

COMMENTARY

Reducing tobacco addiction through tobacco product regulation

J E Henningfield, N L Benowitz, G N Connolly, R M Davis, N Gray, M L Myers, M Zeller

Tobacco Control 2004;13:132–135. doi: 10.1136/tc.2003.006890

Tobacco product regulation has the potential to help reduce tobacco attributable disease by reducing the toxicity of these products and by reducing the prevalence of tobacco use and addiction

There are important efforts underway to regulate tobacco products, such as the World Health Organization's Framework Convention on Tobacco Control¹ (FCTC) and the US Congress' consideration of legislation to give the Food and Drug Administration (FDA) regulatory authority over tobacco. These initiatives aim to reduce the death and disease caused by tobacco by reducing the prevalence of tobacco use and the toxicity of tobacco products.^{1–7} There is an operational assumption, based on scientific studies and tobacco industry documents, that tobacco products could be made less deadly⁸ by controlling their design, content, emissions, and manufacturing.^{5–10}

Using regulation to reduce toxicity is increasingly well accepted, although not without controversy, as long as appropriate safeguards are in place to prevent unintended consequences such as undermining prevention and cessation.^{6–8} Less discussed in the literature, but equally plausible, is using regulation to address the addictiveness of tobacco products.¹¹ Tobacco related diseases caused by toxins in tobacco smoke occur because of long term tobacco use triggered by the powerfully addictive properties of tobacco delivered nicotine.¹² Tobacco industry documents reveal that the industry has gone to great lengths to design and manufacture cigarettes to maximise their addictiveness, facilitate initiation, and undermine cessation.^{7 13–17} Of course, all known nicotine delivering tobacco products are capable of causing and sustaining tobacco addiction, but the deliberate engineering of the products to enhance addictiveness means the industry is increasing the overall harm to public health. There is little reason to believe that tobacco companies will voluntarily modify their products to reduce their addictiveness. In the present commentary we advance the proposition that regulation of the tobacco product design and ingredients that enhance addiction* is as important as the regulation of design and ingredients that directly contribute to disease.

PRIOR PROPOSAL: REDUCING ADDICTION BY GRADUAL ELIMINATION OF NICOTINE

Theoretically, cigarettes could be made less addictive or "non-addictive" by reducing

nicotine levels to values so low that pharmacologic addiction could neither be created nor sustained, as proposed by Benowitz and Henningfield.²³ However, conclusions by the FDA and advisory committees to WHO^{7 14 15 24} and subsequent discussions by Henningfield, Benowitz, and colleagues,²⁵ suggest that progress is needed in several areas in order to implement such a proposal—for example, verification of the threshold nicotine dose per cigarette and per day to sustain nicotine addiction; and education, regulation, and surveillance to reduce unintended effects such as increased toxicity caused by compensatory smoking.²⁶ The relatively poor accessibility and attractiveness of the safest nicotine delivery systems, and tobacco dependence treatment medications such as nicotine gum and patch, are also viewed as limitations to such a strategy because it might then drive smokers to other tobacco products.^{25 27–29} Whereas these issues would appear to pose substantial barriers to immediate implementation of a strategy to eliminate nicotine from cigarettes, the present strategy would not deny smokers their nicotine nor would it be expected to precipitate increased smoking as might be predicted from approaches that decreased the nicotine in cigarettes. Moreover, it is consistent with comprehensive tobacco control efforts intended to reduce the appeal of tobacco products, prevent initiation, foster cessation, and to begin to regulate product design manufacture and ingredients to reduce their toxicity.^{1 5 6 12 15 26 30}

Abbreviations: FCTC, Framework Convention on Tobacco Control; FDA, Food and Drug Administration; FTC, Federal Trade Commission; ISO, International Organization for Standardization

*In the present article we follow the convention^{12 18} of using the term "addiction" in place of the more technical term "dependence", which can also include "withdrawal" as defined by the WHO (1992–ICD10) and American Psychiatric Association.¹⁹ We note that the risk of the development and persistence of addiction, which contribute to addiction prevalence, is related to pharmacological factors, technically referred to as abuse liability,²⁰ as well as factors affecting the acceptability of the formulation, ease of dosing, access, and marketing.^{12 13 21 22} Regulation could exert control over all of these contributors to addiction risk and prevalence; however, the present commentary is focused on characteristics of the product that contribute to its addiction risk and addiction prevalence.

See end of article for authors' affiliations

Correspondence to: Jack E Henningfield, PhD, Pinney Associates, Inc, 4800 Montgomery Lane, Suite 1000, Bethesda, MD 20814, USA; jhenning@pinneyassociates.com

SCIENTIFIC FOUNDATION FOR REDUCING TOBACCO ADDICTIVENESS

The scientific foundation for the present proposal flows from understanding the determinants of tobacco product addictiveness (that is, abuse liability) and the prevalence and spread of addiction.^{18 20 31–33} The FDA investigations and plaintiffs' lawsuits against the tobacco industry in the 1990s resulted in the release of millions of previously secret tobacco industry documents. Many of these documents described the sophisticated technologies used to ensure that virtually any cigarette brand or type could create and sustain nicotine addiction by delivering adequate and highly palatable doses of nicotine.^{7 14–17} We now know that these deliberate product refinements enabled smokers to continue to obtain high levels of tar and nicotine, despite reductions in machine measured nicotine yields using testing parameters established by the International Organization for Standardization (ISO) and Federal Trade Commission (FTC).^{8 34 35}

The tobacco industry uses a vast array of technologies to fine tune the addictive nature of the modern cigarette. For example, ventilated cigarette filters provide cooler and more dilute smoke that enables the smoker to readily inhale larger quantities more deeply into the lungs.^{8 34 35} Additives, such as levulinic acid, ammonia, urea, chocolate, and various sugars, can mask the noxiousness of the smoke while providing more readily absorbable nicotine to the smoker.^{13–15} An extraordinary application of particle physics to the study of cigarette smoke particles produced various technologies to ensure that the particles were optimally absorbable deep into the lung.³⁶

These efforts were presumably intended to enhance or at least maintain the nicotine kick while FTC/ISO nicotine ratings declined. They may have contributed to increased lung cancers by enabling deep lung exposure to the smoke particles. They almost certainly increased all forms of smoking attributable mortality by forestalling declines in the prevalence of tobacco use that might otherwise have occurred.

The adverse public health consequences of their product engineering should have been evident to the tobacco industry. As far back as the 1950s the industry recognised that “increasing the size of smoke particles to get them to a size range which will go into the buccal cavity but not into the lungs [underlined words in original document]... would allow the smoker to taste the smoke but not get a large mass of smoke in the lungs”.³⁷ Could the industry have engineered smoke particles to reduce absorption? Could smoke particle size be regulated today to reduce lung exposure to toxins?

The answers to these questions are not clear. But it was clear to the FDA that the industry understood that part of the key to maximising the addictiveness of cigarettes was the design and manufacture of cigarettes to optimise nicotine delivery.^{15 38 39} Techniques described by the FDA and in other reports included the use of ammonia compounds to increase the free base nicotine in the smoke, and adding menthol and other substances to facilitate the absorption of addictive doses of nicotine. Research by Philip Morris demonstrated that synergistic reinforcing effects could be produced by combining nicotine and acetaldehyde.^{15 38 39} Many questions remain regarding the actual impact of the physical design and manufacture on cigarette addictiveness, but there is little question that the intent was to increase and not decrease the likelihood that initial cigarette use would lead to persistent and addictive use. Similarly, as concluded by the FDA, smokeless tobacco companies engineered their products by physical design and chemical ingredients to facilitate the development and maintenance of addiction.^{15 38 39} It is clear that none of this sophisticated control of tobacco ingredients and design occurred by mere happenstance.

These carefully engineered chemical cocktails could contribute to the strength of addiction in individuals as well as the prevalence of addiction in the population. The effects on the individual could be enhanced by a cocktail that produced a stronger overall effect on brain reinforcement systems, as is apparently produced by nicotine and acetaldehyde. This could also be accomplished by combinations that make it easier to ingest large daily quantities of nicotine and thus maintain higher levels of tolerance and dependence.^{7 28 38} This could contribute to persistence of the addiction and resistance to treatment. In fact, heavily addicted tobacco users often find currently available medications to be inadequate substitutes for tobacco delivered nicotine.⁴⁰ In theory the chemical cocktails can also contribute to prevalence of addiction by enabling more people, including young persons, to ingest addicting doses of nicotine by reducing the noxious effects of tobacco and nicotine that might otherwise discourage some from progressing from experimentation to addiction.

PUBLIC HEALTH AND REGULATORY ISSUES

There are numerous examples of domestic and global efforts to regulate products to control their addictiveness and addiction prevalence.^{11 41} In principle, many of these same strategies could be applied to tobacco, although we are not recommending the regulation of tobacco products as controlled substances under the provisions of the US Controlled Substance Act or the WHO Psychotropic Convention.⁴¹

The product engineering we have discussed has led to increasing calls for regulation to curtail the unmitigated efforts of the industry to design its products to maximise their addictiveness and appeal.^{2–4 7 11 26 42} None of these proposals contends that tobacco products should be banned or made unpalatable. And although reducing nicotine in cigarettes to “non-addicting” levels is a policy option we have discussed previously,^{23 25} a more politically feasible option is that regulated products would retain the capacity to sustain addiction in existing tobacco users and hence some level of tobacco addiction risk. Thus, strong warnings regarding the addictiveness of tobacco products would still be needed. This is parallel to the conclusion that tobacco product toxins should be reduced in order to make the products less deadly; but because tobacco products would undoubtedly remain extraordinarily deadly, they should remain labelled as such, at least until a thorough and regulated evaluation determined conditions under which a claim for reduced toxicity or addictiveness might be made.^{5 6 8 11 30}

One potential danger to public health is that the tobacco industry would attempt to support their marketing efforts by claiming to meet newly promulgated government standards for safety and addictiveness. Some companies may even try to imply that the modified products are less harmful or less addictive. Such claims could adversely impact public health by undermining prevention and cessation efforts if current users kept smoking rather than trying to quit.^{6 8 11 30} This is why strong and effective regulation by the FDA in the USA, and by comparable regulatory agencies elsewhere, is so important.^{5 6 8 11 30} Surveillance will also be needed to document intended and unintended effects.^{43 44} Regulating tobacco products to reduce addictiveness could also help narrow the wide gap between tobacco products and addiction treatment medications with respect to their acceptability and appeal.^{40 45} It has frequently been observed that the “nicotine product playing field” is enormously tilted in favour of tobacco products.^{28 44 45}

While some regulatory authorities may hesitate before accepting over-the-counter marketing of substantially more appealing medications, incremental improvements in the acceptability of the medications and incremental reductions in the addictiveness of tobacco products may be possible. Furthermore, just as medications for treating tobacco

dependence are routinely required to be tested for their addictiveness,^{5 20 28 32 43 45 46} such requirements could also be made for new products from the tobacco industry, including products employing new designs, ingredients, or manufacturing methods. Methods for abuse liability assessment are objective, standardised, and routinely used to assess the addictiveness of a wide range of drugs including nicotine delivering products.^{20 32 43 46}

CONCLUSIONS

The most ancient and crude nicotine delivering tobacco products carry some risk of engendering and sustaining addiction. However, it is evident that the tobacco industry has designed and manufactured products to maximise the likelihood that initial use would lead to persistent use and addiction—in other words, the industry designed its products to increase the risk that use would lead to addiction. Tobacco product regulation has the potential to contribute to reduced tobacco attributable disease by reducing the toxicity of the products and by reducing the prevalence of tobacco use and addiction. The WHO FCTC, and potential legislation in the USA to enable the FDA to assert jurisdiction over tobacco products, will provide opportunities to explore these potential regulatory approaches.^{1 5} Effective regulation is needed to guide the process, to detect unintended consequences, and to mandate appropriate modifications. Comprehensive surveillance is important to monitor the effects of regulatory efforts to maximise their benefits relative to any adverse consequences. Without such regulation and surveillance, the tobacco industry might use efforts to reduce the toxicity of products as marketing tools, making claims about safety and addictiveness that go beyond the science. We are concerned about such unintended consequences but believe they can be minimised so as to not offset the gains achieved from reductions in tobacco use.

As we draw closer to the day of tobacco product regulation, it is time to consider how such regulation can most effectively rein in the application of tobacco product engineering to reduce the prevalence of tobacco use and tobacco attributable disease. Efforts to reduce product addictiveness should be one of the central components of comprehensive tobacco control efforts, and should be viewed as no less important a strategy than efforts to reduce product toxicity. In the context of comprehensive tobacco control programming such product regulation has potential to contribute to reduced premature death and disease.

ACKNOWLEDGEMENTS

Preparation of this paper was supported by the Robert Wood Johnson Foundation Innovators Combating Substance Abuse Awards program, which is directed by JEH. Additional support was provided by unrestricted support for public health issues analysis by GlaxoSmithKline Consumer HealthCare to Pinney Associates. Efforts by NG were within the framework of support from the *Associazione Italiana per la Ricerca sul Cancro*. We are greatly appreciative of the efforts of R. Popovici and C.R. Rose for editorial assistance. JEH and MZ provide consulting services regarding treatments for tobacco dependence to GlaxoSmithKline Consumer Health Care through Pinney Associates. JEH has a financial interest in a nicotine replacement product under development, and serves as an expert witness in litigation against the tobacco industry by the US Department of Justice and other plaintiffs. NLB has provided consulting services regarding treatments for tobacco dependence to GlaxoSmithKline Consumer Health Care and Pfizer Consumer Health Care (Formerly Pharmacia and Upjohn) and he serves as an expert witness in litigation against the tobacco industry.

Authors' affiliations

J E Henningfield, Pinney Associates Inc, Bethesda, Maryland, USA and Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

N L Benowitz, University of California San Francisco, San Francisco, California, USA
 G N Connolly, Harvard University School of Public Health, Boston, Massachusetts, USA
 R M Davis, Henry Ford Health System, Detroit, Michigan, USA
 N Gray, International Agency for Research on Cancer, Lyon, France
 M L Myers, Campaign for Tobacco-Free Kids, Washington, DC, USA
 M Zeller, Pinney Associates, Inc, Bethesda, Maryland, USA

REFERENCES

- 1 **World Health Organization.** *Framework Convention on Tobacco Control.* Geneva: WHO, 2003. http://www.who.int/tobacco/fctc/text/en/fctc_en.pdf. 2003.
- 2 **Gray N, Boyle P.** The regulation of tobacco and tobacco smoke. *Ann Oncol* 2000;**11**:909–14.
- 3 **Gray N, Boyle P.** Regulation of cigarette emissions. *Ann Oncol* 2002;**13**:19–21.
- 4 **Gray N, Boyle P, Zatonski W.** Tar concentrations in cigarettes and carcinogen content. *Lancet* 1998;**352**:787–8.
- 5 **Kennedy EM.** The need for FDA regulation of tobacco products. *Yale Journal of Health Policy, Law and Ethics* 2002;**III**:101–8.
- 6 **Myers ML.** Could product regulation result in less hazardous tobacco products? *Yale Journal of Health Policy, Law and Ethics* 2002;**III**:139–47.
- 7 **World Health Organization.** *Advancing knowledge on regulating tobacco products.* Geneva: WHO, 2001.
- 8 **Stratton K, Shetty P, Wallace R, Bondurant S, eds.** *Clearing the smoke: assessing the science base for tobacco harm.* Washington DC: National Academy Press, 2001.
- 9 **Parrish SC.** Bridging the divide: a shared interest in a coherent national tobacco policy. *Yale Journal of Health Policy, Law and Ethics* 2002;**III**:109–18.
- 10 **World Health Organization, Scientific Advisory Committee on Tobacco Product Regulation SACTob.** Geneva: WHO, 2003. Recommendation on tobacco product ingredients and emissions. http://www.who.int/tobacco/sactob/recommendations/en/ingredients_en.pdf
- 11 **Henningfield JE, Zeller M.** Could science-based regulation make tobacco products less addictive? *Yale Journal of Health Policy, Law and Ethics* 2002;**III**:127–38.
- 12 **Royal College of Physicians.** *Nicotine addiction in Britain: a report of the tobacco advisory group of the Royal College of Physicians.* London: Royal College of Physicians of London, 2000.
- 13 **Bates C, Jarvis M, Connolly G.** *Tobacco additives: Cigarette engineering and nicotine addiction.* London: Action on Smoking and Health, 1999.
- 14 **Food and Drug Administration.** Regulations restricting the sale and distribution of cigarettes and smokeless tobacco products to protect children and adolescents; proposed rule analysis regarding FDA's jurisdiction over nicotine-containing cigarettes and smokeless tobacco products; notice. *Federal Register* 1995;**60**:41314–792.
- 15 **Food and Drug Administration.** Regulations restricting the sale and distribution of cigarettes and smokeless tobacco to protect children and adolescents; final rule. *Federal Register* 1996;**61**:44396–5318.
- 16 **Hurt RD, Robertson CR.** Prying open the door to the tobacco industry's secrets about nicotine: the Minnesota Tobacco Trial. *JAMA* 1998;**280**:1173–81.
- 17 **Slade J, Bero LA, Hanauer P, et al.** Nicotine and addiction. The Brown and Williamson documents. *JAMA* 1995;**274**:225–33.
- 18 **US Department of Health and Human Services.** *The health consequences of smoking: nicotine addiction, A report of the Surgeon General, 1988.* Rockville, Maryland: Public Health Service, Centers for Disease Control, Office on Smoking and Health, 1988. (DHHS Publication No (CDC) 88-8406.)
- 19 **American Psychiatric Association.** *Diagnostic and statistical manual of mental disorders.* Washington DC: American Psychiatric Association, 1994.
- 20 **Schuster CR, Henningfield J.** Conference on abuse liability assessment of CNS drugs. *JG and Alcohol Dependence* 2003;**70**:S1–4.
- 21 **Bachman JG, O'Malley PM, Schulenberg JE, et al.** *The decline of substance use in young adulthood: changes in social activities, roles, and beliefs.* Mahawah, New Jersey: Lawrence Erlbaum Associates, 2002.
- 22 **Hertz S.** Presentation to the FDA Anesthetic and Life Support Drugs Advisory Committee, September 10, 2003. 2003. Bethesda, Maryland: FDA Dockets, 2003. Transcripts.
- 23 **Benowitz NL, Henningfield JE.** Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *N Engl J Med* 1994;**331**:123–5.
- 24 **World Health Organization, Scientific Advisory Committee on Tobacco Product Regulation SACTob.** Recommendation on nicotine and the regulation in tobacco and non-tobacco products. http://www.who.int/tobacco/sactob/recommendations/en/nicotine_en.pdf, 2002.
- 25 **Henningfield JE, Benowitz NL, Slade J, et al.** Reducing the addictiveness of cigarettes. *Tobacco Control* 1998;**7**:281–93.
- 26 **Bates C, McNeill A, Jarvis MJ, et al.** The future of tobacco product regulation and labeling in Europe: implications for the forthcoming European Union directive. *Tobacco Control* 1999;**8**:225–35.
- 27 **Gray N, Boyle P.** The future of the nicotine-addiction market. *Lancet* 2003;**362**:845–6.
- 28 **Novotny TE, Cohen JC, Yurekli A, et al.** Smoking cessation and nicotine-replacement therapies. In Jha P, Chaloupka FJ, eds. *Tobacco control in developing countries*, 287–307. Oxford: Oxford University Press, 2000.
- 29 **Warner KE, Peck CC, Woosley RL, et al.** Treatment of tobacco dependence: innovative regulatory approaches to reduce death and disease: preface. *Food and Drug Law Journal* 1998;**53**(suppl):1–8.

30 **Henningfield JE**, Moolchan ET, Zeller M. Regulatory strategies to reduce tobacco addiction in youth. *Tobacco Control* 2003;**12**(suppl 1):i14-24.

31 **Committee on Opportunities in Drug Abuse, Research Division of Neuroscience and Behavioral Health, Institute of Medicine.** *Pathways of addiction: opportunities in drug abuse research.* Washington DC: National Academy Press, 1996.

32 **Expert Panel, (Henningfield JE, Johanson CE Sellers EM, rapporteurs).** Abuse liability assessment of CNS drugs: conclusions, recommendations, and research priorities. *Drug Alcohol Dependence* 2003;**70**:S107-14.

33 **O'Brien CP.** Drug addiction and drug abuse. In: Hardman JG, Limbird LE, Molinoff PB, et al, eds. *Goodman & Gilman's the pharmacological basis of therapeutics.* New York: McGraw-Hill, 1996:557-77.

34 **Henningfield JE**, Kozlowski LT, Benowitz NL. A proposal to develop meaningful labeling for cigarettes. *JAMA* 1994;**272**:312-4.

35 **National Cancer Institute.** Risks associated with smoking cigarettes with low-machine measured yields of tar and nicotine. *Smoking and Tobacco Control Monograph No. 13.* Bethesda, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer Institutes, 2002. (NIH Publication No. 02-5074.)

36 **Ingebretsen BJ.** Deposition provided in litigation brought on behalf of "The People of the State of California, et al. versus Philip Morris, Inc. et al." March 24 and 25, 1998.

37 **Holmes JC**, Seligman RB, and Philip Morris, Inc. Idea No. 99—Means of controlling particle size of cigarette smoke and of incorporating volatile flavors. American Legacy Foundation Tobacco Documents website. Bates No.2021627703, 2021627706. 1957.

38 **Douglas CE.** Taking aim at the bull's eye: the nicotine in tobacco products. *Tobacco Control* 1998;**7**:215-8.

39 **Kessler D.** *A question of intent: a great American battle with a deadly industry.* New York, NY: Public Affairs, 2001.

40 **Henningfield JE**, Fant RV, Gitchell J, et al. Tobacco dependence. Global public health potential for new medications development and indications. *Ann NY Acad Sci* 2000;**909**:247-56.

41 **Balster RL**, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug and Alcohol Dependence* 2003;**70**:S13-40.

42 **Slade J**, Henningfield JE. Tobacco product regulation: context and issues. *Food and Drug Law Journal* 1998;**53**:43-74.

43 **Houtsmuller EJ**, Fant RV, Eissenberg TE, et al. Flavor improvement does not increase abuse liability of nicotine chewing gum. *Pharmacology, Biochemistry and Behavior* 2002;**72**:559-68.

44 **Warner KE**, Slade J, Sweanor DT. The emerging market for long-term nicotine maintenance. *JAMA* 1997;**278**:1087-92.

45 **Henningfield JE**, Slade J. Tobacco dependence medications: public health and regulatory issues. *Food and Drug Law Journal* 1998;**53**:75-114.

46 **Schuh KJ**, Schuh LM, Henningfield JE, et al. Nicotine nasal spray and vapor inhaler: abuse liability assessment. *Psychopharmacology (Berl)* 1997;**130**:352-61.

The lighter side



© King Features Syndicate. Reprinted with permission of Torstar Syndication Services.