

UCSF

WHO Tobacco Control Papers

Title

Statement of Principles Guiding the Evaluation of New or Modified Tobacco Products

Permalink

<https://escholarship.org/uc/item/65n3687f>

Author

World Health Organization

Publication Date

2003

Statement of Principles Guiding the Evaluation of New or Modified Tobacco Products

A number of new tobacco products for which reduced exposure, reduced toxicity and reduced health risk claims are being made are being introduced in markets worldwide. These products include cigarettes modified to purportedly reduce their toxicity, including cigarettes with modified tobacco from which established carcinogens are reduced/removed, products designed employing unconventional technologies, and a variety of oral tobacco products.

In the past, tobacco companies have marketed products that claimed lower emissions (1); but in fact, these cigarettes did not deliver reduced uptake of toxicants or lower risks to those who smoked them (2, 3, 4). Harm reduction claims for some products are currently being made in some markets (5, 6), and future claims are likely to be made without regulatory oversight. There is no existing regulatory structure to evaluate the scientific validity of these claims (2).

Member States face the need to make decisions and formulate policies with regard to these products as they come to market. This statement by SACTob is intended to provide guidance on issues identified by the scientific community that may form the basis for regulatory and other decisions about these products.

There are three general categories of products for which claims are being made:

The first such category contains products that resemble conventional cigarettes but which claim to reduce the toxicity or addiction potential of the smoke generated by altering the tobacco used or the filter characteristics, or by adding new substances. These products include cigarettes that use reduced nitrosamine tobacco, add catalysts to reduce the polycyclic aromatic hydrocarbon carcinogens produced in the smoke, genetically modify the tobacco plant to reduce nicotine and nitrosamines, use tobacco from which the nicotine has been extracted, utilize filters able to selectively reduce toxicants in the smoke or utilize a combination of these technologies.

The second category is made up of products in which the principal means of delivering nicotine is heating rather than burning the tobacco. The heat sources utilized include either charcoal elements at the tip of the product or electrically heated rods inserted into the tobacco. The area heated may contain tobacco but the nicotine is volatilized with markedly reduced combustion of the tobacco. These products claim to reduce the carcinogenic constituents of smoke and to reduce second hand smoke emissions.

Lastly, oral tobacco products are offered, in general, as products less hazardous than cigarettes. These products make claims of reduced carcinogenic tobacco specific nitrosamines in the tobacco used, are offered for use when smoking is not permitted, and are combined with sweeteners and flavoring agents in candy-like formulations which may make them appealing to younger users.

Estimating the potential for these products to cause/reduce harm is complex, even if real changes occur in the emission profile when they are used. A change in the emission profile

is only one piece of the assessment. Such changes may not translate to reductions in addiction potential or toxicity, and reduced toxicity does not automatically translate into reduced harm for the individual smoker. The assessment of harm modification also needs to consider changes in cessation behavior by the smoker and the fact that introduction and marketing of purportedly safer products may create harm for the population as a whole through increased initiation and deceptive marketing messages.

EXISTING SCIENTIFIC KNOWLEDGE

Extensive reviews of the relative hazard of using existing cigarettes, and changes in cigarettes over the past several decades, have led to the conclusion that the evidence does not support a difference in disease risks with the use of cigarettes with different levels of machine measured tar and nicotine yields or with product modifiers such as light or mild (2, 3, 7). The evidence available for newer tobacco products is more limited and is largely based on chemical measurements, toxicological risk assessment, and *in vitro* toxicity assays. The U.S. Institute of Medicine reviewed the science available to determine differences in harm that might result from use of newer tobacco products and the scientific methods that might be used to examine harm reduction (2). They concluded that existing scientific evidence is not sufficient to allow definition of differences between newly engineered tobacco products and currently existing products for human uptake of toxicants, toxicity, or harm (2). In addition they concluded that a scientific methodology to establish toxicity and harm differences for these products does not currently exist and that a structure for regulatory oversight would be essential to any scientific assessment of claims for reduced harm (2). However, the report also concludes that emerging scientific understanding of disease mechanisms offers the promise of new and more specific methods of assessing tobacco toxicity and harm. The potential for defining differences in harm of specific products is greater for tests of carcinogenicity in the near term than it is for other forms of tobacco related injury; but the evidence supporting a reduction in carcinogenicity for a product must be interpreted in light of the potential effects changes in the product may have on the other major diseases caused by cigarette smoking.

Evaluation of the toxicity of different tobacco products is difficult because of the broad array of factors that may influence toxicity and/or potential for addiction. Product characteristics are critically important; these include ingredients (particularly the type and blend of tobacco), design and engineering characteristics of the product, and elements of the manufacturing processes that may alter the ingredients used. Quantities of these ingredients by brand and the design and manufacturing techniques used for the cigarette brand are usually not provided by tobacco manufacturers, but they are essential for evaluation of toxicity; they could be provided without any increased cost to the manufacturer. Characteristics of product use are also important determinants of toxicity, since they influence the actual delivery of toxicants and addictive constituents to the smoker. Once delivered to the smoker, the uptake of toxicants is influenced by the pattern of smoking, depth of inhalation, duration of breath holding at the end of the puff and other characteristics of how the smoker responds to the smoke delivered. This response is complicated by the reality that smokers adjust their pattern of smoking to maintain a consistent level of uptake of nicotine, which is the addictive agent in tobacco (3, 8, 9). This compensation leads smokers to use products differently based on the amount, rate and form in which nicotine is provided (10, 11, 12, 13, 14).

Assessment of differences in human exposure and harm is complicated by differences in the demographic characteristics and intensity of use of those who choose to use different products (3, 15, 16); the reality that how products are marketed determines who uses the product, what the alternatives are for the person switching to the product, the context in which the product is used (5, 17, 18), and the difficulty in extrapolating from forced switching studies to actual use exposures (19). A final complexity is introduced by the reality that consumer understanding of marketing message, rather than a narrow reading of the text, is what determines the impact of a given marketing approach on consumers.

Perspectives On Harm Reduction

The major acceptable public health rationale for development of new or modified tobacco products is the potential for a reduction in the harm caused by existing tobacco products. This harm can be viewed as occurring in various contexts.

Harm To The User

Harm can be examined within the narrow perspective of effects on the individuals currently using the product. Estimates of the harm reduction that can occur when shifting from one product to another are commonly derived from risk data derived from populations who are lifelong users of the different products. For example, comparison of the risks of cigarette smokers and cigar smokers as a measure of the risk reduction that might occur if smokers switched from smoking cigarettes to smoking cigars is an approach which is deeply flawed by two constraints. First, for the individual, initiation of use of any tobacco product can only increase the harm he or she is likely to experience in comparison with continued abstinence; therefore, recommending initiation with a less hazardous form of tobacco use cannot be considered a harm reduction approach for someone who has never used tobacco products. Only the population which switches to a potentially less harmful product can experience a reduction in harm. The difference in risk that accrues with switching from one product to another is not well estimated from the risks of those who have only used the less hazardous product. Second, smokers who switch from cigarettes to potentially less harmful products carry with them levels of addiction and patterns of use that may differ from those who have only used the less harmful product. For example, those who have only smoked cigars tend not to inhale and this difference is felt to be responsible for much of the difference in risks of lung cancer and heart disease between those who have only smoked cigars and those who smoke cigarettes (20). However, cigarette smokers who switch from smoking cigarettes to smoking cigars do tend to inhale, eliminating much of the theoretical benefit that might be achieved from switching to smoking cigars.

Difference in toxicity with switching from cigarettes to other tobacco products should be examined by comparing those who switch to those who continue to smoke cigarettes. An alternative behavior that also needs to be part of this examination of potential harm reduction is a comparison of those who switch with those who quit using any tobacco product instead of switching. This comparison defines the maximum benefit available to the user so that the benefits of switching can be placed in appropriate context, bounded by the risks of continuing and the benefits of quitting.

For a purported harm reduction product to benefit the user who switches to using it, the product must reduce the intensity of exposure to tobacco or tobacco smoke toxicants,

maintain that reduced intensity for a sufficient duration, and have a reduction in intensity sufficient to outweigh the impact of an increased duration of exposure on disease risks. When estimating the differences in intensity of exposure with switching to a new product, it is necessary to account for compensatory and other changes in the actual use of the new product. For example, in some epidemiological studies the risk of lung cancer declines for smokers of lower tar cigarettes when estimated on a constant number of cigarettes smoked per day basis (21). However, if smokers compensate for the reduced nicotine yield by increasing the number of cigarettes that they smoke per day, the risk could potentially increase.

The frequency and timing of relapse to the previous tobacco product must also be evaluated when considering the likelihood that reduced intensity of exposure will be of sufficient duration and magnitude to meaningfully effect disease risks. Finally, the effect of prolonging the duration of exposure needs to be considered when examining the impact of reduced intensity of exposure. Duration is a much more powerful determinant of disease risk than is intensity of smoking for cancer and lung disease (22), and modest prolongation of duration of use may overwhelm the effect of a substantial reduction in intensity of exposure in determining the risk for individual smokers. Therefore, a product with lower levels of toxic emissions (e.g., smokeless product) which enabled a person to continue his or her use of a more toxic product (e.g., cigarette) may result in increased harm if cessation of the more toxic product is delayed.

Harm To Non-Users/By-Standers

Many of the new products may claim reductions in generation of environmental tobacco smoke and there is clear reduction when shifting from burned tobacco products to products that heat rather than burn tobacco or to smokeless tobacco use. However, there may be an increase in secondhand smoke exposure if smoking duration or prevalence increases or if new products result in an increase in toxicants present in either sidestream smoke or exhaled mainstream smoke. An additional concern is that the reduction in smoke emissions may be used to justify delay or reversal of restrictions on smoking in indoor environments.

Harm To The Population

The harm to the population is the net effect of the changes in harm to the individual users and the changes in number of users who are exposed. A principal concern for all harm reduction products is that their presence on the market will offer alternatives to cessation for those who are interested in quitting. If the only users of a reduced harm product are those who would have quit in the absence of the product, or if the number of smokers whose cessation is delayed or aborted by use of the product exceed the number of those who would never have quit who are using the product, then it is likely that there would be a net increase in harm to the population. This would occur even from the introduction of a product that could actually reduce the harm for those individual smokers who would not otherwise quit. Conversely, it is possible that offering harm reduction products might induce some smokers who would not otherwise have quit to use the product and then begin a path that leads to successful long-term abstinence from tobacco. These products may also play a role in enhancing the cessation success of those who are having difficulty achieving abstinence. The potential benefits described here are theoretical, as no tobacco product has currently demonstrated such benefits.

Population harm, therefore, is the net of the combined effects that harm reduction products and their marketing have on the use of tobacco products and resultant population exposure to toxicants. This calculus involves consideration of who is using the newer products and why; what the users' alternative behavior might have been; whether the availability of the new product increases the initiation of tobacco use with that product; and whether, once initiated, users then transition to products with a greater degree of toxicity. These concerns cannot be addressed without considering the marketing approaches and messages utilized for harm reduction products as they are introduced in the markets of the individual member states. The experience with the so called "light", "mild" and "ultralight" cigarettes is not only that their marketing messages were misleading but also that their marketing target included those who were thinking about quitting smoking (1). The risk that marketing messages may be used to intercept smokers who are on the way to cessation, or to increase the initiation of tobacco use, must be part of any estimate of the net harm produced by newer tobacco products. Monitoring of the rates of initiation and cessation are critical elements of any post-market surveillance program.

Harm Due To Marketing Messages

Messages used to market purportedly less harmful tobacco products can create harm not measured by changes in rates of tobacco initiation, use and cessation. Creation of a false perception of safety alters population norms and beliefs about tobacco, may be used by young smokers to continue tobacco use since they can switch to a safer alternative in the future, and may alter the perceived need for regulatory control of products or of smoking behavior. In addition, the offer on the market of purportedly safer products may be used by the tobacco companies as a demonstration that they have changed their corporate behavior and are now acting responsibly, even if there is no meaningful effort to actually market the products. Harm to society may accrue if these marketing messages slow the changes in social norms and development of regulatory controls that are effective in altering tobacco use.

A Framework For Evaluating New Products

No operational regulatory model exists to adequately address the evaluation of the harm reduction claims being made for products currently on the market or for products that are likely to be introduced in the near future. There is also no scientifically validated testing protocol that would allow comparison of the injury caused by modified (reduced toxicant) cigarettes with that of older, more conventional cigarette brands (2). However, it is possible to provide a scientific framework of questions that would need to be answered in examining the claims made for newer products. The questions vary somewhat for the different types of products.

Modified (reduced carcinogen/toxicant) Cigarettes

The ideal evaluation of any purported harm reduction product would be based on measures of disease outcomes from human epidemiological studies of individuals followed before and after they switched to the new product. For most disease outcomes, such studies would require very large populations followed for long intervals and could therefore only provide information on changes that occurred many years in the past. More timely examination of new products is important for both regulatory oversight and for providing accurate public

health advice to consumers. The data upon which this evaluation is made will, of necessity, be more limited than that which would be available from epidemiological and other observations made over a long duration of the use of the new product. Limitations of the data likely to be available make it useful to conceptualize the evaluation as a set of questions that can be answered in series and which allow a progressively more complete understanding of the actual benefits likely to be experienced by those who switch to a new product. Conceptually, this sequence would involve five measures: measures of smoke emissions under conditions reflecting actual use, measures of smoke uptake in actual users of the product, measures of addiction potential of the product, measures of injury from use of the product, and measures of disease outcome.

Careful independent scientific review of existing data for each of these questions allow conclusions to be drawn (and claims to be validated) for each question independently at a point in time when the data are sufficient to support the claim. The separation of the questions, and of the data to support them, will also avoid confusion about the type of claim that can be made from the data presented. For example, data on the emissions generated by a cigarette might allow claims about differences in smoke composition but would not, without experimental data on measures of injury, allow claims for reduced toxicity. Allowing measures of smoke emissions (machine measured tar and nicotine yields by the FTC/ISO method or even more) to be extrapolated to enable claims of reduced uptake and reduced harm (light and mild brand designators) resulted in the consumer being misled (4), and this experience should not be repeated with new tobacco products. If claims are to be made by the manufacturer, it should be the responsibility of the manufacturer to provide evidence supporting the claim to an independent scientific review before the claim is made. The claims must be validated by the data presented, and claims that go beyond the data presented must not be allowed. Absence of evidence, or absence of scientific methods to measure toxicity or harm, are not legitimate scientific bases to allow claims of harm reduction from measures of smoke emissions.

The first logical step in examining a product having potential to reduce the harm produced by tobacco use is to examine the characteristics of the product. Consideration of the ingredients used, both quantitatively (type and amounts of ingredients, the blend of tobacco, reconstituted sheet tobacco) and qualitatively (toxicity of burned ingredients), are likely areas of scientific concern as well as a description of the engineering design and characteristics of the product. This information is currently available to the manufacturer and can be provided at no additional cost.

The next step is to examine emissions from the product, again both quantitatively and qualitatively. There are two dimensions to this question. The first is a comparison of the emissions of a product to other products under standardized conditions, and the second is the evaluation of the emissions under conditions of actual use. Smokers may vary in the way they use a single product (11), and different products may be used differently by the same smoker, rendering misleading machine measured values derived using a single set of smoking conditions as an estimate of the smoke emissions actually arriving at the smokers mouth when the product is used (4). A companion concern is quantitative and qualitative measures of second hand smoke emissions.

Smoke uptake by the smoker, rather than smoke emissions, is the measure of intensity of exposure important for predicting disease risk. Since smokers often change their smoking behaviors in the laboratory setting, measures of uptake with actual (rather than laboratory)

use of the product are key to estimating uptake for populations of individuals who are likely to use a product. As they are developed and validated, measures of the biologically effective dose (levels of toxicants in critical target organs or tissues) may offer even more precise measures of smoke uptake for predicting smoke toxicity (2). An additional key to assessing differences in uptake resulting from differences in actual use of different products involves understanding who is using the product and why. Measures of uptake derived from comparisons of groups of users may be misleading if a large fraction of those who switch to a new product are doing so in an effort to quit or cut down the amount that they smoke. Valid comparisons of the differences in uptake attributable to differences in the products used must ensure that the populations studied are using the products with similar intentions for maintaining the intensity of their smoking behavior.

Bioassays using accepted toxicological methods for injury related to cancer, lung disease, heart disease, reproduction and development, or neurobehavioral systems are essential to any examination or validation of claims of reduced toxicity. At present, the evidence linking existing biomarkers of injury to ultimate disease outcomes remains incomplete, and no biomarkers have been validated for use in distinguishing the relative injury caused by different levels of cigarette smoke uptake (2). The potential exists for evolving scientific techniques to make a meaningful contribution to the definition of early tobacco smoke related injury, but these approaches remain future rather than current solutions. The absence of existing validated biomarkers of injury from tobacco smoke is a scientific challenge to be overcome, but the absence of measurement tools should not be used to justify claims of reduced injury or reduced harm based on smoke emission or smoke exposure data.

One of the principal harms caused by tobacco use is addiction, and evaluation of the potential to create and sustain addiction is an important component of any consideration of the potential harm that can accrue from new and modified tobacco products. Some new products claim greatly reduced nicotine delivery. However, there remains a distinct possibility that chemical factors other than nicotine influence addiction. For this reason, bioassays that specifically target biochemical mechanisms known or suspected to be related to nicotine or other chemical dependence should be further developed and brought to bear on evaluation of new tobacco products.

Rates of disease outcomes following tobacco use are the ultimate measure of harm from tobacco use. The long time period required to generate this information for many of the diseases caused by smoking may preclude its use in making regulatory decisions surrounding the introduction of new tobacco products, but the importance of this information in understanding the harm caused by tobacco use makes collection of this information a scientific imperative. No claim for harm reduction should be allowed in the absence of evidence demonstrating reduced harm. The length of time required to generate such data is a reality that results from the biology of disease, and is not a justification for allowing claims in the absence of evidence.

Once products are introduced into the market, there is a continuing need to monitor who is using the products and why, changes in the product design and ingredients, and changes in marketing approaches after the product is initially evaluated. The impact of the availability and marketing of the product on rates of smoking initiation and cessation are important measures of its net harm to the population. Who the target populations are for the marketing messages, what those target populations actually understand those marketing messages to mean, and the effect for populations other than the target population are concerns requiring

ongoing monitoring. Many reduced toxicant products may have the potential to either increase or decrease harm depending on who uses them and the alternatives to their use. If these trends are not monitored it will likely be impossible to determine whether use of reduced toxicant cigarettes by smokers provides a benefit or a cost to the population in terms of the damage and disease caused by smoking.

Products That Allegedly Heat Instead Of Burn Tobacco.

The issues for products that use processes other than tobacco combustion to deliver nicotine are similar to those for reduced toxicant cigarettes. However, much greater attention is necessary to the technology being employed and how it functions under a variety of smoking conditions. Assumptions that these new technologies will be smoked with the same pattern of puffing as conventional cigarettes, will continue to heat rather than burn the tobacco under all of the puffing conditions likely to be encountered by consumers, or will not contain new constituents with undefined risks are not warranted and must be tested. These products may also have different potential for creating or sustaining addiction than conventional cigarettes.

Oral Tobacco Products (including smokeless tobacco, but not including NRT products already regulated for a therapeutic purpose)

Differences in the process by which tobacco ingredients are delivered to the user, sites of delivery and time course of uptake make comparisons of emissions from oral tobacco products and cigarettes difficult. Even comparisons of uptake of the same constituent (e.g. nicotine) can be difficult to interpret. However, the same general concerns described above for reduced toxicant cigarettes also apply for defining the harm reduction potential of oral tobacco products. Some particular concerns exist with oral tobacco products.

It remains to be demonstrated that large numbers of adult cigarette smokers who would not otherwise quit will switch to oral tobacco products. The rate at which adults are willing to switch is important in calculating the net effect for harm reduction of marketing oral tobacco products because of the likely effects of marketing on those not yet using any tobacco product. As a new product is introduced, or an existing tobacco product is marketed as offering less risk for the smoker who is unwilling to quit, the initiation of use of that product among adolescents may increase. Existing data on current use suggests that users of oral tobacco products are much more likely to transition to cigarette smoking than are cigarette smokers to transition to smokeless products (23). Initiation of oral tobacco use also occurs largely among the young, raising further concerns about which age groups might be influenced most by marketing messages. A real concern is that a marketing message of lower risk might not change the behavior of adult smokers but might increase the rate of adolescent initiation of oral tobacco use, increasing rather than decreasing the fraction of the population using tobacco products.

A second issue is that the data available on the risks of using oral tobacco products are derived from populations of individuals who use only oral tobacco, and little is known about the magnitude and timing of any change in risk among those who switch from smoking cigarettes to use of oral tobacco. The fraction who switch who might otherwise quit, the fraction who relapse back to smoking, the fraction who continue dual use, and the impact of dual use on disease risks are all unanswered questions in the context of offering these products as vehicles for harm reduction.

A similar concern exists for existing oral tobacco users. Will harm reduction messages reduce cessation or delay cessation attempts?

Oral tobacco products are marketed as temporary alternatives to smoking that sustain nicotine addiction in those circumstances where smoking is prohibited (24). The potential for these products to sustain a high level of nicotine addiction, or to otherwise reduce the interest in quitting or success in achieving abstinence, are real concerns. These effects, if present, could cause a net harm to the population even if the products themselves have low levels of toxicity.

Principles and Conclusions

The existing scientific understanding of risks caused by tobacco use, and the framework of questions to be considered in evaluating the harm reduction potential of new tobacco products presented above, lead to the following principles and conclusions.

1. Existing scientific evidence is not sufficient to assess the differences in health risk potential between newly engineered tobacco products and existing products for composition, exposure, toxicity, or harm (2).
2. Regulatory oversight of cigarette and cigarette-like products should include examination of at least five separate aspects of the new products: physical chemical characteristics of the tobacco and tobacco smoke, uptake of toxicants (both by smokers and by non-smokers), toxicity, addiction potential, and disease risk.
3. Regulatory oversight of smokeless tobacco products should also include examination of at least five separate aspects of the new products: physical chemical characteristics of the product and its constituents, uptake of toxicants, toxicity, addiction potential, and disease risk.
4. Claims of reduced exposure or reduced harm should be supported by adequate scientific data provided by the manufacturer who intends to make the claim.
5. Each type of claim requires a substantive body of evidence; an independent regulatory body capable of examining the claims should determine whether the claims are valid.
6. No claim should be permitted for any tobacco product unless found to be valid by an independent regulatory body on the basis of adequate scientific data submitted by the manufacturer.
7. Regulatory oversight, including post-market surveillance, is necessary to assess and monitor changes in newly modified tobacco products.
8. Demonstration of reductions in smoke emissions or reduced uptake of toxicants alone is not sufficient to support claims or implications of reduced toxicity or harm.

9. Claims of reductions in smoke emissions or reduced uptake of toxicants need to be examined in post market surveillance to determine what smokers and non smokers actually understand from those messages.
10. Evidence supporting a reduction in carcinogenicity must be interpreted in light of the potential effects of the changes in the product on the other major diseases caused by cigarette smoking.

References

- (1) Pollay RW, Dewhirst T. The dark side of marketing seemingly “Light” cigarettes: successful images and failed fact. *Tobacco Control* 2002, 11 Suppl 1: ii18-31.
- (2) Stratton K, Shetty P, Wallace R, Bondurant S. *Clearing the smoke. Assessing the science base for tobacco harm reduction*. Washington D.C., National Academy Press, 2001.
- (3) National Cancer Institute. *Risks associated with smoking cigarettes with low machine yields of tar and nicotine*. Bethesda, U.S. Department of Health and Human Services, 2001. (Smoking and Tobacco Control Monograph No.13).
- (4) Scientific Advisory Committee on Tobacco Product Regulation (SACTob). *Recommendation on health claims derived from ISO/FTC method to measure cigarette smoke*. Geneva, World Health Organization, 2002.
- (5) Environics Research Group Limited. *Knowledge, attitudes and behavior of light and mild brand smokers*. Prepared by Environics Research Group limited. POR-01-26 March 2002.
- (6) Slade J, Connolly GN, Lymperis D. Eclipse: does it live up to its health claims? *Tobacco Control* 2002, 11 Suppl 2: ii64-70. .
- (7) Canadian Expert Panel. *Putting an end to deception: Proceedings of the International Expert Panel on Cigarette Descriptors*. A report to the Canadian Minister of Health from the Ministerial Advisory Council on Tobacco Control, 2001.
- (8) Benowitz NL, Hall SM, Herning RI, Jacob P 3rd, Osman AL. Smokers of low-yield cigarettes do not consume less nicotine. *New England Journal of Medicine*, 1983, 309(3): 139-142.
- (9) Jarvis MJ, Boreham R, Primatesta P, Feyerabend C, Byrant A. Nicotine yield from machine-smoked cigarettes and nicotine intakes in smokers: evidence from a representative population study. *Journal of the National Cancer Institute*, 2001, 93: 134-138.
- (10) Djordjevic MV, Fan J, Ferguson S, Hoffman D. Self regulation of smoking intensity. Smoke yields of the low-nicotine, low-‘tar’ cigarettes. *Carcinogenesis*, 1995, 16(9): 2015-2021.
- (11) Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *Journal of the National Cancer Institute*, 2000, 92(2): 106-111.
- (12) Kozlowski LT, Pillitteri JL, Sweeney CT. Misuse of “light” cigarettes by means of vent blocking. *Journal of Substance Abuse*, 1994, 6(3): 333-336.
- (13) Kozlowski LT, Pope MA, Lux JE. Prevalence of the misuse of ultra-low-tar cigarettes by blocking filter vents. *American Journal of Public Health*, 1998, 78(6): 694-695.

- (14) Kozłowski LT, O'Connor RJ. Cigarette filter ventilation is a defective design because of misleading taste, bigger puffs and blocked vents. *Tobacco Control*, 2002, 11 Suppl 1: i40-i50.
- (15) Giovino GA, *et al.* Attitudes, Knowledge, and Beliefs about Low-Yield Cigarettes among Adolescents and Adults. In: *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Smoking and Tobacco Control Monograph 7*. U.S. DHHS, Public Health Service, National Cancer Institute, Office of Smoking and Cancer Control. NIH Publication No. 96-4028, 1996: 39-57.
- (16) Haddock CK, Talcott GW, Klesges RC, Lando H. An examination of cigarette brand switching to reduce health risks. *Annals of Behavioral Medicine*, 1999, 21(2): 128-134.
- (17) Ashley MJ, Cohen J, Ferrence R. "Light" and "Mild" cigarettes: Who smokes them? Are they being misled? *Canadian Journal of Public Health*, 2001, 92 (6): 407-411.
- (18) Les Études de Marché Créatec. Effect of "light" and "mild" labels on perceived strength and brand image of cigarettes. Prepared for Health Canada Tobacco Control Program. February 2002.
- (19) Benowitz N. Compensatory Smoking of Low-yield cigarettes. In: *National Cancer Institute. Risks associated with smoking cigarettes with low machine yields of tar and nicotine. Smoking and Tobacco Control Monograph No.13*. Bethesda, U.S. Department of Health and Human Services, 2001: 39-63.
- (20) National Cancer Institute. *Cigar Smoking in the United States: Health Effects and Trends. Smoking and Tobacco Control Monograph No. 9*. USDHHS NIH NCI, 1998.
- (21) Hammond, EC. The long term benefits of reducing tar and nicotine in cigarettes. In: Gori GB, Bock FG, eds. *A Safe Cigarette? Banbury Report 3, Proceedings of a Meeting Held at the Banbury Center, Cold Spring Harbor Laboratory, NY, Oct. 14-16, 1979*. Cold Spring Harbor, Cold Spring Harbor Laboratory, 1980: 13-18.
- (22) Doll R, Peto R Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *Journal of Epidemiology and Community Health*, 1978, 32: 303-313.
- (23) Tomar S. Snuff use and smoking in U.S. men. Implications for harm reduction(1). *American Journal of Preventive Medicine*, 2002, 23(3): 143.
- (24) Henningfield J, Rose C, Giovino G. Brave new world of tobacco disease prevention. Promoting dual tobacco-product use? *American Journal of Preventive Medicine*, 2002, 23(3): 226.