The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US

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ABSTRACT

The issues related to tobacco harm reduction continue to challenge the tobacco control research and policy communities. The potential for combusting tobacco products to reduce exposure and risk remains largely unknown, but this has not stopped manufacturers from offering such products making these claims. The role of oral tobacco products in a harm reduction regimen has also been a source of dialogue and debate. Within the last few years, major cigarette manufacturing companies have begun selling smokeless products for the first time, claiming to target current cigarette smokers. Other cigarette manufacturers are also offering smokeless products in markets around the world. The harm reduction debate has at times been divisive. There has been no unifying set of principles or goals articulated to guide tobacco control efforts. In particular, the research needs are extraordinarily high in order to drive evidence-based policy in this area and avoid the mistakes made with "light" cigarettes. This paper discusses recommendations from a strategic dialogue held with key, mostly US-based tobacco control researchers and policy makers to develop a strategic vision and blueprint for research, policy and communications to reduce the harm from tobacco for the US. Short-term and long-term objectives are described.

For more than 2 years a group of tobacco control researchers, policy and communications experts participated in a process called the Strategic Dialogue on Tobacco Harm Reduction (henceforth referred to as the Dialogue). The purpose of this document is to distil a wide variety of views that emerged from the Dialogue into a platform of principles for examining the future of harm reduction in the tobacco control context. Because this document reflects input almost exclusively from US tobacco control experts, its application and acceptability is primarily pertinent within the US. The intention was not to exclude input from the rich experiences of other countries, but at the same time it would be presumptuous to suggest that this document can answer the difficult questions of harm reduction in an international context. Nevertheless, we hope this document will spur other nations to examine tobacco harm reduction within their own boundaries.

BACKGROUND

Most smokers in the US want to quit[1] and a significant number have tried to quit.[2] Although research shows that with repeated attempts, smokers can successfully quit, a new generation of tobacco products has entered the marketplace in the last decade that may jeopardise these efforts. Offering promises of reduced exposure to toxicants in tobacco smoke and oral tobacco and even making implied or direct claims to reduce the risk of cancer or other diseases, these products raise important public health policy questions.

The new tobacco products that are being offered take various forms. Some use conventional means to burn tobacco, while others employ novel technologies such as computer chips and heating blades to burn or heat tobacco. Advertisements for a number of novel combustible products promise to reduce or eliminate exposure to a subset of toxicants in tobacco smoke or to reduce exposure to second-hand smoke. Increasingly, non-combustible oral tobacco products, many low in nitrosamines compared with conventional products, are being marketed with promises of tobacco satisfaction in situations (eg, at work or at home) where smoking is not possible. However, whether they combust or not, all of these products are apparently aimed at health-concerned smokers and/or addicted smokers unable or not wanting to quit.

From a public health perspective, there is concern about tobacco products bearing unsubstantiated claims to reduce exposure and risk.[3] They have entered the marketplace without governmental scrutiny and in the absence of any independent scientific evaluation of their claims. The greatest danger is that these products may pose a significant threat to tobacco cessation and prevention efforts. Smokers concerned about their health who see the claims for novel combustible products may now think that a safer cigarette genuinely exists, making them less interested or less inclined to try to quit smoking. There is the added concern that ex-smokers may start smoking again, thinking they can now safely consume tobacco products. Likewise, those who never used tobacco products previously may initiate tobacco use with one of these new products under the assumption that a safe tobacco product exists.

In theory, the application of harm reduction principles to the tobacco control armamentarium has potential to reduce tobacco's toll. In its broadest conception, tobacco harm reduction consists of all methods used to reduce tobacco-related morbidity and mortality. The most effective efforts to reduce harm from tobacco use are those directed at preventing initiation of tobacco use, encouraging cessation among existing users, and protecting non-smokers from exposure to second-hand smoke. For the purposes of this report—and more generally within the field of tobacco control—we use the term "tobacco harm reduction" much more narrowly to refer to strategies that would reduce morbidity and mortality, at the individual and population levels, resulting from continued use of

tobacco or other nicotine-containing products. For other perspectives on harm reduction, see Reuter P, Caulkins JP;[4] International Harm Reduction Association: What is harm reduction? (http://www.ihra.net/popups/articleswindow.php?id=2); Harm Reduction Coalition: Principles of Harm Reduction (http://www.harmreduction.org/); Marlatt GA.[5]

There is a very pronounced continuum of risk depending upon how toxicants and nicotine, the major addictive substance in tobacco, are delivered. Cigarette smoking is undoubtedly a more hazardous nicotine delivery system than various forms of non-combustible tobacco products for those who continue to use tobacco, which in turn are more hazardous than pharmaceutical nicotine products.[6 7] There is potential for an ever-wider range of consumer-acceptable alternatives to the cigarette for smokers who will not otherwise cease their dependence on nicotine. With US status quo trends in smoking estimated to lead to 10 million additional deaths in the next 25 to 30 years, with virtually all of these to occur among people already smoking, and with the vast majority of them motivated to reduce their risks, the primary reduction in tobacco-related death will come from increased cessation. But the intelligent application of harm reduction principles has the potential to achieve public health gains.

However, in the absence of public health-based regulation, there is no way to know whether the promotion of any of the new or existing products will actually reduce exposure and risk when used by smokers or increase the number of tobacco users and weaken the impact of prevention and cessation efforts. The major concern held by some public health experts is that these new products may be nothing more than a more scientifically sophisticated version of the "light" cigarette. Experts learned—decades too late to be of any help to the health-concerned smoker who switched to "lights"—that "lights" were deliberately designed to reduce tar and nicotine emissions when tested by smoking machines, but not necessarily when smoked by human beings, because they allowed for compensatory smoking.[8]

Worse, these so-called "light" products did not reduce the morbidity and mortality from smoking. Because of the unregulated marketplace 30 years ago, tobacco companies controlled much of the information related to cigarette design, product performance and consumer behaviour. Well intentioned public health officials, without the necessary scientific information, followed the industry's message and encouraged health-concerned smokers to switch to "lights".[9] Today, "lights" and "ultralights" account for nearly 85% of all the cigarettes sold in the US.[10] Yet data now show little or no reduction in deaths, and perhaps an increase in adenocarcinoma of the lung.[8] With today's products, we must avoid repeating the mistakes made with "lights" decades ago. That experience, and the need to look at population-level impacts, must inform our deliberations and analysis of the new generation of products purporting to reduce individual exposure or risk. We also recognise that, at the time this report is being written, there exists an unregulated marketplace where the tobacco companies continue to control the information related to cigarette design and consumer behaviour.

GOALS AND OBJECTIVES OF THE DIALOGUE PROCESS

The topic of tobacco harm reduction is complex and, at times, contentious. No unified vision or strategy has guided research and policy. No opportunities have existed for individuals with diverse perspectives, such as researchers, policy experts, communications experts and advocates to come together to produce a strategic vision on issues related to this area. Instead, while there is broad support for the need to regulate tobacco products, there has been a fractured and sometimes divisive debate over issues such as the appropriate role of regulation as it relates to harm reduction and, particularly, the roles of smokeless tobacco and nicotine replacement therapy (NRT) in harm reduction.

A forum was needed to identify strategies to avoid the previous mistakes with "lights" and not lose another generation of health-concerned smokers to the potentially false hope offered by the tobacco industry. Such a forum would examine ways in which effective product regulation and appropriate consumer information could lead to significant reductions in the predicted deaths and disease from tobacco use. At the same time, it was important to ensure that the public health community explored whether and/or what possible role existed for some tobacco-based products or pure nicotine containing medicinal products in a harm reduction regimen. Other pharmacological agents can also play a role in harm reduction, but in order to limit the focus or our deliberations, we considered only nicotine-containing products.

In 2005, with funding from the American Legacy Foundation and the Robert Wood Johnson Foundation, such a forum for discussion, debate and strategic planning was created: the Strategic Dialogue on Tobacco Harm Reduction. The goals and objectives of the Dialogue included systematically addressing critically important aspects of the harm reduction debate including research priorities, communication methods, policy recommendations and overarching strategic considerations. The Dialogue was launched in the spirit of attempting to build a shared blueprint that would lead to better-defined roles, responsibilities and opportunities for collaboration between researchers, policy makers and advocates. Although the deliberations of the dialogue were focused on the US and we acknowledge that the application of some of our recommendations may not apply in some countries, we hope that some of these principles will have worldwide applicability.

THE DIALOGUE PROCESS

Four Dialogue meetings took place between December 2005 and August 2007. The participants included policy and communications experts and scientists representing different areas of expertise including toxicology, biomarkers across disease states, risk and consumer perception, nicotine addiction, behavioural pharmacology, epidemiology and clinical sciences (see Appendix for participants). They also had differing views on tobacco harm reduction. At the initial meeting, key questions emerged that guided the work of the Dialogue and the end product, this report. Additional participants and areas of expertise were identified for inclusion in subsequent meetings. At the final Dialogue meeting, this report was reviewed and all participants had the opportunity to comment on each of the multiple drafts of the final report. This vision and the report were endorsed by all the members of the group and the report is being released as the collective vision of the participants.

The strategic goal of the Dialogue process was to discuss the development of a long-term vision for tobacco harm reduction and short-term policy objectives to begin the lengthy process of achieving the shared long-term vision. Discussion of these short-term objectives yielded an identification of key issues to research in order to properly evaluate all products in the tobacco marketplace. Research will also help to determine the feasibility and potential impact of the proposed long-term vision.

THE POLICY AND REGULATORY CONTEXT

The Dialogue process took place when—for the first time—there were legitimate prospects for comprehensive tobacco product

regulation. Globally, the World Health Organization (WHO) Framework Convention for Tobacco Control (FCTC) mandates such regulation.[11] In the US, legislative efforts have been mounted to give regulatory authority over tobacco products to the Food and Drug Administration (FDA).[12] FDA had previously asserted jurisdiction over tobacco products in the mid-1990s, but that action was overruled by the Supreme Court in 2000.

Effective product regulation has the potential to be an important complement to the evidence-based policy interventions already in place that have helped drive down US tobacco use over the past 40 years. These existing policies include proven prevention programs such as aggressive counter-marketing efforts, encouragement of use and provision of cessation products and services to help tobacco users quit, legislative initiatives to raise excise taxes, implementation of comprehensive smoke-free air laws, restrictions on tobacco marketing, stronger and more visible graphic warning labels, and improvement of access to treatments for tobacco dependence.[11 13] The primary goal of product regulation would be to reduce morbidity and mortality associated with the use of tobacco products.

THE LONG-TERM VISION AND SHORT-TERM POLICY OBJECTIVES OF THE DIALOGUE

Throughout the Dialogue process, participants engaged in a discussion and exploration of key principles to guide a unified approach to dealing with issues surrounding harm reduction. The following four principles were identified as an essential foundation for subsequent discussions and recommendations:

- The primary goal of tobacco control is to reduce mortality and morbidity associated with tobacco use.
- "Tobacco free" should be the norm. Policy interventions such as clean indoor air laws, sustained media campaigns and excise tax hikes, coupled with expanded prevention and treatment efforts, should continue to be at the forefront of tobacco control efforts to denormalise tobacco use.
- Achieving the primary goal might entail continued use of selected nicotine-containing products if doing so would deter the use of more toxic tobacco products and would result in a significant reduction in tobacco-related morbidity and mortality.
- Any company marketing nicotine-containing products needs to be accountable for the toxicity of its products and must bear the burden of proof for any product claims. There needs to be an adequate science base to support claims, and they must be truthful and not misleading.

If the primary goal of tobacco control is to eliminate morbidity and mortality associated with the use of tobacco products, the most effective means is abstention from all tobacco products. This was judged to be a population outcome that would take time to accomplish. In this context, Dialogue participants with differing views on the role of smokeless tobacco use in harm reduction were able to reach a consensus on one long-term vision: a world where virtually no one uses combustible tobacco products. This is not a recommendation to ban cigarettes and embrace a policy of prohibition, nor does it reflect any agreement about recommending that smokers switch to smokeless tobacco products. Rather, it is a clarion call to alter the current marketplace to reduce the number of people who use cigarettes. Given the currently widespread use of combustible tobacco products, this is obviously a highly ambitious long-term vision, subject to controversy and scepticism regarding its feasibility.

Dialogue participants also identified two key short-term policy objectives to help achieve the primary goal of reducing the morbidity and mortality from tobacco by reducing tobacco use and the number of tobacco users. These are:

- Establish effective public health-based regulatory control of all tobacco products.
- Shift current tobacco users who are unable or unwilling to become nicotine-free toward the least harmful products (ie, medicinal nicotine).

RATIONALE FOR THE LONG-TERM VISION WHERE NO ONE USES COMBUSTIBLE TOBACCO PRODUCTS

A world in which no one uses combustible tobacco products would have a profound impact on reducing death and disease from tobacco use. Perhaps in response to the prospect of significant reductions in tobacco use, tobacco product manufacturers have introduced many new products known as potential reduced exposure products (PREPs)[3] with the dual goals of appearing to address the health concerns of smokers while simultaneously maintaining overall tobacco use.

The discussions and controversies evolving around the recent introductions of PREPs have led to a closer examination of the health risks associated with all tobacco products. This examination has caused many to conclude that combustible PREPs are unlikely to significantly contribute to a reduction in the death and disease from tobacco use.[6 7 14–17]

How to determine the likely reduction in individual-level risk and population-level harm across various PREPs is still an open scientific question. Research in several areas is being conducted to evaluate the following factors as potential determinants: (1) toxic constituents in tobacco products and smoke emissions, (2) preclinical cytotoxicity and genotoxicity in cell cultures and animal models for toxicity and disease, (3) biomarkers of exposure and effect in humans and (4) actual health outcomes across various morbidity factors. The convergence of the results in all these areas of testing is likely to constitute the evidence base for determining the reduced risk potential of a product, with the ultimate evaluation criteria resting on actual health outcomes.

Because of the many years that would be required to directly observe the health effects of a PREP, evaluation currently relies on shorter-term clinical and laboratory measurements, including assessment of toxic chemical delivery, biomarkers of exposure and biomarkers of effect. Toxic chemical delivery is a measure of the level of chemical constituents of concern to which a user of the product is exposed. Usually these measurements are carried out using external devices that smoke or extract the chemicals of concern before analysis of their amounts. Preferably, the delivery process is designed to mimic how people use the product; however, all too often this has not been the case and has led to false estimates of exposure.[8 18] This is also complicated because of intraindividual and interindividual variability in product use. Biomarkers of exposure measure a "constituent or metabolite of the product that is obtained in biological fluid or tissue". Biomarkers of effect refer to "a measured effect including early subclinical biological effects, alterations in morphology, structure or function; or clinical symptoms consistent with the development of health impairment and disease".[19] To date, a few clinical trials that have used these biomarkers suggest that there is a spectrum of potential harm across different types of tobacco or nicotine-containing products,[6 20 21] with the greatest harm associated with the conventional combustible tobacco products and the least harm associated with therapeutic nicotine replacement products.

Based on current knowledge, novel combustible products are unlikely to substantially reduce risk for disease because of the number of toxic combustion constituents associated with

cigarette smoke. Human studies on modified, reduced-toxicant cigarette products have shown only moderate or modest reductions of some toxicants, no significant reductions of other toxicants and even some increases in other toxicants.[22–25]

Some have concluded that a cigarette product that may lead to significant reduction in risk is one with a nicotine content that is too low to promote initiation, sustain addiction, or lead to compensation. (Compensation occurs when smokers engage in behaviours to defeat product modifications such as lowered nicotine content. Such compensatory behaviours include smoking more cigarettes, taking more puffs, or taking larger puffs.)[8] The harm reduction potential from such a product is not a consequence of a reduction in toxic constituents, but rather a reduction in the addiction potential of the product. A gradual reduction in the nicotine content of all cigarettes was proposed in 1994 by Benowitz and Henningfield.[26] This approach could theoretically lower the prevalence of smoking by reducing initiation by adolescents and increasing abstinence rates among addicted adult smokers.

Preliminary evidence has suggested that smokers using specially designed test cigarettes with lowered nicotine content in the tobacco show a dose-related reduction in nicotine intake, with only modest compensation.[27 28] This finding points to the potential feasibility of reducing nicotine addiction through reduced-nicotine cigarettes. The test cigarettes used are different from the commercial ''low-yield'' cigarettes that have similar levels of nicotine as the higher yield cigarettes but achieve lower machine-determined yields due to ventilated filters. Ventilated filters have one or more rings of small perforations that allow air to dilute smoke, thereby reducing machine-based yields of tar, nicotine and carbon monoxide.[8] Unlike machines, smokers can achieve higher levels of nicotine by smoking harder on a cigarette and/or blocking the ventilated filters.[8]

Considerable research needs must be addressed before the nicotine reduction approach can be recommended. Reducing the nicotine content in cigarettes should be pursued only if it reduces smoking prevalence and does not lead to a significant increase in toxicant exposure in continuing smokers due to compensatory smoking. It should also only be considered in a regulated environment where addicted adult smokers would be provided easily accessible products, programs and services to stop using cigarettes.[29]

THE STATE OF THE SCIENCE ON OTHER TOBACCO AND NICOTINE-BASED PRODUCTS

Cigarette-like delivery devices that heat rather than burn cigarettes, such as Philip Morris' Accord and Reynolds American Inc.'s Eclipse, are being sold in the US and other countries. To date, there have not been sufficient studies of these products to determine their value in reducing exposure and disease. The results from studies conducted by Roethig and associates, testing one of the cigarette-like delivery devices, showed significantly lower levels of some carcinogen-related toxicants compared with conventional combustible products in residential and non-residential settings and in short and long-term trials.[30–33] One study also showed significant improvements in some of the cardiovascular risk factors that were measured.[32] To date, it is unknown if the extent of the observed reductions and if reductions in some but not all biomarkers would lead to relative reductions in disease risk compared to continued smoking on conventional cigarettes. Furthermore, not all of these devices are alike. For example, in studies with another electronically heated cigarette-like device, significant increases in some of the biomarkers of exposure and effect were observed.[20 34]

On the continuum of risk, non-combustible tobacco products are more likely to reduce harm than a smoked form of tobacco for individuals who would otherwise be using conventional cigarettes. Though Dialogue participants did not fully agree on the role of smokeless tobacco products as a harm reduction agent, there was a consensus about the value and the concept of this continuum of risk.

To reduce harm, these non-combustible nicotine-containing products will need to expose users to significantly fewer and lower levels of toxicants than cigarettes, and their use should not discourage or delay quitting combustible products. Any discussion of the harm reduction potential of smokeless tobacco products must take into account a series of individual and population-level policy issues including (1) the relative toxicity and risks of any oral tobacco products compared with cigarettes; (2) concomitant use of oral tobacco products and cigarettes with the potential for increased exposure to toxicants; (3) increased prevalence of oral tobacco use due to increased uptake among those who would otherwise never use tobacco, maintenance of oral tobacco use in consumers who would have otherwise quit and/or relapse to tobacco use; and (4) potential as a gateway product to or from cigarette smoking.[21 35–37]

Smokeless tobacco companies and cigarette manufacturing companies in the US are marketing reduced-toxicant (lower tobacco-specific nitrosamines (TSNAs)) and spitless oral tobacco packets or lozenges. Some of these newer US products are lower in TSNA levels than some conventional and most popular brands of smokeless tobacco sold in the US or in other parts of the world such as India and comparable to or lower in TSNAs than the smokeless tobacco products sold in Sweden.[21 38 39] One study showed that tobacco carcinogen exposure (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)) can be reduced when smokers switch to smokeless tobacco products;[40] however, human clinical studies on the effects of oral tobacco products on biomarkers of exposure and effect are limited.

Smokeless tobacco has been found by the US Surgeon General, the American Cancer Society and International Agency for Research on Cancer (IARC) to be a cause of oral cancer and possibly pancreatic cancer.[41] Nonetheless, if smokers who cannot or will not quit their dependence on nicotine switched completely to smokeless tobacco products, they would likely experience a reduction in tobacco-caused mortality and morbidity. The extent of this reduction is unknown. Nevertheless, these persons would not be risk-free, and their risk would be higher than if they switched to medicinal nicotine.

Several published reports and articles describe a significantly lower risk for disease from using smokeless tobacco compared with cigarettes.[7 21 36 42] Unlike cigarette smoking, smokeless tobacco use has not been linked to many of the smoking-related cancers[41] or to pulmonary disease.[43]

Interestingly, those who believe that smokeless tobacco can be used to reduce population-level harm caused by tobacco and others who challenge these claims as unproven have both cited the so-called ''Swedish experience''. Those who contend that the Swedish experience supports the use of smokeless tobacco for harm reduction cite studies that have found, for example, that rates of lung cancer in men in Sweden were significantly lower than the rates found in men in Norway, which has higher rates of cigarette smoking. Authors of those studies attributed this dramatic reduction in lung cancer to increased prevalence of consumption of snus, Sweden's low-nitrosamine form of smokeless tobacco, which was associated with and may have led to reduced prevalence of cigarette smoking.[44] A study conducted in Sweden with men in a twin study observed that

the use of the form of snus sold in Sweden was associated with smoking cessation but not initiation,[45] suggesting to the authors that there were no adverse effects of snus on smoking prevalence and smoking-induced disease. Further, proponents of the use of snus for harm reduction point to studies that demonstrate that snus switchers achieve greater health gains compared with smokers who did not switch, and similar gains to those who quit all tobacco products.[46] It is important to keep in mind that the Swedish studies were conducted in an environment with stronger tobacco regulation that included an advertising ban. Some experts question whether these results, even if widely accepted, are generalisable to other countries.

Other researchers have pointed to other tobacco control factors that may have led to reduction in lung cancer rates in Swedish men and which may have contributed to the low smoking prevalence rates in places such as California.[47] Tomar[47] also notes that some states in the US have high rates of smokeless tobacco use without a corresponding reduction in the prevalence of cigarette smoking. This finding is likely to be true in a culture that aggressively markets cigarettes and smokeless tobacco products. Furthermore, unlike the switchers to snus products, in one study smokers who switched to US smokeless tobacco products were found to be at greater risk for mortality compared with smokers who quit completely.[48]

The safest nicotine-based products are likely to be therapeutic nicotine products such as the gum, patch and lozenge. They contain nicotine but none of the other toxicants found in tobacco. These products are not considered absolutely safe because of the risk for fetal toxicity and increased levels of cardiovascular risk factors, such as effects on blood lipids, endothelial dysfunction and insulin resistance.[49 50] Nevertheless, these products are less hazardous than tobacco products. Medicinal nicotine and other approved products are at a significant marketing disadvantage compared to tobacco products. They must undergo a rigorous federal approval process and are designed to minimise addiction. By contrast, tobacco products are currently subjected to no product regulation.[51]

To facilitate a transition of smokers from the most toxic to the least toxic form of nicotine delivery, consideration should be given to looking at the nicotine market as a whole and developing a more coherent policy that explores the impact of promoting the use of the least toxic forms of nicotine delivery and discourage the most toxic forms. This should include the possibility of making the therapeutic nicotine products more consumer acceptable and effective.[52] Technically, this can be performed by making the products more palatable through improved taste and sensory perception, and by increasing the amount and the delivery speed of nicotine.[6] However, the health and behavioural risks of a pure nicotine delivery that has these characteristics are unknown and require study; although the occurrence of greater health risks, with the exception of long-term or dependent use, seems unlikely.

In summary, the consensus among Dialogue participants and other researchers[7] is that the use of combustible tobacco products will always pose the greatest risks. The tobacco harm reduction approach that will lead to the greatest reduction in tobacco-related morbidity and mortality is cessation of use of all tobacco products. Short of this goal, shifting from combustible tobacco products to the long-term and exclusive use of non-combustible products, particularly therapeutic products, with the right controls and post-market surveillance is likely to create less harm among continuing users. This shifting of product use should be part of a comprehensive approach that includes the regulation of all nicotine products, whether or not they contain tobacco. For cigarette users who switch to smokeless tobacco products, maximal potential reduction in harm could only occur with products that result in the lowest exposure to toxicants, are subject to government regulation, and that avoid adverse consequences such as increased initiation of tobacco use or decreased cessation.

KEY ELEMENTS TO ACHIEVE SHORT-TERM POLICY OBJECTIVES

Dialogue participants identified two short-term policy objectives in addition to prevention and cessation likely to achieve harm reduction as defined in this report: (1) effective tobacco product regulation and (2) promoting a shift by tobacco users toward the least harmful products (ie, medicinal nicotine). Product regulation is a critical component in the efforts to reduce harm associated with tobacco use and is a mechanism to facilitate the long-term vision of the Dialogue, where no one uses combustible tobacco products. As stated in the 2001 Institute of Medicine (IOM) report, *Clearing the smoke*, "Regulation of all tobacco products…is the necessary basis… for assuring that the health of the public is protected".[3]

Dialogue participants reached a consensus on a series of key elements in a regulatory scheme for tobacco products. The regulatory tools that have been recognised by the WHO Study Group on Tobacco Product Regulation (TobReg; http://www.who.int/tobacco/global_interaction/tobreg/tsr/en/index.html) and in the legislation pending in the US Congress in 2008 that would grant regulatory authority over tobacco products to the Food and Drug Administration provide useful guidance.[12] The consensus regulatory elements include:

- *Disclose all known toxicants to regulatory agencies.* Disclosure of the type and amount of all toxicants in tobacco products by brand and brand subtype is not currently required from tobacco companies, although most other consumer products are subject to such requirements. Disclosure of all toxicants would serve several functions: (1) educating public health officials and policymakers about the types and relative amounts of toxicants contained in tobacco products, (2) providing a basis for monitoring toxicants in tobacco products by the government and (3) establishing a platform for regulating these toxic constituents. Regulators would have to make a science-based decision on whether and how this information should be disclosed to consumers.
- *Identify toxicants targeted for reduction.* Toxicants should be identified based on whether they are known to cause adverse effects and the extent to which they are linked to tobacco-related disease and/or addictive behaviour.[3] TobReg has been working to identify known emissions toxicants that should be reduced in cigarette products. Toxicants were identified by TobReg based upon their carcinogenic and toxic activities, their known effects in humans and their concentrations in cigarette smoke. The toxicants identified by TobReg for regulation are acetaldehyde, formaldehyde, benzene, 1,3-butadiene, acrolein, benzo[a]pyrene, carbon monoxide, *N*-nitrosonomicotine (NNN) and NNK. Several other toxicants were also recommended as candidates for reporting to governments.[53] They are acrylonitrile, 4-aminobiphenyl, cadmium, catechol, crotonaldehyde, hydrogen cyanide, hydroquinone, 2-naphthylamine and nitrogen oxides. As products and science evolve, these targeted toxicants will need to be revisited.
- *Develop a science-based rationale for reducing toxicants in all tobacco products.* Cigarettes and smokeless tobacco products vary tremendously in their toxicant levels. This is a function of the type of tobacco leaves in the product, the curing and manufacturing processes, and how the products are consumed. For example, the variability in tobacco-specific

nitrosamines—a potent carcinogen—can range over a 20-fold difference in cigarettes worldwide[54] and greater than a 48-fold difference among US oral tobacco products (0.19 to 9.2 μg/g product wet weight).[38] Although no studies have been conducted on the relationship between tobacco-specific nitrosamine levels in different brands of cigarettes and uptake of these carcinogens in humans, preliminary results in an experimental setting show a relationship with smokeless tobacco products.[21] Therefore, depending on factors the preliminary tests did not examine, it may be that reducing levels of toxicants in smokeless tobacco products can potentially result in reduction of exposure to these toxicants.[25 55] Smokeless tobacco products (snus) in Sweden tend to be lower in tobacco-specific nitrosamines and other toxicants compared with the most popular brands in the US, primarily because the Swedish tobacco companies have self-imposed performance standards. As a result, in Sweden there are studies that conclude that the risk for disease associated with snus tends to be lower, particularly in contrast with risk for disease observed in India and the US, where the smokeless tobacco products tend to have higher levels of toxicants.[21] Because of nicotine's role in cigarette use,[56] reducing levels of toxicants without taking into account nicotine levels may not lead to significant reduction in toxicant exposure. In the case of higher ventilation cigarettes, machine-measured tar and nicotine were reduced over the past 30 years and, as a consequence, smokers increased their intake of toxicants per cigarette to compensate for the reduced levels of nicotine.[8] Reducing toxicants on a per-mg of nicotine basis, as proposed by TobReg, may circumvent this problem, although no proof of concept study has been conducted. Furthermore, measures must be taken to ensure that nicotine yields are not increased in cigarettes in order to maintain a specified toxicant to nicotine yield ratio. While increasing nicotine levels might reduce the number of cigarettes smoked and lead to reduced exposure,[57] this method may increase the number of tobacco users addicted to their product. Any adjustment of nicotine levels—up or down—requires careful study and monitoring and should only be performed in a regulated environment.

- *Establish a standard for the maximum level of specific toxicants and prohibit the sale of tobacco products that exceed the established standards.* Although Dialogue participants were not asked to endorse the quantification of toxicant reduction during the Dialogue process, it is important to note that performance standards should be determined by a body of experts independent of the tobacco companies and that Gray *et al*,[6] commented that the performance standards can become more stringent over time. At this point, there are no mandatory performance standards in the US or globally, thus leaving the companies free to deliver any level of toxicants they choose. Once in place, tobacco companies should not be allowed to publicise mere compliance with any such standards.
- *Establish a standard for nicotine yields across tobacco products.* This regulatory approach would prevent tobacco companies from independently increasing nicotine in tobacco products, as has been observed over several years in a study conducted by the Harvard School of Public Health.[58] Furthermore, it would give regulatory authorities the power to alter levels of nicotine in tobacco products based upon the best available science.[26 29 59]
- *Assess the human exposure impact for toxicant reduction.* The recommendations to develop performance standards must remain fluid. Determination as to whether the proposed standards result in exposure reduction must be based on evidence from human clinical exposure trials and will evolve from data produced by the tobacco companies and by independent scientists. Results from studies may necessitate revisions to previously established performance standards.
- *Prohibit exposure reduction claims associated with reductions in level of toxicants.* Exposure reduction claims are likely to mislead consumers into thinking that a product is "safer" or "safe".[60 61] This is one of the lessons learned from the experience with "light" cigarettes.[62–66] Until there are data to demonstrate that specific levels of toxicant exposure lead to reduction in risk at the population level, tobacco companies should not be allowed to make exposure reduction claims alone. Post-marketing surveillance of any approved risk reduction claims will be necessary to determine the impact of these claims on initiation, relapse, cessation and health.
- *Educate the public about exposure versus risk reduction.* Regulation of tobacco products and efforts to reduce toxicant levels in tobacco products could lead the public to perceive the tobacco products as "safer" or "safe" or "endorsed" by the government. A well designed public education program, grounded in science-based information, needs to be developed. It should include media campaigns that explain the differences between exposure and risk reduction and emphasise the benefit of total cessation of tobacco use.
- *Regulate the promotion, advertising and labelling of tobacco products.* The goal of this regulation is to prevent false or misleading claims, implied or direct. Studies will be needed to provide the evidence base for a proper evaluation of promotion, advertising and labelling.
- *Establish research priorities to achieve the nine regulatory elements listed above.* Research needs for the assessment of PREPs and tobacco products in general have been clearly described in other reports and articles.[3 36 67] These include development of (1) animal models and in vitro assays of the pathogenesis of tobacco-attributable diseases; (2) human biomarkers of exposure and effect and the relationship between these biomarkers with disease risk; (3) methods and measures for short-term clinical and epidemiological studies, including consumer perception testing; and (4) post-marketing surveillance or long-term studies to determine the impact of PREPs on a population level.
- Research is needed to provide guidance for regulation addressing such issues as (1) whether and how to best educate consumers about the toxicant level in tobacco products so that an informed decision can be made on product use or choice of products and so the consumer is not misled; (2) the impact of reducing toxicants on machine-determined yields and in preclinical (animal and in vitro assays) and clinical human exposure studies; (3) the process, impact and viability of gradually reducing nicotine yields of tobacco products, particularly in conjunction with reducing toxicant yields per mg of nicotine; and (4) the best way to educate the public on reduced exposure versus reduced risks and on relative risks, without compromising public health. In all these research questions, the effects on a heterogeneous population (eg, gender, racial/ethnic, socioeconomic status, tobacco use status, concern about health, motivation to quit) must be considered.

To shift the population who cannot or will not quit altogether toward the use of the least harmful products (the second short-term policy objective), a number of methods were identified for further exploration. These were:

- *Substantially raise the tax on combustible tobacco products on a regular basis over time.* Increasing the cost of the most dangerous compared to the least dangerous products (eg, medicinal nicotine) can switch preferences toward the less costly products. For example, studies have been conducted with unhealthy versus healthy food products in schools and

worksites in which low-fat, low-calorie foods were priced lower than high-fat, high-calorie foods.[68] An increase in intake was observed for the more healthy foods with a decrease in consumption of less healthy foods.

- *Institute different levels of availability and packaging based on risk in accordance with a system established by an independent regulatory agency.* More toxic products should be made less available. For example, tobacco products could be placed below the counter at retail outlets, completely out of view of the public, especially from children and adolescents. In addition, research on label statements should be conducted to more effectively communicate relative toxicity (eg, tobacco products vs medicinal products).
- *Consider providing appropriate incentives and/or disincentives for manufacturers.* No company should be able to make an exposure reduction claim. However, if there is a documented decrease in risk, it may be possible to create appropriate incentives. These could include granting a "pioneer" company a period of time where it has exclusive use of an approved claim, or ordering mandatory cross-licensing of technologies that have been proven to reduce exposure and risk with royalty payments guaranteed to the "pioneer". This could create a financial incentive for innovators of genuinely reduced-risk products. Other potential financial incentives should be explored.
- *Expand anti-tobacco advertising, label all cigarettes as deadly and addictive and educate the public accurately on the precise risks of different products.* All of these steps should be taken in a regulated environment. The third of these recommendations stems from the principle that consumers deserve accurate and evidence-based information on the toxicity and relative risk for disease of different products.[69] For example, the public has misconceptions that medicinal nicotine products are associated with risks for certain tobacco-caused diseases that should be corrected.[62 70 71]
- *Strong messages and programs for cessation of all tobacco products.* No tobacco product should be considered safe. Tobacco users who are unable or unwilling to quit tobacco should be encouraged to move toward the least hazardous form of nicotine delivery available, therapeutic nicotine products, or other therapeutic products for cessation. Cessation programs and products should be universally available and widely promoted.
- *Establish research priorities to achieve the five elements listed above.* The critical research questions to address for these short-term policy recommendations are the following: (1) the relative risk across different types of tobacco products and methods to determine relative risk; (2) a better understanding of the relationship between increasing the cost of a highly toxic product and consumers' decisions to switch to less toxic products; (3) optimal methods to educate the public and to correct consumer misperceptions about the relative risk of products; and (4) the population impact of the proposed measures on increasing initiation or decreasing cessation.

Three additional initiatives were identified by Dialogue participants as worthy of further exploration and research.

- Explore whether reducing nicotine exposure in combustible products to non-addicting levels is likely to lead to a reduction in smoking prevalence; accounting for the potential unintended consequences of such a strategy, including whether such a step would result in the creation of a black market for higher nicotine cigarettes.
- Explore the effects of low-toxicant smokeless tobacco products as a harm reduction tool and determine the safety and impact, on individual and population levels, of informing the public about the relative risk of oral tobacco products compared with combustible tobacco products.
- Explore issues surrounding long-term use of nicotine at the population level; account for the trade-offs that may be inherent in this approach, such as a reduction in overall disease toll but an increase in initiation or persistence of nicotine use due to the knowledge that a "safer" alternative exists.

Finally, the following significant infrastructure needs were identified by Dialogue participants:

- Enhanced surveillance of tobacco product use. Surveillance to assess population impact (eg, rates of initiation and cessation, and concurrent product use) is a critical component to achieve a short-term rapid response capability that will support the long-term vision of the Dialogue. As described in several publications,[3 67] short-term and long-term continuous surveillance is critical to assess the patterns of tobacco use and impact of policies and products on health outcomes. Surveillance should include an assessment of biomarkers of tobacco toxicant exposure in individuals using different products and whether there is any correlation between those measurements and health outcomes.
- Creation of a research consortium. In the US, this would ideally include relevant government agencies—the Centers for Disease Control and Prevention (CDC), Environmental Protection Agency (EPA), National Institutes of Health (NIH)—and a range of private and academic research facilities for product testing, human exposure studies and consumer perception studies. The CDC can contribute its expertise in product testing, toxicology and surveillance; the EPA can contribute hazard identification, risk assessment and risk management; and the NIH can generate the research base for addressing critical questions about viable and effective methods for tobacco harm reduction. The contracted research centres would be composed of a consortium or network of independent scientists and testing facilities to test tobacco products using animal and human protocols. This research consortium would closely interact with international efforts in this area, including the WHO Committee on Tobacco Product Regulation and Tobacco Laboratory Network initiatives.

CONCLUSIONS

Dialogue participants reached a consensus that, based on the currently available evidence, significant tobacco harm reduction can be achieved over the long term only in a world where virtually no one uses combustible tobacco products. In such a world, smokers would either quit completely or switch to the least harmful form of nicotine delivery (ie, medicinal nicotine). Steps toward achieving this ambitious vision would include policies that discourage the use of combustible products through taxation and access, marketing and promotion. It might also be possible over time to employ product regulation to permit the sale only of non-addicting combustible tobacco products so that young people who experiment with cigarettes would not become addicted.

Decreasing tobacco initiation and increasing tobacco cessation are proven harm reduction strategies. Current efforts in these areas are woefully underfunded. Implementing the recommendations of the recent IOM report[13] to fully fund comprehensive tobacco prevention and control funding at CDC-recommended levels is a required first step. Tobacco product regulation is also needed to provide a mechanism to reduce the harmfulness of tobacco products. In a regulated environment:

- Tobacco constituents and additives should be disclosed to and monitored by regulatory agencies.
- Performance standards should be established so that all tobacco products would have maximum limits on nicotine and toxic tobacco constituents and emissions.

- Exposure reduction claims should be prohibited in the absence of adequate evidence of risk reduction. Mechanisms should also ensure that claims are examined based on the impact on the population as a whole, as well as individual consumers.
- Risk reduction claims should have an adequate scientific base, including evidence of anticipated population-level effects (eg, on initiation and cessation).
- Any risk reduction claims should be evaluated and approved by a regulatory agency on a pre-market basis.
- Post-marketing surveillance should be used to re-evaluate the claims.
- Consumers should be accurately informed and educated about relative risks of the use of different types of nicotine containing products.
- Combustible products that reduce nicotine exposure to non-addictive levels should be investigated.
- Individual risk and population health impacts of long-term use of nicotine-only products should be examined.
- Policies that shift the population to less harmful products should be explored taking into account their impact on prevention and cessation efforts and overall tobacco-related mortality.
- The effects of regulatory policies on prevalence of tobacco use and tobacco-caused mortality and morbidity should be monitored.

In the short term, the following action steps need to be taken: (1) pass effective legislation for tobacco product regulation, (2) develop the proposed infrastructure and network for product testing and scientific inquiry, (3) coordinate national and international efforts and (4) address the research questions necessary to determine the feasibility and impact of fulfilling the long-term vision. Much is already known about the building blocks required to achieve the long-term vision and short-term policy objectives identified by the Dialogue. What is missing is the requisite degree of public and political support to dare to envision a future world where almost no one uses a combustible tobacco product.

APPENDIX

Strategic Dialogue on Tobacco Harm Reduction participants

Cathy Backinger, National Cancer Institute, Bethesda, Maryland, USA; Neal Benowitz, University of California, San Francisco, California, USA; Lois Biener, University of Massachusetts, Boston, Massachusetts, USA; David Burns, University of California, San Diego, California, USA; Pamela Clark, University of Maryland, College Park, Maryland, USA (during the Dialogue process PC was with the Battelle Centers for Public Health Research and Evaluation, Baltimore, Maryland, USA); Greg Connolly, Harvard School of Public Health, Boston, Massachusetts, USA; Mirjana Djordjevic, National Cancer Institute, Bethesda, Maryland, USA; Thomas Eissenberg, Virginia Commonwealth University, Richmond, Virginia, USA; Gary Giovino, University at Buffalo, SUNY, Buffalo, New York, USA; Dorothy Hatsukami, University of Minnesota, Minneapolis, Minnesota (cochair); Cheryl Healton, American Legacy Foundation, Washington, DC, USA; Stephen Hecht, University of Minnesota, Minneapolis, Minnesota, USA; Jack Henningfield, Pinney Associates, Bethesda, Maryland, USA; Corinne Husten, Partnership for Prevention, Washington, DC (during the Dialogue process CH was with the Centers for Disease Control and Prevention, Atlanta, Georgia, USA); Kimberly Kobus, University of Illinois, Chicago, Illinois, USA; Scott Leischow, University of Arizona, Tucson, Arizona, USA; David Levy, Pacific Institute for Research & Evaluation, Calverton, Maryland, USA; Stephen Marcus, National Cancer Institute, Rockville, Maryland, USA; Matthew Myers, Campaign for Tobacco-Free Kids, Washington, DC, USA; Mark Parascandola, National Cancer Institute, Rockville, Maryland, USA; Prabhu Ponkshe, Health Matrix Inc., McLean, Virginia, USA; Peter Shields, Georgetown University, Washington, DC, USA; Paul Slovic, Decision Research, Eugene, Oregon, USA; David Sweanor, University of Ottawa, Ottawa, Ontario, Canada; Kenneth Warner, University of Michigan, Ann Arbor, Michigan, USA; Mitchell Zeller, Pinney Associates, Bethesda, Maryland (cochair).

Dialogue members participated in their individual capacity. Organisational affiliations are provided for informational purposes only. The views expressed here are those of the authors only and do not represent any official position of the US National Cancer Institute or US National Institutes of Health.

What this paper adds

- There has never been a systematic exploration of the key research, policy and communications issues related to tobacco harm reduction. This document describes the deliberations and consensus reached by a diverse group of experts that yielded a blueprint for action on tobacco harm reduction.
- This blueprint includes a long-term vision and a series of shorter-term policy and research activities to achieve that vision, a world where virtually no one uses combustible tobacco products.

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Competing interests: CB: no conflicts of interest; NB: serves as a paid consultant to several pharmaceutical companies that market or are developing smoking cessation medications and also serves as a paid expert witness in litigation against tobacco companies; LB: no conflicts of interest; DB: testified against tobacco industry in multiple lawsuits; PC: no conflicts of interest; GC: no conflicts of interest; MD: no conflicts of interest; TE: consulted with the National Association of Attorneys General on issues related to potential reduced exposure products (PREPs) and PREP testing, and has received free of charge smokeless tobacco products from RJ Reynolds to test them in his laboratory (neither RJ Reynolds nor any other company has ever had any input into any work performed in his laboratory nor have they had any input into any reporting of results); GG: no conflicts of interest; DH: consulted for pharmaceutical companies (Pfizer, Abbott) that are marketing or developing smoking cessation medications (no honorarium received), received research grant from Nabi Biopharmaceuticals for clinical trial; CH: no conflicts of interest; SH: served as an expert witness for the plaintiff in a case in which US Smokeless Tobacco Company is being sued by the family of a man who died from oral cancer after years of using smokeless tobacco; JH: Pinney Associates (employer) provides consulting services to GlaxoSmithKline Consumer Healthcare on issues related to treating tobacco dependence. JH has interest in a nicotine delivering smoking cessation product under development; CH: owns pharmaceutical stock (Johnson and Johnson, Pfizer); KK: no conflicts of interest; SL: consultant/advisory committee member, speaker for Pfizer pharmaceutical company; consultant for Johnson and Johnson; DL: no conflicts of interest; SM: no conflicts of interest; MM: no personal conflicts of interest. The Campaign for Tobacco-Free Kids (employer) has received donations from pharmaceutical companies that make cessation products, albeit those donations are a very small percentage of the campaign's budget; MP: no conflicts of interest; PP: no conflicts of interest; PShields: served as expert witness in tobacco litigation; PSlovic: no conflicts of interest; DS: receives, directly or indirectly, fees from the marketers of smoking cessation medicines. None of this money is significant enough in relation to his personal financial resources to be considered material; KW: Chair of the Pfizer Tobacco Independence Global Policy Advisory Board, for which an honorarium is received (which is immediately endorsed to a scholarship fund via employer); MZ: Pinney Associates (employer) provides consulting services to GlaxoSmithKline Consumer Healthcare on issues related to treating tobacco dependence.

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