WHO Technical Report Series
955

WHO STUDY GROUP ON TOBACCO PRODUCT REGULATION

Report on the Scientific Basis of Tobacco Product Regulation: Third Report of a WHO Study Group

World Health Organization

WHO Technical Report Series
955

WHO STUDY GROUP ON TOBACCO PRODUCT REGULATION

report on the scientific basis of tobacco product regulation: third report of a WHO study group

World Health Organization

WHO Library Cataloguing-in-Publication Data

WHO study group on tobacco product regulation: report on the scientific basis of tobacco product regulation: third report of a WHO study group.

(WHO technical report series ; no. 955)

1.Tobacco use disorder - prevention and control. 2.Tobacco industry - legislation. 3.Tobacco control campaigns. 4. Tobacco-derived products labelling. 5.Tobacco-derived products packing. I.World Health Organization. II.Series.

ISBN 978 92 4 120955 7 (NLM classification: QV 137)

ISSN 0512-3054

Typeset in India
Printed in Switzerland

Contents

WHO Study Group on Tobacco Product Regulation

Durban, South Africa, 12–14 November 2008

Members

Dr D.L. Ashley, Chief, Emergency Response and Air Toxicants Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

Dr O.A. Ayo-Yusuf, Associate Professor, School of Dentistry, University of Pretoria, South Africa

Dr D. M. Burns, Professor Emeritus of Family and Preventive Medicine, School of Medicine, University of California at San Diego, San Diego, California, United States of America

Dr Vera Luiza da Costa e Silva, Independent Consultant, Senior Public Health Specialist, Rio de Janeiro, Brazil

Dr M. Djordjevic, Program Director, National Cancer Institute, Division of Cancer Control and Population Sciences, Tobacco Control Research Branch, Bethesda, Maryland, United States of America

Dr N. Gray, Honorary Senior Associate, Cancer Council Victoria, Melbourne, Australia

Dr S.K. Hammond, Professor of Environmental Health Sciences, School of Public Health, University of California at Berkeley, Berkeley, California, United States of America

Dr J. Henningfield, Professor (Adjunct), Behavioral Biology, Johns Hopkins University School of Medicine; Vice President, Research and Health Policy, Pinney Associates, Bethesda, Maryland, United States of America

Dr M. Jarvis, Principal Scientist, Cancer Research UK, Health Behaviour Unit, Royal Free and University College London Medical School, London, England

Dr A. Opperhuizen, Head of the Laboratory for Health Protection Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

Dr K.S. Reddy, Professor of Cardiology, All India Institute of Medical Sciences, New Delhi, India

Dr C. Robertson, Ruth G. and William K. Bowes Professor in the School of Engineering, Department of Chemical Engineering, Stanford University, Stanford, California, United States of America

Dr G. Zaatari (*Chair*), Professor, Department of Pathology and Laboratory Medicine, American University of Beirut, Beirut, Lebanon

Secretariat

Dr D.W. Bettcher, Director, Tobacco Free Initiative, WHO, Geneva, Switzerland

Mr R. Minhas, Technical Officer, Tobacco Free Initiative, WHO, Geneva, Switzerland

Ms E. Tecson, Administrative Assistant, Tobacco Free Initiative, WHO, Geneva, Switzerland

Ms G. Vestal, Technical Officer, Tobacco Free Initiative, WHO, Geneva, Switzerland

1. Introduction

The fifth meeting of the WHO Study Group on Tobacco Product Regulation (TobReg) was held in Durban, South Africa on 12–14 November 2008. TobReg is mandated to provide the WHO Director-General with scientifically sound, evidence-based recommendations to Member States about tobacco product regulation. In line with the provisions of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control, TobReg identifies approaches for regulating tobacco products that pose significant public health issues and raise questions for tobacco control policy.

At its fifth meeting, the Study Group addressed regulation of electronic cigarettes, smokeless tobacco toxicants, 'roll-your-own' products, products marketed as cessation aids, particles in smoke and menthol. The meeting followed a WHO press release on 19 September 2008, which asserted that WHO does not consider electronic cigarettes to be a legitimate tobacco cessation therapy. The press release stressed that, as no rigorous, peer-reviewed studies have been conducted to show that electronic cigarettes are a safe, effective nicotine replacement therapy (NRT), there is no evidence to support marketing of these products for tobacco cessation.

This report presents the conclusions and recommendations of the Study Group at its fifth meeting on two products, both of which represent potential harm to public health and the promotion, sale and use of which are inadequately regulated:

- electronic nicotine delivery systems (ENDS), which deliver nicotine and other substances directly to the lung without products of tobacco combustion; and
- smokeless tobacco products, which are marketed in various regions of the world and vary substantially in their content and carcinogenicity.

The following two sections of this report present the Study Group's recommendations in relation to each product. Its overall recommendations are summarized in section 4.

1.1 Background

Regulation of tobacco products is essential for tobacco control and is endorsed by the WHO Framework Convention on Tobacco Control in provisions of its Articles 9, 10 and 11. Regulation serves public health goals by providing an understanding of tobacco products and meaningful surveillance of their manufacture, packaging, labelling and distribution. The scientific basis of the principles that guide implementation of the Articles creates synergy and mutual reinforcement of the regulatory practices described in each Article.

Tobacco product regulation includes regulation of the contents and emissions of tobacco products by testing, measuring and mandating disclosure of the results and regulating their packaging and labelling. Governmental supervision is required of manufacture and of enforcement of the regulations governing the design, contents and emissions of tobacco products, as well as their distribution, packaging and labelling, with the aim of protecting and promoting public health.

Chemical consumer products are usually regulated after a review of the scientific evidence on the hazards presented by the product, the exposure likely to occur, the patterns of use and the marketing messages of the manufacturer. Many jurisdictions require manufacturers to classify and label products according to their hazardous properties, to control the hazardous contents or to limit the advertising, promotion and sponsorship of such products. ENDS deliver nicotine and other substances but do not contain tobacco, and smokeless tobacco is produced in 'cottage' industries or can be modified significantly by the end user. Both therefore pose a significant challenge to regulation, as they may fall outside the scope of domestic regulatory regimes for tobacco products. Nevertheless, their popularity and the fact that they are marketed as alternatives to cigarette smoking indicate the need to characterize them, regulate them and establish appropriate educational programmes to limit their use.

TobReg reviews the scientific evidence on topics related to tobacco product regulation and identifies the research needed to fill regulatory gaps in tobacco control. The Study Group is composed of national and international scientific experts on product regulation, treatment of tobacco dependence and laboratory analysis of tobacco ingredients and emissions. As a formalized entity of WHO, the Study Group reports to the WHO Executive Board through the Director-General to draw the attention of Member States to the Organization's work in tobacco product regulation, which is a complex area of tobacco control.

The Study Group hopes that the recommendations contained in this report, as well as its other recommendations and advisory notes, will be useful to countries in implementing the product regulation provisions of the WHO Framework Convention on Tobacco Control.

2. TobReg Scientific Recommendation: Devices designed for the purpose of nicotine delivery to the respiratory system in which tobacco is not necessary for their operation

2.1 Preface

This Scientific Recommendation addresses electronic nicotine delivery systems (ENDS) designed for nicotine delivery to the respiratory system. This designation encompasses products that contain tobacco-derived substances but in which tobacco is not necessary for their operation. ENDS are marketed under a variety of brand names and descriptors, including 'electronic cigarettes', 'ecigarro', 'electro-smoke', 'green cig' and 'smartsmoker'.

This recommendation is being made because ENDS pose significant public health issues and raise questions for tobacco control policy and regulation. Manufacturers have not fully disclosed the chemicals used in ENDS; there are few data on their emissions or actual human exposure; their health effects have not been studied; and their marketing and use could undermine public smoking bans, which are important tobacco control interventions. The products could also undermine smoking cessation efforts by proposing unproven devices for smoking cessation in the place of products of proven efficacy. ENDS might also undermine the prevention of tobacco use because of their appearance and marketing as safe alternatives to tobacco products for non-tobacco users, including children.

ENDS are marketed internationally on the Internet and by direct consumer marketing in some countries. Market penetration of unregulated ENDS has expanded rapidly to most WHO regions, primarily from China, where most of the products are manufactured. Increasing access to these largely unregulated products must be addressed by rational regulatory policy.

ENDS fall into a regulatory gap in most countries, escaping regulation as drugs and avoiding the controls levied on tobacco products. Thus, policymakers and consumers lack evidence-based information and recommendations. Regulatory control of ENDS is confounded by their international availability from online retailers and distributors. In Bulgaria, for example, a number of online retailers sell the product for the equivalent of US$70, and nicotine cartridges retail for US$10 each, independently of the labelled nicotine content. In addition, ENDS are being introduced in countries such as

Lebanon as products that are imported from China. Thus, it has become urgent to evaluate the safety of the products and the data supporting the claims for their safety and efficacy.

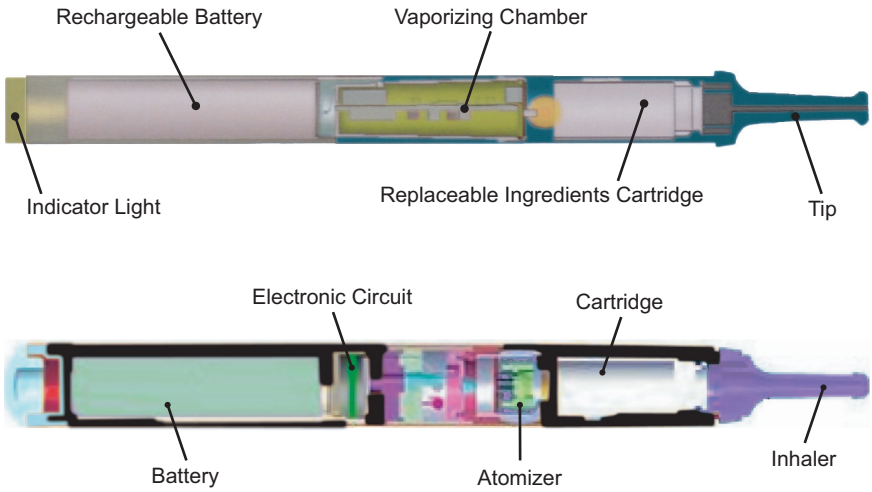
Policy-makers in many countries have sought guidance from WHO on the scientific evidence and regulatory approaches with regard to ENDS, enquiring whether they should be regulated as tobacco products, drugs or a combination of drugs and medical devices, and what information on safety should be communicated to consumers. An important regulatory consideration is the validity of the marketing claims made for the products, which include statements that ENDS are smoking cessation aids and that they deliver safer nicotine but at variable levels compared to those in cigarettes. Other practical regulatory questions include whether use of ENDS should be exempt from restrictions in places where smoking is prohibited, a claim supported by some manufacturers and distributors.

This Recommendation includes conclusions and recommendations for regulatory policy and recommendations for clinical trials and other research. It is an extension of earlier recommendations from the Scientific Advisory Committee on Tobacco Product Regulation (SACTob) and TobReg and is designed to provide a foundation for regulation that will advance tobacco control in general. This Recommendation was formulated in the context of the WHO Framework Convention on Tobacco Control, particularly to aid Parties to the treaty in implementing Articles 9, 10, 11 and 14. In addition, further guidance for implementation of Article 8, which requires protection from exposure to tobacco smoke, is vital, because the advertisements of many of the manufacturers of ENDS state that they can be used in environments where smoking is prohibited, on the basis of their claim that these products do not produce smoke.

2.2 Definition of ENDS

Electronic nicotine delivery systems (ENDS) are a category of consumer products designed to deliver nicotine to the lungs after one end of a plastic or metal cylinder is placed in the mouth, like a cigarette or cigar, and inhaled to draw a mixture of air and vapours from the device into the respiratory system. They contain electronic vaporization systems, a rechargeable battery and charger, electronic controls and replaceable cartridges that may contain nicotine and other chemicals. Some brands are claimed to deliver a range of nicotine concentrations or no nicotine at all, and some are claimed to provide sensory experiences similar to those obtained with major cigarette brands. The chemicals used to produce the odours and flavours that simulate those of cigarettes have not all been identified, although some products claim to include ‘menthol’. Some devices have light-emitting diodes, to reproduce the

appearance of a burning cigarette tip. The premise stated by some marketers of the products is that ENDS provide nicotine that would otherwise be obtained by tobacco use. The figures below show prototype devices.



2.3 Types and distribution

It is not clear how many manufacturers of ENDS exist, but an Internet search revealed at least 24 licensed companies and many more brands and model names. It is not clear whether products of similar appearance from other companies have identical contents, deliveries and effects on the body; it is possible that different devices represent different hazards and effects. The number of product types and brands described and marketed on the Internet and by retail stores is increasing rapidly. In addition, the inadequacy of customs product codes makes it difficult for regulators to track importation accurately.

Distributors market ENDS in many countries and regions, including Australia, Brazil, China, Europe, the Republic of Korea and the United States of America. In view of the number and diversity of ENDS, the content, design and delivery characteristics of each product must be measured, as it cannot be assumed that their effects are similar. Regulation should ensure that every product marketed to the public has been approved after disclosure of content, manufacturing method and data on safety appropriate to each product.

2.4 Substances in addition to nicotine

Various ENDS marketers claim that their products mimic the sensory effects of cigarettes with markedly different characteristics, suggesting that ENDS cartridges contain several chemicals in addition to nicotine. The manufacturers have not fully disclosed the chemical combinations included during

manufacture or synthesized during electronic vaporization that produce such sensory effects. Furthermore, the manufacturers have not proven that the constituent chemicals—which include organic chemicals that may be acceptable for use in foods and cosmetics—are safe for inhalation when vaporized and delivered to the lung. Although some manufacturers have disclosed the identity of some chemicals, full disclosure of the chemical components of ENDS and their evaluation for potential toxicity are regulatory priorities.

The United States Food and Drug Administration recently analysed the chemicals in 18 varieties of ENDS cartridges marketed with two different brands of ENDS and found significant variation in contents and deliveries. Several contained "detectable levels of nitrosamines, tobacco-specific compounds known to cause cancer" (*1*). The Administration's testing also revealed that the nicotine levels were inconsistent with the information on the cartridge labels and that some cartridges that were stated not to contain nicotine actually did.

2.5 Concern about lung delivery

Other products target the lung for safe, effective drug delivery (e.g. insulin inhalers), and scientific advances in the delivery of drugs to the lungs of animals and humans could be adapted to develop safe systems for delivering nicotine to the lung. Although the medical advances were gradual and costly, regulatory authorities have consistently required manufacturers to establish a rigorous scientific foundation for product approval.

Delivery of nicotine to the lung raises concern about safety and addiction that go beyond that related to currently approved NRT. Concern about the safety of ENDS is associated with the probable exposure of the lung to repeated dosing, perhaps hundreds of times a day for many months, if these products are used as a smoking cessation aid, or for years, for smokers who use them as long-term cigarette substitutes. An added concern is the safety of the chemical combinations in various ENDS cartridges, which have not been evaluated for either short-term or long-term safety. Potential long-term toxicity would not necessarily preclude short-term use of such products for smoking cessation, but it is essential to measure the risk associated with exposure to determine how such products could be used and what information should be stated on the labels.

2.6 Nicotine addiction as the basis for ENDS marketing

ENDS marketing promotes the systems to replace nicotine from tobacco. This strategy is based on the fact that tobacco use is driven and sustained by nicotine addiction, as discussed in earlier WHO reports and reports from other

organizations (*2–6*). In addition to nicotine dependence, the sensory effects of the product, social and marketing forces and perceptions of harmfulness and potential benefits should be considered in examining the initiation, patterns of use and development of addiction.

NRT products facilitate smoking cessation by providing controlled doses of nicotine to enable gradual withdrawal and reduce dependence. Certain other drugs, such as bupropion and varenicline, can also be used to treat withdrawal and dependence and thereby aid smoking cessation efforts. All current NRT products include guidance on dosing, use and how to minimize the risks for side-effects specific to that therapy. This guidance is important, because nicotine is a potent drug, and its health effects are related to dosage and patterns of use. Furthermore, if NRT products are not used according to the evidence-based therapeutic guidance, there is no assurance that they will be effective.

Theoretically, nicotine delivery by electronic vaporization and inhalation of combination products could be a safe, effective form of treatment for tobacco addiction. Nevertheless, testing for safety, efficacy and appropriate labelling are required to evaluate such potential, as described in reports by WHO and other organizations (*5–8*).

2.7 ENDS are not nicotine replacement therapy

ENDS should not be confused with NRT products approved for the treatment of tobacco dependence. Some manufacturers have marketed ENDS as smoking cessation aids and have communicated claims to the news media that their products are effective for this use. Furthermore, at least one manufacturer has claimed that WHO has endorsed its product, stating that WHO's inclusion of an NRT device commonly referred to as a nicotine 'inhaler' among products listed as effective smoking cessation aids also includes ENDS. In fact, WHO has not endorsed this manufacturer's products and has made that clear in a formal letter to the sponsor as well as in a press release (*9*). WHO supports evidence-based pharmacotherapy when scientific studies demonstrate that certain applications of products result in predictable outcomes under specified conditions, and the products have been approved as safe and effective by major drug regulatory authorities, such as the European Medicines Agency and the United States Food and Drug Administration.

ENDS and conventional NRT products may differ in design, content and the mode of delivery of nicotine and other chemicals. The contents and design features of currently approved NRT products have been fully disclosed, and their safety and efficacy have been demonstrated under conditions of labelled use, with evaluations of their nicotine delivery and absorption kinetics. No currently approved NRT product, including that referred to as an 'inhaler',

delivers nicotine systemically via the lung. During use of the 'inhaler' product, air is drawn through it, but more than 90% of the nicotine is deposited and absorbed in the oral cavity, and very little reaches the lung, as confirmed by positron emission imaging in published studies (*10*).

2.8 Capacity of ENDS to serve as nicotine replacement therapy

It is possible that at some time in the future ENDS might be developed as smoking cessation aids. Several smoking cessation experts have argued the potential benefits of an NRT device in which the treatment is delivered to the lung (*5*, *11–13*). However, currently, the evidence is insufficient to conclude that any of the ENDS products is an effective smoking cessation aid or that they deliver sufficient nicotine for them to be used in smoking cessation. If ENDS deliver significant amounts of nicotine for lung absorption, concerns about the safety of lung delivery and the addictive potential of the nicotine delivered by this route would have to be addressed (5, *12*). Claims that ENDS are smoking cessation aids have not met the standards of evidence required by scientific organizations and regulatory authorities (e.g. *8*, *14*). Thus, at present, there is insufficient evidence that ENDS are safe for human consumption.

Although ENDS are promoted as smoking cessation aids in some markets, the manufacturers have not provided evidence-based guidance for their efficacy, dosing and duration of use, how they should be combined with behavioural strategies for smoking cessation or guidance for discontinuation. This information would be required if WHO or national regulatory authorities were to make even a preliminary evaluation of the safety and effectiveness of ENDS.

In summary, claims for the effectiveness of ENDS for smoking cessation and other health effects must be substantiated by rigorous studies of pharmacokinetics, trials of safety and efficacy and review and approval by major drug regulatory authorities. The types of data and studies that would be required include a complete listing of the chemicals used in ENDS products; a listing and reporting of the concentrations of chemicals delivered to the consumer; comparisons of the effect of ENDS on smoking cessation with that of approved NRTs and placebo; and the adverse effects of these products.

2.9 Regulatory status

The ENDS products addressed in this recommendation do not require tobacco for operation but are claimed to deliver nicotine to the consumer. According to the regulatory schemes of many countries,[1] this would suggest that ENDS

[1] Canada, Denmark, the Netherlands, Norway, Turkey and the United States (see Annex 1)

products would appropriately be regulated as combination drugs and medical devices and therefore could not be marketed until the regulatory authorities determine that adequate evidence, including data from approved clinical trials, exists to support approval. Some countries have completely banned the sale and marketing of ENDS.[2] Some countries and areas allow marketing within other regulatory frameworks.[3] Internet marketing of ENDS and the inadequacy and misapplication of import product codes, however, impede systematic regulation. Regardless of the regulatory approach taken, this report recommends that claims that ENDS are safer than cigarettes, that they have health benefits and are effective smoking cessation aids or could be marketed as cigarette substitutes be prohibited until such claims are substantiated by sufficient evidence to satisfy their accuracy to independent scientific organizations and regulatory authorities (e.g. 8, *14*).

Some manufacturers have claimed that ENDS can be used legally in environments where smoking is prohibited. TobReg strongly recommends that ENDS not be exempted from 'clean air' laws, which restrict the places in which cigarette smoking is allowed, until adequate evidence is provided to assure regulatory authorities that use of the product will not expose nonusers to toxic emissions (See Article 8 of the WHO Framework Convention on Tobacco Control). WHO strongly encourages its Member States to prohibit manufacturers from marketing electronic cigarettes with claims that WHO endorses them as legitimate tobacco cessation aids. Furthermore, Member States should ensure that the manufacturers of these products comply with all existing regulatory requirements to preclude unsubstantiated claims that may derail public health efforts in tobacco control.

2.10 Other concerns

The conditions under which marketing of ENDS should be allowed is also a concern. ENDS may be considered relatively safe and attractive alternatives to tobacco products by people, including adolescents, who would not otherwise have used a potentially addictive nicotine product. The product might therefore ultimately increase tobacco product use.

ENDS might be used to perpetuate smoking by what has been termed 'dual use', that is, sustaining nicotine dependence in environments where smoking is prohibited. One of the positive consequences of smoking restrictions is the de-normalization of tobacco product use and the subsequent increase in cessation rates. ENDS may discourage people from quitting, as users can maintain their nicotine addiction despite smoking restrictions and resume smoking where such restrictions are absent.

[2] Australia, Brazil, China, Singapore, Thailand and Uruguay (see Annex 1)
[3] European Union, New Zealand and the United Kingdom (see Annex 1)

Smokers trying to quit may use ENDS in place of effective evidence-based treatments. If ENDS are not effective NRT products, their use could delay smoking cessation and contribute to an increased risk for smoking-attributable disease.

2.11 Conclusions

- ENDS products claim to deliver nicotine, an addictive chemical, via the respiratory system with the purpose of facilitating and perpetuating nicotine addiction.
- The safety and extent of nicotine uptake from ENDS products have not been established. Although ENDS may cause and sustain addiction, evidence for potential addiction and the frequency with which addiction occurs does not currently exist.
- Manufacturers have marketed ENDS as smoking cessation aids, and these products might be effective in this respect; however, scientific evidence sufficient to establish their actual nicotine dosing capabilities, their efficacy as smoking cessation aids and safety of use is not yet available.
- There is concern that nicotine delivery to the lung might result in stronger toxicological, physiological and addictive effects, and this concern must be addressed in scientific studies.
- Lung delivery of medications, independent of the effects of nicotine, is of global importance and must be addressed in scientific studies.

2.12 Recommendations for regulatory policy

- ENDS products should be regulated as combination drugs and medical devices and not as tobacco products. Notwithstanding the various marketing strategies, ENDS might facilitate and perpetuate nicotine addiction.
- If ENDS products are regulated under tobacco control laws, the manufacture, sale or importation of these products should be subject to regulation of the contents and labelling (Articles 9–11), prohibition of public use that might expose others to emissions (Article 8) and restrictions on advertising, promotion and sponsorship that appeal to adolescents (Article 13). Countries might consider granting exemption and concurrent jurisdiction with drug regulatory authorities only if ENDS products are proven to be safe and effective as smoking cessation aids.
- Regulators should weigh the theoretical benefits of ENDS as smoking cessation aids against those of current NRT products and the risk that the

products will appeal to nonsmokers, that is, the risk that nonsmokers will be drawn into nicotine addiction.

- Manufacturers and retailers must provide evidence to define the appropriate uses of, exposure to, and safety of ENDS, and regulatory authorities should confirm the accuracy of this evidence before approving these products for sale and marketing.
- Claims implying health benefits or less harm than cigarettes should be prohibited, unless the safety of these devices, when used as intended, is scientifically proven to the satisfaction of regulatory authorities.
- Claims that ENDS assist smoking cessation should be prohibited, unless the efficacy of these devices, when used as intended, is scientifically proven to the satisfaction of regulatory authorities.

2.13 Recommendations for clinical trials and other research required for regulatory approval

- Research should be conducted on the delivery and absorption of nicotine from ENDS use, in both the short and the long term, to enable regulators to establish the dosage and formulation for regulatory approval.
- Research should be conducted on the behavioural and physiological consequences of using ENDS.
- The dependence potential (also known as 'abuse liability') relative to cigarettes and NRTs should be studied.
- Short- and long-term effects of human exposure should be monitored to determine potential harm.
- Post-marketing studies should be conducted to determine patterns of use, such as dual use, to monitor adverse effects and to determine the implications for initiation and cessation at individual and population level.

2.14 References

1. Zezima K. Analysis finds toxic substances in electronic cigarettes. *The New York Times*, 22 July 2009. http://www.nytimes.com/2009/07/23/health/policy/23fda.html.
2. *The scientific basis of tobacco product regulation: report of a WHO study group*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 945).
3. *Neuroscience of psychoactive substance use and dependence. Chapter 4 -- Psychopharmacology of dependence for different drug classes.* Geneva, World Health Organization, 2004.

4. Royal College of Physicians of London. *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.

5. Royal College of Physicians of London. *Harm reduction in nicotine addiction; helping people who can't quit: A report of the Tobacco Advisory Group of the Royal College of Physicians.* London, Royal College of Physicians of London, 2007.

6. Department of Health and Human Services. *Reducing tobacco use: A report of the Surgeon General.* Washington DC, Government Printing Office, 2000.

7. *Policy recommendations for smoking cessation and treatment of tobacco dependence.* Geneva, World Health Organization, 2003.

8. Fiore MC et al. *Treating tobacco use and dependence: 2008 update.* Clinical practice guideline. Rockville, Maryland U.S. Department of Health and Human Services, Public Health Service, 2008.

9. *Marketers of electronic cigarettes should halt unproved therapy claims*. Press Release. Geneva, World Health Organization, media Centre, 19 September 2008.
http://www.who.int/mediacentre/news/releases/2008/pr34/en/index.html.

10. Bergstrom et al. *Regional deposition of inhaled ^{11}C-nicotine vapor in the human airway as visualized by positron emission tomography.* Clinical Pharmacology and Therapeutics, 1995, 57: 309–317.

11. Warner KE et al. The emerging market for long-term nicotine maintenance. *Journal of the American Medical Association*, 1997, 278:1087–1092.

12. Fant RF et al. Pharmacotherapy for tobacco dependence. *Handbook of Experimental Pharmacology*, 2009, 192:487-510.

13. Gray N, Boyle, P. The future of the nicotine-addiction market. *Lancet*, 2003, 362:844-845.

14. www.treatobacco.net

Country	Regulate as medicinal product	Prohibition	Source
Australia Therapeutic Goods Administration	The National Drugs and Poisons Schedule Committee under the Therapeutic Goods Administration concluded that nicotine's classification as a poison should apply to ENDS, effectively prohibiting the sale and marketing of ENDS in all states and territories. *Victoria*: Regulated as a nicotine drug and subject to entry in the Poisons Code under the Victorian Drugs, Poisons and Controlled Substances Act 1981 Substances in the Poisons Code are subject to regulation under the Victorian Drugs, Poisons and Controlled Substances Regulations 2006 (Regulation 65): A person must not manufacture, sell, supply, purchase or otherwise obtain, possess or use a listed regulated poison unless the person is authorized, licensed or permitted under the Act or these Regulations to do so." Penalty: 100 penalty units* *From 1 July 2009, the value of a penalty unit in Victoria is AUS$ 116.82.	*Western Australia*: Prohibited as imitation tobacco products ENDS are prohibited under section 106 of the Western Australia Tobacco Products Control Act 2006, which states: "106. Products resembling tobacco products, packages. A person must not sell any food, toy or other product that is not a tobacco product but is: (a) designed to resemble a tobacco product or a package; or (b) in packaging that is designed to resemble a tobacco product or a package."	Department of Health and Ageing, Therapeutic Goods Administration October 2008, NDPSC Resolution 2008/54 – 21, http://www.tga.gov.au/ndpsc/record/rr200810.pdf

Brazil National Health Surveillance Agency (ANVISA)	Regulates as tobacco product Article 1 Prohibits marketing, importing and advertising of any smoking electronic device (ENDS), known as electronic cigarettes, ecigarettes, eciggy, Ecig among others, especially those that claim to be replacement for cigarettes, cigarillos, cigars, pipes and similar as alternative in the treatment of smoking cessation. Sole Paragraph. Included in the prohibition in the caput of this article are any accessories and refills intended for use in any smoking electronic device (ENDS). Article 2 The admissibility by ANVISA for the Registration of Data on any smoking electronic device (ENDS), especially for the treatment of smoking cessation or the replacement of cigarette, cigar, pipe and similars in the habit of smoking, shall depend upon the submission of toxicological	Import, sale or offer for sale prohibited as imitation tobacco products under RDC 41/09 (August 28th 2009) There shall be the possibility of registering the product as medicinal product after the presentation of all due tests and studies (article 3rd RDC 41/09).	ANVISA RDC 41/09 http://portal.anvisa.gov.br/wps/portal/anvisa/home/derivadostabaco

studies and scientific tests that prove the specific purposes alleged.

§ 1. The toxicological studies and the tests referred to in this article shall be conducted in accordance with protocols and internationally recognized and accepted scientific methods, accompanied by the risk assessment of health damage to the consumer as well as proof of non - environmental contamination with toxic compounds.

§ 2. All results of toxicological studies and tests referred to in this article shall be subject to technical review and approval by ANVISA.

§ 3. Even if the registration of the data of the device (ENDS) shall be approved in accordance with the caput of Article 2 it is forbidden the selling, the supplying, even as means of samples, the delivery or the use in any case, to children or

	adolescent, of any smoking electronic device (ENDS). Article 3 The violation of the provisions under this Resolution shall subject those responsible to penalties under the Act 6437 of 20 August 1997.		
Canada Health Canada	ENDS, as well as ENDS cartridges that contain nicotine, fall within the scope of the Food and Drugs Act and therefore require marketing authorization before they can be imported, advertised or sold. Currently, no ENDS products have been granted marketing authorization.		Health Canada, 27 March 2009 http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_53-eng.php
China, Hong Kong Special Administrative Region	Under the Pharmacy & Poisons Ordinance, ENDS containing nicotine are classified as poison products and strictly prohibited. All products containing nicotine must be registered with the department that assesses them for safety and quality before they can be sold.	Penalty imposed is linked to the Pharmacy & Poisons Ordinance: "Possession or sale of an unregistered pharmaceutical product, and possession of Part I poisons without authority warrants two-years' jail and a $100 000 fine."	Hong Kong Legal Information Institute, Pharmacy and Poisons Ordinance, Cap 138, sec. 21–24; Pharmacy and Poisons (Amendment) (No. 4) Regulation 2008, 234; Poisons List (Amendment) (No. 4) Regulation 2008, 235; http://www.hklii.org/hk/legis/en/ord/cur/138.txt
Denmark Danish Medicines Agency	ENDS are classified as medicinal products that cannot be sold in the country without		Danish Medicines Agency, 9 March 2009 http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=14819

	fulfilling the requirements of Executive Order No. 1268 of 12 December 2005 on medical devices and receiving marketing authorization from the Agency. To date, the Agency has not licensed any ENDS; therefore, any marketing and distribution of ENDS constitutes a violation of the provisions of the Danish Medicines Act.	Danish Medicines Agency, 9 October 2008 http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=14250
European Commission Health & Consumer Protection Directorate-General	Whether ENDS fall under Directive 2001/83 on human medicinal products depends on whether they can be characterized as a human medicine by presentation or by function. ENDS can be regarded as a human medicine by presentation if they are presented as a remedy for nicotine addiction. ENDS can be regarded as a human medicine by function in so far as they qualify as “restoring, correcting or modifying physiological functions” in a significant manner.	Health & Consumer Protection Directorate-General of the European Commission Orientation Note 22 May 2008 http://ec.europa.eu/health/ph_determinants/life_style/Tobacco/D ocuments/orientation_0508_en.pdf

	Whether ENDS could be regarded as falling under Directive 93/42/EEC on medical devices depends on the claimed intended use and whether this intended use has a medical purpose.		
Netherlands Ministry of Health, Welfare and Sport	Advertising of ENDS products is banned. In order to market them legally, manufacturers must register the products with the Medicines Evaluation Board.		Ministry of Health, Welfare and Sport, 28 January 2008, http://www.minvws.nl/en/nieuwsberichten/gmt/2008/klink-seeks-consensus-e-cig.asp
New Zealand New Zealand Medicines and Medical Devices Safety Authority (MedSafe)	Cartridges containing nicotine fall under the requirements of the Medicines Act and are regulated by MedSafe. Nicotine for inhalation can be purchased from a pharmacist without a doctor's prescription. When selling these medicines, pharmacists must fulfil special requirements designed to ensure that the consumer is properly informed about the safe and correct use of the medicine.		http://www.medsafe.govt.nz
Norway Norwegian Directorate of Health		The Norwegian Tobacco Act forbids the import and sale of new tobacco products and/or nicotine products, a classification that encompasses ENDS products.	Regulations concerning prohibition of new tobacco and nicotine products laid down by Royal Decree, 13 October 1989, http://www.regjeringen.no/en/dep/hod/Subjects/The-Department-of-Public-Health/Norways-

			National-Strategy-for-Tobacco-Co.html?id=451948
Singapore Tobacco Regulation Unit, Health Sciences Authority	Medicinal product registration and product licence required for the import and sale or supply of product Poisons licence required, as the product contains nicotine, a substance controlled under the Poisons Act	Import, sale or offer for sale prohibited as imitation tobacco products under Section 16 of the Smoking (Control of Advertisements and Sale of Tobacco) Act. Exemption from prohibition considered if product is registered as medicinal product	Highlights of Licensees' Obligations under the Smoking (Control of Advertisements and Sale of Tobacco) Act and its Regulations. Health Sciences Authority (last updated 29 October 2008) http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/tobacco/legislation/licensee_obligations.html
Thailand Food and Drug Administration	Smoking alternatives are not a tobacco product, according to the law, if they are not produced from *Nicotiana tabacum.* As such, they are classified as a drug containing nicotine, which is an alkaloid. Therefore, ENDS manufacturers must apply to the Food and Drug Administration for import and sale in the country. Before giving permission the Food and Drug Administration would have to examine all scientific evidence about the drug.	In banning alternative cigarettes, Thailand does not have to enact a new law but can use an existing law and regulation.	Thailand: Public Health Ministry orders study of e-cigarettes, Non-aligned Movement News Network, 13 June 2009 (http://www.namnewsnetwork.org/v2/read.php?id=51042)
Turkey Turkish Ministry of Health		In 2008, it was reported that the sale of ENDS was suspended by the Ministry of Health. The Advertisement Board under the Ministry of Industry and Trade	*Hürriyet Daily News*, 3 January 2008, http://arama.hurriyet.com.tr/arsivnews.aspx?id=-621407

		followed suit and banned public advertisement of ENDS, noting that the Ministry of Health had not approved use of the products.	*Hürriyet Daily News*, 17 January 2008, http://arama.hurriyet.com.tr/arsivnews.aspx?id=-622303
United Kingdom Medicines and Healthcare Products Regulatory Agency	If ENDS are marketed as a smoking cessation aid, they are licensable as a medicine by the Medicines and Healthcare Products Regulatory Agency. As a smoking alternative, however, the use of ENDS is unrestricted. Conversely, products that contain nicotine at safe levels but which are presented as a replacement for or alternative to tobacco products, in circumstances where smoking is not permitted, such as air travel, the theatre or cinema, are not licensable.	ENDS manufacturers are prohibited from selling these products under general product safety principles, unless the packaging bears the appropriate safety warnings in terms of the Chemicals (Hazard Information and Packaging for Supply) Regulations 2009. As most manufacturers do not have the appropriate safety warnings (e.g. appropriate packaging, 'highly toxic' labels, tactile warnings, child-resistant fastenings), these products would, in theory, be prohibited. They are, however, currently marketed and distributed in the United Kingdom.	
United States of America United States Food and Drug Administration (FDA)	FDA considers ENDS to be combination drug and medical devices, and marketing of these products is illegal without regulatory approval. FDA has announced that a claim or representation for smoking cessation is not the only element it evaluates in making these	FDA has seized about 50 shipments of ENDS products and is reviewing the new tobacco law that is the basis of the Agency's jurisdiction to regulate tobacco products; the Agency is considering a range of enforcement actions, including recalls and criminal sanctions. A 2009 FDA study found that several cartridges contained detectable levels of	FDA considers ways to short-circuit electronic cigarettes. *USA Today*, 22 July 2009 (http://www.usatoday.com/news/health/2009-07-22-electroniccigarette_N.htm) (last updated 29 July 2009) Federal caution on electronic cigarettes. *The Washington Post*, 23 July 2009 (http://www.washingtonpost.com/wp-dyn/content/article/2009/07/22/AR2009072203558.html).

	determinations. It also focuses on the product's intended uses, on whether they are intended to affect the body's structures and functions and/or to treat, mitigate or prevent disease (e.g. nicotine addiction). FDA has reviewed electronic cigarettes, cigars and pipes and their components and classified them as drug–device combinations under section 503 (g)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 USC § 353(g)(1)) with their 'drug' uses, as defined in section 201(g) of the Act (21 USC § 321 (g)), as the primary mode of action, which are intended to affect the body's structures and functions and, in some cases, to treat or prevent withdrawal symptoms of nicotine addiction.	nitrosamines, which are carcinogens, and diethlyene glycol, a common ingredient of antifreeze that is toxic to humans. In addition, the study showed that the levels of nicotine vary even in cartridges with labels that claim to have the same amount, including those labelled as not containing nicotine.	Analysis finds toxic substances in electronic cigarettes. *The New York Times*, 23 July 2009 (http://www.nytimes.com/2009/07/23/health/policy/23fda.html). FDA: Electronic cigarettes contain toxic chemicals. *The Associated Press*, 22 July 2009 (http://www.google.com/hostednews/ap/article/ALeqM5iFxte-Xw6qPRQqUJmEnNTkDqGoJQD99JOJA00).
Uruguay		Sale in Uruguay is banned via a decree issued in November 2009.	

3. Report on setting regulatory limits for carcinogens in smokeless tobacco

3.1 Background

The WHO Study Group on Tobacco Product Regulation (TobReg) has prepared a series of reports to provide a scientific foundation for tobacco product regulation (*1*, *2)* to support the provisions of Article 9 of the WHO Framework Convention on Tobacco Control. The reports identify approaches for regulating cigarettes, including mandated reductions in the concentrations of toxicants present in smoke. The most recent report suggests that reducing the concentrations of toxicants present in smokeless tobacco products would be a logical scientific extension of this regulatory strategy (*2*).

Smokeless tobacco products are used widely in Asia (particularly South-East Asia), Africa, North America and parts of Europe (*3*). There are well documented differences in the contents and formulations of smokeless tobacco products used in different countries, and there are scientifically documented differences in the adverse health outcomes resulting from use of these different products (*3*). Smokeless tobacco has been causally associated with oropharyngeal cancer, pancreatic cancer and heart disease (*3*, *4)*; but these risks vary dramatically by geographic location and composition of the smokeless tobacco product used, with very high risks evident for products used in Africa and the Indian subcontinent and lower risks occurring in studies conducted in the U.S. and Scandinavian countries, particularly in Sweden where low nitrosamine snuff has been in widespread use (*3*).

The content of smokeless tobacco is substantially less complex than the emissions of combusted tobacco products. Smokeless tobacco contains fewer carcinogens, but some formulations have substantial amounts of some carcinogens common to cigarette smoke emissions (*3–6*). Differences of several orders of magnitude in the concentrations of carcinogens have been found between products with the lowest levels, which are most commonly marketed in the developed world, and those produced in ‘cottage’ industries in Asia and Africa. The differences among manufactured smokeless tobacco products used in different regions are more modest, but even within the same region there are substantial differences in products (*3*). Differences in the

content and formulation of the smokeless tobacco products used in different geographical areas might reasonably explain the different health outcomes observed with their use. The disease outcomes indicate a public health benefit of regulation. Regulatory lowering of the concentrations of carcinogens in smokeless tobacco products might reduce the numbers of cancers resulting from their use.

Differences in the concentrations of two groups of powerful carcinogens in smokeless tobacco, tobacco-specific *N*-nitrosamines (TSNA) and polycyclic aromatic hydrocarbons (PAH), might explain the diverse cancer risks seen with use of these products in different regions. The carcinogenic potency of these compounds and the possibility for substantially lowering their concentrations in smokeless tobacco with existing techniques make these carcinogens priorities for regulatory consideration.

At a meeting of TobReg held in Durban, South Africa, in November 2008, consideration was given to regulatory approaches by which the concentrations of carcinogens in smokeless tobacco could be lowered. After reviewing the evidence, the Study Group concluded that it is both desirable and feasible to regulate smokeless tobacco by setting regulatory limits on the concentrations of selected carcinogens. It further recommended that regulation begin with PAH and TSNA. This TobReg report presents the scientific evidence for regulating smokeless tobacco products and makes recommendations for the initial regulatory levels.

3.2 Carcinogens present in smokeless tobacco

Smokeless tobacco is taken orally or nasally without burning the product at the time of use. Oral smokeless tobacco products are placed in the mouth, cheek or lip and sucked ('dipped') or chewed. Tobacco pastes or powders are used in a similar manner and placed on the gums and teeth. Fine tobacco mixtures may be inhaled nasally and the contents absorbed in the nasal passages.

Smokeless tobacco has been classified by the International Agency for Research on Cancer (IARC) as 'carcinogenic to humans' (Group 1) (*3*). There are, however, many forms of smokeless tobacco, which differ considerably in their composition and carcinogenic potential. Available information indicates the presence of 28 potential or known carcinogens (*5*). The list below contains only those identified in smokeless tobacco that meet the criteria for inclusion as IARC group 1 carcinogens ('sufficient' evidence of carcinogenicity in humans):

benzo[*a*]pyrene

formaldehyde

N′-nitrosonornicotine (NNN)
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
arsenic
nickel compounds
polonium-210
uranium-235
uranium-238
beryllium
cadmium
chromium

3.3 Tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons

Tobacco-specific nitrosamines (TSNA) are formed from tobacco alkaloids and nitrosating agents, such as nitrite. They are found only in tobacco products. Seven TSNA have been detected in smokeless tobacco: NNN, *N*′-nitrosoanabasine, *N*′-nitrosoanatabine, NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 1-(methylnitrosamino)-1-(3-pyridyl)-4-butanol and 4-(*N*-nitrosomethylamino)-4-(3-pyridyl)butyric acid. Of these, NNN and NNK are considered the most important because of the levels at which they occur in smokeless tobacco and their carcinogenic potency. Procedures exist for dramatically limiting the formation of TSNA in smokeless tobacco, including those used by some manufacturers of smokeless tobaccos sold in Sweden (*7*) and the manufacturer of the Russian *nass* (*8*). A comprehensive review of the techniques available was prepared by O'Connor and colleagues (*9*). The procedures include a short ageing process, use of tobacco with a low nitrate content, a pasteurization-like process that destroys bacteria implicated in the formation of nitrosamines and changes in the methods for curing tobacco. Refrigeration of the product also helps limit the formation of nitrosamines during storage.

Polycyclic aromatic hydrocarbons (PAH) are carcinogenic constituents of smokeless tobacco (*3*, *5*, *10–12*), which are products of incomplete combustion of organic matter. They are not found in raw tobacco leaf, except in areas where there are high levels due to ambient air pollution. The commonest source of PAH in smokeless tobacco is smoke from wood (or other organic matter) burnt during tobacco curing; therefore PAH can be viewed as unnecessary contaminants of smokeless tobacco that should not be present, rather than intrinsic constituents which should be minimized.

3.4 Differences in carcinogens present in smokeless tobacco by region

A working group convened by IARC (*3*) reviewed studies on the concentrations of TSNA in a variety of smokeless tobacco products in different regions (Table 1). The measurements were made on products sold during different decades, with different methods and reported by different laboratories; however, even with these sources of variation, the levels of TSNA clearly varied considerably among products sold in different parts of the world. Relatively low levels of NNN and NNK were reported in products described as 'low-TSNA smokeless tobacco', for instance in South Africa and Sweden, and in some products from Thailand and Uzbekistan. Even some of the products used in Sweden have been reported to have relatively high levels of NNN. Generally, moist snuff products used in Europe and the United States contain lower levels of TSNA than products on the Indian market or those imported from South Asia to the United Kingdom (*3*, *5*, *11*, *12*). A wide range of concentrations is reported, however, even in products on the market in Europe and the United States, ranging from undetectable to levels comparable to those of the more toxic products available on Asian markets. The IARC review makes it clear that, while the products used in developed countries generally have lower TSNA levels, some have high TSNA levels. Conversely, some products with relatively low levels of TSNA are available in almost all countries in which a substantial number of products have been examined, even in those countries where most products have high TSNA levels and where there is a high burden of disease due to smokeless tobacco use. The concentrations of NNN and NNK in Sudanese *toombak* are extremely high: the concentration of NNN was reported to be 141–3085 µg/g of tobacco dry weight and that of NNK was 188–7870 µg/g of tobacco dry weight (*13–15*).

The moist snuff (*snus*) currently manufactured, marketed and used in Sweden has been well studied and is produced to a standard (*7*) that results in a lower nitrosamine content. In the United States, there are both 'traditional' products, which have relatively high concentrations of TSNA, and newer products, which have levels closer to those of the Swedish product (*12*).

In Asia, especially India, and in other developing countries, there are many tobacco mixtures, which are administered in various ways and often prepared and marketed by individuals or small manufacturers (cottage industry). Differences in the composition of the products on these markets are therefore difficult to define. Certain products have been described by IARC (Table 1) (*3*).

Table 1
Concentrations of tobacco-specific *N*-nitrosamines in selected smokeless tobacco products (µg/g dry weight of tobacco)

Country	Type of product	NNK	NNN	NAB	NAT
Belgium	Chewing tobacco	0.13	7.38		970 (includes NAB)
Canada	Moist snuff	3.2–5.80	50.4–79.1	4–4.8	152.0–170.0
Canada	Chewing tobacco	0.24	2.09	0.1	1.58
Germany	Chewing tobacco	0.03–0.3	1.42–2.30	0.03–0.05	0.33–3.7 (upper value includes NAB)
Germany	Dry snuff	0.58–6.43	2.93–18.75	NR	1.03–7.83
India	Chewing tobacco	0.13–0.6	0.47–0.85	0.03–0.07	0.3–0.5 (upper value includes NAB)
India	*Zarda*	0.22–24.1	0.4–79.0	NR	0.78–99.1 (includes NAB)
India	*Mishri*	0.294–1.1	0.3–6.995	NR	0.488–14.15
India	*Khiwam*	0.1–1.03	2.5–8.95	NR	1.83–10.36
India	*Zarda*	0.22–24.1	0.4–79	NR	0.78–99.1
India	*Khaini*	0.11–5.29	25.8–40	1.24–2.48	0.66–18.8
South Africa	Low-TSNA moist snuff	0.27–0.29	1.05–2.07	0.09–0.11	
Sudan	*Toombak*	188–7870	141–3080	139–2370	20–290
Sweden	Moist snuff	0.19–2.95	1.12–154	0.04–1.7	0.9–21.4
Thailand	Chewing tobacco	0.1	0.5	NR	0.5
United Kingdom	Moist snuff	0.4–13.0	1.1–52.0	0.086	2.0–6.5 (upper value includes NAB)
United Kingdom	Chewing tobacco	0.3	0.9	NR	1.5 (upper value includes NAB)
United Kingdom	Dry snuff	0.58–4.3	2.39–16.0	NR	1.03–7.83
United States	Moist snuff	ND–18.0	ND–147.0	0.02–10.67	0.24–339.0
United States	Chewing tobacco	ND–1.1	0.67–6.5	0.02–0.14	0.67–12,4
United States	Dry snuff	0.88–84.4	9.37–116.1	0.52–1.53	11.2–238.8 (upper value includes NAB)
Uzbekistan	*Naswar*	0.02–0.13	0.12–0.52	0.008–0.03	0.032–0.3

From reference *2*

NAB, *N*′-nitrosoanabasine; NAT, *N*′-nitrosoanatabine; ND, not detected; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, *N*′-nitrosonornicotine; NR, not reported

This report is concerned with the concentrations of TSNA and benzo[*a*] pyrene found in products currently being marketed, rather than the historical ranges important for disease causation. The concentrations in products obtained more recently are shown in tables 2 and 3. A wide range of concentrations was found for both TSNA and benzo[*a*]pyrene in various products, and substantial differences were found in the levels in new and traditional smokeless tobacco products.

Table 2
Concentrations of tobacco-specific nitrosamines (TSNA) and benzo[*a*]pyrene in smokeless tobacco products purchased in the United Kingdom and elsewhere

Product	TSNA[a] (µg/g dry weight)	Benzo[*a*]pyrene (ng/g dry weight)
Products purchased in the United Kingdom		
Guthka products		
Manikchard	0.289	0.4
Tulsi mix	1.436	1.28
Zarda products		
Hakim Pury	29.705	0.32
Dalal Misti Zarda	1.574	8.89
Baba Zarda (GP)	0.716	2.04
Tooth-cleaning powder: A. Quardir Gull	5.117	5.98
Dried tobacco leaf	0.223	0.11
Products purchased outside the United Kingdom		
Baba 120 (India)	2.361	2.83
Snus (Sweden)	0.478	1.99
Ariva (United States)	ND	0.4
Copenhagen (United States)	3.509	19.33

From reference *11*

[a] *N*′-nitrosoanabasine, *N*′-nitrosoanatabine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone ND, not detected

PAH originate primarily from fire-curing of tobacco and are therefore avoidable contaminants of smokeless tobacco. They are generally locally acting carcinogens and have been extensively evaluated for carcinogenicity in mouse skin models (*16*). The carcinogenicity of PAH varies considerably because of differences in relative molecular mass and biochemical properties. As PAH always occur as complex mixtures, the concentration of benzo[*a*] pyrene is commonly used as a proxy for that of PAH.

Table 3
Concentrations of tobacco-specific nitrosamines (TSNA) and benzo[*a*]pyrene in smokeless tobacco products sold in the United States

Product	NNN + NNK		Benzo[*a*]pyrene	
	No. of samples	µg/g dry weight	No. of samples	ng/g dry weight
Taboka, Marlboro Snus, Camel Snus	8	1.04–1.82		
Taboka, Marlboro Snus, Camel Snus, Skoal Dry			11	ND–2.1
Camel Snus Original			1	10.5
General Snus	1	2.3	1	ND
Skoal Dry	3	2.81–5.61		
Mint Marlboro Snus	1	3.50		
Traditional smokeless tobacco	4	4.86–8.27	4	30.1–57.3
United States moist snuff	39	5.5–98.6		

From reference *12*
NNN, *N*′-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; ND, not detected

The concentration of benzo[*a*]pyrene in natural tobacco and snuff in the United States was < 0.1–90 ng/g of tobacco (unspecified as to wet or dry weight) (*5*). Products in the United Kingdom and some other countries (Table 2) were found to contain 0.11–19.33 ng/g dry weight, with the lowest levels in tobacco leaf and the highest in Copenhagen smokeless tobacco in the United States. A recent study of smokeless tobacco products available in the United States (Table 3) showed that General Snus and newer test-marketed brands had lower concentrations of PAH than a selected set of other brands, including Copenhagen (*12*). The other brands had on average 12 times more acenaphthylene, 71 times more phenanthrene, more than 300 times more anthracene, 40 times more fluoranthene, 50 times more pyrene, 14 times more benzofluoranthenes and 12 times more benzo[*a*]pyrene than the newer products.

The observations that smokeless tobacco products can be manufactured with relatively low levels of TSNA and benzo[*a*]pyrene and that products with high levels of these carcinogens remain on the market suggest that the composition and toxicity of smokeless tobacco will continue to vary markedly in the absence of regulatory control. The availability of techniques to produce products low in TSNA and benzo[*a*]pyrene and the existence of voluntary programmes intended to reduce the concentrations of those carcinogens has not resulted in uniformly low TSNA levels in most products. These realities suggest that regulatory control could reduce the levels of carcinogens in smokeless tobacco.

3.5 Targets for regulation

In most parts of the world where smokeless tobacco is widely consumed, the products used include both those sold by large manufacturers and those produced by individuals and in cottage industries. The products most amenable for initial regulatory control are those produced by large manufacturers. TobReg recognizes that these companies represent only a fraction of the market and do not produce the products with the highest carcinogen content. Nevertheless, we recommend that initial regulatory efforts be focused on large manufacturers and importers of smokeless tobacco, who can change products rapidly. The more complex problem of limiting the levels of carcinogens in products produced by cottage industries should not be used as an excuse to allow higher levels than needed in manufactured products. Rather, companion programmes to educate cottage industry producers and to design improved production processes for small producers should be set up. In particular, attention should be given to the use of tobacco with a low nitrate content, use of a pasteurization process that destroys the bacteria implicated in the formation of nitrosamines, avoidance of wood-smoke curing and use of refrigeration during storage before sale. These techniques, while not yet available in poor villages, may become available in coming decades.

The inability of cottage industries to produce smokeless tobacco with lower concentrations of toxicants should not be used as a justification on the part of developing countries for tolerating the presence of tobacco products with higher levels of carcinogens in the manufactured segment of the market, as this segment can readily reduce levels. The levels of TSNA and PAH shown in tables 1–3 clearly show that manufacturers in both developed and developing countries can make smokeless tobacco products with low concentrations of TSNA and benzo[*a*]pyrene.

Lower carcinogen levels may be more easily achieved in wealthy countries, but TobReg considers that higher toxicant levels in manufactured products should not be accepted in countries with fewer economic resources.

3.6 Selection of metric for regulation

Although the users of cigarettes adjust their pattern of puffing to achieve the desired dose of nicotine, the delivery of substances from smokeless tobacco is influenced mainly by the product itself rather than the user. Users can adjust the quantity of smokeless tobacco they use, the placement of the product and the duration of use, but the delivery of toxicants is largely a function of the product composition and formulation. The levels of toxicants in smokeless tobacco could be normalized by a variety of approaches, each of which has its advantages and limitations.

- *Per typical dose used:* One advantage of this approach is that it might approximate the amount of toxicant presented to a user with each use. The limitations include the fact that there is substantial variation in the amount actually used by individuals, limited data on the quantities actually used per use of many products, and no accepted international standard for typical dose used. The advantage of approximating the dose presented to the user is diminished by the reality that the exposure of individuals per dose is also a function of the time they hold the dose in their mouths and by other actions that may be taken to increase delivery. This approach would be complex to administer, as it would require a different standard for each formulation of smokeless tobacco, and perhaps for different brands or groupings within the same formulation, on the basis of differences in patterns of use, making comparisons of products problematic.
- *Per gram as sold:* The advantage of this approach is that the product tested would approximate the product acquired by the user. Thus, the sample tested would be what the user actually encounters. Furthermore, the same quantity of product would be measured in comparisons of different products. Different products have different moisture levels, however, and the moisture level in the same product might vary with the humidity of the environment in which it is stored. Therefore, samples of smokeless tobacco would have to be stored at a standardized humidity before measurement, as is done for cigarettes. The question that arises is whether the measure actually reflects the product available for purchase. Also, manufacturers might vary the moisture in their products to achieve the desired regulatory level.
- *Per gram dry weight:* This approach has the advantages of standardization to the same quantity of product for comparisons and avoiding the variation created by differences in moisture content among products and by differences due to the humidity of the storage environment. One concern is that manufacturers might add non-tobacco components to smokeless tobacco in order to meet the standard. The levels proposed by TobReg are not intended to result in small incremental changes in the product, however, and the addition of small amounts of non-tobacco material would not reduce the concentrations of nitrosamines by the orders of magnitude necessary to meet the regulatory standard for products with the high levels found in Asia and Africa. Additionally, measurement per gram dry weight is a long-accepted method of standardizing measurements of smokeless tobacco constituents, and there are abundant data in the literature on the levels of various toxicants in different smokeless tobacco products from different regions based on this metric.

- *Per gram nicotine:* This approach is similar to that used by TobReg in the proposed standards for cigarette emissions. It presupposes that users adjust their use patterns to differences in nicotine levels and that normalizing the amount of nicotine will remove the differences in formulation intended to exploit this compensatory behaviour. Compensatory behaviour is somewhat less of a concern with smokeless tobacco, as the principal form of compensation is use of increased amounts, as opposed to cigarettes, with which the intake of nicotine is increased largely by altering puffing behaviour. One concern is that manufacturers might simply add nicotine to the product to meet the standards. An unresolved question with respect to this approach is whether the normalization should be to total nicotine or to nicotine in the free (unprotonated) form. While the free form of nicotine is the form of greatest concern for blood nicotine levels, it is possible to alter the free nicotine levels independently of the total nicotine levels, in ways that might result in dramatic changes in free nicotine levels when the product is mixed with saliva. Manufacturers might be able to increase the amount of nicotine in a product but reduce the pH, thus reducing the fraction in the free form. This approach would be appropriate only if the regulation also included a standard for nicotine.
- *Per gram of residual weight:* This approach normalizes measurements to the weight of product remaining after all of the extractable components have been extracted. It is being evaluated by the United States National Cancer Institute for use in normalizing measurements of smokeless tobacco toxicants. Few data are available, however, on use of this approach, and it would be premature to recommend it.

TobReg considered each of the above approaches and, after weighing their strengths and limitations, recommended that the amount of toxicant be normalized per gram of dry weight of smokeless tobacco. This metric is intended to be a product performance standard rather than a measure of human exposure to toxicants. It is in accordance with currently established laboratory practice and may be modified as that practice is improved.

3.7 Selection of achievable levels for tobacco-specific *N*-nitrosamines and benzo[*a*]pyrene in smokeless tobacco

The criterion used in selecting a level of TSNA for regulation was to identify the low concentrations that have been achieved in existing products, as reported in the literature. That literature includes measurements made over several decades and with various methods in different laboratories, and is for products currently being marketed as well as older products. Some of the differences in reported levels may be due to use of different methods by

different laboratories. In order to identify the concentrations that could be achieved with existing techniques in a range of current products, TobReg concentrated on recent studies in two well-respected laboratories (*12*, *17*) (Table 3).

Examination of the concentrations in current products, including products stated to have low TSNA levels (*12*), showed that a number of products have concentrations of NNN and NNK < 2 µg/g dry weight. Equally important, the results show that the concentrations in other traditional smokeless tobacco products on the market substantially exceed this value. It was TobReg's judgement that concentrations < 2 µg/g dry weight of tobacco could be achieved for NNN and NNK in most major manufacturing markets. While the moist snuff products on the United States market do not include any with a combined concentration of NNN and NNK < 2 µg/g dry weight, the concentration in low-TSNA moist snuff sold in South Africa and other countries (see Table 1) is lower than this level. The lower levels of TSNA reported in products sold in most developing countries (Table 1) include concentrations that are below the recommended upper limit, suggesting that achieving that limit is not beyond the capability of those manufacturers who are currently marketing in Africa and Asia.

The concentrations of TSNA increase in smokeless tobacco during storage at room temperature due to microbial action. Therefore, TobReg recommends that smokeless tobacco be stored and sold under conditions of refrigeration whenever possible and be attributed an expiration or sell-by date to minimize any increase in the levels of TSNA between manufacture and sale.

The regulatory limit recommended for TSNA is a maximal concentration of:

- **NNN plus NNK: 2 µg/g dry weight of tobacco.**

When considering a recommended concentration of benzo[*a*]pyrene, TobReg investigated whether there was justification for any benzo[*a*]pyrene in smokeless tobacco, as it is a product of combustion, and combustion does not occur in smokeless tobacco use. The sources of benzo[*a*]pyrene in smokeless tobacco are curing of tobacco with wood smoke (exposure to benzo[*a*]pyrene as a combustion product of wood) and, to some extent, high ambient general air pollution (*3*). Both sources are avoidable in the production of manufactured smokeless tobacco. Examination of tables 2 and 3 shows that low concentrations of benzo[*a*]pyrene are present (often below the threshold for detection) in most of the newer smokeless tobacco products and in some traditional products. The tables show higher levels in other manufactured products, indicating that there is an opportunity to reduce the benzo[*a*]pyrene levels through regulation.

As benzo[*a*]pyrene is an avoidable contaminant, which is introduced into smokeless tobacco during tobacco growth and curing, TobReg recommends that the concentration be based on the lower level of detection that can be achieved by most laboratories in which tobacco constituents are measured. While sophisticated methods can detect extremely low levels of this toxicant, most can detect concentrations > 4.5 ng/g dry weight of tobacco with readily available techniques, even when testing for PAH in general rather than using methods specific to benzo[*a*]pyrene. TobReg therefore recommends a regulatory level of < 5 ng/g dry weight of tobacco for benzo[*a*]pyrene. As lower detection limits for benzo[*a*]pyrene become technically feasible, TobReg recommends that this recommendation be revised.

The regulatory limit recommended for benzo[*a*]pyrene is a maximal concentration of:

- **benzo[a]pyrene: 5 ng/g dry weight of tobacco.**

3.8 Regulatory considerations and communication of regulatory values and testing results to the public

The purpose of this recommendation is to reduce the concentrations of carcinogens currently present in many smokeless tobacco products to the low levels readily achievable with existing techniques through altered manufacturing practices. This recommendation is not intended to address questions of reduction in risk or harm that may occur when shifting from one tobacco product to another, or the question of whether use of smokeless tobacco should be recommended as a harm reduction strategy to current cigarette smokers.

The mandated limits on carcinogen concentrations recommended in this report constitute a first step towards regulation of smokeless tobacco products by setting performance standards. The immediate next steps would include methods to address the carcinogen levels present in products produced by cottage industries, which might initially have to focus more on education and technology transfer than on regulatory levels.

Mandating levels and disallowing brands with higher levels from the market does not imply that the remaining brands are safe or less hazardous than the brands that are removed. It also does not represent government recognition of the safety of the products that remain on the market. The proposed strategy for limiting carcinogens is based on sound precautionary approaches, similar to those used for other consumer products. As an essential part of this proposal, regulators must assume responsibility to ensure that consumers are not told directly or indirectly or led to believe that smokeless tobacco products that meet the carcinogen limits established pursuant to this proposal are less

hazardous than similar products, have been approved by the government or meet government-established health or safety standards. In particular, ranking of brands by the metric proposed in this report could be interpreted by users as reliable differences in the probable exposure or harm that will result from using different smokeless tobacco brands. Communicating such rankings to the consumer or allowing them to be communicated directly or indirectly is likely to influence user behaviour in ways that will cause harm, similar to that currently caused by communicating the ratings of the International Organization for Standardization (ISO) for tar, nicotine and carbon monoxide to cigarette smokers.

The proposed strategy must be applied in ways that will prevent the new standards from being used as marketing tools to misinform consumers. Unsubstantiated claims for health or exposure on the basis of the proposed testing should be prohibited, as a companion condition essential to responsible implementation of this regulatory strategy.

Measurements of carcinogen levels by brand and all the costs associated with testing and reporting are expected to be the responsibility of tobacco product manufacturers. The results should be reported to the regulatory authority, and a sample of the results should be verified by an independent laboratory. Alternatively, some regulators may wish to conduct the testing themselves, with funding from taxation or licensing of tobacco products.

Given the existing scientific limitations, regulatory authorities have an obligation to ensure that the public is not misled by the results of the recommended testing and regulatory strategy. TobReg recommends that any regulatory approach specifically prohibit use of the results of the proposed testing in marketing or other communications with the consuming public, including product labelling. TobReg also recommends that manufacturers be prohibited from making statements that a brand has met government regulatory standards or from publicizing the relative ranking of brands by testing level. Because information is often transmitted to tobacco users through the kinds of news stories that accompany the implementation of new regulations, it is a responsibility of the regulatory structure to monitor:

- the accuracy of news reports,
- tobacco industry marketing,
- smokeless tobacco users' understanding of the new regulations,
- what smokeless tobacco users interpret the new regulations to mean relative to the hazard of the products remaining on the market and

- whether understanding about the hazard of the remaining products is influencing initiation or cessation rates.

Regulators should pursue whatever corrective action is necessary to prevent consumers from being misled. These monitoring and surveillance concerns are described in more detail in the WHO report, *Evaluation of new or modified tobacco products* (*18*).

3.9 Recommendations

- All products that deliver nicotine for human consumption should be regulated.
- Smokeless tobacco products should be regulated by controlling the contents of the products.
- The metric for measuring toxicants in smokeless tobacco should be the amount per gram of dry weight of tobacco.
- Initially, upper limits should be set for two nitrosamines N′-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and one polycyclic aromatic hydrocarbon, benzo[*a*]pyrene.
- The combined concentration of NNN plus NNK in smokeless tobacco should be limited to 2 μg/g dry weight of tobacco.
- The concentration of benzo[a]pyrene in smokeless tobacco should be limited to 5 ng/g dry weight of tobacco.
- Regulation of the distribution and sale of smokeless tobacco products should include a requirement for affixation of the date by which the product must be sold or returned to the manufacturer and a requirement for refrigeration of the product before sale in order to limit the increase in the concentration of nitrosamines that occurs over time of storage.

3.10 Acknowledgement

This report was prepared on the basis of a discussion paper written for TobReg by Stephen S. Hecht, Ph.D., American Cancer Society Research Professor and Wallin Land Grant Professor of Cancer Prevention at the University of Minnesota Masonic Cancer Center, Minneapolis, Minnesota.

3.11 References

1. *The scientific basis of tobacco product regulation: report of a WHO study group*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 945).
2. *The scientific basis of tobacco product regulation: second report of a WHO study group*. Geneva, World Health Organization, 2008 (WHO Technical Report Series, No. 951).
3. International Agency for Research on Cancer. *Smokeless tobacco and some tobacco-specific* N-*nitrosamines*, 2007. Lyon, IARC Press (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 89).
4. Teo KK et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case–control study. *Lancet*, 2006, 368:647–658.
5. Brunnemann KD, Hoffmann D. Chemical composition of smokeless tobacco products. In: *Smokeless tobacco or health. An international perspective*. Bethesda, Maryland, National Cancer Institute, 1992 (Smoking and Tobacco Control Monograph No. 2).
6. International Agency for Research on Cancer. *Tobacco smoke and involuntary smoking*. Lyon, IARC Press, 2004 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83).
7. *Gothiatek standards. 4-12-2008*. Stockholm, Swedish Match Company. http://www.swedishmatch.com/en/Snus-and-health/Our-quality-standard-GothiaTek/GothiaTek-standards/ Access 4-12-2008
8. Zaridze DG et al. Carcinogenic substances in Soviet tobacco products. In: O'Neill IK, Chen J, Bartsch H eds. *Relevance to human cancer of* N-*nitroso compounds, tobacco smoke and mycotoxins*, Lyon, IARC Press, 1991 (IARC Scientific Publications No. 105:485–488).
9. O'Connor RJ, Hurley PJ. Existing technologies to reduce specific toxicant emissions in cigarette smoke. *Tobacco Control*, 2008, Suppl 1:i39–48.
10. International Agency for Research on Cancer. *Polynuclear aromatic compounds. Part 1, chemical, environmental, and experimental data*, 1983. Lyon, IARC Press (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 32).
11. McNeill A et al. Levels of toxins in oral tobacco products in the UK. *Tobacco Control*, 2006, 15:64–67.
12. Stepanov I et al. New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels. *Nicotine and Tobacco Research*, 2008, 10:1773–1782.
13. Idris AM et al. Unusually high levels of carcinogenic tobacco-specific nitrosamines in Sudan snuff (*toombak*). *Carcinogenesis*, 1991, 12:1115–1118.
14. Idris AM, Ahmed HM, Malik MO. Toombak dipping and cancer of the oral cavity in the Sudan: a case–control study. *International Journal of Cancer*, 1995, 63:477–480.
15. Idris AM, Prokopczyk B, Hoffmann D. Toombak: a major risk factor for cancer of the oral cavity in Sudan. *Preventive Medicine*, 1994, 23:832–839.
16. Straif K et al. Carcinogenicity of polycyclic aromatic hydrocarbons. *Lancet Oncology*, 2005, 6:931–932.

17. Richter P et al. Surveillance of moist snuff: total nicotine, moisture, pH, unionized nicotine, and tobacco-specific nitrosamines. *Nicotine and Tobacco Research*, 2008, 10:1645–1652.

18. WHO Scientific Advisory Committee on Tobacco Product Regulation. *Statement of principles guiding the evaluation of new or modified tobacco products*. Geneva, World Health Organization, 2003.

4. Overall recommendations

This report addresses two types of products that currently concern scientists because of their potential for harming public health and the inadequacy of regulations governing their promotion, sale and use. Electronic nicotine delivery systems (ENDS) deliver nicotine and other substances directly to the lung, unaccompanied by tobacco smoke. They are marketed under a variety of brand names and descriptions around the world but fall into a regulatory gap in most countries. Few studies have documented their content or emissions, and claims that WHO approves their use for smoking cessation have been circulated. Smokeless tobacco products are also used in many countries, and scientifically documented differences have been found in their content and formulations that may explain the observed differences in adverse health outcomes. Substantial variation in carcinogen levels has been found in smokeless tobacco products marketed in different regions and among products marketed within a region. It is desirable and feasible to lower these levels through better manufacturing and sales practices.

Of the topics discussed at the fifth meeting of TobReg, ENDS and smokeless tobacco were deemed to be most important for issuing recommendations for regulation.

4.1 Electronic nicotine delivery systems (ENDS): regulatory recommendations and research needs

4.1.1 *Main recommendations*

ENDS designed for direct nicotine delivery to the respiratory system fall into a regulatory gap in most countries, escaping regulation as drugs and avoiding the controls on tobacco products. There is currently insufficient evidence to assess whether ENDS products could be used to aid cessation, create or sustain addiction, or deliver constituents other than nicotine to smokers. Clinical trials, behavioural and psychological studies and post-marketing studies at individual and population levels are needed to answer these questions. Claims imputing health benefits, reduced harm or use in smoking cessation should be prohibited until they are scientifically proven. ENDS products should be

regulated as nicotine delivery devices; when such regulation is not possible, they should be subjected under tobacco control laws to regulation of contents and labelling, prohibitions against public use and restrictions on advertising, promotion and sponsorship.

4.1.2 *Significance for public health policies*

ENDS might benefit public health if they promote smoking cessation, but they might create public health risks if they sustain nicotine dependence by allowing nicotine intake where smoking is prohibited or if they increase initiation and transition to cigarette smoking among people who would not otherwise have used tobacco. Smokers who attempt to quit may use ENDS in place of evidence-based treatments, potentially delaying smoking cessation and increasing the risks for smoking-attributable disease if they are ultimately ineffective as nicotine replacement therapy devices.

4.1.3 *Implications for WHO programmes*

WHO continues to support pharmacotherapy only when scientific studies have demonstrated predictable outcomes under specified conditions and when products have been approved as safe and effective by major drug regulatory authorities. WHO strongly encourages its Member States to prohibit manufacturers of ENDS from issuing claims that WHO endorses their products as legitimate tobacco cessation aids. Member States should ensure that the manufacturers of these products comply with all existing regulatory requirements to preclude unsubstantiated claims that may derail public health efforts in tobacco control.

4.2 Smokeless tobacco: setting regulatory limits for carcinogenic components

4.2.1 *Main recommendations*

The regulatory strategy previously advocated by TobReg for cigarettes should be extended to mandating reductions in toxicant levels in smokeless tobacco. Two groups of toxicants should take priority for regulatory limits because of their carcinogenic potency and the possibility of achieving substantially lower concentrations in smokeless tobacco with existing techniques: tobacco-specific *N*-nitrosamines (TSNA) and polycyclic aromatic hydrocarbons (PAH). Upper limits should be set for the combined concentrations of *N*′-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone at 2 μg/g dry weight of tobacco and for benzo[*a*]pyrene as a marker for carcinogenic PAH at 5 ng/g dry weight of tobacco. Regulators should inform consumers that, like cigarettes, smokeless tobacco products that meet

safety standards may be no less hazardous, and they should prohibit product ranking or publicizing test results that are likely to influence user behaviour in ways that will cause harm. Measuring, testing and reporting should be verified by independent laboratories or government agencies, and expiration dates and refrigeration requirements should be enforced to limit the accumulation of TSNA.

4.2.2 *Significance for public health policies*

Differences in the disease risks associated with smokeless tobacco use in different parts of the world reflect differences in the toxicity of the products available on various markets. While existing evidence has not established that lowering TSNA or PAH levels in smokeless tobacco products will lower cancer risks, it is difficult to justify allowing high levels of known carcinogenic constituents in a product that is known to cause cancer, when lower levels are readily achievable with existing technology. As they do for other consumer products, regulators should lower the concentrations of carcinogens present in smokeless tobacco by limiting the concentrations that can be present in products that are marketed. As lower detection limits become technically feasible, more aggressive targets for mandated lowering can be set by regulatory authorities.

4.2.3 *Implications for WHO programmes*

WHO should begin by advising the regulation of manufactured smokeless tobacco products, even though individuals and cottage industries, which are not easily regulated, often dominate the use and production of smokeless tobacco. WHO should recommend that companion programmes be set up to educate cottage industry producers and to improve production approaches for small producers, in order to address the more difficult problem of limiting carcinogen concentrations in non-manufactured smokeless tobacco. Finally, WHO should reject the notion that manufactured products with higher toxicant levels are acceptable in countries with few economic resources.

This report presents the conclusions reached and recommendations made by the members of the WHO Study Group on Tobacco Product Regulation at its fifth meeting, during which it reviewed two background papers specially commissioned for the meeting and which dealt, respectively, with the following two themes.

1. Devices designed for the purpose of nicotine delivery to the respiratory system in which tobacco is not necessary for their operation.

2. Setting regulatory limits for carcinogens in smokeless tobacco.

The Study Group's recommendations in relation to each theme are set out at the end of the section dealing with that theme; its overall recommendations are summarized in section 4.

ISBN 978 92 4 120955 7