of both production lines and API.

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