

UCSF

WHO Tobacco Control Papers

Title

WHO TobReg: report on the scientific basis of tobacco product regulation: 5th report of a WHO study group. WHO Technical report series, 989

Permalink

<https://escholarship.org/uc/item/81m4m677>

Author

World Health Organization

Publication Date

2015

WHO STUDY GROUP ON TOBACCO PRODUCT REGULATION

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



World Health
Organization

WHO STUDY GROUP ON TOBACCO PRODUCT REGULATION

Report on the Scientific Basis of
Tobacco Product Regulation:
Fifth 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: fifth report of a WHO study group.

(WHO Technical report series; 989)

1.Tobacco Use Disorder – prevention and control. 2.Tobacco Industry – legislation. 3.Tobacco Control Campaigns. 4.Tobacco – chemistry. 5.Metals, Heavy – adverse effects. 6.Metals, Heavy – toxicity. 7.Metals, Heavy – standards. I.World Health Organization. II.WHO Study Group on Tobacco Product Regulation. III.Series.

ISBN 978 92 4 120989 2

(NLM classification: QV 137)

ISBN (PDF) 978 92 4 069380 7

ISSN 0512-3054

© World Health Organization 2015

All rights reserved. Publications of the World Health Organization are available on the WHO website (www.who.int or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int). Requests for permission to reproduce or translate WHO publications –whether for sale or for non-commercial distribution– should be addressed to WHO Press through the WHO website (www.who.int/about/licensing/copyright_form/en/index.html).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the policies of the World Health Organization.

Printed in Italy

Contents

Participants in the seventh meeting of the WHO Study Group on Tobacco Product Regulation, Rio de Janeiro, Brazil, 4–6 December 2013	7
Acknowledgements	9
1. Introduction	13
2. Novel tobacco products, including potential reduced exposure products: research needs and regulatory recommendations	17
2.1 Introduction	17
2.2 Results of the WHO tobacco products survey, 2014	18
2.3 Impact on public health	20
2.4 Research needs	21
2.4.1 Monitoring	21
2.4.2 Framework for risk assessment	22
2.4.3 Marketing and consumer perception	24
2.4.4 Risk communication	25
2.4.5 Regulatory issues	25
2.5 Regulatory recommendations	27
2.6 References	27
3. Smokeless tobacco products: research needs and regulatory recommendations	31
3.1 Introduction	31
3.1.1 Wide range of products	32
3.1.2 Limited data	33
3.1.3 Novel products and marketing	33
3.1.4 Impact on young people and development of tobacco use	34
3.1.5 Limited treatment options	34
3.1.6 Tobacco “harm reduction”	34
3.2 Results of the WHO tobacco products survey, 2014	35
3.3 Current regional and national regulations	36
3.3.1 WHO African Region	36
3.3.2 WHO Region of the Americas	37
3.3.3 WHO Eastern Mediterranean Region	37
3.3.4 WHO European Region	37
3.3.5 WHO South-East Asia Region	38
3.3.6 WHO Western Pacific Region	39
3.4 Conclusions	39
3.5 Research needs	41
3.5.1 Surveillance and monitoring	41
3.5.2 Product characterization	41
3.5.3 Health effects	41
3.5.4 Economics and marketing	42
3.5.5 Interventions	42
3.6 Regulatory recommendations	42
3.6.1 Interventions and policy	42

3.6.2	Challenges and recommendations for creating a regulatory framework	45
3.6.3	Building capacity	45
3.7	References	47
4.	Reduced ignition propensity cigarettes: research needs and regulatory recommendations	51
4.1	Introduction	51
4.2	Background	52
4.3	Findings	52
4.3.1	New studies since the previous report	53
4.3.2	Country and regional experiences in legislation and its implementation	53
4.3.3	Data on product compliance	54
4.3.4	Risk assessment and perceptions of safety and risk	56
4.3.5	Trends in cigarette-ignited fires before and after adoption of the standard	58
4.3.6	Relevance and shortcomings of the standard	61
4.4	Conclusions	61
4.5	Results of the WHO tobacco products survey, 2014	62
4.6	Research needs	63
4.7	Regulatory recommendations	64
4.8	References	64
	Appendix 4.1. Methods	66
	Appendix 4.2. Summary of ISO 12863	67
	Appendix 4.3 Recent CORESTA presentations by industry relevant to the technology of reduced ignition propensity cigarettes	68
5.	Non-exhaustive priority list of toxic contents and emissions of tobacco products	71
5.1	Introduction	71
5.2	Findings of the review	72
5.3	Recommendations	73
5.4	Non-exhaustive list of priority toxic contents and emissions of tobacco products	74
5.5	References	75
6.	Overall recommendations	77
6.1	Novel tobacco products	77
6.1.1	Main recommendations	77
6.1.2	Significance for public health policies	78
6.1.3	Implications for WHO programmes	78
6.2	Smokeless tobacco	78
6.2.1	Main recommendations	78
6.2.2	Significance for public health policies	79
6.2.3	Implications for WHO programmes	79
6.3	Reduced ignition propensity cigarettes	79
6.3.1	Main recommendations	79
6.3.2	Significance for public health policies	79
6.3.3	Implications for WHO programmes	79
6.4	Non-exhaustive list of toxic contents and emissions of tobacco products	80

6.4.1	Main recommendation	80
6.4.2	Significance for public health policies	80
6.4.3	Implications for WHO programmes	80
7.	Regulation of tobacco smoke: commentary on the status quo	81
7.1	Background	81
7.2	Proposed actions	84
7.3	Issues relevant to setting upper limits	85
7.4	References	87
Annex 1.	Novel tobacco products, including potential reduced exposure products: research needs and recommendations	89
	Abstract	90
	Background	91
	Concept of “harm reduction”	92
	Methods	93
	Data sources	93
	Selection criteria	93
	Data extraction and synthesis	94
	New marketed and test-marketed products and products with emerging use	94
	Oral tobacco products	95
	Modified or alternative smoked products	106
	Waterpipes	119
	Notable alterations to traditional products	122
	Technologies under development	125
	Substitution of traditional tobacco burning by heating	126
	Combination of changed tobacco processing and filter structure	126
	Modification of filter structure	132
	Research in progress as presented at the 2013 CORESTA meeting	134
	Summary	136
	Non-combustible oral products	136
	Cigarettes and cigarette-like devices	139
	Conclusions	143
	Acknowledgements	143
	References	145
	Appendix. Questionnaire on new tobacco products, including products with potentially “modified risk”	157
Annex 2.	Role of ammonia in delivery of free nicotine: recent work and analytical challenges	161
	Introduction	161
	Recent publications on nicotine transfer to smoke	162
	Recent publications on nicotine uptake	164
	Current role of ammonia technology	166
	References	169
Annex 3.	Reducing the dependence potential of manufactured cigarettes by reducing their nicotine content to levels that cannot cause or sustain addiction	173
	Introduction	174
	Tobacco addictiveness model	175

Nicotine addiction	176
Individual variation in response to nicotine	177
Delivery of nicotine from tobacco	178
Dual reinforcement model of addiction	179
Drug expectancy	181
Social and contextual factors	181
Summary	182
Establishing a threshold for addiction	183
Nicotine self-administration	183
Acquisition of nicotine dependence	185
Reinforcing effects of low-nicotine cigarettes	185
Addiction threshold versus reinforcement threshold	186
Threshold for conditioned stimulus	187
Summary	188
Feasibility of reducing nicotine	189
Cigarette nicotine delivery	189
Methods for reducing nicotine in tobacco	190
Denicotinized or reduced-nicotine cigarettes	191
Free-base nicotine in low-delivery cigarettes	192
Products that lead to compensatory smoking	193
Product formulation and approaches to nicotine reduction	194
Summary	195
Potential behavioural and population outcomes	196
Potential effects on cigarette consumption	197
Potential effects on topography and smoking behaviour	197
Potential effects on abstinence and quitting	198
Potential effects on acquisition of cigarette use	199
Potential unintended behavioural consequences	200
Potential population differences	200
Potential health effects	201
Potential illicit sales of nicotine-containing cigarettes	202
Models of population effects	202
Summary	204
Policy approaches to nicotine reduction	205
Comprehensive regulation of nicotine	205
Performance standards	206
Gradual versus sudden reduction	207
Alternative forms of nicotine	208
Cessation and behavioural treatment	208
Surveillance	209
Consumer education and beliefs	210
Public support for a reduced nicotine policy	210
Unintended market consequences	211
Summary	212
Conclusions	213
Recommendations	214
References	215

Participants in the seventh meeting of the WHO Study Group on Tobacco Product Regulation

Rio de Janeiro, Brazil, 4–6 December 2013

Members

- Dr D.L. Ashley, Director, Office of Science, Center for Tobacco Products,
US Food and Drug Administration, Rockville, Maryland, United States of
America
- Professor O.A. Ayo-Yusuf, Dean, School of Oral Health Sciences, Sefako
Makgatho Health Sciences University, Pretoria, South Africa
- Professor A.R. Boobis, Biochemical Pharmacology, Centre for Pharmacology
and Therapeutics, Department of Medicine, Imperial College, London;
Director, Public Health England Toxicology Unit, Imperial College, London,
United Kingdom
- Dr Vera Luiza da Costa e Silva, Independent Consultant, Senior Public Health
Specialist, Rio de Janeiro, Brazil
- Dr M.V. Djordjevic, Program Director/Project Officer, Tobacco Control
Research Branch, Behavioral Research Program, Division of Cancer
Control and Population Sciences, National Cancer Institute, Bethesda,
Maryland, United States of America
- Dr N. Gray, Honorary Senior Associate, Cancer Council Victoria, Melbourne,
Australia†
- Dr P. Gupta, Director, Healis Sekhsaria Institute for Public Health, Mumbai,
India
- Dr S.K. Hammond, Professor of Environmental Health Sciences, School of
Public Health, University of California, Berkeley, California, United States
of America
- Dr D. Hatsukami, Professor of Psychiatry, University of Minnesota,
Minneapolis, Minnesota, United States of America
- Dr J. Henningfield, Professor (Adjunct), Behavioral Biology, The Johns
Hopkins University School of Medicine; Vice President, Research, Health
Policy, and Abuse Liability Pinney Associates, Bethesda, Maryland, United
States of America
- Dr A. Opperhuizen, Director, Office for Risk Assessment and Research,
Utrecht, The Netherlands
- Dr G. Zaatari (Chair), Professor and Chairman, Department of Pathology and
Laboratory Medicine, American University of Beirut, Beirut, Lebanon

Facilitators of the WHO FCTC Conference of the Parties Working Group on Articles 9 and 10

- Dr P. Altan, Tobacco Control Department, Ministry of Health, Ankara, Turkey
- Ms A.C. Bastos de Andrade, Head of Tobacco Products Control Department, Agência Nacional de Vigilância Sanitária, Rio de Janeiro, Brazil
- Dr Katja Bromen, Policy Officer, Tobacco Control Team, European Commission, Directorate-General for Health and Consumers, Unit D4, Substances of Human Origin and Tobacco Control, Brussels, Belgium
- Mr D. Choinière, Director, Tobacco Products Regulatory Office, Controlled Substances and Tobacco Directorate, Health Canada, Ottawa, Ontario, Canada

Presenters

- Dr G. Ferris Wayne, California, United States of America
- Dr R. Grana, Postdoctoral Fellow, Center for Tobacco Control Research and Education, University of California, San Francisco, California, United States of America
- Dr M. Parascandola, Epidemiologist, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Maryland, United States of America
- Dr R. Talhout, National Institute for Public Health and Environment, Centre for Health Protection, Bilthoven, The Netherlands

Convention Secretariat of the WHO FCTC (Geneva, Switzerland)

- Ms K. Brown, Programme Officer

WHO Regional Office for the Americas

- Dr A. Blanco, Regional Advisor, Tobacco Control, Washington DC, United States of America

WHO Secretariat (Prevention of Noncommunicable Diseases, Geneva, Switzerland)

- Ms M. Aryee-Quansah, Administrative Assistant, Tobacco Free Initiative
- Dr A. Peruga, Programme Manager, Tobacco Free Initiative
- Dr V.M. Prasad, Project Manager, Tobacco Free Initiative
- Ms G. Vestal, Technical Officer (Legal), Tobacco Free Initiative

Acknowledgements

WHO has many people to thank for the production of this fifth report of the WHO Study Group on Tobacco Product Regulation (TobReg). Ms Gemma Vestal coordinated the production, with the supervision and support of Dr Armando Peruga and Dr Douglas Bettcher.

Work on the report began shortly after the fifth session of the Conference of the Parties to the WHO Framework Convention on Tobacco Control (WHO FCTC) in Seoul, Republic of Korea, 12–17 November 2012, and continued after the sixth session, in Moscow, Russian Federation, 13–18 October 2014. This report will be presented by the Director-General of WHO to the 136th session of the Executive Board in Geneva, Switzerland, to be held 25 January–3 February 2015.

We thank all the members of TobReg for their full, whole-hearted dedication, time and unfailing commitment to fulfilling their mandate to advise WHO on tobacco product regulation, a highly complex area of tobacco control. As independent experts, members of TobReg serve WHO without remuneration. In response to the requests to WHO made by the Conference of the Parties at its fifth session, TobReg members provided guidance in drafting the terms of reference for commissioning a series of reviews to serve as background documents and as a basis for discussions at TobReg's seventh meeting, held in Rio de Janeiro, Brazil, in December 2013.

We thank the authors of the background paper on novel tobacco products, Dr Irina Stepanov, Dr Lya Soeteman-Hernández and Dr Reinskje Talhout, for their highly informative document. Their work was overseen by Dr Mirjana Djordjevic (TobReg). The full background paper is appended as Annex 1 to this report.

We also recognize our colleagues Dr Samira Asma, United States Centers for Disease Control and Prevention, and Dr Mark Parascandola, United States National Cancer Institute, for providing WHO with a draft of their report

entitled *Smokeless tobacco and public health: a global perspective*. This authoritative, voluminous report, published in 2014, was ably synthesized by Dr Dorothy Hatsukami (TobReg) and Ms Lindsay Pickell, BLH Technologies, and subsequently presented to TobReg at its seventh meeting.

We also acknowledge the authors of the background paper on reduced ignition propensity cigarettes, Dr Greg Connolly and Dr Hillel Alpert, both at the Harvard School of Public Health. They thoroughly and enthusiastically updated the original TobReg paper on reduced ignition propensity cigarettes, which was published in 2008. The work on this background paper was overseen by Dr Alan Boobis (TobReg) and Professor O.A. Ayo-Yusuf (TobReg).

The background paper on reducing the dependence potential of manufactured cigarettes by reducing their nicotine content to levels that cannot cause or sustain addiction was written by Mr Geoff Ferris Wayne. It is appended as Annex 3 to this report. WHO thanks Mr Wayne for the time and effort invested in writing the paper, which was presented to TobReg in December 2013, and for continuing to work with TobReg in finalizing their conclusions and recommendations on this important topic. Work on the background paper was overseen by Dr Jack Henningfield, who unfortunately resigned from TobReg in January 2014. WHO would like to take the opportunity to express its deepest gratitude to Dr Henningfield for his years of dedicated, effective service to TobReg. He was one of TobReg's "thought leaders" and a prolific writer.

The Conference of the Parties at its fifth session also requested WHO to draw up a non-exhaustive priority list of toxic contents and emissions of tobacco products. Work on this chapter was led by three TobReg members, Dr David Ashley, former Chair of the WHO Tobacco Laboratory Network (TobLabNet), Dr Antoon Opperhuizen, current Chair of TobLabNet, and Dr Ghazi Zaatari, current Chair of TobReg.

At its seventh meeting, TobReg discussed the role of ammonia in increasing the rate of delivery of nicotine to the brain. The background paper on this topic was written by Ms Christina Watson, United States Centers for Disease Control and Prevention. For the benefit of academics and policy-makers, this paper is appended to the report as Annex 2. Work on this paper was overseen by Dr David Ashley (TobReg).

The report also includes a commentary by Dr Nigel Gray, one of the pioneers of TobReg, on regulation of tobacco smoke and the status quo. Dr Gray, in his ninth decade, passed away peacefully on 20 December 2014. Dr Gray was renowned in the international tobacco control community as an activist, scholar and visionary. As a TobReg member, Dr Gray provided leadership and invaluable insight in an area that is often highly complex, as most studies have been conducted by the tobacco industry, and many Member States did

not have the capacity to analyse them thoroughly. The WHO Tobacco Free Initiative considered that inclusion of Dr Gray's commentary in this report was a fitting tribute to the life of a prime "thought leader" in TobReg. Dr Gray's legacy can be found in the many TobReg recommendations that have been published throughout the years.

To ensure that WHO delivered the information requested on tobacco product regulation to the Conference of the Parties, through the Convention Secretariat, WHO and TobReg worked closely with the facilitators of the Working Group on Articles 9 and 10 of the WHO FCTC. WHO acknowledges the significant contributions of Ms Ana Claudia Bastos de Andrade (Brazil), Mr Denis Choinière (Canada), Dr Katja Broman (European Union) and Dr Peyman Altan (Turkey).

WHO also acknowledges the assistance of colleagues of the Convention Secretariat throughout production of this document, namely: Ms Karlie Brown, Ms Guangyuan Liu and Dr Tibor Szilagyi (Technical Officers), Dr Haik Nikogosian (former Head of the Convention Secretariat) and Dr Vera da Costa e Silva (current Head of the Convention Secretariat).

Administrative support throughout the years of production was provided by WHO colleagues Ms Miriamjoy Aryee-Quansah, Mr Gareth Burns, Ms Elaine Alexandre Caruana, Mr Luis Madge, Ms Elizabeth Tecson and Ms Rosane Serrao.

Special thanks go to Dr Adriana Blanco, Tobacco Control Regional Adviser, WHO Regional Office for the Americas, for ensuring a smooth TobReg meeting in Brazil. We also sincerely thank Ms Ana Claudia Bastos de Andrade, Agência Nacional de Vigilância Sanitária (ANVISA), Brazil, for heroically hosting the seventh meeting of TobReg in Rio de Janeiro, Brazil, in December 2013, while at the same time defending ANVISA from a number of lawsuits instigated by the tobacco industry. In addition, ANVISA provided much needed financial assistance to make the meeting become a reality.

We also express our appreciation to the WHO editor, copy-editor and proof-reader and to the layout and typesetter company, Talk Infosystems, in India, for their eye for detail and their patience with the various rounds of editing.

Last but not least, WHO expresses its profound gratitude to former interns at the Tobacco Free Initiative who contributed large amounts of their internship time to the fruition of this document: Ms Aurelie Abrial, Ms Colleen Ciciora, Mr Adrian Diaz, Dr Richelle Duque, Ms Mary Law, Ms Christina Menke, Ms Hannah Patzke and Ms Angeli Vigo. It is our hope that they continue to work passionately in some aspects of tobacco control, regardless of the bright careers they follow in the future.

Undoubtedly, many people to whom we are indebted are not mentioned here, because there were so many people involved in production of this report. We apologize for any omission. We therefore thank both those who are named and those who are not named. Without your assistance and support, none of this would have been possible. Thank you very much.

1. Introduction

The WHO Study Group on Tobacco Product Regulation (TobReg)¹ is mandated to provide the WHO Director-General with scientifically sound, evidence-based recommendations for Member States about tobacco product regulation. In line with the provisions of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control (WHO FCTC), TobReg identifies approaches for regulating tobacco products that pose significant public health issues and raise questions for tobacco control policy.

Regulation of tobacco products is essential for tobacco control and is endorsed by the WHO FCTC in provisions of its Articles 9, 10 and 11. Regulation serves public health goals by meaningful surveillance of the manufacture, packaging, labelling and distribution of tobacco products. Scientifically based principles for implementing the provisions create synergy and mutual reinforcement of the regulatory practices described in each article.

Tobacco product regulation includes regulating their contents and emissions by testing, measuring and mandating disclosure of the results and regulating their packaging and labelling. Government supervision is required for manufacture and for enforcement of regulations on 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 associated with them, the probable exposure, 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 content or to limit the advertising, promotion and sponsorship of such products.

TobReg reviews the scientific evidence on topics related to tobacco product regulation and identifies the research necessary to fill regulatory gaps in

¹ http://www.who.int/tobacco/industry/product_regulation/tobreg/en/

tobacco control. It is composed of national and international scientific experts on product regulation, treatment of tobacco dependence and laboratory analysis of tobacco contents and emissions. As a formalized entity of WHO, TobReg 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 seventh meeting of TobReg was held in Rio de Janeiro, Brazil, on 4–6 December 2013. The discussions mainly addressed the request of the Conference of the Parties (COP) of the WHO FCTC at its fifth session (Seoul, Republic of Korea, 12–17 November 2012) to WHO to:

- Monitor and follow closely the evolution of new tobacco products, including products with potentially “modified risks”, and to report any relevant development to the COP.
- Direct some of its activities towards aspects of addictiveness (or dependence liability) of both smoked and smokeless tobacco products that remain to be studied.
- Monitor and research country experience and scientific developments with respect to reduced ignition propensity cigarettes.
- Identify measures likely to reduce the toxicity of both smoked and smokeless tobacco products, and describe the evidence supporting the effectiveness of such measures and the experience of Parties on the matter for consideration by the COP.
- Compile, make available to Parties and update a non-exhaustive list of the toxic contents and emissions of tobacco products, and provide advice on how such information could be best used by Parties.
- Prepare draft fact sheets on measures recommended in the partial guidelines for implementation of Articles 9 and 10 of the WHO FCTC.
- Continue and report on progress in validation of analytical chemical methods for testing and measuring cigarette contents and emissions.

Subsequent to this request, a number of background documents were commissioned. In addition, information on the availability and regulation of novel tobacco products, smokeless tobacco products and reduced ignition propensity cigarettes was collected in a WHO survey of tobacco products sent to all Member States. Ninety countries responded, representing approximately 77% of the world's population.

This report focuses on four main topics for which TobReg has issued clear recommendations: novel tobacco products, smokeless tobacco, reduced ignition propensity cigarettes and a non-exhaustive priority list of toxic contents

and emissions of tobacco products. The document that served as the basis for discussions on novel tobacco products is included in this report as Annex 1, and a background paper on the industry practice of adding ammonia to increase the rate of delivery of nicotine to the brain is included as Annex 2. At its eighth meeting, TobReg will review the topic of “reducing the dependence potential of manufactured cigarettes by reducing their nicotine content to levels that cannot cause or sustain addiction”, as the discussions on this topic did not result in fully agreed recommendations for research and regulation. The background document for the discussion at the seventh meeting in December 2013 is nevertheless provided as Annex 3 for the information of researchers and policy-makers.

The report also includes a commentary, which is based on a paper written independently by Dr Nigel Gray, one of the pioneers of TobReg, on regulation of tobacco smoke and the status quo, which was presented at the seventh meeting in December 2013. Unfortunately, Dr Gray, in his ninth decade, passed away peacefully on 20 December 2014.² TobReg members unanimously recommended that his thoughtful commentary be included in recognition of the importance of its content and goals and of Dr Gray as a leader and visionary in public health and tobacco control.

TobReg hopes that the conclusions, recommendations and advisory notes contained in this report will be useful to countries in implementing the product regulation provisions of the WHO FCTC.

² See WHO’s tribute to Dr Nigel Gray at <http://www.who.int/tobacco/communications/highlights/nigelgray/en/>.

2. Novel tobacco products, including potential reduced exposure products: research needs and regulatory recommendations

- 2.1 Introduction
- 2.2 Results of the WHO tobacco products survey, 2014
- 2.3 Impact on public health
- 2.4 Research needs
 - 2.4.1 Monitoring
 - 2.4.2 Framework for risk assessment
 - 2.4.3 Marketing and consumer perception
 - 2.4.4 Risk communication
 - 2.4.5 Regulatory issues
- 2.5 Regulatory recommendations
- 2.6 References

2.1 Introduction

This section of the report is based on a background paper commissioned by WHO (appended as Annex 1 to this report), which served as the basis for discussion on the topic at the seventh meeting of the WHO Study Group on Tobacco Product Regulation (TobReg) in Rio de Janeiro, Brazil, in December 2013.

A wide variety of novel tobacco product types and technologies have entered world markets since 2000. According to WHO, “new” or “novel” tobacco products, in addition to containing tobacco, must meet at least one of the following criteria:

- New or unconventional technology is used, such as vaporization of tobacco into the lungs or use of menthol pellets in a cigarette filter.
- The product type has been on the market for less than 12 years; these include dissolvable tobacco products.
- The product type has been on the market for longer, but the market share has increased in areas in which the type was not traditionally used, such as smokeless tobacco products being introduced into countries where they were not previously available.
- The product is marketed, or work has been published to allow it to be marketed, with the claim that it could reduce exposure to harmful chemicals.

Some novel products are designed for oral use, such as dissolvable tobacco products and “snus” manufactured in the USA (1–3). Others are in essence modified cigarettes that may include specially treated tobaccos, novel filters or

novel ways of delivering inhaled tobacco (e.g. at a lower burning temperature or by heating rather than burning tobacco) (4–6). At least some novel products reflect an industry effort to reduce exposure to harmful tobacco or smoke constituents and have been marketed with corresponding implicit or explicit health claims. Industry research suggests that more novel products are likely to be introduced in the near future (7, 8).

New tobacco products and types and their unique physical or chemical characteristics may alter consumers' exposure to harmful and addictive tobacco constituents. The results of these changes, whether positive or negative, may be difficult to anticipate. The characteristics of novel products and any associated health claims may potentially increase their addictiveness and appeal, thereby promoting continued use. Even when a novel product is relatively less toxic than conventional cigarettes, it may be marketed or adopted primarily as an adjunct to smoking, delaying cessation for some people by providing a means to relieve nicotine craving temporarily when smoking is not possible (3, 9). Novel products may also appeal to new users, including adolescents who would not otherwise initiate tobacco use (2, 3). In order to address the public health issues related to novel products adequately, all products that can be used as a means to facilitate cessation, lead to initiation and addiction or result in maintenance of smoking through dual use—both those that contain tobacco and those that do not—should be regulated to maximize any benefits and minimize harm.

A systematic approach to monitoring novel tobacco products entering international markets is instrumental to guiding tobacco control and assessing their potential public health impact. Basic principles for the evaluation of new and potentially reduced-harm tobacco products require consideration of the actual exposure to and intake of the constituents, behavioural adaptation to the product, marketing approaches, consumer perceptions and modes and populations of use (5, 10).

2.2 Results of the WHO tobacco products survey, 2014

A questionnaire on smokeless tobacco products, electronic nicotine delivery systems, reduced ignition propensity (RIP) cigarettes and novel tobacco products³

³ Products that represent variations on cigarettes, cigars, pipe tobacco, roll-your-own tobacco or oral tobacco in markets that traditionally carry these types of products were excluded. Also, for the purposes of this report, electronic nicotine delivery systems, such as electronic cigarettes, and herbal cigarettes are not included; a specific document covers such products (document FCTC/COP/6/10 Rev., http://apps.who.int/gb/ctc/PDF/cop6/FCTC_COP6_10Rev1-en.pdf, accessed on 10 December 2014).

was sent to all WHO Member States in 2013.⁴ Novel tobacco products were found to be available for sale in 13 Member States representing 28% of the world population. Regulation of novel products may be one factor in their limited availability, as regulations govern the production (in 26 Member States, representing 26% of the world population), distribution (33 Member States, 32%) and sale (39 Member States, 32%) of these products. Only three of the Member States in which novel products are sold reported domestic manufacture; seven reported that all such products are imported, and three did not report the origin of manufacture. Government sales licences for novel products are required by 11 Member States (28% of the world population), and 44 (34%) have policies restricting the sale of these products to minors; when specified, the minimum age for sale to minors was 16–21 years.

Regulation of marketing and promotion of novel products is only slightly more widespread than regulation of sales. Comprehensive bans on tobacco advertising, promotion and sponsorship of novel tobacco products are in place in 41 Member States (35% of the world population), while 32 Member States (38%) reported no such ban. Claims on the packaging of these products that they modify or reduce risk or harm were reported by nine Member States (26%), but the characteristics or contents of these products were regulated for their potential to cause harm in only one of the nine Member States; no health claims were reported in five Member States.

Overall, the worldwide sale of novel products is limited; however, more than half of all Member States, representing more than half the world population, remain open to the introduction of novel products with no restriction on sales, marketing or product characteristics.

⁴ A total of 90 countries, including 86 Parties to the WHO FCTC, had responded to the survey as of 9 April 2014. These countries, representing 77% of the world's population, are:

- WHO African Region: Botswana, Congo, Gabon, Ghana, Kenya, Mali, Mauritania, South Sudan, Zambia;
- WHO Region of the Americas: Barbados, Belize, Bolivia (Plurinational State of), Brazil, Canada, Chile, Colombia, Costa Rica, Dominica, Ecuador, Guatemala, Honduras, Jamaica, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, United States of America;
- WHO European Region: Austria, Belarus, Belgium, Croatia, Czech Republic, Estonia, Finland, France, Georgia, Hungary, Iceland, Latvia, Lithuania, Netherlands, Norway, Poland, Slovakia, Spain, Sweden, Russian Federation, Turkey, Uzbekistan;
- WHO Eastern Mediterranean Region: Bahrain, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Morocco, Oman, Pakistan, Qatar, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates;
- WHO South-East Asia Region: Bangladesh, Bhutan, India, Indonesia, Maldives, Myanmar, Thailand; and
- WHO Western Pacific Region: Australia, Brunei Darussalam, Cambodia, China, Fiji, Japan, Lao People's Democratic Republic, Malaysia, Mongolia, New Zealand, Palau, Philippines, Republic of Korea, Tonga, Tuvalu, Viet Nam.

2.3 Impact on public health

Development of new tobacco products that are less toxic or less addictive could be a component of a comprehensive approach to reducing tobacco-related deaths and disease, particularly among tobacco users who are unwilling to quit or are unable to break their dependence on tobacco. However, new products that increase the risk for exposure or encourage tobacco use could result in greater harm to individual users or to the population as a whole (11).

Evidence of the population impact of novel products is limited. The United States (US) Food and Drug Administration Tobacco Product Scientific Advisory Committee (12) reviewed information on dissolvable tobacco products and concluded that the likelihood of abuse of these products may be lower than that for conventional smoked and smokeless tobacco products, and that exclusive use of dissolvable products should be less hazardous than cigarette smoking. The report noted, however, that no epidemiological data were available to assess absolute or population risks.

Dissolvable tobacco products have undergone significant transformation in both formulation and packaging since they were first introduced onto the US market, but with little commercial success, and it is not clear whether these products will persist in the USA or internationally. In contrast, novel snus products appear to be gaining popularity in the USA (13). These products are differentiated from traditional smokeless products in advertising (9, 13) and are often promoted as versions of popular cigarette brands that can be used discreetly in public, in bars, offices and airplanes, where smoking is banned (9).

Both novel snus and dissolvable products can suppress symptoms of smoking abstinence, although products with different nicotine content have different effects (14–16). Surveys in Scandinavia show that snus has been used effectively for cessation, predominantly among male smokers (17–19), but the extent to which these products can substitute completely for cigarettes in smokers in other countries is unknown because of differences in the context of tobacco use and in populations. While smokers in the USA are generally dissatisfied with the taste of snus and dissolvable products, they may use these products to reduce their risk (20, 21) or to satisfy nicotine craving in locations where smoking is banned. More thorough surveillance of population responses to dissolvable products and snus in test market areas will be essential to provide tobacco control professionals with the data necessary to recommend policy (22).

Modified cigarettes or alternative tobacco-burning or -heating devices developed and marketed as potential harm-reducing devices have generated little public awareness or acceptance (23). Previous studies on use of cigarettes modified to yield fewer toxicants did not find a substantial reduction in actual exposure to these toxicants (e.g. 24). Furthermore, decreasing the content

of a limited number of carcinogens may not decrease the overall health risk and could potentially affect the concentrations of other carcinogens in smoke (23). The introduction of new materials in product construction, in cigarette filler or elsewhere, might generate new chemicals with unknown health consequences. Some other novel cigarette devices, such as those that heat rather than burn tobacco, appear to generate lower yields of toxic constituents than conventional products and lower levels of biomarkers (25); however, no studies have been conducted to determine whether use of these products results in a significantly lower disease burden than use of cigarettes. These types of product may also indirectly encourage cigarette consumption by promoting a safer image of cigarette use overall (5). Population effects are difficult to assess in view of the lack of market penetration and short market life of alternative cigarette designs.

2.4 Research needs

2.4.1 Monitoring

Systematic global surveillance should provide accurate, timely data on new tobacco products and products with emerging or expanding use, including when, where, how and what types of products have been introduced, which populations are targeted, how the products are used and their impact on the use of other tobacco products. The aim of surveillance should be not only to identify novel products but also to assess the likelihood that such products will gain a market share. The data to be collected should include:

- a description of the product (composition, physical parameters, design features, package) from a random sample (e.g. by the International Standards Organization [ISO] method) to account for factors such as storage conditions and differences per production batch;
- marketing and promotion;
- their cost relative to that of other tobacco products;
- awareness and perception of the product and attitudes toward tobacco control policies;
- the prevalence and patterns of use, including use with other products;
- the results of cognitive testing and/or focus groups to determine the best way to describe the product to respondents for full comprehension;
- uptake by young people and whether its use leads to use of other tobacco products;
- development of dependence;

- reasons for use;
- groups targeted for product use, such as young people, women and populations with co-morbid medical and mental disorders;
- behavioural measures (e.g. topography); and
- exposure to toxicants and nicotine in the product.

2.4.2 Framework for risk assessment

A global regulatory framework should be drawn up for assessing new products, in order to evaluate the validity of claims made by industry and to assess potential harm. General guidelines for assessing the risks associated with modified tobacco products have been proposed by the Tobacco Product Scientific Advisory Committee (10) and by the Society for Research on Nicotine and Tobacco (5). The main issues are outlined below.

Conventional machine measurements are not sufficient to assess the delivery of toxicants by novel smoke- or vapour-generating products. Traditional methods, such as smoking machine measurements, used for conventional cigarettes may have to be adapted or new methods developed, because puffing behaviour and the physical and chemical characteristics of new products vary, particularly those with inhaled aerosols, and because exposure time may be different. Human behavioural studies should be conducted to understand better the smoking behaviour associated with each potential reduced-exposure product (PREP).

*Use of standardized machine-generated yields per milligram of nicotine would minimize the variation among methods (26).*⁵ In contrast to smoking machines, smokers tend to adjust their puff volume and inter-puff interval to attain the desired biological level of nicotine. Adjustment of the toxicant level per milligram of nicotine as obtained from smoking machines to a smoker's nicotine intake can provide a better estimate of the actual level of toxicants to which smokers are exposed (27). This approach was an important factor in an assessment of the reduction in risk associated with titanate nanoparticles (7, 28), while a reduction in toxicant levels was not seen after standardization per milligram of nicotine.

A reduction in the toxicant level in mainstream cigarette smoke per milligram of nicotine does not necessarily reduce risk. Even when toxicant levels are normalized to nicotine, product design may alter user behaviour and result in different risks. Taking larger puffs can result in smoke particles being drawn deeper

⁵ The available standards for machine yields are those of ISO and TobLabNet, which pertain only to cigarettes. Although there are tests for yields from e-cigarettes, they have not yet been standardized.

into the lungs. Normalization by level of nicotine does not address these behavioural differences. For example, studies of smoking behaviour of Eclipse cigarettes showed that, in comparison with estimates made from smoking machines, smokers took larger puff volumes and more frequent puffs than of conventional cigarettes (4, 29). Variations in puffing behaviour and in physical and chemical characteristics, particularly of inhaled aerosols, and the differences in exposure time should be considered when evaluating new products.

A method is required to assess changes in risk associated with each PREP. There is no agreed method for assessing the risks associated with toxicants in a complex mixture such as mainstream smoke. At present, the “margin-of-exposure” approach is considered the most appropriate for estimating the risks associated with individual smoke components (30, 31). The margin of exposure is defined as the ratio of a critical toxicological end-point (e.g. a no-observed-adverse-effect level or a benchmark dose) to an appropriate exposure dose metric: the higher the margin of exposure, the lower the risk. Although interpretation of this measure depends on extrapolation (e.g. between and within species and types of exposure), it has been used successfully to assess novel tobacco products (30, 31). A limitation of the margin-of-exposure approach is that it is intended for single compounds, not exposure to mixtures; additive effects can be calculated, but, as synergistic effects cannot be taken into account, the risks may be underestimated. If the margin of error increases because the concentration has decreased in a PREP, the synergistic effects are expected to decrease and the risk will be reduced disproportionately; on the other hand, if the margin of error decreases, the overall outcome is unknown because the impact of synergistic effects cannot be determined without carefully designed studies.

Biomarkers of exposure are toxicant-specific; therefore, biomarkers of effect are needed to assess the health effects of PREPs. Wide variation in the concentrations of biomarkers of exposure are found among individuals using the same PREP, which is presumed to reflect both individual smoking and tobacco use behaviour and inter-individual differences in metabolism. Therefore, while group mean biomarkers of exposure tend to be reduced when comparing the use of a PREP and smoking, the wide variation may result in some users not experiencing a decrease in exposure. Often, only a few biomarkers of exposure are measured, and the possibility of increased levels of unmeasured toxicants in PREPs cannot be excluded. For instance, in a study of a British American Tobacco process (tobacco-blend treatment), the levels of carcinogens such as formaldehyde and benzo[*a*]pyrene were increased (32). Correlations between reduced yields and biomarkers of disease (effect) must be studied to properly assess potential long-term health risks and the full range of tobacco-related diseases, including cardiovascular disease, pulmonary disease, cancer and fetal toxicity (25, 33).

Post-market surveillance of novel products is crucial for determining their effects on population health. Pre-market evaluation cannot fully remove uncertainty about how products will be used and their effects once they are introduced onto the market. Post-market surveillance can help to identify emerging issues once a product is being used by the broader population, such as consumer response, potential for abuse, use by minors, dual use, long-term effects of use or accidental ingestion by children (34). A post-market regulatory framework is also required for monitoring ingredients and constituents, as for conventional cigarettes. Consideration should be given to which contents and emissions of novel products are priorities. For instance, in methods for measuring waterpipe emissions, priority should be given to nicotine, polycyclic aromatic hydrocarbons (PAH), aldehydes and carbon monoxide (CO).

New products should also be assessed for their potential to recruit new users, their potential to discourage smoking cessation and their effects on other forms of tobacco use. Considerations in evaluating the potential public health impact of novel tobacco products include their potential to recruit new consumers who previously did not use tobacco, potential progression to smoking conventional cigarettes, potential to discourage smoking cessation, and whether the products will be used exclusively or will lead to significant dual (or multi-) tobacco product use.

2.4.3 Marketing and consumer perception

Recently, companies have changed the way in which they interact with both current and prospective customers. Web sites promoting specific brands of tobacco are a relatively new form of marketing for tobacco companies (35). Research should be conducted to determine how web sites and other new media are being used to communicate brand identity, advertise brand events and promotions and introduce new products. Social media should also be monitored for new trends.

Packaging plays a significant role in shaping perceptions of novel products. Brand extension of traditional products to novel products may enhance their acceptability through a recognizable brand name. Some novel products may be less expensive than the traditional products, which may favour their acceptance.

Research should be conducted on how tobacco users perceive newly introduced products and the accompanying direct and implicit health claims made by tobacco manufacturers. For example, analysis of smokers' responses to advertisements for potential reduced-exposure cigarettes (Omni, Eclipse and Advance) showed that, although the advertisements did not explicitly state that the products were healthy or safe, smokers perceived them as being associated

with lower health risks and fewer carcinogens than other cigarettes (36). Effective regulation must take into account the perceptions arising from advertisements in addition to the explicit content of the advertising text.

An important aspect of novel tobacco products is whether they are marketed as products as such, as a means of reducing cigarette smoking or for use when smoking is not possible. These different approaches may have substantial effects on the use and public health impact of a new product.

2.4.4 Risk communication

Effective approaches for providing accurate, understandable information to health professionals and the general public should be identified in order to prevent or reverse any misperceptions about novel products. General communication rules with regard to the content of messages, the type of media, the messenger and timing should be considered, and messages should be tailored to different target groups. Correct health information can be effective in changing consumers' and tobacco control professionals' perceptions of products (37, 38). Counter-marketing messages may also be effective in discouraging current and former smokers from becoming dual users of smokeless tobacco and cigarettes (39).

2.4.5 Regulatory issues

Although marketing in the USA has emphasized the Swedish origin of snus (9), snus manufactured in the USA differs from that made in Sweden with regard to moisture content, pouch size and the content of nicotine and other constituents (40–42). Furthermore, the higher levels of tobacco-specific nitrosamines (TSNA) in the latest versions of Camel Snus indicate that either the tobacco type or the tobacco processing method (or both) used in manufacturing this product is different from that for Swedish snus. Therefore, those researchers who advocate replication of the “Swedish experience” in other countries should be cautious. Analysis of the characteristics of these products should be country-specific.

Regulation of tobacco product nomenclature would require tobacco manufacturers to justify the use of existing tobacco product names for newly developed products. Individual and public health may be harmed if brand extension perpetuates use of multiple tobacco products with the same name.

The carcinogenic potential of smokeless tobacco products varies worldwide with the nature of the product used. Promotion of novel smokeless tobacco products as a harm-reduction strategy in countries where the locally marketed products are highly toxic could be particularly detrimental (43–45).

Tobacco control measures such as taxation, smoke-free workplaces and clean air laws may stimulate the development and adoption of novel product types. Research should be conducted on the impact of tobacco control measures on marketed products, such as their toxicity or addictiveness.

Changes in tobacco use from conventional cigarettes to products that do not involve the burning of tobacco suggest that the focus on exposure to “second-hand smoke” should evolve to the more inclusive concept of “second-hand tobacco”. Both psychological and behavioural considerations, such as social acceptability by non-users and initiation by new users, and biochemical aspects, such as accidental ingestion or experimentation by children and exposure to tobacco constituents at home, must be considered. For instance, it has been shown that non-smoking residents, including children, living with smokeless tobacco users can be exposed to high levels of nicotine and other constituents of tobacco by contact with contaminated household surfaces (46).

2.5 Regulatory recommendations

All new and emerging tobacco products should be regulated under the WHO FCTC. The regulatory framework could be extended to include not only existing and emerging tobacco products but also products that are “gateways” to or substitutes for smoking, such as non-tobacco *shisha*, electronic cigarettes, herbal cigarettes and herbal snuff. When regulation under the WHO FCTC is not feasible, novel products should at least be monitored to determine their effects.

A notification or premarket authorization should be required for all novel products. When feasible, a regulatory body should determine which products are allowed on the market, on the basis of scientific evidence of potential public health benefit. In line with criteria developed by the US Food and Drug Administration, the burden of proof should lie with manufacturers, while the established regulatory body should have the authority to decide whether the information provided is sufficient. Any other required scientific data should be provided by manufacturers and audited by independent scientists. The financial burden for establishing such a system should be borne by the industry. Regulatory strategies developed by the US Food and Drug Administration could be used as a basis for deciding on best practices (10).

The prevalence of new tobacco products and their use should be monitored in each country to determine whether a product is a priority for regulation or other tobacco control measures. Novel products that are introduced onto the market should be monitored for unanticipated population outcomes, including

- unrecognized toxicity;

- increased or sustained prevalence of tobacco use by recruitment of new users, relapse of ex-smokers or maintenance of tobacco use in current smokers who might otherwise have quit;
- dual use with cigarettes or another conventional tobacco product; and
- initiation of tobacco use with a novel product by adolescents or other populations at risk and eventual switching to cigarette smoking (“gateway” effect).

Regulatory bodies should prepare strategies for clearly communicating information about novel products to both professionals (such as general practitioners) and the general public.

2.6 References

1. Rainey CL, Conder PA, Goodpaster JV. Chemical characterization of dissolvable tobacco products promoted to reduce harm. *J Agric Food Chem* 2011;59:2745–51.
2. Romito LM, Saxton MK, Coan LL, Christen AG. Retail promotions and perceptions of R.J. Reynolds’ novel dissolvable tobacco in a US test market. *Harm Reduction J* 2011;8:10.
3. Southwell BG, Kim AE, Tessman GK, MacMonegle AJ, Choiniere CJ, Evans SE et al. The marketing of dissolvable tobacco: social science and public policy research needs. *Am J Health Promot* 2012;26:331–2.
4. Slade J, Connolly GN, Lymperis D. Eclipse: does it live up to its health claims? *Tob Control* 2002;11(Suppl 2):ii64–70.
5. Hatsukami DK, Henningfield JE, Kotlyar M. Harm reduction approaches to reducing tobacco-related mortality. *Annu Rev Public Health* 2004;25:377–95.
6. Kleinstreuer C, Feng Y. Lung deposition analyses of inhaled toxic aerosols in conventional and less harmful cigarette smoke: a review. *Int J Environ Res Public Health* 2013;10:4454–85.
7. Deng Q, Huang C, Zhang J, Xie W, Xua H, Wei M. Selectively reduction of tobacco specific nitrosamines in cigarette smoke by use of nanostructural titanates. *Nanoscale* 2013;5:5519–23.
8. Dittrich DJ, Fieblekorn RT, Bevan MJ, Rushforth D, Murphy JJ, Ashley M, et al. Approaches for the design of reduced toxicant emission cigarettes. SpringerPlus 2014;3:374.
9. Bahreinifar S, Sheon NM, Ling PM. Is snus the same as dip? Smokers’ perceptions of new smokeless tobacco advertising. *Tob Control* 2013;22:84–90.
10. Tobacco Product Scientific Advisory Committee. Modified risk tobacco product applications. Draft guidance. Rockville, Maryland: US Food and Drug Administration; 2012.
11. Zeller M, Hatsukami D, Strategic Dialogue on Tobacco Harm Reduction Group. The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for

- action in the US. *Tob Control* 2009;18:324–32.
12. Tobacco Product Scientific Advisory Committee. Summary: TPSAC report on dissolvable tobacco products (Rep. No. March 1, 2012). Rockville, Maryland: US Food and Drug Administration; 2012.
 13. Delnevo CD, Waskowski OA, Giovenco DP, Bover Manderski MT, Hrywna M, Ling PM. Examining market trends in the United States smokeless tobacco use: 2005–2011. *Tob Control* 2014;23(2):107–12.
 14. Blank MD, Eissenberg T. Evaluating oral noncombustible potential-reduced exposure products for smokers. *Nicotine Tob Res* 2010;12:336–43.
 15. Cobb CO, Weaver MF, Eissenberg T. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tob Control* 2010;19:367–73.
 16. Hatsukami DK, Jensen J, Anderson A, Broadbent B, Allen S, Zhang Y, et al. Oral tobacco products: preference and effects among smokers. *Drug Alcohol Depend* 2011;118:230–6.
 17. Ramstrom LM, Foulds J. Role of snus in initiation and cessation of tobacco smoking in Sweden. *Tob Control* 2006;15:210–4.
 18. Lund KE, McNeill A, Scheffels J. The use of snus for quitting smoking compared with medicinal products. *Nicotine Tob Res* 2010;12:817–22.
 19. Scheffels J, Lund KE, McNeill A. Contrasting snus and NRT as methods to quit smoking. an observational study. *Harm Reduction J* 2012;9:10.
 20. Pederson LL, Nelson DE. Literature review and summary of perceptions, attitudes, beliefs, and marketing of potentially reduced exposure products: communication implications. *Nicotine Tob Res* 2007;9:525–34.
 21. O'Connor RJ, Norton KJ, Bansal-Traves M, Mahoney MC, Cummings KM, Borland R. US smokers' reactions to a brief trial of oral nicotine products. *Harm Reduction J* 2011; 8:1.
 22. Biener L, McCausland K, Curry L, Cullen J. Prevalence of trial of snus products among adult smokers. *Am J Public Health* 2011;101(10):1870–6.
 23. McNeill A, Hammond D, Gartner C. Whither tobacco product regulation? *Tob Control* 2012;21:221–6.
 24. Hatsukami DK, Joseph AM, LeSage M, Jensen J, Murphy SE, Pentel P, et al. Developing the science base for reducing tobacco harm reduction. *Nicotine Tob Res* 2007;9(Suppl 4):S537–53.
 25. Hatsukami DK, Feuer RM, Ebbert JO, Stepanov I, Hecht SS. Changing smokeless tobacco products: new tobacco delivery systems. *Am J Prev Med* 2007;33:S368–78.
 26. Burns DM, Dybing E, Gray N, Hecht S, Anderson C, Sanner T, et al. Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization TobReg proposal. *Tob Control* 2008;17:132–41.
 27. Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *J Natl Cancer Inst* 2000;92(2):106–11.

28. Deng Q, Huang C, Xie W, Xu H, Wei M. Significant reduction of harmful compounds in tobacco smoke by the use of titanite nanosheets and nanotubes. *Chem Commun (Camb)* 2011;47:6153–5.
29. Lee EM, Malson JL, Moolchan ET, Pickworth WB (2004) Quantitative comparisons between a nicotine delivery device (Eclipse) and conventional cigarette smoking. *Nicotine Tob Res* 2004;6:95–102.
30. Cunningham FH, Fiebelkorn S, Johnson M, Meredith C. A novel application of the margin of exposure approach: segregation of tobacco smoke toxicants. *Food Chem Toxicol* 49:2921–33.
31. Hernandez LG, Bos PM, Talhout R. Tobacco smoke-related health effects induced by 1,3-butadiene and strategies for reduction. *Toxicol Sci* 2013;136:566–80.
32. Liu C, DeGrandpre Y, Porter A, Griffiths A, McAdam K, Voisine R et al. The use of a novel tobacco treatment process to reduce toxicant yields in cigarette smoke. *Food Chem Toxicol* 2011;49:1904–17.
33. Hatsukami DK, Giovino GA, Eissenberg T, Clark P, Lawrence D, Leischow S. Methods to assess potential reduced exposure products. *Nicotine Tob Res* 2005;7(6):827–44.
34. O'Connor RJ. Postmarketing surveillance for “modified-risk” tobacco products. *Nicotine Tob Res* 2012;14:29–42.
35. Wackowski OA, Lewis MJ, Delnevo CD. Qualitative analysis of Camel Snus’ website message board—users’ product perceptions, insights and online interactions. *Tob Control* 2011;20:e1.
36. Hamilton WL, DiStefano NJ, Ouellette TK, Rhodes WM, Kling R, Connolly GN. Smokers’ responses to advertisements for regular and light cigarettes and potential reduced-exposure tobacco products. *Nicotine Tob Res* 2004;6:S353–62.
37. Biener L, Bogen K, Connolly G. Impact of corrective health information on consumers’ perceptions of “reduced exposure” tobacco products. *Tob Control* 2007;16:306–11.
38. Biener L, Nyman AL, Stepanov I, Hatsukami D. Public education about the relative harm of tobacco products: an intervention for tobacco control professionals. *Tob Control* 2013;22(6):412–7.
39. Popova L, Neilands TB, Ling PM. Testing messages to reduce smokers’ openness to using novel tobacco products. *Tob Control* 2014;23(4):313–21.
40. Foulds J, Furberg H. Is low-nicotine Marlboro snus really snus? *Harm Reduction J* 2008;5:9.
41. Stepanov I, Jensen J, Hatsukami D, Hecht SS. New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels. *Nicotine Tob Res* 2008;10:1773–82.
42. Stepanov I, Biener L, Knezevich A, Nyman AL, Bliss R, Jensen J et al. Monitoring tobacco-specific N-nitrosamines and nicotine in novel Marlboro and Camel smokeless tobacco products: findings from round I of the New Product Watch. *Nicotine Tob Res* 2012;14:274–81.

43. Hatsukami DK, Lemmonds C, Tomar SL. Smokeless tobacco use: harm reduction or induction approach? *Prev Med* 2004;38:309–17.
44. Bedi R, Scully C. Tobacco control—debate on harm reduction enters new phase as India implements public smoking ban. *Lancet Oncol* 2008;9:1122–3.
45. Ayo-Yusuf OA, Burns DM. The complexity of “harm reduction” with smokeless tobacco as an approach to tobacco control in low-income and middle-income countries. *Tob Control* 2012;21:245–51.
46. Whitehead TP, Metayer C, Park JS, Does M, Buffler PA, Rappaport SM. Levels of nicotine in dust from homes of smokeless tobacco users. *Nicotine Tob Res* 2013;15(12):2045–52.

3. Smokeless tobacco products: research needs and regulatory recommendations⁶

- 3.1 Introduction
 - 3.1.1 Wide range of products
 - 3.1.2 Limited data
 - 3.1.3 Novel products and marketing
 - 3.1.4 Impact on young people and development of tobacco use
 - 3.1.5 Limited treatment options
 - 3.1.6 Tobacco “harm reduction”
- 3.2 Results of the WHO tobacco products survey, 2014
- 3.3 Current regional and national regulations
 - 3.3.1 WHO African Region
 - 3.3.2 WHO Region of the Americas
 - 3.3.3 WHO Eastern Mediterranean Region
 - 3.3.4 WHO European Region
 - 3.3.5 WHO South-East Asia Region
 - 3.3.6 WHO Western Pacific Region
- 3.4 Conclusions
- 3.5 Research needs
 - 3.5.1 Surveillance and monitoring
 - 3.5.2 Product characterization
 - 3.5.3 Health effects
 - 3.5.4 Economics and marketing
 - 3.5.5 Interventions
- 3.6 Regulatory recommendations
 - 3.6.1 Interventions and policy
 - 3.6.2 Challenges and recommendations for creating a regulatory framework
 - 3.6.3 Building capacity
- 3.7 References

3.1 Introduction

Smokeless tobacco products present a complex, widespread challenge to public health that has so far received limited attention from researchers and policy-makers. In many regions of the world, such as India, it is the predominant form of tobacco use; and data from the Global Youth Tobacco Survey in 2006 showed that students aged 13–15 surveyed in 132 countries were more likely to report using non-cigarette tobacco products, including smokeless tobacco (11.2%), than smoking cigarettes (8.9%) (2). Data from household surveys,

⁶ The background paper that was the basis for the TobReg deliberations on this issue was a synopsis of a then unpublished report entitled *Smokeless tobacco and public health: a global perspective*, which was published in 2014 (1).

including the Global Adult Tobacco Survey, in a few countries show that use of smokeless tobacco tends to be more frequent among women and people in lower socioeconomic strata, making these populations even more vulnerable to the health and economic consequences of these products. Yet, international tobacco control has focused mainly on cigarettes, with only limited attention to other types of products, including smokeless tobacco.

Smokeless tobacco products have been used worldwide for hundreds of years, and today over 300 million adults worldwide use these products; nearly 270 million of these users live in the WHO South-East Asia Region (3). The serious health effects of smokeless tobacco have been documented: users are at high risk for death from all causes (4–7) and from specific diseases (8–12). In 2004, a working group convened by the International Agency for Research on Cancer (IARC) found that there was sufficient epidemiological and experimental evidence to conclude that smokeless tobacco causes oral cancer, oesophageal cancer and pancreatic cancer in humans (13, 14). At least 28 carcinogens have been identified in smokeless tobacco products, including TSNA, which cause tumours of the nasal cavity, lung, trachea, pancreas, liver and oesophagus in animal models (15). Smokeless tobacco also causes adverse oral health effects, including oral mucosal lesions, leukoplakia and periodontal disease (16, 17). Use of smokeless tobacco increases the risk for cardiovascular diseases (18, 19) and causes adverse reproductive outcomes when used by pregnant women (20, 21). As smokeless tobacco products contain nicotine, users show signs of dependence similar to those of cigarette smokers, including tolerance with repeated use and symptoms of withdrawal upon cessation of use (22). Although smokeless tobacco use, like tobacco smoking, can cause serious damage, it poses substantial challenges for science and public health that are distinct from those presented by tobacco smoking. For example, the extent of health effects may vary by country, with the highest risks in countries including India and lower health risks in Sweden (23), due in part to the types and toxicity of the products used in different countries.

3.1.1 Wide range of products

Understanding the use and effects of smokeless tobacco products is complicated by the diversity of products and the related behaviour. The wide range includes chewing tobacco, snuff, *gutka*, betel quid with tobacco, snus, *toombak*, *iqmik* and tobacco lozenges. Yet, limited data are available on the properties of these products, how they are used and the prevalence of their use in different population groups. It is therefore inappropriate to make generalizations about them as a class. Additionally, the ways in which these products are produced, sold, used and controlled (such as through taxes or marketing restrictions) differ widely by country and region.

3.1.2 Limited data

Although the biological effects of smokeless tobacco are known, the public health impact of its use depends on various factors, including the prevalence and patterns of use of different products, the impact of marketing messages and the effectiveness of prevention and cessation activities. While certain groups have been identified as being at increased risk for use, limited data are available on why particular populations begin to use smokeless tobacco and what factors are most important in preventing or promoting initiation.

3.1.3 Novel products and marketing

Tobacco manufacturers have introduced a new generation of smokeless tobacco products that may have broad consumer appeal because of the addition of attractive flavourings, such as mint or fruit, and new delivery methods, such as lozenges. Products have also been developed that appeal to novice users, new target populations (such as women) or smokers by placing smokeless tobacco in small pouches, thus eliminating the need to spit. Major multinational cigarette companies such as Philip Morris and RJ Reynolds have introduced snus products carrying the well-known Marlboro and Camel brand names, with the marketing expertise of those companies now in the service of smokeless tobacco products. Tobacco control experts warn that increased marketing of these products may have an adverse impact on population health by appealing to young, new users or by inciting current smokers to maintain their nicotine dependence (24). Novel nicotine delivery devices, such as electronic cigarettes, in which heat, rather than combustion, is used to release a vapour containing nicotine, are also being marketed in many countries as an alternative to conventional cigarettes. These products are not addressed in this report, but they may also affect the patterns of tobacco use (25).

Some tobacco companies responded to the widespread smoke-free indoor air laws by advertising smokeless tobacco products to smokers as a temporary alternative to cigarettes for use in situations in which they cannot smoke, using slogans such as “Enjoy tobacco inside the office? You bet” and “Enjoy tobacco on a 4-hour flight? You bet” (26). In addition to increasing smokeless tobacco use, this marketing strategy may impede smoking cessation efforts by making it easier for smokers to maintain their nicotine addiction between cigarettes. This is an example of how progress made in one area of tobacco control, such as through smoke-free indoor air laws, has been followed by adaptation by the tobacco manufacturers, this time by introducing new products and marketing strategies.

3.1.4 Impact on young people and development of tobacco use

Increased initiation of smokeless tobacco use by young people poses a major public health challenge. Smokeless tobacco use among adolescents and young adults rose substantially in the USA during the 1970s after the introduction of products that were more accessible to new users (27). These products had a lower nicotine content and attractive flavourings; evidence suggests that users who begin with low-nicotine “starter” products are more likely to “graduate” subsequently to products with a higher nicotine content (28). In India, marketing of a new smokeless tobacco product, *gutka*, led to increases in the incidences of oral submucous fibrosis and mouth cancer among young people (29, 30). Moreover, a number of studies suggest that smokeless tobacco use is associated with and reinforces use of other tobacco products, including cigarettes. Thus, adolescents who use smokeless tobacco may also be more likely to move on to cigarette smoking (31, 32). The 2014 US Surgeon General’s Report (33) shows that, although US cigarette consumption has decreased substantially, both the consumption and the sale of smokeless tobacco have risen since 2000, with increased use among young adults (18–25 years of age), an overall prevalence of 5.5% and far more common current use among males (10.5%) than females (0.5%).

3.1.5 Limited treatment options

Strategies for cessation of smokeless tobacco use have had mixed success. Behavioural intervention studies in India were successful in rural populations (34, 35) and among schoolteachers (36). Clinical trials of behavioural interventions in settings such as dental offices showed increased abstinence rates among smokeless tobacco users, although the evidence is insufficient to recommend specific intervention components (37, 38). Trials of pharmacotherapy, including nicotine patches, nicotine gum and bupropion, showed no effect on long-term (> 6 months) abstinence rates (39); however, pharmacotherapy may reduce symptoms associated with cessation, such as craving and weight gain (40). Moreover, people who use both cigarettes and smokeless tobacco have higher exposure to nicotine and find cessation more difficult than those who use only smokeless tobacco or who only smoke (41–43). Very few countries have a cessation intervention for smokeless tobacco users in their national programmes. Recently, the National Tobacco Control Programme in India scaled up cessation services for both cigarette and smokeless tobacco users (44).

3.1.6 Tobacco “harm reduction”

The response to the hazards of smokeless tobacco use is complicated by discussions about the possibility of using this form of tobacco as a means to reduce

harm in cigarette smokers. Some forms of smokeless tobacco could provide an alternative to cigarettes; as smokeless tobacco is not associated with the same risks for lung cancer and respiratory diseases as cigarette smoking, it might reduce the overall risk. Although all forms of smokeless tobacco are harmful and cause cancer and other diseases, some forms, including some snus products, have lower concentrations of TSNA and other toxicants than cigarettes and may pose lower overall risks.

This inference requires a number of assumptions, as the health effects of the most widely used forms of smokeless tobacco in a number of Asian countries have not been fully documented, and some smokeless tobacco products used in Bangladesh and India have not been tested. Some products called “snus” in India are highly toxic (45).⁷ Given the wide diversity of smokeless tobacco products and patterns of use around the world, it is inappropriate to make any broad generalization about the level of harm associated with these products as a category, as little is known about their toxic constituents or the exposure of users. Will smokers who begin using smokeless tobacco products completely replace cigarettes, or will they instead become dual product users, which could increase their risk? Additionally, it is essential to consider the overall population impact of increased smokeless tobacco use. For example, will increased promotion of these products increase initiation of tobacco use or adversely affect smoking cessation efforts? While the body of evidence on this topic is growing, definitive studies to answer key questions are lacking, and more research is needed.

3.2 Results of the WHO tobacco products survey, 2014

The WHO questionnaire on smokeless tobacco, electronic nicotine delivery systems, reduced ignition propensity (RIP) cigarettes and novel tobacco products was sent to all WHO Member States in 2013.⁸ The responses indicated that smokeless tobacco products are available in 70 Member States in which 73% of the world population lives. Snuff is widely available in 52 Member States (65% of the world population), snus in 21 (55%), chewing tobacco in 55 (51%), tobacco gum in 17 (49%), dissolvable tobacco in 7 (44%), topical tobacco paste in 5 (40%), dipping tobacco in 10 (29%), creamy snuff in 6 (23%), tobacco water in 8 (20%), *gutka* in 11 (10%), *orbs* in 3 (6%) and blackbull (*iqmik*) in 3 Member States (5%) (dissolvable tobacco products were not distinguished from dissolvable tobacco in the questionnaire). Flavoured smokeless tobacco is also widely available in 34 Member States (61%), the most popular flavours

⁷ See also <http://en.schweden-snus.com/chaini-khaini.html> and <https://www.youtube.com/watch?v=HqOfA7tXhwY>.

⁸ A total of 90 countries, including 86 Parties to the WHO FCTC, had responded to the survey as of 9 April 2014, representing 77% of the world population.

being menthol and mint. It is made available by local manufacturers in three Member States (1%), by cottage industries in 8 (2%), by importation from other countries in 30 (8%), by local manufacture and cottage industries in 5 (26%), by local manufacture and importation in 6 (24%), by cottage industries and importation in 7 (1%) and by local manufacture, cottage industries and importation in 6 Member States (9%). The main countries from which smokeless tobacco products were imported were India, Sweden and the USA.

Smokeless tobacco products are regulated under tobacco laws in 46 Member States (26%), under both tobacco and food safety laws in 8 Member States (19%) and under other laws in 9 (23%); the laws under which these products are regulated were unknown in the remaining Member States. Comprehensive bans on advertising, promotion and sponsorship of smokeless tobacco products are in place in 58 Member States (40%), while there are partial bans in 11 (29%).

The production, distribution and sale of smokeless tobacco products are regulated to some extent in 54 Member States (66%). The production of commercially manufactured smokeless tobacco products is regulated in 41 (60%), the distribution in 43 (59%) and sale in 51 (63%); the production of smokeless tobacco products manufactured in cottage industries is regulated in 24 (31%) Member States, distribution in 30 (33%) and sale in 36 (41%).

The content and ingredients of smokeless tobacco products on the market are regulated in 9 Member States (22%). Governmental sales licences are required in 26 Member States (30%); policies regulating the sale of smokeless tobacco products to minors exist in 64 Member States (72%), and the minimum age for buying these products ranged from 16 to 21 years, when this information was specified.

Taxes are levied on these products as follows: no excise tax in 24 Member States (13%), a uniform ad valorem excise tax in 8 Member States (21%), a uniform specific excise tax in 11 (8%), a mix of uniform ad valorem and uniform specific excise taxes in 4 Member States (2%), uniform ad valorem with minimum specific floors in 3 Member States (1%), a tiered system in 1 Member State (1%), value added tax in 34 Member States (53%) and import duty in 31 (53%).

3.3 Current regional and national regulations

3.3.1 WHO African Region

The introduction of smokeless tobacco products into many eastern and southern sub-Saharan African countries in the past decade or so has gone mainly unnoticed by health and revenue authorities. A number of countries in the Region are now adopting comprehensive tobacco control policies and legislation

to cover all tobacco products, including smokeless products. Sale of these products was officially banned in the United Republic of Tanzania in 2006, although it has been suggested that more stringent monitoring and enforcement are needed. Seychelles has legally mandated pictorial health warnings covering 50% or more of the principal display areas on smokeless tobacco product packaging.

3.3.2 WHO Region of the Americas

In Brazil, smokeless tobacco products may be sold if they are registered with the national health regulatory agency, ANVISA; as none are registered, however, the sale of any such product in Brazil is currently illegal. In Canada, smokeless tobacco products generally fall under broader tobacco product regulations, including prohibition of sale to minors, restrictions on promotion and requirements for manufacturer reporting. Labelling regulations for smokeless tobacco products exist but apply only to chewing tobacco, nasal snuff and oral snuff. In the USA, laws have been enacted that include provisions for product registration, warning labels on all products and enforcement of a minimum age for sale. In addition, under US law, the Food and Drug Administration is authorized to establish limits on the amounts of nicotine, toxicants and additives in smokeless tobacco products, but it has not yet issued any specific regulation on product performance standards. Many countries in the Region, including Chile, Costa Rica, Ecuador, El Salvador, Honduras, Nicaragua, Panama, Peru and Uruguay, have legally mandated pictorial health warnings covering 50% or more of the principal display areas on smokeless tobacco product packaging.

3.3.3 WHO Eastern Mediterranean Region

While the Islamic Republic of Iran has banned importation of smokeless tobacco products and Bahrain has adopted policies banning both the sale and importation of these products, few relevant regulatory controls exist in the Region. Heavy fines have been used to enforce the existing laws. Many countries in the Region, such as Egypt, the Islamic Republic of Iran, Kuwait, Morocco, Oman, Qatar and the United Arab Emirates, have legally mandated pictorial health warnings covering 50% or more of the principal display areas on tobacco product packaging.

3.3.4 WHO European Region

The European Union provides leadership on regulatory practices, including through the recently revised Tobacco Products Directive, which governs the manufacture, presentation and sale of tobacco and related products. The 28

member states of the European Union regulate smokeless tobacco products by prohibiting the sale of tobacco for oral use, which includes all products for oral consumption made of tobacco except those intended for smoking or chewing. Sweden, however, is exempted from this regulation. In many non-European Union countries in Europe, smokeless tobacco is regulated in accordance with regulations on advertising and health warnings similar to those applicable to smoked tobacco products. Turkey has legally mandated pictorial health warnings covering 50% or more of the principal display areas on smokeless tobacco product packaging.

3.3.5 WHO South-East Asia Region

Many Parties in the Region have taken steps to regulate smokeless tobacco (3). Bhutan introduced a policy to ban the manufacture and sale of tobacco products, including smokeless products, in 2004 and in 2010 introduced comprehensive legislation to implement the 2004 policy. Thailand also has provisions to ban the import and sale of these products. Legislation in Bangladesh, India and Nepal requires the display of graphic health warnings on smoked and smokeless products, covering 50%, 85% and 90% of the display area, respectively. Bangladesh, Bhutan, India, Maldives, Myanmar, Nepal, Sri Lanka and Thailand have banned advertisement of smokeless tobacco products. India invoked food safety laws in 2011 to ban *gutka* and *pan masala* containing tobacco, some of the most common forms of smokeless tobacco used in the country. A few states in India, including Maharashtra, have banned production and sale of scented smokeless tobacco products. India has also strengthened pictorial health warnings, used intensive mass media campaigns to inform people of the harm of smokeless tobacco and introduced smokeless tobacco cessation into tobacco dependence treatment guidelines and into the National Tobacco Control Programme. To control illicit trade, India introduced presumptive taxes on smokeless tobacco, based on production capacity; revenue collection on smokeless tobacco products increased by more than fourfold in the past 5 years. Myanmar banned importation of all types of tobacco products, including smokeless tobacco, but illicit trade from neighbouring countries remains a problem. Nepal has banned the use of smokeless tobacco products in public places, and Myanmar banned the sale of these products in certain metropolitan areas and their use in Government workplaces. India, Myanmar and Nepal have policies to prohibit sales of smokeless tobacco products within 100 m of educational facilities. Enforcement is, however, still weak in many countries, and the Region lacks adequate laboratory capacity to test for constituents of smokeless tobacco. The lower taxes on smokeless tobacco than on smoking products lead tobacco users to switch to smokeless tobacco whenever the tax on cigarettes is increased.

3.3.6 WHO Western Pacific Region

In 2010, because of concern about the increasing use of areca (betel nut) and chewing tobacco, the WHO Regional Office for the Western Pacific supported Parties to the WHO FCTC in the Region in preparing a regional action plan, in which specific indicators and actions were identified to reduce betel nut and tobacco use. The report, issued in 2012 (46) was prepared in consultation with countries and territories in which use of betel nut and chewing tobacco is particularly common (Cambodia, Guam, Kiribati, Marshall Islands, Micronesia (Federated States of), Mariana Islands, Palau, Solomon Islands and Vanuatu). The report found that use of betel nut is widespread in parts of Melanesia, principally Papua New Guinea, the Solomon Islands and the Northern Province of Vanuatu, and in the Federated States of Micronesia, particularly in the Northern Mariana islands, the Marshall Islands and Palau and also in the US territory Guam. It recommended that evidence on the harm caused by this type of smokeless tobacco be shared with policy-makers and that community-based strategies be designed to change behaviour in use of smokeless tobacco. Some Parties, such as Singapore, have banned smokeless tobacco products such as chewing tobacco, new tobacco-derivative products such as dissolvable tobacco and nicotine-based products. Singapore has a laboratory for measuring nicotine content in smokeless tobacco products such as chewable tobacco, betel quid and *khaini*. Mongolia and Viet Nam require pictorial health warnings covering 50% or more of the principal display areas on smokeless tobacco product packaging.

3.4 Conclusions

Smokeless tobacco is a global problem, in that the products are used in at least 70 low-, middle- and high-income countries by more than 300 million people. The highest prevalence of use is in South-East Asia, with 89% of users, which also has the highest attributable disease burden and the greatest diversity of product types and forms of use. In Bangladesh, more women use these products than men. In India, use of smokeless tobacco exceeds tobacco smoking among both men and women.

The disease risks directly associated with smokeless tobacco use differ by country and region, due in part to differences in the products and patterns of use. Laboratory analyses have shown widely varying levels of known carcinogens and nicotine in products from different regions, and epidemiological studies have yielded risk estimates for cancer and cardiovascular disease that vary from country to country. Yet data are lacking to quantify these differences in disease risk precisely and to identify the factors that drive them.

Smokeless tobacco use and marketing are public health challenges in a number of countries and regions. While some high-income countries, such as Sweden, have a high prevalence of use of smokeless tobacco with a low nitrosamine content, a reduced prevalence of smoking and strong tobacco control and regulatory frameworks, most countries in which smokeless tobacco is used are low- or middle-income such as Bangladesh, India and other countries in the South-East Asia Region. In these countries, smokeless tobacco products often have very high levels of harmful constituents, marketing of cigarettes is increasing, and a large unorganized business sector makes product control and regulation difficult. Changes in product marketing, patterns of use and tobacco control programmes and interventions may have widely different effects in these different environments.

Changing tobacco industry marketing strategies may influence the future public health impact of smokeless tobacco use. In some high-income countries where restrictions on public smoking have increased and the prevalence of smoking has decreased, tobacco companies have been marketing oral tobacco products to smokers. The impact of this trend on smoking behaviour and possible use of one or more tobacco products together remains uncertain. Multinational tobacco companies are increasingly present, introducing both smoked and smokeless products in low- and middle-income countries.

In many regions, even those in which smokeless tobacco use is highly prevalent, the policies and programmes for prevention and cessation of smokeless tobacco use are generally weaker than those for smoked tobacco products: the prices are lower, the warning labels are weaker, surveillance is less well developed, fewer proven interventions are available, and fewer resources are devoted to prevention and control.

The challenges in monitoring the use and health effects of smokeless tobacco include the diversity of products and types of use, lack of information on the products and their use, the informal, unorganized nature of the market in some regions and limited attention to tailored educational and intervention programmes.

Many gaps remain in research on smokeless tobacco products, including surveillance data, characterization of products, the health consequences of use of the products, including fetal exposure and reproductive outcomes, the economic policies related to smokeless tobacco products and their use and effective region-specific education, prevention and treatment interventions. Various policies have been proposed or implemented in some countries, but data are often lacking on their impact or effectiveness. More evidence-based policies are needed to control smokeless tobacco use, which could include: obliging tobacco companies to disclose the content of smokeless tobacco products; establishing product performance standards for toxicants and maximum pH levels; banning flavourings; requiring effective, relevant health warning

labels; increasing taxes on these products; banning or restricting promotion, sponsorship and marketing of smokeless tobacco; and raising public awareness about the toxicity and health effects of these products. In sum, prevention and cessation of smokeless tobacco use should form an integral part of any comprehensive tobacco control effort.

Capacity for research and public health action on smokeless tobacco is limited in many countries, especially those in which the public health burden is greatest. International infrastructure for research and information-sharing could improve the ability of many countries to reduce the consequences of smokeless tobacco use.

3.5 Research needs

3.5.1 Surveillance and monitoring

Comprehensive surveillance should be conducted to assess the extent of smokeless tobacco use and changes in patterns of use and to evaluate the effectiveness of policies, interventions and other steps that could be taken to reduce its use, even in countries where the products are banned or the prevalence of use is very low. Surveillance and monitoring of trends in use should include information on the populations and subpopulations that use the products, the types of products used, the patterns and intensity of use, combined use with other tobacco products and attitudes, beliefs and perceptions about the products. Surveillance should also include monitoring of changes in use and cessation in use of other tobacco products, including cigarettes.

3.5.2 Product characterization

Given the diversity of products and modes of manufacture around the world, the properties of different products, their constituents and methods of manufacture should be characterized comprehensively. Where the resources are available, biomarker studies to determine actual human uptake (absorption and excretion) of nicotine and other toxicants after active and second-hand exposure (e.g. fetal) to smokeless tobacco would be valuable. Studies should also be conducted on non-tobacco products that are frequently used in conjunction with tobacco, such as areca nut. Products should be tested regularly in order to assess national and regional variations and changes in products over time.

3.5.3 Health effects

The diversity of products, practices and patterns of use also precludes broad generalizations about their health effects. Most studies of health effects have been conducted in India, the Nordic countries and the USA. Because of

differences in the levels of nicotine and other toxicants in smokeless tobacco products, the results from one country cannot be applied to another; even within a country, the products may vary widely. Data are not available for estimating the relative risks for disease associated with the different products, although assessment of country-specific health effects is essential for determining the global burden of disease associated with use of smokeless tobacco.

3.5.4 *Economics and marketing*

Data on pricing, tax structures and sales of smokeless tobacco products and marketing strategies are limited, and there is no information on the cost of health care for treating the diseases caused by use of these products. Such information is necessary to devise policies and programmes for different countries. In view of the high prevalence of smokeless tobacco use in some low- and middle-income countries and among poor and rural populations, information on pricing would be especially important for designing effective public health interventions. Information on prices, taxes, affordability and trade should be collected routinely.

3.5.5 *Interventions*

Population and individual interventions for the prevention and cessation of smokeless tobacco use should be developed and tested, especially interventions tailored to specific populations of users, taking into account cultural differences. Most of the current evidence base for the effectiveness of interventions applies to high-income countries; therefore, interventions designed for use in low- and middle-income countries and in diverse health care settings are necessary.

3.6 Regulatory recommendations

3.6.1 *Interventions and policy*

Tobacco control policies, programmes and interventions applied to cigarettes and smoked tobacco products should also be applied, enforced and monitored, with equal rigor, to smokeless tobacco products, particularly in regions where the prevalence of use is high. Prevention and cessation of smokeless tobacco use should be an integral part of a comprehensive tobacco control programme. Nevertheless, these products pose distinct challenges, and specific policies might depend on the products, patterns of use, marketing and the tobacco control environment. The aspects of smokeless tobacco product regulation listed below should be addressed in particular.

Pay greater attention to smokeless tobacco.

The public health challenge of smokeless tobacco warrants far greater attention and action than it has received so far, considering the extent and complexity of the problem, marketing, trends in patterns of use and lack of effective treatment. Much of the scientific basis for policy to control cigarette use also applies to controlling use of smokeless tobacco.

Make country-specific and product-specific interventions.

No intervention strategy will apply to all countries: approaches must be tailored to the social context, prevalence and trends in consumption of all tobacco products. Furthermore, because of the heterogeneity of the products and how they are made, policy interventions should be specific for each type of product, both manufactured and custom-made.

Apply WHO FCTC requirements to smokeless tobacco products.

Tobacco control policy interventions for cigarettes and other forms of smoking tobacco should also apply to smokeless tobacco products. These interventions include:

- health warnings on product packaging that cover a major proportion of the package and that include text and pictorial depictions, are rotated and are located on the top principal display (Article 11) (Although many countries require health warnings on smokeless tobacco packaging, most labels have only text warnings and lack the graphic images that have been used on cigarette labels.);
- restrictions or bans on advertising, promotion and sponsorship (Article 13);
- restriction of sales to minors (Article 16);
- taxation and pricing policies, with effective compliance, to discourage smokeless tobacco use and to lower demand, including consideration of using taxation of tobacco leaves or a presumptive tax (compounded levy per manufacturing machine), because of the challenge of traditional markets (Article 6);
- obligatory disclosure of the constituents of smokeless tobacco products by manufacturers, comprising all the ingredients and harmful and potentially harmful constituents of the products (Article 10);
- public education about the harms of smokeless tobacco (Article 12), with information, education and communication to raise awareness of the harmful health effects and to dispel myths (Education should be targeted to health professionals, policy-makers, community leaders and the public, with particular attention to young people and women of child-bearing age, especially in geographical areas where tobacco products are made in cottage industries or custom-made at home or at the point of sale.);

- a tracking and tracing mechanism for smokeless tobacco products and prevention of illicit trade (Article 15); and
- promotion and provision of evidence-based interventions for smokeless tobacco cessation (Article 14).

Reduce the hazard associated with smokeless tobacco products.

- *Reduce toxicity:* The levels of known toxicants in smokeless tobacco products vary widely, as do the effects of storage and processing on toxicant levels (25). Requirements that could be introduced to prevent greater toxicity of pre-made and custom-made products include: reducing the use of *Nicotiana rustica*; limiting bacterial contamination, which can promote nitrosation and carcinogen formation; requiring that tobacco be flue- or sun-cured rather than fire- or air-cured; killing bacteria by pasteurization; improving storage conditions, such as refrigerating products before sale; affixing a date of manufacture; and eliminating ingredients such as areca nut and tonka bean, which are known to be carcinogenic (14).
- *Impose product standards (Article 9):* As proposed by TobReg (25), upper limits on toxicants should be mandated for smokeless tobacco products manufactured by industry, with an upper limit for *N*-nitrosornicotine (NNN) plus 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) at 2 µg/g of dry tobacco and an upper limit for benzo[*a*]pyrene at 5 ng/g. Regulatory authorities should require monitoring of levels of arsenic, cadmium and lead in tobacco (47). Implementing such standards does not mean that a product is less hazardous, and tobacco companies should not be allowed to promote products as such.
- *Reduce appeal and addictiveness:* A variety of flavours and other additives are used to enhance the appeal of tobacco products and facilitate uptake (48, 49). Steps to reduce the appeal of and addiction to tobacco products should include banning or regulating sweeteners and flavourings (including herbs, spices and flowers) and setting limits on free nicotine and pH.
- *Apply uniform standards for transnational products:* Exported smokeless tobacco products should be held to the same (or a higher) standard as in the country in which they were manufactured.

No health claim or claim of reduced exposure or harm should be allowed on the basis of currently available evidence. Scientific evidence introduced to support a health claim must be reviewed by an independent, scientific, government regulatory agency (Article 10).

3.6.2 Challenges and recommendations for creating a regulatory framework

Conducting surveillance and research and implementing new policies and interventions to address smokeless tobacco use will require greater scientific and public health capacity in low- and middle-income countries, particularly those with high levels of smokeless tobacco use. Major challenges, however, impede implementation of effective policies and programmes.

Gaps in the evidence base and information

Limited data are available for quantifying the risks associated with smokeless tobacco use, including the burden on health, the economy, the environment and society, in regions and countries. Furthermore, there is almost no information on progress or challenges in smokeless tobacco control.

Recommendation: The Global Tobacco Surveillance System of the US Centers for Disease Control and Prevention and WHO STEP surveys could be extended to provide greater coverage of smokeless tobacco. Smaller, targeted surveys are needed to understand patterns in specific subgroups.

Laboratory testing

Most countries in which smokeless tobacco is widely used lack the technical and financial capacity to evaluate the content and toxicant levels in smokeless tobaccos. Methods, product performance standards and testing regimens should be improved to facilitate inter-country comparisons and to monitor products in countries over time.

Recommendation: Testing methods should be standardized and, ideally, coordinated by region through the WHO Tobacco Laboratory Network (TobLabNet).⁹ Methods for determining nicotine, TSNA and benzo[*a*]pyrene in smokeless tobacco products should be validated. Laboratory capacity should be improved in low- and middle-income countries by partnerships, such as with WHO collaborating centres.

3.6.3 Building capacity

Communication and collaboration among countries are increasingly important. As tobacco use changes, innovative policies and interventions are being introduced in various countries, and the tobacco industry is adopting new marketing strategies. This enormous “natural experiment” provides unique opportunities for research and evaluation, which will require coordinated surveillance, information-sharing and research. With this in mind, the following recommendations are made to enhance collaboration and infrastructure (some of which are described in Article 20 of the WHO FCTC).

⁹ The WHO Tobacco Laboratory Network (TobLabNet) is a global network of government, academic and independent laboratories for strengthening national and regional capacity for testing and research on the contents and emissions of tobacco products, in accordance with Article 9 of the WHO FCTC (http://www.who.int/tobacco/industry/product_regulation/toblabnet/en/).

Create regional knowledge hubs or clearing-houses.

Create regional information hubs or clearing-houses for information on tobacco products, especially smokeless tobacco, that can be readily accessed electronically by people throughout the world. Clearing-houses could provide information about global “best practice” and country experience in regulating smokeless tobacco, product characteristics, patterns of use, policies and interventions and the results of research and evaluations.

Establish an infrastructure for networking, communication and collaboration.

A web portal could be established that would be a repository and index of information on global, regional and country best practice in regulating smokeless tobacco, product characteristics, constituents and ingredients, manufacturing and promotion methods, prices, packaging and marketing. The portal could also bring together the regional hubs or clearing-houses described above and provide a forum for discussion about successes and challenges in smokeless tobacco product regulation, operational and policy research, clinical research design and results and policies.

Encourage collaboration among scientists, tobacco control advocates and policy-makers.

Such collaboration is critical for translating research into policy and ensuring that policy needs inform research. Collaboration among countries and regions will be especially important for comparing different products, environments and interventions. Countries with more mature tobacco control programmes could provide expertise and assistance to countries with newer programmes and policies.

Build research capacity.

Research capacity should be built by better use of existing resources, such as the TobLabNet, the Global Adult Survey and the Global Youth Tobacco Survey. Research capacity could also be enhanced by attracting and training new researchers—especially from middle- and low-income countries—and encouraging collaboration between new and more experienced researchers.

Enhance opportunities for smokeless tobacco product regulation.

Opportunities for evidence-based smokeless tobacco regulation and policy can be increased by international coordination of technical assistance, training and capacity-building; surveillance and enforcement of existing regulations; development and dissemination of testing protocols and product performance standards; and revising existing tobacco control programmes to better address smokeless tobacco.

3.7 References

1. National Cancer Institute and Centers for Disease Control and Prevention. Smokeless tobacco and public health: a global perspective. Bethesda, Maryland: Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, National Cancer Institute (NIH Publication No. 14-7983); 2014 (<http://nccd.cdc.gov/GTSSData/Ancillary/Publications.aspx>).
2. Centers for Disease Control and Prevention. Use of cigarettes and other tobacco products among students aged 13–15 years—worldwide, 1999–2005. *Morb Mortal Wkly Rep* 2006;55:553–6.
3. WHO Regional Office for South-East Asia. Expert group meeting on smokeless tobacco control and cessation, New Delhi, India, 16–17 August 2011. New Delhi.
4. Gupta PC, Bhonsle RB, Mehta FS, Pindborg JJ. Mortality experience in relation to tobacco chewing and smoking habits from a 10-year follow-up study in Ernakulam District, Kerala. *Int J Epidemiol* 1984;13:184–7.
5. Gupta PC, Mehta FS, Pindborg JJ. Mortality among reverse chutta smokers in south India. *Br Med J* 1984;289:865–6.
6. Gupta PC, Mehta HC. Cohort study of all-cause mortality among tobacco users in Mumbai, India. *Bull World Health Organ* 2000;78:877–83.
7. Gupta PC, Pednekar MS, Parkin DM, Sankaranarayanan R. Tobacco associated deaths in Mumbai (Bombay) India. Results of the Bombay Cohort Study. *Int J Epidemiol* 2005;34:1395–402.
8. Rahman MA, Zaman MM. Smoking and smokeless tobacco consumption: possible risk factors for coronary heart disease among young patients attending tertiary care cardiac hospital in Bangladesh. *Public Health* 2008;122:1331–8.
9. Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med* 2009;29:36.
10. Lee CH, Lee KW, Fang FM, Wu DC, Shieh TY, Huang HL, et al. The use of tobacco-free betel-quin in conjunction with alcohol/tobacco impacts early-onset age and carcinoma distribution for upper aerodigestive tract cancer. *J Oral Pathol Med* 2011;40:684–92.
11. Mateen FJ, Carone M, Alam N, Streatfield PK, Black RE. A population-based case–control study of 1250 stroke deaths in rural Bangladesh. *Eur J Neurol* 2012;19:999–1006.
12. Rahman MA, Spurrier N, Mahmood MA, Rahman M, Choudhury SR, Leeder S et al. Is there any association between use of smokeless tobacco products and coronary heart disease in Bangladesh? *PLoS One* 2012;7:e30584.
13. Cogliano V, Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F. Smokeless tobacco and tobacco-related nitrosamines. *Lancet Oncol* 2004;5:708.
14. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 85. Betel quid and areca nut chewing. Lyon: International Agency for Research on Cancer; 2004 (<http://monographs.iarc.fr/ENG/Monographs/vol85/mono85-6>).

pdf, accessed 1 August 2012).

15. Smokeless tobacco or health: an international perspective (Smoking and Tobacco Control Monograph No. 2). Bethesda, Maryland: National Cancer Institute, Department of Health and Human Services; 1992 (Publication No. 92-3461) (<http://www.cancercontrol.cancer.gov/tcrb/monographs/2/index.html>).
16. Shulman JD, Beach MM, Rivera-Hidalgo F. The prevalence of oral mucosal lesions in US adults: data from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Am Dent Assoc* 2004;135:1279–86.
17. Fisher MA, Bouquot JE, Shelton BJ. Assessment of risk factors for oral leukoplakia in West Virginia. *Community Dent Oral Epidemiol* 2005;33:45–52.
18. Boffetta P, Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *BMJ* 2009;339:b3060.
19. Gupta R, Gupta N, Khedar RS. Smokeless tobacco and cardiovascular disease in low and middle income countries. *Indian Heart J* 2013;65:369–77.
20. England LJ, Kim SY, Tomar SL, Ray CS, Gupta PC, Eissenberg T, et al. Non-cigarette tobacco use among women and adverse pregnancy outcomes. *Acta Obstet Gynaecol Scand* 2010;89:454–64.
21. Willis D, Popovech M, Gany F, Zelikoff J. Toxicology of smokeless tobacco: implications for immune, reproductive, and cardiovascular systems. *J Toxicol Environ Health Crit Rev* 2012;15:317–31.
22. Henningfield JE, Fant RV, Tomar SL. Smokeless tobacco: an addicting drug. *Adv Dent Res* 1997;11:330–5.
23. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. *Lancet Oncol* 2008;9:667–75.
24. Henningfield JE, Rose CA, Giovino GA. Brave new world of tobacco disease prevention: promoting dual product use? *Am J Prev Med* 2002;23:226–8.
25. 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). Geneva: World Health Organization; 2009 (http://www.who.int/tobacco/global_interaction/tobreg/publications/tsr_955/en/index.html).
26. O’Hegarty M, Richter P, Pederson LL. What do adult smokers think about ads and promotional materials for PREPs? *Am J Health Behav* 2007;31:526–34.
27. Connolly GN. The marketing of nicotine addiction by one oral snuff manufacturer. *Tob Control* 1995;4:73–9.
28. Tomar SL, Giovino GA, Eriksen MP. Smokeless tobacco brand preference and brand switching among US adolescents and young adults. *Tob Control* 1995;4:67–72.
29. Gupta PC, Sinor PN, Bhonsle RB, Pawar VS, Mehta HC. Oral submucous fibrosis in India: a new epidemic? *Natl Med J India* 1998;11:113–6.
30. Gupta PC. Mouth cancer in India—a new epidemic? *J Indian Med Assoc* 1999;97:370–3.

31. Tomar S. Is use of smokeless tobacco a risk factor for cigarette smoking? The US experience. *Nicotine Tob Res* 2003;5:561–9.
32. Hatsukami DK, Lemmonds C, Tomar SL. Smokeless tobacco use: harm reduction or induction approach? *Prev Med* 2004;38:309–17.
33. The health consequences of smoking—50 years of progress. A report of the Surgeon General. Rockville, Maryland: Department of Health and Human Services; 2014.
34. Gupta PC, Mehta FS, Pindborg JJ, Bhonsle RB, Murti PR, Daftary DK, et al. Primary prevention trial of oral cancer in India: a 10-year follow-up study. *J Oral Pathol Med* 1992;21:433–9.
35. Anantha N, Nandakumar A, Vishwanath N, Venkatesh T, Pallad YG, Manjunath P, et al. Efficacy of an anti-tobacco community education program in India. *Cancer Causes Control* 1995;6:119–29.
36. Sorensen G, Pednekar MS, Sinha DN, Stoddard AM, Nagler E, Aghi MB, et al. Effects of a tobacco control intervention for teachers in India: results of the Bihar School Teachers Study. *Am J Public Health* 2013;103:2035–40.
37. Severson HH. What have we learned from 20 years of research on smokeless tobacco cessation? *Am J Med Sci* 2003;326:206–11.
38. Carr AB, Ebbert JO. Interventions for tobacco cessation in the dental setting. *Cochrane Database Syst Rev* 2006:CD005084.
39. Ebbert JO, Rowland LC, Montori V, Vickers KS, Erwin PC, Dale LC, et al. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev* 2004:CD004306.
40. Dale LC, Ebbert JO, Glover ED, Croghan IT, Schroeder DR, Severson HH, et al. Bupropion SR for the treatment of smokeless tobacco use. *Drug Alcohol Depend* 2007;90:56–63.
41. Hatsukami DK, Severson HH. Oral spit tobacco: addiction, prevention and treatment. *Nicotine Tob Res* 1999;1:21–44.
42. Spangler JG, Michielutte R, Bell RA, Knick S, Dignan MB, Summerson JH. Dual tobacco use among Native American adults in southeastern North Carolina. *Prev Med* 2001;32:521–8.
43. Wetter DW, McClure JB, de Moor C, Cofta-Gunn L, Cummings S, Cinciripini PM, et al. Concomitant use of cigarettes and smokeless tobacco: prevalence, correlates, and predictors of tobacco cessation. *Prev Med* 2002;34:638–48.
44. Varghese C, Kaur J, Desai NG, Murthy P, Malhotra S, Subbakrishna DK, et al. Initiating tobacco cessation services in India: challenges and opportunities. *WHO South-East Asia J Public Health* 2012;1:159–68.
45. Mukherjea A. Tobacco industry co-optation of culture? Converging culturally specific and mainstream tobacco products in India. *Tob Control* 2012;21:63–4.
46. Review of areca (betel) nut and tobacco use in the Pacific. A technical report. Manila: WHO Regional Office for the Western Pacific; 2012 (http://www.wpro.who.int/tobacco/documents/201203_Betelnut/en/).

47. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation. Fourth report of a WHO study group (WHO Technical Report Series, No. 967). Geneva: World Health Organization; 2012 (http://www.who.int/tobacco/global_interaction/tobreg/publications/tsr_967/en/index.html).
48. Henningfield JE, Hatsukami DK, Zeller M, Peters E. Conference on abuse liability and appeal of tobacco products: conclusions and recommendations. *Drug Alcohol Depend* 2011;116(1–3):1–7.
49. Menthol cigarettes and the public health: review of the scientific evidence and recommendations. Washington DC: Tobacco Products Scientific Advisory Committee, Food and Drug Administration; 2011 (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM269697.pdf>).

4. Reduced ignition propensity cigarettes: research needs and regulatory recommendations

- 4.1 Introduction
- 4.2 Background
- 4.3 Findings
 - 4.3.1 New studies since the previous report
 - 4.3.2 Country and regional experiences in legislation and its implementation
 - 4.3.3 Data on product compliance
 - 4.3.4 Risk assessment and perceptions of safety and risk
 - 4.3.5 Trends in cigarette-ignited fires before and after adoption of the standard
 - 4.3.6 Relevance and shortcomings of the standard
- 4.4 Conclusions
- 4.5 Results of the WHO tobacco products survey, 2014
- 4.6 Research needs
- 4.7 Regulatory recommendations
- 4.8 References
- Appendix 4.1 Methods
- Appendix 4.2 Summary of ISO 12863
- Appendix 4.3 Recent CORESTA presentations by industry relevant to the technology of reduced ignition propensity cigarettes

4.1 Introduction

This section addresses emerging issues and provides an update of the work of TobReg on reduced ignition propensity (RIP) cigarettes published in 2008. The document was prepared for the Sixth Session of the Conference of the Parties of the WHO FCTC in October 2014.

Laws have been enacted on the basis of laboratory research conducted by the US National Institute of Standards and Technology, and coalitions of scientists, consumer groups and public health and fire officials have been formed. Countries are enacting legislation and have introduced product-reporting systems for RIP, the costs of testing being paid for by the manufacturers. Despite early claims to the contrary, the marketplace responded by producing reduced-ignition paper and adequate, certified laboratory testing facilities. The costs of manufacture have been minimal. Compliance has been monitored in various countries, and the results are available. Canadian data indicate substantial, sustained compliance by large manufacturers and increasing compliance by smaller ones. Risk assessments indicate little evidence that people smoking RIP cigarettes increased their fire risk-related behaviour and limited evidence of

increased exposure of smokers to toxicants. Evaluations of the impact on fire incidence and casualties are limited by the quality of fire reporting systems, the short time the RIP standard has been in force, secular trends to fewer fires and reduced flammability (e.g. of mattresses and upholstered furniture). Still, the most rigorous evaluations indicate an approximately 30% reduction in fires due to smoking as a result of the RIP regulations. In 2010, the ISO adopted a global standard based on the standard of the US National Institute of Standards and Technology and the American Society for Testing and Materials (1). The scientific evidence from experimental research and emerging population studies show that the current standard is effective in reducing fires and fire deaths. Legislation for RIP cigarettes should nevertheless allow flexibility in improving the standard as the science base grows, particularly with regard to population effectiveness. Countries should adopt the 2010 ISO standard, and manufacturers should all voluntarily adopt RIP cigarette design as part of good manufacturing processes.

4.2 Background

The report of TobReg (2) on the scientific basis for regulating tobacco products included an advisory note on “fire safer” cigarettes. The report concluded that deaths in fires caused by burning cigarettes are a major global problem and that cigarettes with RIP should be mandatory. Standards exist, including the American Society for Testing and Materials E2187 (3), and laboratories accredited according to ISO 17025 are capable of testing RIP cigarettes, the cost being borne by tobacco manufacturers. The report cautioned that, although claims that RIP cigarettes reduce risk should be allowed, the effectiveness of the standard in reducing fires and fire-related deaths should be monitored as the standards are implemented. Any legislation with regard to RIP cigarettes should allow flexibility for strengthening the standard as new research results become available. The report called for international collaboration among interested agencies.

In preparation for the Sixth Session of the Conference of the Parties, TobReg reviewed activities and research since the previous report, including on RIP standards, their adoption, monitoring, their effect on consumer perceptions of the overall risk associated with cigarettes and the effectiveness of RIP cigarettes in reducing fires. As part of this exercise, TobReg requested comments on the relevance of the standard, its shortcomings and areas in which more research is needed (see Appendix 4.1 for details).

4.3 Findings

The regulations for RIP cigarettes are based on a test derived from work performed at the US National Institute for Standards and Technology under the

Cigarette Fire Safety Act of 1991 (4), which led to the development of a repeatable, reproducible test for ignition strength on filter paper, with full-length burn as an indicator of ignition propensity. The method, in which a cigarette is placed flat on a varying number of layers of filter paper in an enclosed chamber, is called the “cigarette extinction method” and is described in detail in the previous report. The test is based on an earlier performance standard, the “mock up furniture ignition method”, in which a burning cigarette was placed on furniture material and tested for fire ignition. The simpler filter paper method correlates well with the furniture test and was codified by ASTM International (1) as ASTM E2187. In 2010, ISO adopted the method as 12863:2010 (5). Neither the National Institute of Standards and Technology nor the ISO standard proscribes the design of the cigarette necessary to meet the standard. The two standards are similar. Appendix 4.2 summarizes the procedure.

4.3.1 New studies since the previous report

Alpert and colleagues (6) reviewed existing patents and literature on RIP-related technologies. Seidenberg et al. (7) conducted tests according to the ASTM method and reported that cigarettes bought in countries that had regulations tended to comply, while those bought in other markets tended to have more full-length burns. Recent meetings of groups on smoke science and product technology of the Cooperative Centre for Scientific Research Relative to Tobacco (CORESTA) in Paris, France, considered a number of abstracts related to RIP (Appendix 4.3), mainly on testing parameters and methods and comparisons of the emissions of RIP cigarettes and other products. Most of the studies on emissions reported no substantial difference between products (8, 9). Studies conducted by independent researchers on changes in toxic emissions of RIP, risk perceptions and population effects are reviewed below.

4.3.2 Country and regional experiences in legislation and its implementation

New York State (USA) was the first jurisdiction to enact RIP regulation, in June 2004. Canada implemented its regulation in October 2005. At the time of the previous report (2), Canada and 18 US states (with 38% of the US population) were the only jurisdictions with active RIP regulations. Since 2008, RIP standards have been implemented in four countries and by all member states of the European Union (10). In South Africa, RIP standards were published as regulations in 2011.¹⁰ In the USA, where 18 states had already adopted the standards, the remaining states did so between 2009 and 2011. Australia adopted the standards in 2010.

¹⁰ <http://www.tobaccocontrollaws.org/files/live/South%20Africa/South%20Africa%20-%20RIP%20Regs%20-%20national.pdf>. See also link to BAT’s communication to customers when the law was implemented in 2012: http://www.batsa.co.za/group/sites/BAT_7N3ML8.nsf/vwPagesWebLive/DO8QVAU2?opendocument&SKN=1.

This experience illustrates a number of legislative strategies for passing RIP laws (11). A coalition including scientists, “burn” advocates, legislators, consumer groups and public health and fire safety officials should be formed to collect data on fires related to cigarette use and the scientific basis of the standard; they should then formulate comprehensive, consistent legislation, conduct public education campaigns and interact with policy-makers. The coalition should be closely advised by experts in science and legislation and take note of progress in other jurisdictions and public information, including information to refute tobacco industry opposition (11, 12).

In the USA, first, a series of international meetings and workshops attended by representatives of countries that later adopted RIP legislation was convened, including scientists, consumer groups, legislators, public health and fire safety officials, to exchange information and form policy. The meetings were supported by grants and contracts from fire and public health agencies. Secondly, use of a uniform standard in all states facilitated adoption of and research on RIP laws and eliminated the industry argument that they would have to design several types of RIP cigarette. Thirdly, hard data were available on the actual harm caused by cigarette fires, and, in some campaigns, “heroes” who had been injured in fires caused by cigarettes were spokespersons. Finally, consensus was achieved that uniform, comprehensive laws must be drafted and reviewed by legal experts; the actual design of the cigarette should not be dictated, but a uniform standard should be complied with. Legislation should allow alteration of the standard in the light of new findings, require that fees for testing be paid by the tobacco industry, prohibit claims of reduced risk and require fees for national implementation and follow-up research. A centralized rapid response team was formed to track progress, refute industry arguments and prevent attempts to weaken legislation. These activities facilitated passage and implementation of RIP laws and eased the passage of subsequent laws. Once the law was passed, states shared their methods of implementation; however, data on actual fires, which would improve the RIP standard, have not yet been shared or reported.

A European Union directive has been adopted, requiring the ISO standard but not compliance of industry with laboratory testing. The laws requiring RIP cigarettes in Australia, the European Union and South Africa cover approximately 20% of the world’s population, who consume approximately 20% of the world’s manufactured cigarettes. Most are high-income countries; adoption by low- and middle-income countries has been limited.

4.3.3 Data on product compliance

Health Canada’s website shows the results of RIP testing in the period 2005–2011, with test results for specific brand styles (13). For simplicity, TobReg has

classified manufacturers as the three major companies (Imperial, Rothmans and JTI) and “other” (which encompasses small importers and local manufacturers). The three major manufacturers have about 97% of the market share (14).

Figure 4.1 shows raw data on full-length burns. A clear difference in RIP compliance can be seen between the major manufacturers and others: the products of the major manufacturers have been well under the RIP standard from the beginning, while the others took longer. The results of binary logistic regression (events/trials) analysis to model the effects of manufacturer group and sampling year (2005–2011) on full-length burns are illustrated in Figure 4.2, which confirms the initial finding that the rate of change in full-length burns was greater for other manufacturers than for the major companies (manufacturer × year interaction, $\chi^2(6) = 241.6, p < 0.001$). It is unclear, however, whether this is due to the effectiveness of the regulation or the number of fires observed, as the major manufacturers hold such a dominant share of the market.

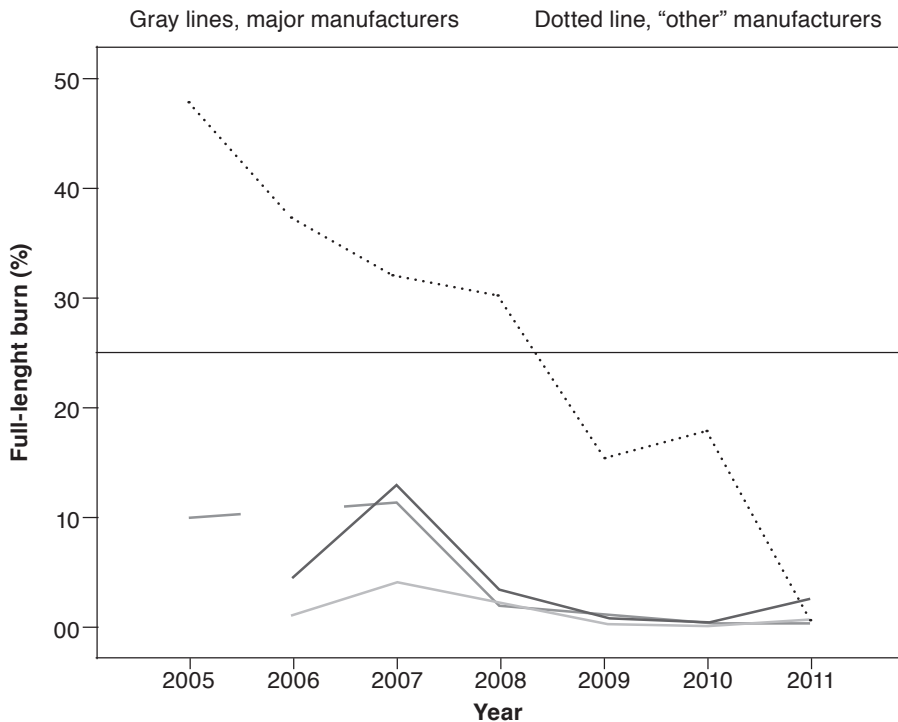


Figure 4.1. Proportions of tested brands showing full-length burn in the ASTM E2187 test method, by manufacturer, Canada, 2006–2011. RIP legislation was introduced in October 2005. Horizontal line, RIP standard (25% full-length burn)

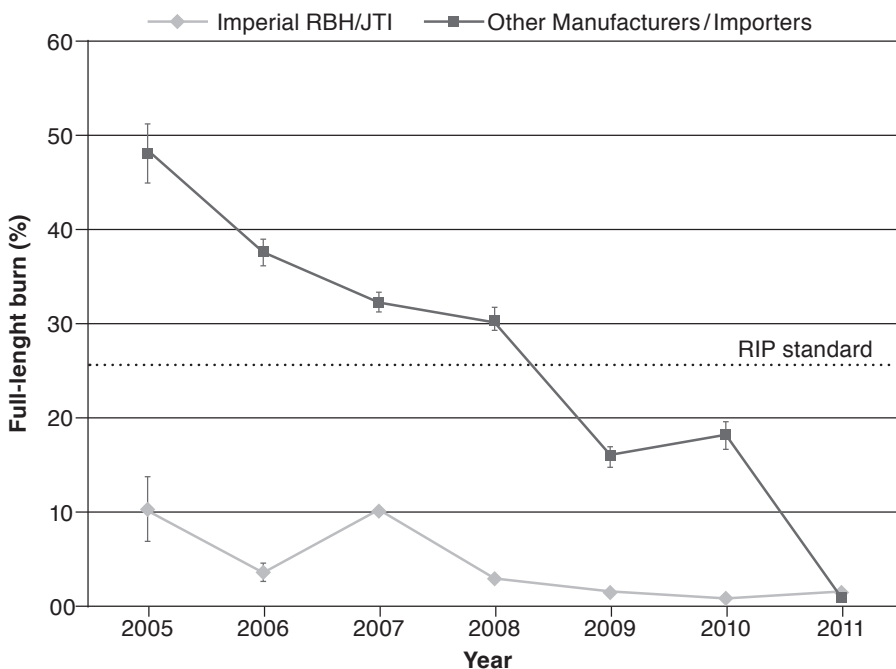


Figure 4.2. Estimated proportions of tested brands with full-length burns in the ASTM E2187 test, by binomial regression on year and manufacturer, Canada, 2006–2011. RIP legislation was introduced in October 2005. Horizontal line, RIP standard (25% full-length burn)

4.3.4 Risk assessment and perceptions of safety and risk

The behavioural and health correlates of introducing RIP cigarettes have been addressed in a few studies. O'Connor et al. (15) examined Canadian smokers' beliefs and behaviour before and 1 year after implementation of the regulation. Using random-digit dialling telephone surveys, they obtained information from 435 smokers aged ≥ 18 years (73% follow-up rate) and found similar levels of fire-risk behaviour, such as smoking in bed (14.7% before and 13.1% after the legislation) and dozing off while smoking (2.3% versus 2.1%). No difference was found in worry about starting a fire with a cigarette. Smokers more frequently reported that their cigarettes self-extinguished "often" after implementation of the law (3.7% before and 14.7% after; $p < 0.001$), but there was no difference in reports of "coal drop-off" (36.4% before, 31.3% after). Seidenberg et al. (16) reported a similar study among smokers in Massachusetts, USA, before and after implementation of the law and found a broadly similar pattern. Of 620 initial respondents, 352 (57%) completed both surveys. The frequency of reports of leaving a cigarette unattended (26.5% vs 28.1%, $p = 0.567$) and smoking in bed (19.2% vs 19.6%, $p = 1.000$) was unchanged; the

proportion of respondents who smoked more than 20 cigarettes per day decreased (21.5% vs 15.6, $p < 0.001$), reports of self-extinction “often” increased (22.3% vs 44.2%, $p < 0.001$), while no increase was reported in “coal drop-off” (43.2% vs 33.7%). There was no change in reported intention to quit.

Adkison et al. (17) studied the effects of RIP cigarette regulation on consumer behaviour and intention to quit between 2004 and 2011 from data obtained in a survey conducted in Australia, Canada, the United Kingdom and the USA (total N = 12 492). This dataset is unique, as it allows assessment of both initial and time-lagged effects, since laws were introduced at different times in each (and in the USA, within) country. Perceptions of cigarette self-extinction increased concurrently with RIP cigarette legislation (odds ratio = 2.7, $p < 0.001$), as did the intention to quit smoking (odds ratio = 1.02, $p < 0.05$), but no effect was seen on the number of cigarettes smoked per day. The intention to quit was more frequent among people who reported that their cigarettes self-extinguished (odds ratio = 1.02, $p < 0.05$). Overall, the RIP safety standards did not have an impact on consumer acceptability, and the study did not indicate any “wear-out” effect (i.e. loss of market share because of implementation of RIP safety standards).

O'Connor et al. (18) reported the results of an 18-day study among 160 smokers in two US cities, in which smokers in one city switched from their usual brand to the RIP version, while those in the other city smoked RIP cigarettes throughout the study. The outcomes of interest included the number of cigarettes smoked per day, smoking topography (puff volume, duration, interval), exhaled CO, saliva cotinine and urine metabolites of selected PAH (pyrene, naphthalene, phenanthrene and fluorene). The authors reported no significant difference in smoking topography, exhaled CO, PAH metabolites (with the exception of phenanthrene) or cotinine as a result of switching to RIP versions. The smoking rate decreased by approximately two cigarettes per day, from 18 to 16. There was a 35% increase in the level of urinary metabolites of phenanthrene, which is an irritant but is not known to be carcinogenic.

June et al. (19) reported the findings of a study of the behaviour and exposure of 42 daily smokers before and 18 months after introduction of the Canadian RIP regulation. The outcomes of interest were the same as in the study of O'Connor et al. (18). No significant differences were seen in smoking topography, exhaled CO, the number of cigarettes smoked per day or urinary cotinine. Significant increases of 14–25% in selected PAH metabolites were noted; if this result is confirmed, it would be a concern because these biomarkers indicate the presence of benzo[*a*]pyrene, a known human carcinogen.

Côté et al. (20) conducted a study supported by Imperial Tobacco Canada of oral exposure to tar and nicotine, using machine smoking estimates and the “part-filter” method (21). Half of the total of 1086 smokers who used 10

specific brands were recruited before and half after introduction of the RIP regulation. Participants were given up to two packs of their usual brand and a kit for collecting filters and were asked to smoke *ad libitum* but to return the kit when 15 filters had been collected. The filters were tested for nicotine retention by gas chromatography with a flame ionization detector, and the results were used to estimate exposure by comparison with calibration curves for each brand, generated from machine smoking parameters. Although the mean number of cigarettes smoked per day was significantly higher before introduction of the law than after (22.1 vs 20.6, $p = 0.0003$), no difference in oral exposure to tar or nicotine was observed. It should be noted that this was a cross-sectional and not a cohort study.

4.3.5 Trends in cigarette-ignited fires before and after adoption of the standard

Research on the effects of the RIP standard on the frequency of cigarette-ignited fires is essential for validating the effectiveness of a laboratory standard in reducing cigarette-related fires and deaths. Studies on the causes of and casualties due to fires confirm that cigarette-associated fires are more likely than other causes to result in injury or death (22–24). Such studies are difficult to conduct because of the quality and number of fire-reporting systems, the short time the RIP standard has been in force and other trends that affect the incidence of fires, including increased resistance of mattresses and upholstery to ignition, smoke detectors, public education, decreased smoking prevalence and changes in where people smoke because of indoor smoking restrictions (25). Such research is also difficult to conduct because legislation on RIP does not require that such studies be conducted or funded, and there is no centralized reporting system in which compliance with the RIP standard is linked to reports of fires. At the time this report was written, neither Australia nor the European Union had published data on fire incidents.

The US National Fire Protection Association reported in 2013 that incidents and deaths in fires related to smoking were at their lowest levels since monitoring began, in 1980 (26). Furthermore, the report commented that adoption of the RIP standard by the 50 US states appeared to be the “principal reason for a 30% decline in smoking material fire deaths from 2003 to 2011”, taking into account the percentage of smokers covered and changes in the resistance of mattresses and upholstery to ignition. Figure 4.3 illustrates the trends in incidents, deaths and injuries found in the study.

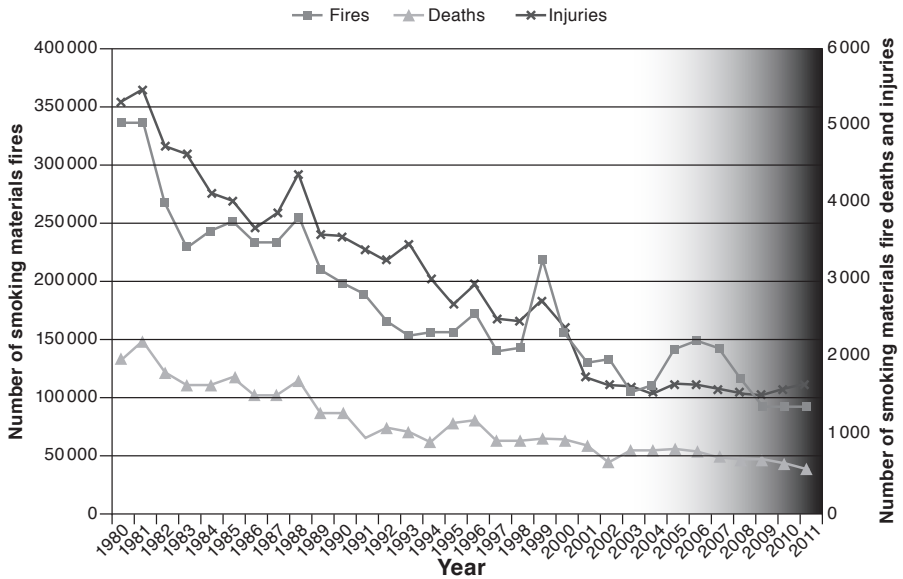


Figure 4.3. Incidents, deaths and injuries related to fires ignited by smoking materials, USA, 1980–2011. The shading indicates the increasing number of states that adopted the standard after 2004. Adapted from Hall (26)

A report prepared by TriData on behalf of Philip Morris International examined the impact of the RIP laws in Ontario and Alberta, Canada, and in New York State, USA, up to 2008–2009 (27). The authors concluded that there was “no substantive decrease attributable to reduced ignition propensity cigarettes”. Trends in Ontario and Alberta are shown in Figure 4.4. Their analysis has a number of serious flaws (D. Hemenway, personal communication); broadly speaking, their evaluation appears to be designed to find no effect (28). Evaluations of regulatory policies must include a counterfactual approach (i.e. What would have happened in the absence of the law?), because there is no control group. Epidemiological approaches and statistical analyses were not, however, used. A major problem in the TriData analyses is the assumption of a straight-line trend, with the absolute number of incidents on the vertical axis, which is then projected to continue unabated. This assumes a rapidly increasing *rate* of decrease and indeed leads to the inference that the number of incidents will fall to zero within a few years and become negative, which is clearly absurd (see their figures 18 and 22). Note, however, that when the trend before RIP implementation is upwards (in New York), they do not draw a trend line for comparison (their figures 36 and 37). They also overlook evidence of possible beneficial effects in Vermont, Massachusetts, New York (their figure 34) and Alberta (their figures 18, 20 and 29).

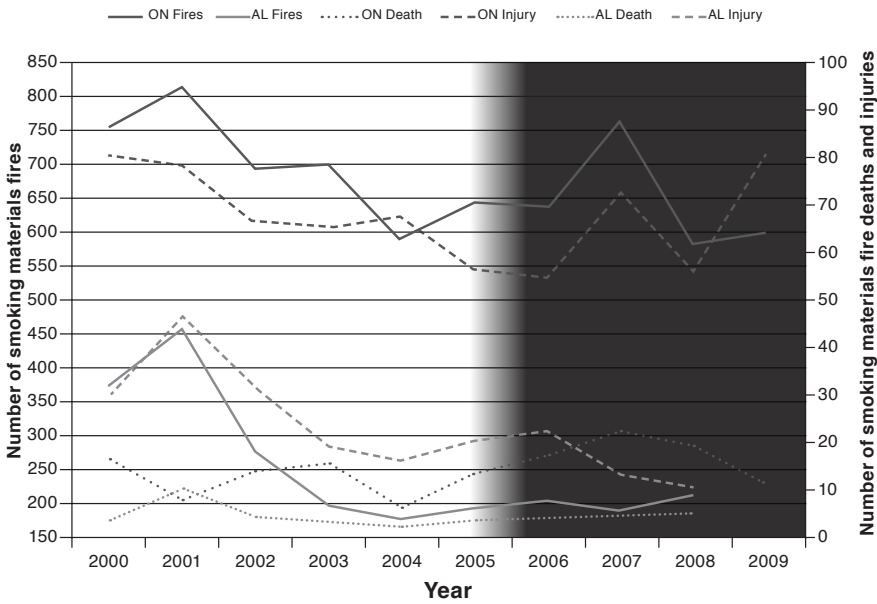


Figure 4.4. Incidents, deaths and injuries from fires associated with smoking materials in Alberta and Ontario, Canada, 2000–2008 or 2009. Shading indicates implementation of the RIP law. Adapted from Frazier et al. (27)

Perhaps the best evidence to date on the population effect of the RIP standard comes from a recent evaluation by Alpert et al. (29) of the effectiveness of the Massachusetts (USA) Fire Safe Cigarette Law in preventing residential fires. The analysis effectively controlled for most potential sources of confounding, other than an increased use of flame retardants, on which information was not available. Massachusetts already had one of the best fire-reporting systems in the USA, and the reporting characteristics did not change after the law came into effect on 1 January 2008. Unintentional residential fires reported to the system in 2004–2010 were analysed to determine which of them were caused by cigarettes, and effect modification by fire scenario factors was analysed in an interrupted time series regression model. Poisson regression was used to analyse the effect of the law on monthly fire rates. Cigarettes caused 1629 unintentional fires during the period. The greatest reductions were in fires in which human factors were involved: ignited on furniture, bedding or soft goods, occurred in living areas or occurred in summer or winter (rather than in spring or autumn). The authors concluded that the RIP standard adopted into law and enforced in Massachusetts had decreased the likelihood of residential fires by 28% (95% confidence interval, 12–41%), particularly in the scenarios for which the RIP standard was set. This study is one of only a few high-quality, reliable population studies on the impact of the RIP standard on cigarette fires.

In summary, despite the difficulty of conducting research on the population effects of the standard, particularly in view of the short time it has been in force and the quality of fire-reporting systems, the RIP standard appears to be effective in reducing the incidence of cigarette-associated fires by approximately one third; however, more research is needed to validate this initial finding.

4.3.6 *Relevance and shortcomings of the standard*

The current standard is based on over 30 years of research, beginning with the “mock-up upholstery method”, the cell paper ignition method and emerging research on population health. More research is needed, including on the possible effects of changes in smoking behaviour and increased resistance of substrates to ignition. In high-income countries, the standard has been found to be effective, regardless of national factors; however, the standard could be altered as new scientific results, testing standards and cigarette features emerge.

4.4 Conclusions

Experience in countries in which RIP laws have been introduced suggests that the steps necessary for successful passage of such laws are:

- constitution of a coalition of relevant groups, including scientists, consumer groups and public health and fire safety officials, to collect data on cigarette-related fires, to formulate appropriate legislative proposals and to interact with policy-makers;
- a uniform standard for all legislative entities to facilitate adoption and to eliminate industry arguments that multiple RIP cigarettes would have to be designed;
- hard data on the actual harm caused by cigarette fires; and
- legislation that requires compliance with a uniform standard but does not dictate actual cigarette design.

Data on compliance have been collected in countries in which RIP laws have been introduced. Studies in Canada indicate substantial, sustained compliance by large manufacturers and increasing compliance by smaller ones. The three large manufacturers, which comprise 97% of the market in Canada, readily met the performance target of $\leq 25\%$ of cigarettes in a sample that failed to meet the standard, soon after the RIP law was implemented. For all manufacturers, 10% or less of samples failed to reach the standard within a few years of the RIP law being enacted.

Few studies have been conducted on behavioural and health effects after introduction of RIP cigarettes. There is little, if any evidence of any change in

smoking topography (puff volume, puff duration, interval between puffs) or any increase in fire risk-related behaviour, such as leaving a burning cigarette unattended or smoking in bed. A consistent observation was that RIP cigarettes self-extinguish more often, but there was no difference in the reported frequency in coal drop-off. Inconsistent evidence was presented that more people who smoke RIP cigarettes express an intention to quit smoking and smoke fewer cigarettes per day. The yields of CO, tar and nicotine are similar in RIP and non-RIP cigarettes.

In two studies in which urinary biomarkers of exposure to hydrocarbons were measured, use of RIP cigarettes was associated with a modest ($\leq 25\%$) increase in metabolites of pyrene, fluorenes and phenanthrenes; however, the data were not consistent, and the significance of the finding is unclear.

Evaluation of the impact of RIP laws on the incidence of cigarette-caused fires and the related casualties is limited by factors including lack of or poor quality data on fires, the relatively short time the RIP standard has been in force, particularly in some regions, such as the European Union, a general decrease in the prevalence of fires in recent decades, the introduction of clean air laws and the reduced flammability of substrates such as mattresses and soft furnishings. Despite these limitations, some rigorous studies have been conducted in high-income countries, which indicate an approximate 30% reduction in cigarette-caused fires as a result of RIP regulations. While it is anticipated that the numbers of deaths and injuries would be decreased as a result, there is only limited evidence in support of this assumption. It has been noted that the effectiveness of RIP cigarettes in reducing fire-related harm would vary with the effectiveness of fire-fighting departments. No information was available on the impact of RIP legislation on the frequency of outdoor fires or the resulting human or environmental impact.

4.5 Results of the WHO tobacco products survey, 2014

The WHO questionnaire on smokeless tobacco products, electronic nicotine delivery systems, RIP cigarettes and novel tobacco products was sent to all WHO Member States.¹¹ Eighteen Member States (5%) reported that they had a legal mandate requiring cigarettes sold to have RIP characteristics; and 19 Member States (5%)—18 with a mandate and one without—in four of the six WHO regions (the African Region, the Region of the Americas, the European Region and the Western Pacific Region) reported having adopted technical standards for RIP. RIP cigarettes are made available by commercial manufacturers in 13 Member States (8%) and by importation in 19 (8%). The exporting countries identified in the survey were Canada, China, the Czech Republic, Hungary, Lithuania, the Netherlands, New Zealand, the Republic of Korea and the USA.

¹¹ A total of 90 countries, including 86 Parties to the WHO FCTC, had responded to the survey as of 9 April 2014, representing 77% of the world's population.

Fires or deaths in fires due to smoking materials were recorded in 24 Member States (7%). Of those Member States in which reliable data were available over a 10-year period (2003–2012), the Czech Republic reported a total of 8129 fires due to cigarettes and 177 deaths, while Norway reported 74 deaths in the same period. Lithuania reported an average of 79 deaths per year, Oman reported an average of 48 fires per year, and Sweden reported an average of 25 deaths due to smoking-related fires each year. In general, 30% of all residential fire deaths in high-income nations are attributable to smoking.

4.6 Research needs

Research should be conducted at national, subnational or combined levels to predict population effects, including:

- factors that contribute to a general reduction in the number of fires, with specific studies on the effects of educational campaigns, sprinkler systems and reducing the flammability of substrates (upholstery, mattresses, etc.);
- cigarette-related issues, such as the impact of changes in smoking behaviour, including decreasing prevalence, the impact of clean indoor air laws on where people smoke, the number of cigarettes smoked and their disposal;
- emerging paper design techniques to enhance RIP performance, standards and possible alterations in emissions and toxicity;
- fires lit by cigarettes in settings not addressed by the standard (outdoors, brush fires, outdoor rubbish bins); and
- the applicability of the standard to novel RIP cigarettes that are not wrapped in paper.

Regarding infrastructure, research capacity, funding and support for universal RIP standards for all cigarettes, WHO FCTC Parties and fire officials should be surveyed about the significance of the RIP standard in their overall tobacco control or fire safety plans and asked to assess the resources required and potential funding.

In order for RIP standards to be considered good manufacturing process, the cost–benefit of having one global design rather than multiple designs should be calculated, including the time required to develop manufacturing capacity and compliance costs. Research should be conducted to find simpler compliance testing methods at the site of manufacture rather than in individual markets, thus reducing industry costs, and to determine the applicability to cigarettes of good manufacturing processes already recommended by WHO for drugs and other products.

4.7 Regulatory recommendations

- Universal RIP standards should be applied to all cigarettes.
- The RIP design should be adopted universally by manufacturers as standard manufacturing practice for cigarettes.
- All costs for implementation of the RIP standard should be borne by manufacturers. Countries with limited capacity for compliance testing should consider asking manufacturers to file a statement of conformity with the government or to use third-party certification.
- Implementation of these recommendations will require close collaboration between agencies and fire departments, the establishment of a central clearing-house for RIP standards, a survey of WHO FCTC Parties and fire officials on the impact of RIP standards, introduction of a consistent standard for reporting fires and determining how these activities will be funded.
- Research should be continued to obtain data on the population impact of RIP legislation on cigarette-associated fires, deaths and injuries in all countries and regions in which RIP laws have been implemented.

4.8 References

1. Standard test method for measuring the ignition strength of cigarettes. West Conshohocken, Pennsylvania: ASTM International; 2004.
2. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: second report of a WHO study group (WHO Technical Report Series, No. 951). Geneva: World Health Organization; 2008 (http://www.who.int/tobacco/global_interaction/tobreg/publications/tsr_951/en/index.html).
3. Gann RG, Hnetkovsky EJ. Modification of ASTM E 2187 for measuring the ignition propensity of conventional cigarettes. *Fire Technol* 2011;47:69–83.
4. Barillo DJ, Brigham PA, Kayden DA, Heck RT, McManus AT. The fire-safe cigarette: a burn prevention tool. *J Burn Care Rehabil* 2000;21:162–70.
5. Standard testing method for assessing the ignition propensity of cigarettes. Geneva: International Organization for Standardization; 2010.
6. Alpert HR, O'Connor RJ, Spallete R, Connolly GN, Rees VW, Alpert HR, O'Connor RJ, Connolly GN. Recent advances in cigarette ignition propensity research and development. *Fire Technol* 2010;46: 275–89.
7. Seidenberg AB, Rees VW, Alpert HR, O'Connor RJ, Connolly GN. Ignition strength of 25 international cigarette brands. *Tob Control* 2011;20:77–80.
8. Connolly GN, Alpert HR, Rees V, Carpenter C, Wayne GF, Vallone D, et al. Effect of the New York State cigarette fire safety standard on ignition propensity, smoke constituents, and the consumer market. *Tob Control* 2005;14:321–7.

9. Pang Y, Jing Y, Jiang X, Chen Z, Tang G, Xing J. Effects of low ignition propensity cigarette paper on deliveries of harmful components in mainstream cigarette smoke (in Chinese). *Tob Sci Technol* 2013;2:52–6.
10. Arnott D, Berteletti F. Europe: agreement on reducing cigarette fires. *Tob Control* 2008;17:4–5.
11. Goldstein AO, Grant E, McCullough A, Cairns B, Kurian A. Achieving fire-safe cigarette legislation through coalition-based legislative advocacy. *Tob Control* 2010;19:75–9.
12. Barbeau EM, Kelder G, Ahmed S, Mantuefel V, Balbach ED. From strange bedfellows to natural allies: the shifting allegiance of fire service organisations in the push for federal fire-safe cigarette legislation. *Tob Control* 2005;14:338–45.
13. Laboratory analysis of cigarette for ignition propensity. Ottawa: Health Canada; 2012 (<http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/legislation/reg/ignition-allumage/analys-eng.php>, accessed 20 November 2013).
14. Smoking and Health Action Foundation, Non-smokers' Rights Association. Backgrounder on the Canadian tobacco market. Toronto, Ontario.; 2013 (http://www.nsra-adnf.ca/cms/file/files/2013_Canadian_Tobacco_Market.pdf, accessed 20 November 2013).
15. O'Connor RJ, Fix BV, Hammond D, Giovino GA, Hyland A, Fong GT, et al. The impact of reduced ignition propensity cigarette regulation on smoking behaviour in a cohort of Ontario smokers. *Inj Prev* 2010;16:420–2.
16. Seidenberg AB, Rees VW, Alpert HR, O'Connor RJ, Giovino GA, Hyland A, et al. Smokers' self-reported responses to the introduction of reduced ignition propensity (RIP) cigarettes. *Tob Control* 2012;21:337–40.
17. Adkison SE, O'Connor RJ, Borland R, Yong HH, Cummings KM, Hammond D, et al. Impact of reduced ignition propensity cigarette regulation on consumer smoking behavior and quit intentions: evidence from 6 waves (2004–11) of the ITC Four Country Survey. *Tob Induced Dis* 2013;11:26.
18. O'Connor RJ, Rees VW, Norton KJ, Cummings KM, Connolly GN, Alpert HR, et al. Does switching to reduced ignition propensity cigarettes alter smoking behavior or exposure to tobacco smoke constituents? *Nicotine Tob Res* 2010;12:1011–8.
19. June KM, Hammond D, Sjödin A, Li Z, Romanoff L, O'Connor RJ. Cigarette ignition propensity, smoking behavior, and toxicant exposure: a natural experiment in Canada. *Tob Induced Dis* 2011;9:13.
20. Côté F, Letourneau C, Mullan G, Voisine R. Estimation of nicotine and tar yields from human-smoked cigarettes before and after the implementation of the cigarette ignition propensity regulations in Canada. *Regul Toxicol Pharmacol* 2011;61(3 Suppl):S51–9.
21. Shepperd CJ, Eldridge AC, Mariner DC, McEwan M, Errington G, Dikon M. A study to estimate and correlate cigarette smoke exposure in smokers in Germany as determined by filter analysis and biomarkers of exposure. *Regul Toxicol Pharmacol* 2009;55:97–109.

22. Mulvaney C, Kendrick D, Towner E, Brussoni M, Hayes M, Powell J. Fatal and non-fatal fire injuries in England 1995–2004: time trends and inequalities by age, sex and area deprivation. *J Public Health* 2009;31:154–61.
23. Smith J, Bullen C, Laugesen M, Glover MP. Cigarette fires and burns in a population of New Zealand smokers. *Tob Control* 2009;18:29–33.
24. Anderson A, Ezekoye OA. A comparative study assessing factors that influence home fire casualties and fatalities using state fire incident data. *J Fire Prot Eng* 2013;23:51–75.
25. Markowitz S. Where there's smoking, there's fire: the effects of smoking policies on the incidence of fires in the USA. *Health Econ* 2013;25:1353–73.
26. Hall JR Jr. The smoking-material fire problem. Quincy, Massachusetts: National Fire Protection Association; 2013:54.
27. Frazier P, Schaeffer P, Jones E. Initial evaluation of the effectiveness of reduced ignition propensity cigarettes in reducing cigarette-ignited fires: case studies of the North American experience. Arlington, Virginia: TriData Division, System Planning Corp; 2011 (http://www.fdma.go.jp/html/life/yobou_contents/info/pdf/tabaco/kentou01/sanko04.pdf).
28. Hemenway D. How to find nothing. *J Public Health Policy* 2009;30:260–8.
29. Alpert HR, Christiani D, Orav EJ, Dockery D, Connolly GN. Effectiveness of the cigarette ignition propensity standards in preventing unintentional residential fires in Massachusetts. *Am J Public Health* 2014;104:e56–61.

Appendix 4.1. Methods

For this review, we searched a number of publicly accessible databases, including PubMed, the Africa Index Medicus, the Index Medicus for the Eastern Mediterranean Region, the Index Medicus for the Western Pacific Region, the Pan American Health Organization Library, Biblioteca virtual em Saúde, the Index Medicus for the South-East Asia Region, the Web of Science and Engineering Village, using the search terms “cigarette” and “fire” or “burn”, published since 2008. This search of the published literature was supplemented with a search on Google to identify “grey” literature, such as conference abstracts, consultant organization reports and news reports. Public health and fire safety officials in countries that were known to have adopted or were considering adopting RIP standards for cigarettes were contacted, and information was collected from the WHO regional offices. Interviews were conducted with key informants in countries in which RIP laws have been adopted. A total of 26 relevant publications were identified.

Appendix 4.2. Summary of ISO 12863

1 test = 40 determinations, one cigarette per determination

Outcome = full-length burn (lit cigarette burns past the end of the tipping paper for filter-tipped cigarettes, or past metal pins placed in non-filter cigarettes)

Environmental conditions: humidity $55\% \pm 5\%$, temperature $23\text{ °C} \pm 3\text{ °C}$

Polymethylmethacrylate test chamber dimensions: height, $340 \pm 25\text{ mm}$; width, $292 \pm 6\text{ mm}$; depth, $394 \pm 6\text{ mm}$; chimney height, $165 \pm 13\text{ mm}$ with inside diameter $152 \pm 6\text{ mm}$

Polymethylmethacrylate substrate holder dimensions: outer diameter, $165 \pm 1\text{ mm}$; inner diameter, $127 \pm 1\text{ mm}$; height, $50 \pm 1\text{ mm}$; a recess in the top, $10 \pm 2.5\text{ mm}$ deep, extending the inner diameter to $152 \pm 1\text{ mm}$; three or four legs to raise the bottom holder approximately $20 \pm 1\text{ mm}$ above the chamber floor; a metal rim made of brass, with an outer diameter of $150 \pm 1\text{ mm}$

Filter papers (Whatman #2) should be selected such that the combined mass of 15 sheets is $24.7 \pm 0.5\text{ g}$.

Test procedure:

1. Before testing, mark cigarettes in pencil at 5 mm and 15 mm from the lighting end to establish a uniform pre-burn period.
2. Light cigarette, and place with seam facing upwards in the holder. Close chamber door and remove chimney cover.
3. If cigarette goes out in the holder (i.e. between 5-mm and 15-mm marks), record as self-extinguished.
4. If cigarette burns to the 15-mm mark, remove from holder and place seam up on substrate.
5. Record stopping point of burn. If burn has reached tipping paper (or metal reference pins for non-filter cigarettes), record as full-length burn; otherwise, record as non-full-length burn.
6. Remove cigarette and filter papers, and dispose of them.
7. Repeat procedure until 40 determinations have been made.
8. Calculate proportion of determinations in which a full-length burn was observed.

Appendix 4.3 Recent CORESTA presentations by industry relevant to the technology of reduced ignition propensity cigarettes

2013

Wilkinson P, Colard S, Verron T, Cahours X, Pritchard J. Control or monitoring of the LIP testing process: the fitness for purpose of the LIP standard products.

Wanna J. Alternate test substrate for ASTM test method E2187-09.

Mayr M, Vizee H. Impact of using a metal sheet as an “alternative substrate for ISO 12863” on SE performance.

Verron T, Cahours X, Colard S. LIP cigarettes: proposal for an alternative sampling design.

Gleinser M, Bachmann S, Rohregger I, Vizee H, Volgger D. Puff-by-puff analysis of mainstream smoke constituents of non-LIP and LIP-cigarettes.

Verron T, Cahours X, Colard S, Taschner P. Some key points to assess LIP regulation impact.

2012

Bachmann S, Gleinser M, Möhring D, Rohregger I, Volgger D. Puff-by-puff analysis of mainstream smoke constituents of non-LIP/FSC and LIP/FSC cigarettes.

Guyard A, Meier D, Cecchetto A, Hofer R, Li P. Impact of cigarette paper properties on smoke constituents’ delivery under Health Canada Intense smoking regime.

Hesford MJ, Volgger D, Case P, Vanhala A. A further experimental design to investigate the influence of the LIP test substrate parameters on LIP pass rates and residual length measurements.

Mayr M, Volgger D. Influence of band width and band material coverage rate (total band area / total paper area) on smoke yields, SE test and free burn.

Verron T, Cahours X, Colard S. LIP cigarettes: effect of band positioning.

Verron T, Cahours X, Colard S. Trend analysis: a relevant tool to assess post-regulation impacts.

Wanna J, Le Moigne C, Le Bec L. Tobacco column influence on cigarette paper.

2011

Hesford M. A 24 factorial experimental design to investigate the influence of LIP testing substrate parameters (basis weight, permeability and roughness) on LIP pass rates and residual length measurements.

Mayr M, Volgger D. The impact of different physical and chemical cigarette paper base sheet parameters on smoke yields, and testing of an alternative substrate for Whatman #2 using the ASTM method E.2187-09.

Inoue Y, Hasegawa Y, Kominami T. Study of heat transfer of a cigarette relating to the ignition propensity.

Loureau JM, Le Bec L, Kraker T, Le Moigne C, Wanna J, Le Bourvellec G. Influence of base paper citrate and filler amount and of band diffusion on smoke deliveries, ASTM and FASE.

2010

Eitzinger B, Volgger D. Some statistical considerations regarding the testing of LIP cigarettes.

Hesford M, Case P, Coburn S, Larochelle J, Cabral JC, DeGrandpré Y, Wanna J. A factorial experimental design to investigate the influence of band diffusivity and filler, fibre and citrate contents on the machine smoking yields and LIP performance of banded LIP papers.

Wanna J. Influence of humidity, number of filter papers, and orientation of the filter paper on ASTM results.

HAMPL V Jr. Effect on ASTM test results and carbon monoxide deliveries when sodium alginate bands are on the outside of cigarettes.

Mason T, Tindall I. Correlation between manual and semi automatic measurements of ignition propensity to ASTM E2187-04.

Vincent J, Tindall I. Factors affecting the design of paper diffusivity measurement apparatus with particular reference to the design of transfer standards.

5. Non-exhaustive priority list of toxic contents and emissions of tobacco products

- 5.1 Introduction
- 5.2 Findings of the review
- 5.3 Recommendations
- 5.4 Non-exhaustive list of priority toxic contents and emissions of tobacco products
- 5.5 References

5.1 Introduction

This document was prepared in response to a request by the Conference of the Parties at its Fifth Session (Seoul, Republic of Korea, 12–17 November 2012) to the Convention Secretariat to “compile, make available for Parties and update jointly with WHO’s Tobacco Free Initiative a non-exhaustive list of toxic contents and emissions of tobacco products and advise how such information could best be used by Parties” for consideration at the Sixth Session of the Conference of the Parties (decision FCTC/COP5(6)) (1). In the same decision, the Conference of the Parties further decided to mandate the Working Group on Articles 9 and 10 to submit draft partial guidelines or a progress report on testing and measuring contents and emissions with analytical chemical methods validated by WHO, for consideration at the Sixth Session of the Conference of the Parties.

TobReg, at its meeting in Rio de Janeiro, Brazil, on 4–6 December 2013, selected a priority list of 38 toxicants from among more than 7000 chemicals found in cigarette smoke on the basis of qualitative and quantitative analyses. The list of toxicants was based on eight non-exhaustive lists of toxicants: from Health Canada,¹² the National Institute for Public Health and the Environment in The Netherlands (2), the US Food and Drug Administration (3), Counts et al. (4), Fowles and Dybing (5), the “Hoffman analytes” (6), Philip Morris Australian brands¹³ and Philip Morris Canadian brands¹⁴ in order to balance the identified concerns with the practical reality of a regulatory structure.

The list of tobacco contents and emissions of cigarette smoke was drawn up on the basis of the following criteria:

¹² For constituents: <http://laws-lois.justice.gc.ca/eng/regulations/SOR-2000-273/page-13.html>; for emissions (mainstream smoke): <http://laws-lois.justice.gc.ca/eng/regulations/SOR-2000-273/page-14.html>.

¹³ <http://www.health.gov.au/internet/main/publishing.nsf/Content/health-tobacco-ingredients-philip-2013>.

¹⁴ Available from Health Canada upon request or at tfi@who.int.

- the presence of specific chemicals in cigarette smoke at levels that are toxic for smokers as determined by well-established scientific toxicity indices;
- variations in concentrations among cigarette brands that are substantially greater than the variation in repeated measurements of the toxicant in a single brand; and
- the availability of technology to reduce the concentration of a given toxicant in smoke, should an upper limit be mandated.

The 7000 chemicals in cigarette smoke were analysed according to the same criteria when sufficient data on smoke emissions and data on toxicity relevant to humans were available.

The Conference of the Parties at its Third Session requested the Convention Secretariat to invite the WHO Tobacco Free Initiative to validate the analytical chemical methods for testing and measuring priority emissions and contents in cigarette smoke (decision FCTC/COP3(9) (7). TobLabNet has undertaken validation of the methods for three contents (nicotine, ammonia and humectants) and four emissions (aldehydes, benzo[*a*]pyrene, TSNA and volatile organic compounds). To date, validation of the methods for CO, humectants, benzo[*a*]pyrene, nicotine and TSNA has been completed, while the methods for ammonia, volatile organic compounds (benzene and 1,3-butadiene) and aldehydes (acetaldehyde, acrolein and formaldehyde) are still being validated.

5.2 Findings of the review

TobReg evaluated the lists of harmful and toxic chemicals associated with cancer, cardiovascular and pulmonary diseases published by several regulatory bodies, including Health Canada, the National Institute for Public Health and the Environment in The Netherlands and the US Food and Drug Administration, and reviewed the list of toxicants in the report of TobReg (8). TobReg subsequently drew up a modified non-exhaustive list of priority toxic contents and emissions of tobacco products, as outlined in section 5.4; however, it should be noted that this list represents only a small fraction of the total complex mixture of chemicals present in combustible tobacco products and that the overall toxicity of the emissions of tobacco products is not necessarily related to the toxicity of the individual chemicals.

Experience gained by the Agência Nacional de Vigilância Sanitária in Brazil, Health Canada and the US Food and Drug Administration should be used by Parties and non-Parties to the WHO FCTC to urge the tobacco industry to disclose information about the emissions of tobacco products, in accordance with the Partial Guideline for Articles 9 and 10.

While several Parties include tar in their regulatory policies, it is not on the priority list of toxicants in tobacco smoke emissions, as the composition of tar varies qualitatively and quantitatively in each type of product, limiting the possibility for validated testing and measurement.

TobReg previously expressed concern about the presence of cadmium, lead, nickel, arsenic and polonium in tobacco smoke. Although these metals present a high risk when present in smoke, there are no currently interlaboratory-validated standardized methods for testing and monitoring them (9).

Because of the increasing worldwide use of waterpipes (*shisha*), TobReg concludes that there is an urgent need for an interlaboratory-validated method for determining nicotine in waterpipe smoke and that the relative concentrations of nicotine and other priority emissions in the smoke should be studied.

Some of the emissions from smoked tobacco products on the priority list are irrelevant or less relevant for smokeless tobacco products. For example, CO is produced during burning and is thus not present in smokeless tobacco. The priority list for smokeless products is currently limited to nicotine, TSNA and benzo[*a*]pyrene; however, no standardized, interlaboratory-validated methods are available for measuring these chemicals in smokeless products. TobReg concludes that methods for testing these components in smokeless tobacco should be fully validated.

TobReg concludes that the upper limits of emissions of toxicants from tobacco products should be regulated on the basis of the scientific knowledge and principles that have been applied to food and other consumer products, often on the basis of the principle of reasonable assurance of safety. TobReg concludes that the same principle should apply to tobacco products.

5.3 Recommendations

- The Conference of the Parties should request WHO to mandate TobLab-Net to develop standardized methods for determining the arsenic, cadmium and lead content of tobacco products.
- Tar need not be measured, as it is not a sound basis for regulation, and the levels can be misleading.
- Although the recommended priority list of contents and emissions was drawn up for standard cigarettes, TobReg recommends use of the same list for other smoked tobacco products, such as non-standard cigarette (slims, for example), cigars, waterpipes, pipes and roll-your-own or “make-your-own” cigarettes.

- For both standardized cigarettes and other tobacco products, the concentration of a chemical in emissions should also be reported relative to the concentration of nicotine in the smoke, as advocated previously (8).
- The Conference of the Parties should request WHO to mandate TobLabNet to issue a validated method for the determination of nicotine in the smoke of waterpipes (*shishas*).
- Countries should regulate nicotine, TSNA and benzo[*a*]pyrene in smokeless tobacco products.
- The Conference of the Parties should request WHO to mandate TobLabNet to develop validated methods for determining nicotine, TSNA and benzo[*a*]pyrene in smokeless tobacco products.
- The list of priority contents and emissions should be used, with validated TobLabNet methods, as a basis for regulating contents and emission, as stated in Article 9 of the WHO FCTC.
- As an initial step in regulating contents and emissions, as stipulated in Article 9, Parties may start monitoring the priority contents and emissions of cigarettes on their markets. Data on each brand and each content and emission should be made available by the tobacco industry, and the cost of compliance testing should be covered by the tobacco industry, as agreed in the Partial Guideline of Article 10.
- Regulatory steps should include setting upper limits for emissions of toxicants in tobacco products on the basis of established toxicological principles.
- Tobacco emissions contain many chemicals; therefore, the list of priority emissions and contents is only a first step to help Parties fulfil the requirements of Articles 9 and 10.
- The priority list of contents and emissions in cigarettes, other smoked tobacco products and smokeless tobacco products should be re-evaluated periodically, as appropriate, on the basis of new scientific knowledge.

5.4 Non-exhaustive list of priority toxic contents and emissions of tobacco products¹⁵

Acetaldehyde

Acetone

Acrolein

¹⁵ This list contains one compound more than the 38 listed in the WHO report to the Sixth Session of the Conference of the Parties to the WHO FCTC (10), because, on the basis of the weight of the scientific evidence and further deliberations by TobReg, arsenic was added to the list.

Acrylonitrile
1-Aminonaphthalene
2-Aminonaphthalene
3-Aminobiphenyl
4-Aminobiphenyl
Ammonia
Arsenic
Benzene
Benzo[*a*]pyrene
1,3-Butadiene
Butyraldehyde
Cadmium
Carbon monoxide
Catechol
m-Cresol
p-Cresol
o-Cresol
Crotonaldehyde
Formaldehyde
Hydrogen cyanide
Hydroquinone
Isoprene
Lead
Mercury
Nicotine
Nitric oxides
N-Nitrosoanabasine
N-Nitrosoanatabine
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
N'-Nitrosornicotine (NNN)
Phenol
Propionaldehyde
Pyridine
Quinoline
Resorcinol
Toluene

5.5 References

1. Decision FCTC/COP5(6). In: Decisions. Fifth Session of the Conference of the Parties to the WHO Framework Convention on Tobacco Control. Geneva: World Health Organization; 2012 (document FCTC/COP/5/DIV/5) (<http://apps.who.int/>)

gb/fctc/PDF/cop5/FCTC_COP5%286%29-en.pdf).

2. Talhout R, Schulz T, Florek E, van Benthem J, Wester P, Opperhuizen A. Hazardous compounds in tobacco smoke. *Int J Environ Res Public Health* 2011;8:613–28.
3. Harmful and potentially harmful constituents in tobacco products and tobacco smoke: established list. Silver Spring, Maryland: Food and Drug Administration; 2012.
4. Counts ME, Morton MJ, Laffoon SW, Cox RH, Lipowicz PJ. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. *Regul Toxicol Pharmacol* 2005;41:185–227.
5. Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical toxicants of cigarette smoke. *Tob Control* 2003;12:424–30.
6. Thielen A, Klus H, Müller L. Tobacco smoke: unraveling a controversial subject. *Exp Toxicol Pathol* 2008;60:141–56.
7. Decision FCTC/COP3(9). In: Decisions. Third Session of the Conference of the Parties to the WHO Framework Convention on Tobacco Control. Geneva: World Health Organization; 2008 (document FCTC/COP/3/DIV/3) (http://apps.who.int/gb/fctc/PDF/cop5/FCTC_COP5%286%29-en.pdf).
8. Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation. Geneva: World Health Organization; 2008 (WHO Technical Report Series, No. 951) (http://www.who.int/tobacco/publications/prod_regulation/trs_951/en/).
9. Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation. Fourth report of a WHO study group. Geneva: World Health Organization; 2012 (WHO Technical Report Series, No. 967) (http://www.who.int/tobacco/publications/prod_regulation/trs_967/en/).
10. Work in progress in relation to Articles 9 and 10 of the WHO FCTC. Report by WHO. In: Sixth Session of the Conference of the Parties to the WHO Framework Convention on Tobacco Control. Geneva: World Health Organization; 2014 (document FCTC/COP/6/14).

6. Overall recommendations

- 6.1 Novel tobacco products
 - 6.1.1 Main recommendations
 - 6.1.2 Significance for public health policies
 - 6.1.3 Implications for WHO programmes
- 6.2 Smokeless tobacco
 - 6.2.1 Main recommendations
 - 6.2.2 Significance for public health policies
 - 6.2.3 Implications for WHO programmes
- 6.3 Reduced ignition propensity cigarettes
 - 6.3.1 Main recommendations
 - 6.3.2 Significance for public health policies
 - 6.3.3 Implications for WHO programmes
- 6.4 Non-exhaustive list of toxic contents and emissions of tobacco products
 - 6.4.1 Main recommendations
 - 6.4.2 Significance for public health policies
 - 6.4.3 Implications for WHO programmes

TobReg commissioned a series of reports to provide a scientific foundation for tobacco product regulation. In line with Articles 9 and 10 of the WHO FCTC,¹⁶ these reports identify approaches on which to base the regulation of tobacco products, which pose significant public health threats.

The seventh meeting focused on issues critical to advancing the regulation of tobacco products, particularly as outlined at the Fifth Session of the Conference of the Parties to the WHO FCTC.¹⁷ The topics discussed included the evolution of novel tobacco and related products, smokeless tobacco, reduced ignition propensity (RIP) cigarettes, nicotine reduction and addictiveness and a non-exhaustive priority list of toxicants.

6.1 Novel tobacco products

6.1.1 *Main recommendations*

A tobacco product is considered novel if it contains tobacco and if at least one of the following applies: it has been on the market for less than 12 years; it has been on the market for a longer time but with market share increases in countries or regions that traditionally did not use the product; it is based on a new technology; and it is marketed as being less hazardous to health than other tobacco products.

¹⁶ For more information, see: http://www.who.int/fctc/text_download/en/ (accessed 28 November 2014).

¹⁷ For more information, see decision FCTC/COP5(6), paragraph 3(b) and decision FCTC/COP5(10), paragraphs 1– 4 (<http://www.who.int/fctc/cop/en/> (accessed 28 November 2014)).

Novel tobacco products should be evaluated for toxicity, association with disease risk, consumer awareness and perception, pattern of use and the demographics of use. Standardized evaluation of such products is needed, and regulators should approve them only if pre-market testing shows a probably public health benefit. The concept of “harm reduction” used by the industry and the impact and effectiveness of strategies promoting the use of products that are allegedly less hazardous to health should be evaluated and communicated effectively to the general public in order to prevent misperceptions.

6.1.2 Significance for public health policies

The main concern related to the use of novel tobacco products includes unknown toxicity, changes in product use behaviour, decreased cessation, increased initiation, sustained prevalence of tobacco “dual use”¹⁸ and public misunderstanding about the actual risk associated with allegedly less hazardous products.

6.1.3 Implications for WHO programmes

The approach to monitoring should be more comprehensive and consistent and the collection of research data on novel tobacco products more systematic.

6.2 Smokeless tobacco

6.2.1 Main recommendations

Clearer policy is required to address the challenges presented by smokeless tobacco products. In comparison with smoked tobacco products, smokeless tobacco products are more readily affordable, they carry weaker warning labels, and fewer resources are spent on their surveillance, prevention and control. Evidence-based control policies must be strengthened, such as ensuring disclosure of product content, establishing performance standards for toxicants and maximum pH levels, banning flavourings, using effective, relevant health warning labels, increasing product taxes, restricting or banning marketing of such products and increasing public awareness of the harm associated with their use.

¹⁸ Concomitant use of two forms of tobacco is an increasing public health concern. As yet, however, there is no consensus on a consistent definition of such “dual use”. For the present purposes, the term refers to use of both cigarettes and smokeless tobacco or of cigarettes and a novel tobacco product, either product being used daily or not daily.

6.2.2 Significance for public health policies

More attention should be given to the overall impact of smokeless tobacco products, including their use by adolescents, dual use, “poly-use” and the growth in targeted marketing for indoor use.

6.2.3 Implications for WHO programmes

Additional data are needed on the use, surveillance and characteristics of smokeless tobacco products, as well as on the health consequences of the use of individual products. Further, better understanding is required of the market for such products and on effective region-specific education, prevention and treatment interventions. Resources and collaborative work are required to obtain such data.

6.3 Reduced ignition propensity cigarettes

6.3.1 Main recommendations

Laws relating to RIP have now been enacted in Australia, Canada, South Africa, the USA and the European Union, but this pattern has yet to be followed in many middle- and low-income countries. Ideally, this technology would be applied to all cigarette manufacture; to achieve this, testing must be standardized in accredited laboratories, paid for by the tobacco industry. Claims of reduced risk to health should not be allowed. Monitoring should be established to determine whether this technology is effective in reducing the numbers of fires, deaths and injuries related to cigarettes. Monitoring should also be conducted for toxicity and for behavioural changes related to a heightened awareness of RIP in cigarette manufacture.

6.3.2 Significance for public health policies

Fires caused by smoking are a major public health risk and cause many deaths. A reduction of approximately 30% in smoking-related fires was shown in areas with RIP laws, when data were available. Testing has shown no consistent difference in smoke emissions between cigarettes manufactured by RIP technology and classical cigarettes. These findings refute the claims of the tobacco industry.

6.3.3 Implications for WHO programmes

More research is needed on the toxicity and emissions of RIP cigarettes, on possible changes in smoking behaviour and on the potential reduction in the numbers of fires and deaths associated with cigarettes.

6.4 Non-exhaustive list of toxic contents and emissions of tobacco products

6.4.1 Main recommendation

From among the chemicals found in cigarette contents and emissions (as many as 7000), TobReg identified a non-exhaustive priority list of 39 contents and emissions of cigarette smoke and recommended that these 39 toxicants be monitored in all tobacco products. The criteria included their potential toxicity to smokers and variation in concentrations among cigarette brands. As the scientific basis grows, this list is likely to be modified or extended.

6.4.2 Significance for public health policies

The list will guide regulation of contents and emissions, as stated in Articles 9 and 10 of the WHO FCTC. The list should be re-evaluated periodically as new knowledge becomes available.

6.4.3 Implications for WHO programmes

The contents and emissions of tobacco products should be monitored and regulated by the validated methods of TobLabNet. Laboratories in the Network have already validated methods for measuring tar, nicotine, CO, TSNA, benzo[*a*]pyrene and humectants, and validation of methods for measuring ammonia, volatile organic compounds and aldehydes is under way. Priority should be given to laboratories in the Network that are developing standardized methods for measuring cadmium and lead in tobacco, nicotine in the smoke of waterpipes and nicotine, TSNA and benzo[*a*]pyrene in smokeless tobacco products.

7. Regulation of tobacco smoke: commentary on the status quo¹⁹

- 7.1 Background
- 7.2 Proposed actions
- 7.3 Issues relevant to setting upper limits
- 7.4 References

7.1 Background

This commentary addresses those elements of cigarette design that are well understood, for which there is clear evidence of harm and which could certainly be reduced on the basis of existing evidence.

Nicotine delivery systems have evolved over the centuries, leaving the cigarette as the victor since the development of efficient machinery in 1880. Not a great deal changed between the two world wars, but, since then, the cigarette has remained the nicotine delivery system of choice. It has been developed into a highly sophisticated chemical melange of tobacco and additives that is certainly more addictive (1), more adenocarcinogenic (2, 3) and more “attractive” (1) than the relatively simple “gasper” that addicted the troops during the First and Second World Wars.

The cigarette’s competitors in the western world have universally failed to displace it as first choice. In the developing world, there is a galaxy of smokeless products that are highly toxic and carcinogenic and also have a high nicotine content, but even these cannot challenge the cigarette. Even in India, where the mixtures are diverse and abundant, the cigarette has claimed 40% of the smoking market (4). There are probably two reasons for this situation: the existence of a globally powerful group of corporate bodies with a serious vested interest in the cigarette, which is cheap to make and sell, and the technical brilliance of the modern cigarette.

¹⁹ This commentary by Dr Nigel Gray is based on the thoughtful paper that he independently produced for the seventh TobReg meeting in December 2013 without commission by WHO. It does not necessarily represent the views of WHO or TobReg. However, TobReg members unanimously recommended that it be included as a commentary recognizing the thought-provoking nature of its content and goals, and recognizing Dr Gray as a public health and tobacco control leader and visionary. Dr Gray served TobReg since its inception in 2000 as SACTob (Scientific Advisory Committee on Tobacco Product Regulation) and he significantly guided its direction and reports. WHO TobReg has been honoured by his service, and global tobacco control has advanced significantly by his contributions. Dr Nigel Gray passed away peacefully on 20 December 2014 surrounded by his loved ones. WHO’s tribute to Dr Gray can be found at: <http://www.who.int/tobacco/communications/highlights/nigelgray/en/>.

In developed countries, public health authorities have considered alternatives, with the expensive development of therapeutic nicotine and, in some cases, other alternatives, such as snus and, more recently, electronic cigarettes. None of these has made a significant inroad into the market of the cigarette, which dominates the battlefield of nicotine addiction and probably has about 65–85% of the global market (5).

Much of the literature on harm reduction involves comparisons of cigarette alternatives, such as smokeless tobacco and therapeutic nicotine, with “the cigarette” (6–8). The implication of many such comparisons is that “the cigarette” is a standard form of product. This is patently not true, as shown in Table 7.1. Although comparisons between “cigarettes” and less toxic products such as snus are reasonable for promoting the possibility of harm reduction by change of product, they avoid the reality that the cigarette of today is a highly variable product, which presumably causes various degrees of harm. As cigarette recipes are not published but certainly change over time and users also change brands, there has been, and can be, no study in which specific brands are compared with specific disease outcomes. As a result, there is no precise way of determining whether Marlboro is more or less carcinogenic, adenocarcinogenic or squamocarcinogenic than Virginia Slims. Modern epidemiology was built on use of “the cigarette” as the unit of dose, with occasional studies of differences in levels of tar. It is probable that the main findings of the major studies have withstood the test of time because they are actually serious understatements.

Table 7.1. Levels of carcinogens and other toxins found in cigarettes

Toxin	Variation			
	Lowest	Highest	(fold)	Threefold
NNK (ng/cigarette)	12.4	107.8	9	37.2
NNN (ng/cigarette)	5.0	195	19	15
Benzo[<i>a</i>]pyrene	6.6	29.3	4	19.8
Acetaldehyde (μ g/cigarette)	32	643	20	94
Acrolein (μ g/cigarette)	2.4	61.9	24	7.2
Benzene (μ g/cigarette)	6.1	45.2	7	18.3
Butadiene (μ g/cigarette)	6.4	54.1	8	19.2
Formaldehyde (μ g/cigarette)	1.6	52.1	30	4.8
CO (mg/cigarette)	1.1	13.4	13	3.3

The passage of legislation permitting interference with cigarette design in Canada and the USA offers hope but has so far produced only changes in flavourings. This is probably a reflection of the relative powers of the manufacturers and of government agencies. A side-effect of that relative power has

been a consequential failure by public health authorities to establish actual rather than theoretical control of product design. Even more serious is the disconnection between the excellent research done by non-industry scientists and the development of public health policy that could have led to changes in cigarette design.

There is an obvious role for TobReg and WHO in this situation, where they could reasonably aspire to establish some parameters for cigarette design that could be introduced immediately in those countries that do not have sophisticated public health establishments or tobacco research facilities. Such countries need advice about immediate action on cigarette design that is research-based, scientifically solid and unarguable. WHO has the deficiency that it cannot make laws and can only advise Member States. It has the parallel virtue, however, that its advice is widely accepted. Within WHO, only TobReg has independent expertise in the field of tobacco product design. For this reason, it is proposed that TobReg establish a set of parameters for cigarette design that could be accepted routinely and immediately by interested countries, just as WHO advice on influenza vaccines is accepted.

The report of TobReg (1) covered virtually all the qualities and chemicals that are known to contribute to dependence on cigarettes. Although they were named and described, TobReg did not suggest any action. That publication does, however, set the stage for specific regulatory actions, which can now be recommended. It should be noted that the manufacturers have shown extraordinary skill in using *chemical* changes to achieve alterations in *qualities*. A review of the text of the TobReg document reveals the following qualities. The proposals are fully referenced in WHO (1), and some new references are added.

Factors (qualities) that affect initiation and maintenance of addiction:

- attractiveness
- smell
- flavour
- taste
- coolness
- smoothness

Factors (qualities) that affect the strength of the “fix”:

- filter ventilation
- speed of delivery
- efficiency of absorption
- pH
- particle size
- starter products with low nicotine and high flavour

Chemicals that facilitate dependence:

- nicotine
- anabasine
- nornicotine
- menthol
- acetaldehyde
- ammonia
- laevulinic acid
- monoamine oxidase inhibitors
- urea
- chocolate

WHO (1) list of carcinogens and toxicants for which upper limits could be set:

- NNK
- NNN
- acetaldehyde
- acrolein
- benzene
- benzo[*a*]pyrene
- 1,3-butadiene
- CO
- formaldehyde

Now is an ideal time to consider the actions that should be taken on the basis of what we know.

7.2 Proposed actions

As an initial step in regulating cigarettes, the following measures, which have a strong evidence base, could be taken.

- Cigarettes should contain a relatively standard dose of nicotine, delivered to the smoker with a minimum of carcinogens and other toxins. This is not discussed further here, as the issue of nicotine dosing, including the alternative approach of reduction of nicotine to non-addictive levels, is addressed in Annex 3 of this report.
- Elements that facilitate compensatory smoking should be discouraged; filter ventilation is an obvious example.
- Additives that increase the addictiveness or the attractiveness of tobacco smoke should be prohibited.
- There is a strong case for prohibiting all additives, unless there is a public health reason for their presence, such as the additives required to make RIP cigarettes.

- Upper limits should be set for those carcinogens and other toxins about which there is knowledge and for which the necessary technology is available.
- A measuring system that gives consistent results is needed. The current Canadian system (9) meets this need and has the advantage that the filter is taped over, thereby reducing the incentive to use filter ventilation.
- Manufacturers should be required to meet the performance standards proposed here and should disclose relevant levels of carcinogens and other toxins. The current Canadian system also meets this need.

This leads to the consideration of the following performance standards:

- *Nitrosamines*: The tobacco industry has established a standard method for reducing the levels of nitrosamines, the Gothatiek standard (10, pp. 23–41), pioneered by Swedish Match. It is used for such products as snus and could be accepted as an initial step, although the levels of these carcinogens could be reduced still further (S.S. Hecht, personal communication).
- *PAH*: The levels of these compounds could also be reduced significantly with the standard Gothatiek procedure.

Other major carcinogens and other toxins that were considered by TobReg (11) are listed in Table 7.1, which shows the high and low levels in cigarettes on the international market in 2002, as reported by Counts et al. (12). The range of levels is astonishing; conveniently, it covers an international sample, although it is limited by the choice only of Philip Morris brands.

7.3 Issues relevant to setting upper limits

There are no precedents for setting limits for carcinogens and other toxins in a consumer product, for the simple reason that the normal public health approach would be to set these at zero. Any regulator would require considerable persuasion to accept that a limit other than that which is the lowest achievable would be acceptable. Acceptance of levels that are multiples of the lowest levels achievable would be clearly ridiculous, as shown in Table 7.1: e.g. eightfold for NNK, 19-fold for acetaldehyde, 24-fold for acrolein, sevenfold for benzene, sixfold for butadiene, 30-fold for formaldehyde and 12-fold for CO.

If the upper limit was set at three times the lowest level achieved on the market, it would be up to the manufacturer to prove that such a (generous) limit should be increased. Thus, the onus of proof that any such limit should be exceeded should lie with the manufacturer, and the only acceptable reason for any increase would be that achieving the set limit is biochemically impossible. Permitting a threefold variation above the lowest level achievable, while

clearly generous, would establish a precedent and should be established for a trial period of 2 years, after which time the levels would be reviewed and, where practical, set lower.

These simple actions would:

- reduce the incentive for compensatory smoking, as the cigarette would provide the smoker's chosen dose;
- remove much of the sophistication that underlies addictiveness;
- be consistent with fire risk reduction;
- reduce the relative risk for adenocarcinoma (which has been clearly related to exposure to nitrosamines: 2, 3); and
- reduce the total carcinogenic burden by removing nitrosamines and PAH.

Ten nitrosamines could be almost completely removed, and the levels of nine PAH would be substantially reduced. This change, with those in the levels of the other substances shown in the table, might well be described as dramatic, but it actually reflects the views first stated 6 years ago (11).

While it cannot and should not be denied that cigarettes that meet these performance standards would be less dangerous than current products, there is nothing here that could allow "health" claims to be made, as the benefits cannot be quantified, nor could the period over which effects would be seen be firmly established in any ethical trial. The cigarette will still be the most dangerous consumer product in the world as well as, probably, the greatest cause of tobacco-related disease.

Nevertheless, we should be clear that what we are attempting to do is "harm reduction" applied to the cigarette. This principle was the basis for the low-tar cigarette campaign, which started with harm reduction as an objective but was a failure because the industry cheated and public health authorities lacked the knowledge and laboratory facilities to call them to account.

Times have changed.

Thus, these changes are justified not only by the precautionary principle, which is a normal feature of public health regulation, but also because there can be no doubt that the substantial changes proposed would reduce cancer rates and addictiveness over time. The fact that we do not know by how much or over what time is no excuse for accepting the status quo.

7.4 References

1. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation. Fourth report of a WHO study group (WHO Technical Report Series, No. 967). Geneva: World Health Organization; 2012.
2. Burns DM, Anderson CM, Gray N. Has the lung cancer risk from smoking increased over the last fifty years? *Cancer Causes Control* 2011;22:389–97.
3. Burns DM, Anderson CM, Gray N. Do changes in cigarette design influence the rise in adenocarcinoma of the lung? *Cancer Causes Control* 2011;22:13–22.
4. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 89. Smokeless tobacco and some tobacco-specific *N*-nitrosamines. Lyon: International Agency for Research on Cancer; 2007.
5. Jha P, Chaloupka F. Tobacco control in developing countries. Oxford: Oxford University Press; 2000.
6. Fox BJ, Cohen JE. Tobacco harm reduction: a call to address the ethical dilemmas. *Nicotine Tob Res* 2002;4(Suppl 2):S81–7.
7. Gilpin EA, Pierce JP. The California tobacco control program and potential harm reduction through reduced cigarette consumption in continuing smokers. *Nicotine Tob Res* 2002;4(Suppl 2):S157–66.
8. Foulds J, Ramstrom L, Burke M, Fagerstrom K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob Control* 2003;12:349–59.
9. Canadian tobacco reporting regulations. Ottawa: Health Canada; 2003.
10. WHO Study Group on Tobacco Product Regulation. Report on setting regulatory limits for carcinogens in smokeless tobacco. Geneva: World Health Organization; 2010 (WHO Technical Report Series No. 955).
11. WHO Study Group on Tobacco Product Regulation. Contents and design features of tobacco products: their relationship to dependence potential and consumer appeal. Geneva: World Health Organization; 2007 (WHO Technical Report Series, No. 945).
12. Counts ME, Morton MJ, Laffoon SW, Cox RH, Lipowicz PJ. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. *Regul Toxicol Pharmacol* 2005;41:185–227.

Annex 1

Novel tobacco products, including potential reduced exposure products: research needs and recommendations

*Dr I. Stepanov, Division of Environmental Health Sciences and Masonic
Cancer Center, University of Minnesota, Minneapolis, Minnesota, USA*

*Dr L. Soeteman-Hernández, Centre for Health Protection, National Institute for
Public Health and the Environment, Bilthoven, The Netherlands*

*Dr R. Talhout, Centre for Health Protection, National Institute for Public Health
and the Environment, Bilthoven, The Netherlands*

Abstract

Background

Concept of “harm reduction”

Methods

Data sources

Selection criteria

Data extraction and synthesis

New marketed and test-marketed products and products with emerging use

Oral tobacco products

Dissolvable tobacco

Novel snus products

Oral tobacco types resembling snus on the market in the
European Union

Modified or alternative smoked products

Potential reduced exposure cigarettes

“Low-tar” cigarettes promoted in some countries as “less harmful”
products

Reduced-nicotine cigarettes

Super-slim cigarettes

Little cigars and cigarillos

Herbal-tobacco cigarettes

Bidis

Waterpipes

Product description and marketing strategies

Consumer awareness, product use and perceptions

Constituents, toxicity and disease risk

Addictive potential

Regulatory considerations

Notable alterations to traditional products

Swedish snus with reduced tobacco content

- Moist snuff with bioactive additives
- Menthol capsules in filters
- No-additive, or organic, cigarettes
- Branding with a brand name
- Less-smoke-smell cigarettes
- Technologies under development
 - Substitution of traditional tobacco burning by heating
 - Combination of changed tobacco processing and filter structure
 - Tobacco substitute sheet with a carbon or cellulose acetate filter
 - Tobacco-blend treatment and filters containing functionalized resin or carbon
 - Combination of tobacco substitute sheet and a two-segment carbon filter
 - Modification of filter structure
 - An amine functionalized ion-exchange resin in filters
 - Titanate nanosheets, nanotubes and nanowires in filters
 - Charcoal filters
- Research in progress as presented at the 2013 CORESTA meeting
 - Tobacco additives
 - Filter additives
 - Precursor studies
- Summary
 - Non-combustible oral products
 - Cigarettes and cigarette-like devices
- Conclusions
- Acknowledgements
- References
- Appendix. Questionnaire on new tobacco products, including products with potentially “modified risk”

Abstract

This annex provides an overview of novel marketed and test-marketed products and products with emerging use, including oral tobacco products, modified or alternative cigarettes, waterpipes and notable alterations to traditional products. New technologies in development, such as substituting traditional burning of tobacco by heating, changing tobacco processing and alterations to filter structure are also discussed.

Analysis of published research on these products brought us to the conclusion that the impact of the newest tobacco products on public health is not clear. Potential unrecognized toxicity, increased or sustained prevalence of tobacco use by recruitment of new users, relapse of ex-smokers or maintenance of tobacco use by current smokers who might otherwise have quit, dual use of a novel tobacco product and cigarettes and potential initiation with a novel product followed by switching to cigarette smoking are major concerns voiced

by many public health researchers and advocates. The current state of research does not provide sufficient evidence to dismiss any of these concerns.

We recommend improved systematic global surveillance of new tobacco products and development of a standard approach to assess the risks associated with their use, research on marketing and on consumer perceptions of novel products, development of effective approaches to communicate information on these products to professionals and the general public, introduction of consistent nomenclature and assessment of the impact of policies on the prevalence of novel product use. We also suggest that regulatory bodies consider expanding their regulatory framework to include not only all existing and emerging tobacco products but also products that are used in similar ways (such as herbal cigarettes) and accessories for tobacco use (such as waterpipe charcoal), establish requirements for premarket authorization of novel products, monitor the prevalence of new tobacco product use in each country in order to prioritize tobacco control and regulation measures properly, and develop regulatory strategies to decrease the toxicity, attractiveness and addictiveness of new products.

Background

During the past decade, a range of new tobacco products and product types has been introduced onto markets worldwide. Some of the new products, such as dissolvable tobacco products and “snus” manufactured in the USA, are designed for oral use. Other innovations are in essence modified cigarettes that contain specially treated tobacco or novel filters or deliver inhaled tobacco in novel ways, such as at a lower burning temperature or by heating instead of burning the tobacco. Some of these products may be the result of attempts by the tobacco industry to manufacture and market products that decrease exposure to harmful tobacco constituents, and some have been or are being marketed with corresponding implicit or explicit health claims. While the general concept of exposure reduction is constructive, use of such products or misperception of the health benefit of using a “reduced exposure” product could have unintended health consequences. For instance, marketing of “light” cigarettes raised false expectations of reduced exposure, and they have not decreased health risks. Cigarettes with reduced nicotine content are another innovation in tobacco products; such cigarettes could be less addictive and lead to a decrease in smoking prevalence. Other innovations, such as menthol capsules in cigarette filters, are not associated with reduced risk. Further alterations to or processing of tobacco plants and new tobacco delivery products may be developed. The emerging use of some tobacco products in countries where those products have not been used previously, with potential unrecognized consequences, is another concern.

The increase in the diversity of new tobacco products should be accompanied by rigorous research on their effects at both individual and population level. A significant amount of independent research has been conducted on some of these products during the past decade, and tobacco companies publish the results of testing of products that may appear on the market. Summarizing existing knowledge on the toxicity and marketing of these products is important for understanding the current state of science and for identifying any gaps and future directions, thus providing an adequate basis for tobacco control policies and regulations. Our objective was to systematically identify and evaluate published peer-reviewed publications and other sources on the types, properties and effects of new and emerging tobacco products, including those with potentially “modified risks”.

Concept of “harm reduction”

A “harm reduction” strategy to develop tobacco products that are less toxic and addictive could be an effective element of a comprehensive approach to reducing tobacco-related deaths and disease. Such a strategy might not only be beneficial on a population scale but might also be necessary to reduce the risk for disease of tobacco users who are unwilling or unable to break their dependence on tobacco.

The concept of “harm reduction” may have different meanings for the tobacco industry and for researchers in public health and tobacco control. Until now, the industry has focused on reducing the measured yields of harmful constituents in cigarette smoke; however, from a public health perspective, marketing of such tobacco products might imply reduced exposure and risk on the basis of insufficient or unverified information. The history of the manufacture and marketing of “light” or “low-tar” cigarettes is a well-known example in which consumers were misled by invalid assurances of reduced harm. Public health researchers and tobacco control professionals are therefore concerned about the actual exposure and intake of consumers to constituents, the possible recruitment of new users and the addictive potential of products (1, 2). As both addiction and the risks for many tobacco use-associated diseases are related to the level of exposure to tobacco constituents, reducing exposure should be an important component of tobacco control. Several basic principles have been proposed by the Society for Research on Nicotine and Tobacco (3) for approaches to exposure reduction.

- The purpose of the approach must be to reduce deaths and disease caused by tobacco.
- The long-term goal of the approach should be to make smokers both tobacco- and nicotine-free.

- The approach should not add any risk, and the data on safety should be extensive, including in long-term use.
- The approach should not exacerbate individual nicotine dependence.
- It should not reduce the likelihood of eventual cessation of tobacco use.
- The approach should not increase the population prevalence of tobacco dependence.
- It should not appeal to adolescents or increase the risk for misuse or abuse by adolescents.
- Any promotion or marketing of this approach should provide consistent messages about smoking cessation and offers of help in quitting smoking and in terminating use of the product.

Use of these basic principles in designing exposure reduction approaches might accelerate assessment of products with reduced toxicant levels and provide consumers with less harmful options than the currently available conventional cigarettes.

Methods

Data sources

Literature was sought primarily on the PubMed database and with the SciFinder search tool, which retrieves data from the Medline and C.Aplus databases. Relevant articles cited in publications obtained from the databases were also included. In addition, the Internet was searched for websites that provide product characteristics and marketing information, the websites of major tobacco manufacturers, tobacco research websites, blogs and news articles. Information was obtained from 2002 on, as the background document on new or modified tobacco products (4) was finalized in November 2002 and issued in 2003. A period of around 11 years is therefore covered.

In addition, experts in the field, including regulators and tobacco scientists, were consulted through a questionnaire (see Appendix). Contributors are listed in the acknowledgements. The Internet was searched for products identified in the questionnaire survey.

Selection criteria

We used the following criteria to define “new” or “novel” tobacco products:

- The product contains tobacco (e.g. e-cigarettes and herbal cigarettes were not included).

- The product is manufactured by a new or unconventional technology and/or is marketed as a “reduced harm” product.
- The product type has been on the market for less than 12 years.
- The product type has been on the market for longer, but its market share has increased in countries or regions in which this type was not used previously. Emerging use of unconventional tobacco products jeopardizes tobacco control efforts worldwide.

While some of the products described are no longer available, we summarized the research on those products to improve understanding of current and future innovations in tobacco product development and for interpreting any health claims by the industry.

We excluded products that are just variations of traditional or regular cigarettes, cigars, pipe tobacco, roll-your-own or oral tobacco in markets that carry these types of product.

Data extraction and synthesis

The search was performed with the initial keywords “snus”, “waterpipe”, “dissolvable tobacco”, “low nicotine cigarette”, “reduced (tobacco product or cigarette)”, “modified (tobacco product or cigarette)”, “tobacco harm reduction” and “novel (tobacco or cigarettes)”, followed by the “snowball” method. We collected information on the products, approaches used in marketing them, including health claims, how the products are used and perceived, their chemical composition and toxicity, their addictive potential, their effectiveness in suppressing withdrawal symptoms (which may hinder smoking cessation or complete substitution) and any regulations specific to the product.

New marketed and test-marketed products and products with emerging use

Although some of the products described in this section have been discontinued by their manufacturers and are no longer available, a substantial amount of research has been done, which is important for understanding current and future innovations in tobacco product development and for evaluating the potential public health impact of future modified products. Products that do not involve new technologies but are beginning to be used in new markets are also included, as expanding use by new types of consumer raises new challenges and new questions that must be addressed by rigorous scientific research.

The majority of the published papers included in this report originated in Europe and the USA. Furthermore, the feedback to the questionnaires did not provide sufficient information for a geographically comprehensive overview, as some respondents reported no information on new or emerging tobacco products in their region. Therefore, information is provided on product type rather than on trends by geographical region.

Oral tobacco products

Dissolvable tobacco

Product description and marketing strategies

Dissolvable tobacco products appeared on the US market in 2001, with the introduction of Ariva and Stonewall (Figure A1.1).

Figure A1.1. Examples of dissolvable tobacco products



Their manufacturer, Star Scientific, made only a limited investment in marketing and promoting these products (5). In 2009, RJ Reynolds introduced Camel dissolvable products, and in 2011 Philip Morris introduced Marlboro and Skoal dissolvable tobacco (Figure A1.1). These products are made from finely milled tobacco and are sold in the form of pellets, sticks or strips. For example, Camel Orbs are small, oval-shaped pellets, Camel Sticks are rods of dissolvable tobacco that resemble toothpicks, and Camel Strips are brown tobacco strips similar to breath-freshening strips (6). Dissolvable Camel

products were initially introduced in mellow and fresh flavours, but the latest version has been reformulated and has a single mint flavour (7). Dissolvable tobacco products of a size, shape and packaging similar to those of the Camel dissolvable series were introduced into markets of Taiwan, China, under the brand name Revo in 2010 (8). Marlboro Sticks and Skoal Sticks produced by Philip Morris differ from Camel Sticks in that they contain a toothpick-like wooden rod covered with a layer of finely milled tobacco. Figure A1.1 demonstrates the evolution of this category of product.

Camel dissolvable products were test-marketed in several US states, including Indiana, which has the highest tobacco use and the second highest adult smoking rate in the USA (9, 10). Advertising in shops carrying dissolvable tobacco products included phrases such as “dissolvable tobacco”, “free trial”, “special price” and “What’s your style?”, and the products were shelved near smokeless tobacco, cigarettes or sweets (10). Like the approaches for promoting US snus, some of the advertisements for dissolvable products emphasize their unique features (for example, do not require spitting or disposal after use), their discreet nature and the ease of use in bars, airplanes and other places where smoking is not permitted (5). Although the primary audience for retail advertising of these products appears to be current smokers, some researchers raised the concern that their promotion, the fact that they can be used discreetly and the packaging, which many refer to as “candy-like”, may appeal to new, young users who have not previously used tobacco (5, 10). The study by Romito et al. (10) in Indiana showed that most shops that sold Camel dissolvables carried promotional items, including offers of free trial packs with another Camel purchase. The authors also reported that various university campuses held events at which dissolvable products were promoted, with free samples, coupons and other promotional items. Of participants who had received any promotion, 11% had tried the products, whereas only 3% of the total sample had done so.

Consumer awareness, product use and perceptions

Early research on Ariva showed little appeal or uptake by smokers, although some research participants thought the products would appeal to groups such as new smokers, young adults and women (5, 11). Concern has been raised that the “candy-like” appearance of these products and the added flavours might be attractive to young children (12). Analysis of data from Florida, USA, suggested that 18- to 34-year-old smokers are more likely to have tried dissolvables than older adult smokers (5). Another study of consumer awareness, interest and perception of Camel dissolvables in Indiana, USA, showed that consumer interest was very low, but respondents < 40 years were more familiar with Camel dissolvables (60%) than those > 40 years (45%; $p < 0.01$). As for snus,

males and current and former smokers showed more interest and more often tested dissolvable products. Both smokers and nonsmokers perceived that the advertisements targeted smokers (10).

Constituents, toxicity and disease risk

The first versions of dissolvable products, Ariva and Stonewall, contained the lowest levels of tobacco-specific *N*-nitrosamines (TSNA)—a major group of tobacco carcinogens—of all US commercial tobacco products (13). For instance, the *N*'-nitrosonornicotine (NNN) content of Ariva was 19 ng/g, and that of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was 37 ng/g, whereas the traditional moist snuff Kodiak Wintergreen contained 2200 ng/g NNN and 410 ng/g NNK. In a study of Ariva and medicinal nicotine, the TSNA intake of smokers who switched to Ariva was comparable to that of a nicotine lozenge (14). Slightly higher TSNA levels have been reported in more recent Ariva and Stonewall products, although they are still much lower than those in traditional moist snuff (15, 16). The TSNA levels in the dissolvable Camel products that initially appeared on the market were generally comparable to those of Ariva and Stonewall, Camel Strips having the lowest TSNA content, followed by Camel Orbs and Sticks (15). More recent versions of Camel dissolvables, however, contain higher levels of TSNA (17). The new dissolvable products Marlboro Sticks and Skoal Sticks contained TSNA at the levels found in conventional US moist snuff (16, 17). Table A1.1 summarizes the concentrations of nicotine and TSNA reported in dissolvable tobacco products.

Table A1.1. Concentrations of nicotine and tobacco-specific *N*-nitrosamines in dissolvable tobacco products

Product	Free		NNN (ng/g)	NNK (ng/g)	References
	Nicotine (mg/g)	nicotine (mg/g)			
Ariva	4.4–6.3	0.3–1.5	19–98	37–71	13, 15, 16, 18
Stonewall	6.8–8.7	0.7–1.6	56–133	43–73	13, 15, 16, 18
Camel Orbs	2.7–4.1	1.2–1.8	190–280	260–1060	15, 16, 18; Stepanov, unpublished data
Camel Sticks	3.1–4.7	1.4–1.9	221–260	220–780	15, 16; Stepanov, unpublished data
Camel Strips	2.2–4.1	1.1–2.0	150–340	194–780	15, 16; Stepanov, unpublished data
Marlboro Sticks	5.9–7.1	2.7–3.5	1760–2070	472–800	16; Stepanov, unpublished data
Skoal Sticks	4.5–5.9	0.8–1.1	1820–2420	485 – 790	16; Stepanov, unpublished data

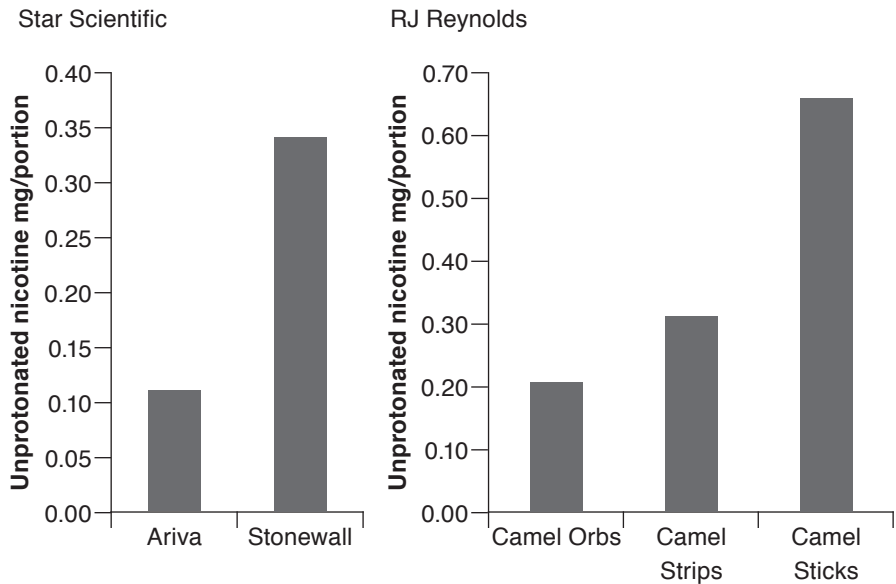
Extensive chemical screening of Camel dissolvable tobacco products showed that they contain mainly tobacco, mixed with binders, fillers and flavours (6, 7). The chemical composition of the version of Camel dissolvable products released in 2010 showed a changed flavour (mint instead of fresh and mellow flavours); thus, all the new products contained menthol but no cinnamaldehyde or coumarin, which were previously present in mellow-flavoured dissolvables, and threitol instead of glycerol. The level of free nicotine (biologically available form) was statistically significantly higher in the new Orbs than in the older version, but no significant change was found in sticks or strips. More comprehensive screening showed the presence of 163 chemicals in dissolvable Camel Orbs, indicating their chemical complexity (16).

Because of the suggested resemblance of dissolvable tobacco products to “candies” (sweets), there is concern that children might accidentally ingest these products. Connolly et al. (12) analysed data on child poisoning due to ingestion of tobacco products and found an increasing rate of ingestion of smokeless tobacco between 2006 and 2008, with a case of ingestion of Orbs by a 3-year-old child and two cases of mild poisoning in children aged 2 and 3 years resulting from ingestion of snus.

Addictive potential: effectiveness in smoking substitution or cessation

According to the promotional literature, Camel Orbs contain 1 mg of nicotine per pellet, Camel Sticks contain 3.1 mg of nicotine per stick, and Camel Strips contain 0.6 mg of nicotine per strip. Connolly et al. (12) analysed Camel Orbs (fresh and mellow flavours) sold in three test markets in the USA and found that they contained an average of 0.83 mg of nicotine per pellet. The average pH was 7.9, which resulted in an average of 42% nicotine in the biologically available free, or unprotonated, form. Analysis of Camel dissolvable products in another study (6) showed that the nicotine content was 0.82 mg in Orbs mellow flavour, 0.77 mg in Orb fresh flavour, 0.91 mg in sticks and 0.21 mg in strips; the pH of these products ranged from 7.50 to 8.02. These products have much lower levels of total and free nicotine than traditional smokeless tobacco, which is likely to determine their acceptability by current or new tobacco users. Low-nicotine products may have lower addictive potential and thus may be more readily accepted by young people who are initiating tobacco use, but they may be rejected by smokers who are seeking a good substitute for cigarette smoking. Smokeless products with a higher nicotine content potentially lead to abuse and sustain addiction but may more effectively satisfy smokers and more completely substitute for cigarettes than those with less nicotine (19, 20). Dissolvable products can provide gradually increasing levels of biologically available free nicotine, so that different formulations may appeal to different potential consumers (Figure A1.2).

Figure A1.2. Nicotine gradient in dissolvable tobacco products



Free nicotine levels have been intentionally maintained in various smokeless tobacco products in order to offer low-nicotine products to new users and also products with gradually higher levels of nicotine to sustain the addiction of established consumers (“graduation strategy”) (21). It is important to understand how differing free nicotine levels in new dissolvable products affect their use by consumers.

Studies of switching from smoking to the use of dissolvable tobacco show that the physiological and subjective effects of some dissolvable products on withdrawal and craving may be comparable to those of medicinal nicotine (14). These products may, however, delay cessation by providing a means for smokers to relieve their nicotine craving temporarily when they cannot smoke rather than to quit tobacco use completely (5).

US Food and Drug Administration Tobacco Products Scientific Advisory Committee report on dissolvable tobacco products

In March 2012, this Committee reviewed the published material, submissions and presentations relevant to dissolvable products and submitted a report to the Food and Drug Administration on “...the nature and impact of the use of dissolvable tobacco products on the public health, including such use among children” (22). The Committee concluded that (i) products vary in the content of various constituents, including nicotine and TSNA; (ii) the liability for abuse of dissolvable tobacco products may be lower than that of conventional

US cigarettes and most conventional smokeless tobacco products; (iii) use of dissolvable tobacco products may reduce cigarette consumption but does not completely substitute for smoking by most regular cigarette smokers; (iv) while exclusive use of dissolvable tobacco products should be less hazardous than regular smoking of cigarettes, no epidemiological data are available on the absolute health risks posed by these products as they are currently used in the population; (v) data on consumer perceptions and response are limited, but, in general, consumers have not responded positively to current products; and (vi) few cases of accidental ingestion with serious consequences have been reported.

Novel snus products

Snus traditionally manufactured in Scandinavia is a finely ground moist tobacco snuff usually processed by pasteurization, which leads to lower levels of carcinogenic TSNA than in other traditional moist snuff. Snus is placed between the cheek and gum, and the juices produced in the mouth are swallowed rather than expectorated. In this section, we focus on the novel versions of snus manufactured and marketed in the USA.

Product description and marketing strategies

In 2006, two leading US cigarette manufacturers, RJ Reynolds and Philip Morris, began to market new smokeless tobacco products also called “snus” (Figure A1.3).

Figure A1.3. Examples of US-manufactured snus



The US version of snus is also produced from pasteurized tobacco and differs from traditional US chewing tobacco, dip and snuff in that it does not require spitting and is packaged in small teabag-like pouches that are placed under the upper lip and are relatively unobtrusive (23). Differentiation of US snus from

traditional smokeless products was part of the product advertising (24, 25). The marketing of US snus has emphasized the Swedish origins, but US snus products have been promoted as extensions of the popular cigarette brands Camel and Marlboro. With increasing application of clean indoor air laws, snus has been marketed as a product that can be used discreetly in public and in bars, offices and airplanes “when smoking isn’t an option” (24). Therefore, although much of snus advertising appears to position the product as an alternative to smoking (25), there is concern that snus is marketed primarily as an adjunct to smoking rather than a replacement (24). Examination of Camel snus advertisements (26) indicated that, while between 2007 and 2009 this product was promoted to cigarette smokers, the marketing strategy shifted in October 2009, when new “Break free” advertisements appeared in magazines. The authors suggested that the new advertisements give an ambiguous message that could appeal to a broader spectrum of consumers, including young potential new users. A limited study of a small sample of neighbourhoods and schools in New York City, USA, showed that about 20% of probable tobacco-selling businesses around schools sold snus (27).

Since the restriction of traditional broadcast tobacco advertising in the USA, snus has been promoted by tobacco companies to consumers by direct mail, e-mail and other means and also by promotions and free samples in bars and clubs and magazine advertising (23, 24, 28, 29). Direct mailing has been used to promote Marlboro and Camel snus, with coupons and free packages of the product (24). The marketing also included new websites, such as www.camelsnus.com for Camel snus (28). The messages posted on the message board of the Camel snus brand website by consumers during test-marketing may have influenced RJ Reynolds’ decisions on product modifications, such as discontinuing Spice flavour and revising pouch size (28). Delnevo et al. (25) suggested that the ranking of Camel snus as one of the top 10 selling US smokeless brands after only a few years on the market might be attributable to this aggressive marketing.

Snus products carrying popular cigarette brand names such as Lucky Strike and Peter Stuyvesant have also been promoted in Canada, Japan and South Africa (24).

Consumer awareness, product use and perceptions

Biener et al. (30) reported that 10% of smokers in test markets had tried snus in 2010, the trial rate among young adult men being as high as 29%. Products were tested more frequently by whites than by minorities, by respondents with lower education than by those with higher education and by those without immediate plans to quit smoking than by those intending to quit within the next 30 days. Similar results were obtained in a study of snus use in 8472 pupils

aged 11–18 in Texas, USA: 7.1% reported ever trying snus, and, of these, 77% were male, 68% were in school, and 46% were white (31). In a study of the awareness, use and perception of snus among 2607 young adults aged 20–28 after snus became available nationwide, 64.8% of participants were aware of snus, 14.5% had ever used it, and 3.2% had used it in the past 30 days; all three outcomes were associated with being male and having smoked > 100 cigarettes in a lifetime ($p < 0.05$) (29). In a study of the Camel snus website message board, marketing was found to play a significant role in deciding to try this product; many participants said that they had tried the product after receiving a free sample (28).

Most smokers viewed using smokeless tobacco products such as Camel snus and Marlboro snus as a temporary rather than a complete substitution for smoking; furthermore, trying snus was reported to reinforce a preference for smoking (24). The participants considered the main benefits of snus to be its use in smoke-free environments and avoiding the social stigma attached to second-hand smoke. Participants were sceptical of the idea that snus is safer than cigarettes and did not consider it an acceptable substitute for cigarettes or as a cessation aid. In other studies, however, snus users and people exposed to snus marketing in bars and clubs were more likely to agree that snus is less harmful than cigarettes (29, 31).

The overall market share of snus in the USA increased from 0.1% in 2007 to 3.7% in 2011 (25). Camel, Marlboro and Skoal snus accounted for 99.7% of all snus sales in 2011 (63.3% Camel, 24.2% Marlboro and 12.3% Skoal snus). Most snus sold in 2011 (86.7%) was spearmint or mint flavoured. Habitual users of Camel snus reported using other tobacco products concurrently and consumed an average of 3.3 ± 1.9 pouches/day. Some users reported using two or more pouches simultaneously (32).

Constituents, toxicity and disease risk

The levels of TSNA, nicotine, benzo[*a*]pyrene (a representative of carcinogenic polycyclic aromatic hydrocarbons [PAH]) and several metals in Camel snus were reported by RJ Reynolds researchers (32). In an independent study, Stepanov et al. (2012a) analysed TSNA and nicotine levels in various novel products, including Camel and Marlboro snus, purchased in various parts of the USA in 2010. Camel snus had significantly higher TSNA levels than Marlboro snus, while the levels of unprotonated nicotine in the two products varied significantly by region. The amounts of total nicotine, unprotonated nicotine and the sum of NNN and NNK in Camel and Marlboro snus determined in the authors' laboratory between 2006 and 2010 were significantly higher in the large Camel snus pouches released in 2010 than in the original, smaller

pouches that entered the market in 2006, due to the increase in pouch size. The total and unprotonated nicotine contents of the later version of Marlboro snus pouches were also higher, but the sum of NNN and NNK was lower than in the original version (33). Table A1.2 summarizes the concentrations of nicotine and TSNA reported in US-manufactured snus.

Table A1.2. Concentrations of nicotine and tobacco-specific *N*-nitrosamines in US-manufactured snus

Product	Nicotine (mg/g)	Free nicotine (mg/g)	NNN (ng/g)	NNK (ng/g)	References
Taboka	14.0–18.3	0.7–1.1	822–933	67–84	18, 34
Marlboro Snus	11.5–19.7	0.3–1.0	330–2950	100–233	15, 34; Stepanov, unpublished data
Camel Snus	8.7–13.9	1.6–6.1	369–1320	84–480	15, 18, 34; Stepanov, unpublished data
Skoyal Dry	10.1–11.4	0.6–1.6	929–4750	80–323	18, 34
Skoyal Snus	17.2–19.0	0.6–1.0	1410–1710	246–378	Stepanov, unpublished data

Mouth-level exposure to various constituents of Camel snus was studied in a group of adult habitual snus users (32). On average, 60–90% of the nicotine, TSNA and benzo[*a*]pyrene initially present in a snus pouch remained in the pouch after use. The calculated mean mouth-level exposure was 9.4 mg/day for nicotine, 527.7 ng/day for TSNA and 0.68 ng/day for benzo[*a*]pyrene. In contrast, researchers at the British American Tobacco in Sweden reported that only 33–38% of nicotine and TSNA were extracted from Swedish snus by habitual users (35). The Camel snus studied by Caraway and Chen (32) is, however, different from the Lucky Strike snus tested by Digard et al., with a lower moisture content, a smaller portion size and perhaps other differences in content and manufacture.

Potential changes in the exposure of smokers who switched to snus were investigated in a comparison of Taboka, an early version of a US snus-like product, Camel snus and medicinal nicotine. The concentrations of exhaled CO, urinary cotinine, urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a biomarker of exposure to the tobacco-specific lung carcinogen NNK, and urinary total NNN were lower after 4 weeks of product use in each group. The decrease in total NNAL concentration was greater in the group given medicinal nicotine than in that given Camel snus (20). Switching to Marlboro snus was investigated in a study that included partial substitution, complete switching and control groups of smokers who continued to smoke or

did not use any tobacco products (36). Metabolites of TSNA, nicotine (urine and plasma), aromatic amines, benzene and PAH, urine mutagenicity and carboxyhaemoglobin were measured at baseline and at various times after switching or quitting. Significant reductions were found in all urinary biomarkers in both the “complete” and “partial” substitution groups as compared with smokers who continued to smoke.

Epidemiological evidence indicates that people who use exclusively low-TSNA Swedish snus have a lower overall risk for cancer than regular cigarette smokers (37–39). An increased risk for pancreatic cancer was reported in snus users as compared with people who never used tobacco, but the risk for oral cancer was low or inexistent (38, 39). Snus-induced leukoplakia is common in Scandinavian snus users, but the risk for subsequent development of cancer is not clear (40). Use of smokeless tobacco may increase the risk for death after a myocardial infarct, but it does not increase the risk for myocardial infarction. The data on the reproductive effects of smokeless tobacco use during pregnancy are too sparse to allow conclusions. No information on these health effects is available for users of US-manufactured snus; however, the individual risks of exclusive users may be similar to those of Swedish snus users.

Addictive potential; effectiveness in smoking substitution or cessation

In a study in which smokers were asked to stop smoking and to choose General snus (a Swedish product), Camel snus, Marlboro snus, Stonewall or Ariva and use it for 2 weeks, Camel snus was generally associated with greater relief from craving, greater satisfaction, reduced use of cigarettes and longer abstinence during follow-up than the other products (19). The dissolvable products Ariva and Marlboro snus were least effective in encouraging abstinence, suppressing cigarette use and lowering the rate of product use. These differences could be due to the levels of nicotine in the products studied: the free nicotine content of a single portion of Camel snus was 1.74–1.97 mg, while that of Ariva was 0.24–0.25 mg and that of Marlboro snus was 0.14–0.38 mg. In a study of pharmacokinetics, the intake of nicotine tended to parallel the nicotine content of the products: use of Camel snus resulted in a higher peak plasma concentration of nicotine (7.7 ng/mL) than Ariva (3.4 ng/mL) or Marlboro snus (2.9 ng/mL) (41). Measures of craving and intention to smoke were significantly decreased with use of Camel snus but not with the lower-nicotine Ariva or Marlboro snus. In a pilot comparison of medicinal oral nicotine replacement with Camel snus and Taboka, Camel snus was associated with less cigarette smoking, greater product use and greater abstinence than the lower-nicotine Taboka (20).

The effect of the level of nicotine in snus products on subjective responses to the products is not clear. In one study of the pharmacokinetics of different oral

tobacco products, products with a higher nicotine content resulted in greater relief of craving (42), while another study involving 5 days of product administration showed no difference in craving or anticipation of withdrawal relief between Ariva and Camel snus (43). Similarly, in a study with randomization of smokers to Taboka, Camel snus or medicinal nicotine, no difference in craving or withdrawal was seen (20). In general, snus products have not been found to be superior to medicinal nicotine in reducing withdrawal symptoms (19, 20).

Oral tobacco types resembling snus on the market in the European Union

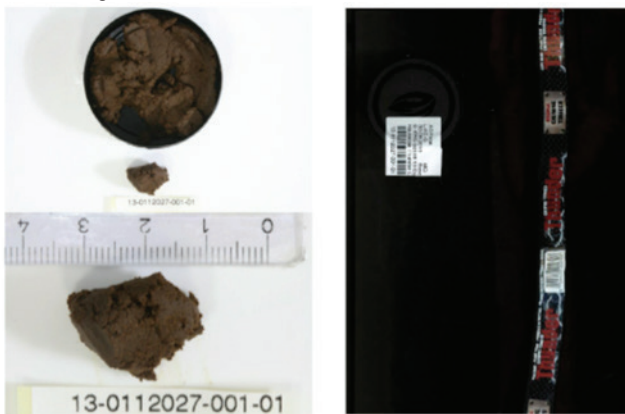
According to Article 8 of the European Tobacco Product Directive 2001/37/EC (44), selling tobacco for oral use, except for chewing tobacco, is forbidden in the European Union, except in Sweden.

“Tobacco for oral use” means all products for oral use, except those intended to be smoked or chewed, made wholly or partly of tobacco, in powder or in particulate form or in any combination of those forms, particularly those presented in sachet portions or porous sachets, or in a form resembling a food product.

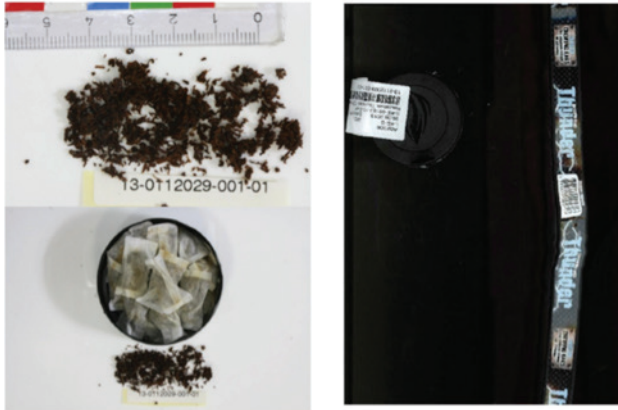
In our questionnaire survey, Austria, the Czech Republic, Germany and Switzerland reported products that resemble both chewing tobacco and snus. For instance, Thunder Chewing Tobacco (Figure A1.4A), a strongly flavoured tobacco paste manufactured by V2 Tobacco in Denmark (<http://www.v2tobacco.com/>), contains 41% tobacco and 59% of “texture agent”; this is a relatively low tobacco content. The same manufacturer produces Thunder Chewing Bags (Figure A1.4B), consisting of cut tobacco in small sachets that are strongly flavoured with aroma of spearmint.

Figure A1.4. Examples of products that resemble snus

A. Chewing tobacco



B. Chewing bags



Another product of this type is Makla Africaine reported in Switzerland and the United Kingdom (e.g. http://www.sifaco.be/Engl/Site_engl.htm and <http://www.makla-ifrikia.com/shop/kautabak-makla-ifrikia-kautabakshop.html>).

On a snus consumer forum (<http://www.snuson.com/forum/archive/index.php/t-16456.html>, accessed 5 October 2013), Thunder Chewing Tobacco is described as unsuitable for chewing, but “Its technically *makla*, which is classed as chewing tobacco, European chewing tobacco is different to US chewing tobacco, if it wasn’t intended to be chewed, it would be banned by the EU”.

As the product resembles snus, its regulatory status must be assessed. In Germany, authorities are examining whether the product falls under the Tobacco Law (implemented from Article 8 of Directive 2001/37/EC). Switzerland considers that the product is not a typical chewing tobacco product but is similar to snus, although it does not fit the definition, as it is more a paste than a powder. In Finland, the authorities are assessing whether a similar product should be regarded as snuff or as chewing tobacco.

Modified or alternative smoked products

In this section, we review information on cigarettes and cigarette-like products and devices that have either recently been introduced onto the market or have an expanding market share in regions in which they were not used previously. Research on cigarettes designed to reduce the exposure of smokers to toxins and on reduced-nicotine cigarettes is described. Alternative size cigarettes (super-slim), herbal tobacco cigarettes and other products are also described briefly.

Potential reduced exposure cigarettes

Product description and marketing strategies

Several attempts have been made by the tobacco industry to develop cigarettes that result in lower exposure to toxins than traditional cigarettes, potentially reducing the health risks of smokers and nonsmokers associated with smoking (3, 45). Three main approaches are used in the manufacture of such cigarettes.

Substituting burning for heating of tobacco. Examples are Eclipse cigarettes, introduced by RJ Reynolds, and Accord, developed by Philip Morris. Eclipse consists of a filter, tobacco (in two plugs) and a carbon-based heating element wrapped in aluminium foil surrounded by a fibreglass insulator at the tip, which is lit like a conventional cigarette but does not burn the tobacco (46). Once it is heated, the carbon element transfers heat along the wrapped core, first reaching a light reconstituted tobacco high in glycerine and then reaching the tobacco; thus, the smoke is rich in glycerol and water (47). Eclipse was claimed to potentially “reduce the risks of smoking-associated cancers and lower the risk of lung disease” (48). Other advertisements stated that Eclipse “may present less risk”, “may present less risk of cancer”, “reduces levels of carcinogenic compounds”, “produces less respiratory inflammation” and is less offensive to passive smokers because it releases vapour instead of smoke (45). Accord consists of a filter plug, a hollow tube and a segment filled with pressed tobacco; the tube is inserted into a hand-held chamber that heats the tobacco without burning it (46). Accord was marketed as a product intended to reduce second-hand smoke and which may decrease the mutagenicity and cytotoxicity associated with normal tobacco smoke (48). While Accord has been discontinued, Eclipse is still available on the US market.

A recent prototype of cigarettes that heat rather than burn tobacco is the Ploom modelTwo (Figure A1.5), a combination of an electronic cigarette (e-cigarette) and a conventional cigarette, which vaporizes actual tobacco rather than the propylene glycol used in e-cigarettes (49; <http://www.ploom.com/modeltwo>).

Figure A1.5. Ploom



The motto of the Ploom company is “It’s time to rethink tobacco”, and their most popular product, the Ploom modelTwo, is advertised as a “revolutionary way to enjoy real tobacco in style”. It is a handheld device for warming tobacco pods in many different flavours and inhaling the warm tobacco vapour. According to the product description, the Ploom modelTwo takes 20–30 s to heat up, and each tobacco pod is designed to be smoked over 5–10 min rather than being puffed steadily for a longer time. The vapour generated appears to be appreciated by consumers due to its similarity to conventional tobacco smoke: “The vapor is great, thick and milky, almost like actual smoke...” (49). A reported disadvantage is that the heating element is placed close to the mouthpiece, which becomes very hot (49).

Changing tobacco processing. This approach was used in Advance™ and Omni cigarettes, released by Brown & Williamson and Vector Tobacco, respectively, which have been discontinued. Advance™ was marketed as a product with “all of the taste...less of the toxins” and, according to the manufacturer’s claims, was made of tobacco cured by a special process that “significantly inhibits the formation of tobacco-specific nitrosamines” (50, 51). Omni was made with tobacco treated with palladium to increase its burning efficiency, which was expected to reduce the levels of toxic and carcinogenic products of incomplete combustion in the smoke (52). Omni was marketed as containing significantly reduced levels of PAH, TSNA and catechols, which are “among the most potent and dangerous substances in tobacco smoke in relation to lung cancer incidence” (51).

Modifying filter structure. For example, Marlboro UltraSmooth, which entered the US commercial test market in 2005, had a filter that contained activated carbon. While carbon was already used in US cigarettes, the novelty of Marlboro UltraSmooth was that it contained more carbon than other brands (53), suggesting enhanced potential to reduce toxic smoke constituents. This brand was also discontinued.

Consumer awareness, product use and perceptions

In studies of smokers’ and ex-smokers’ reactions to Eclipse cigarettes, most smokers believed that they were safer than regular, low-tar or low-nicotine cigarettes or even “completely safe”, for the health of both smokers and those around them (45, 54, 55). In one study, many smokers viewed Eclipse as a step towards quitting (45). Another group showed that Eclipse appealed to smokers who were contemplating quitting but that claims of reduced risk appeared to reduce their readiness to quit (54). Thus, such claims can undermine adult cessation and prevention of uptake by young people, possibly increasing harm even if the products are less toxic. A study by the same group in the United

Kingdom had similar findings, indicating that the effects of such products and of the claims of quitting by smokers and relapse by ex-smokers must be evaluated as a matter of public health urgency worldwide (55). Despite smokers' perception that Eclipse cigarettes are "safer", they rated Eclipse as less satisfying and less rewarding than their own brand of cigarettes (56).

Constituents, toxicity and disease risk

According to industry investigations, the lower pyrolysis temperature of electrically heated cigarette smoking systems like Accord leads to a significant reduction (25–90%) in the measured concentrations of 44 mainstream smoke (MSS) constituents, including nicotine and carbon monoxide (CO), in comparison with a standard reference cigarette (46, 57). When tested with the Federal Trade Commission method, Accord yields 0.1 mg nicotine and 2 mg tar, and Eclipse yields 0.2 mg nicotine and 4.0 mg tar (46); however, because of differences in design and potential differences in human smoking topography from that of conventional cigarettes, the requirements for measuring the doses of chemicals and toxicants delivered from this type of product must be carefully evaluated. For instance, although the machine-measured nicotine yield of Eclipse was reduced, the levels of nicotine in the blood of smokers were similar to those after smoking conventional cigarettes (58). An evaluation of exposure based on urinary biomarkers, however, showed that switching to Eclipse reduced exposure to nicotine and NNK (59).

Early research reported by the manufacturer RJ Reynolds showed that, in comparison with regular cigarettes, the MSS condensate of Eclipse was less genotoxic in a mouse dermal application study (47) and caused less inflammation and pulmonary toxicity in the rat nasal inhalation model (60); they also reported that switching to Eclipse reduced the mutagenicity of the urine of smokers (61). An independent study of the acute effects of Eclipse in smokers who had switched to these cigarettes showed that their exposure to CO was approximately 30% higher than that from regular cigarettes (46). Other studies showed that smokers take larger puff volumes and more frequent puffs when smoking Eclipse than with conventional cigarettes and confirmed the increase in exhaled CO (56, 59, 62). Long-term smokers of Eclipse exhaled 45% more CO than people who used a Nicorette oral inhaler (63, 64). Rennard et al. (65) investigated the effect in heavy smokers of switching from regular cigarettes to Eclipse for 2 months on lower respiratory tract inflammation and observed a significant reduction, although the improvement did not reach the state found in nonsmokers. In a study of the effect on pulmonary epithelial permeability, airway inflammation and blood leukocyte activation in current smokers, switching to Eclipse reduced alveolar epithelial injury in some smokers but may have increased carboxyhaemoglobin levels and oxidative stress (66). In

the same study, Accord reduced exposure to CO from that with regular cigarettes, even though smokers take larger, longer puffs when using Accord (46).

Smoking Advance™ cigarettes produced a lower CO “boost” but increased the heart rate, like regular cigarettes (67). Modest reductions in the uptake of tobacco toxins were observed when smokers switched for 4 weeks from their usual conventional cigarette brand to Omni cigarettes; the total level of NNAL, but not that of 1-hydroxypyrene (a PAH biomarker), was statistically significantly reduced. The overall mean total NNAL level of smokers who used a nicotine patch was statistically significantly lower than that of smokers who used the Omni cigarette (68). Tests in mouse embryonic stem cells showed that smoke from Advance™ cigarettes was as toxic as smoke from a traditional brand (Marlboro Red) (69). In a study of the effect of Omni and Advance™ cigarettes on oviduct functioning in hamsters, it was found that these cigarettes contain sufficient amounts of oviductal toxicants to inhibit biological processes, potentially affecting reproductive outcomes (70).

Like “low tar” cigarettes, Marlboro UltraSmooth was shown to lead to compensatory smoking, although it produced a lower CO “boost” than regular cigarettes. Measures of salivary cotinine and cardiac function after smoking Marlboro UltraSmooth were similar to those with conventional brands, suggesting that switching to this brand is unlikely to reduce exposure to smoke constituents (53).

Effectiveness in smoking substitution or cessation

In a study in which smokers of regular cigarettes abstained overnight and then smoked Eclipse or Accord, withdrawal symptoms were suppressed fully with Eclipse, while Accord was less effective (46). Studies on the long-term effects of Eclipse showed that it can decrease cigarette consumption without causing withdrawal symptoms, decreasing nicotine concentrations or decreasing the motivation to quit altogether (63, 64). Advance™ produced withdrawal suppression and higher plasma nicotine concentrations, similar to those produced by regular cigarettes (67).

“Low-tar” cigarettes promoted in some countries as “less harmful” products

Product description and marketing strategies

These cigarettes—currently banned from being designated as “light”—include several elements (for example filter ventilation and paper porosity) that reduce smoking machine-measured tar and nicotine yields by diluting the smoke with air. Because smokers increase their intensity of smoking in response to

the reduced nicotine content of the smoke, however, these cigarettes did not reduce smokers' exposure to tobacco carcinogens and did not lower the risks for smoking-induced diseases (71–73). Nevertheless, this type of cigarette is being promoted actively in China. For example, analysis of the annual reports of the State Tobacco Monopoly Administration and the Chinese National Tobacco Corporation after 2000 shows a proposal to “actively proceed with ‘less harmful, low-tar’ cigarettes” (74).

Consumer awareness, product use and perceptions

Since the tobacco industry launched the “less harmful, low-tar” strategy in China, overall tobacco production was reported to have increased by nearly 40% between 2000 and 2009, due largely to the production and sale of low-tar cigarettes. During the first 10 months of 2011, low-tar cigarette production in China increased by 408%, and sales increased by 386% over those in 2010 (74).

Constituents, toxicity and disease risk

Cigarettes with low tar and low nicotine yields are designed to produce lower levels of smoke constituents than regular cigarettes in smoking machine measurements. It is well established that the smoker–cigarette interaction is driven primarily by the smoker's pursuit of nicotine and is therefore much more complex than any machine-based regimen (75–77). To control their nicotine intake, smokers adjust their puff volume, duration, frequency and depth of inhalation, which affects their exposure to other constituents present in cigarette smoke. Smokers also regulate their nicotine intake by blocking filter ventilation holes, which reduces dilution of cigarette smoke with air (78). Therefore, smoking low-tar cigarettes does not reduce smokers' exposure to tobacco carcinogens and does not lower their risk for smoking-induced diseases (71–73).

Addictive potential

Smokers adjust their smoking intensity, for example by drawing larger volumes of smoke and inhaling more deeply, when smoking low-tar cigarettes. Therefore, as “low-tar, low-nicotine” cigarettes deliver regular doses of nicotine to the user, their addictive potential is similar to that of regular cigarettes.

Regulatory considerations

Misleading labelling of these cigarettes as “lights” has been banned in many countries. Article 5 of the law of China's Tobacco Monopoly states that “The

State shall strengthen the scientific research and technical development of tobacco monopoly commodities, so as to improve the quality of tobacco products and reduce the content of tar and other hazardous ingredients in such products”. As a result of this requirement, the Chinese Cigarette Science and Technology Development Outline was developed in 2003, and manufacturers were ordered to reduce the tar level in cigarettes to an average of 12 mg by 2010. A report of the State Tobacco Monopoly Administration annual meeting in 2010 stated that implementing the “less harmful, low-tar” strategy would be the overall approach to improving competitiveness in China (74).

Reduced-nicotine cigarettes

Product description and marketing strategies

Unlike the “reduced-yield” cigarettes, in which the nicotine yield in smoke is modified by changing the cigarette or filter structure, low-nicotine cigarettes are made with tobacco that contains less nicotine than traditional tobaccos. For example, a brand of low-nicotine cigarettes named Quest, introduced onto the US market in 2003, was available in three varieties—low nicotine, extra-low nicotine and nicotine free. They contained genetically modified low-nicotine tobacco blended with normal tobacco to provide nicotine levels of 0.6–0.05 mg/cigarette (79), offering smokers the opportunity to reduce their nicotine intake gradually. The yields of other constituents in such cigarettes are expected to be similar to those of regular commercial cigarettes; therefore, from the point of view of exposure to toxicants and carcinogens, these cigarettes should not be considered “harm reduction” products. Analysis of internal industry documents, however, reveals that the tobacco industry has invested substantial resources in the development of low-nicotine cigarettes (80) because of their consumer appeal and their economic importance in a highly competitive cigarette market for “healthier” products. Investigation of smokers’ reactions to Quest advertisements showed that some held false beliefs about these cigarettes, such as “lower in tar”, “healthier” and “less likely to cause cancer” (81).

Dutch Magic, a brand of cigarettes with virtually no nicotine (< 0.04 mg) but a “normal” level of tar, is expected to enter the Dutch market (<http://www.dutch-magic.com/>). According to the manufacturer’s website, the product allows smokers the experience of smoking a cigarette with the characteristic tobacco taste but without the addictive effects of nicotine. The website also cites specific target consumer groups: people who want to quit smoking with an aid, occasional smokers, people who would like to try smoking but do not want to get addicted and cannabis smokers who do not otherwise smoke tobacco or currently use nicotine-containing tobacco to roll their joints but do not want to get addicted. Dutch Magic is prepared under license of 22nd Century, which

is, according to their website, committed to developing and commercializing consumer-acceptable reduced-risk tobacco products and a prescription-based smoking cessation aid consisting of a kit of very low-nicotine cigarettes (<http://www.xxiiicentury.com/>). The company offers to supply cigarettes with virtually any nicotine content level, from very low (approximately 0.50 mg/cigarette) to high (approximately 30 mg/cigarette).

Consumer response

In studies of switching to commercially available low-nicotine Quest cigarettes, study participants reported that the research cigarettes were less satisfying and of poorer quality than their usual brands (82–84).

Constituents, toxicity and disease risk

The level of nicotine in Quest cigarettes reported by the manufacturer ranged from 0.05 to 0.6 mg/cigarette, with a tar content of 10 mg tar/cigarette (85). Chen et al. (86) generally confirmed these values, although, interestingly, they found that the level of NNN was higher in the smoke of nicotine-free than low-nicotine Quest. Analysis of the tobacco filler revealed no significant difference in NNN levels among Quest varieties with different nicotine levels (13). One possibility is that the levels of nornicotine in nicotine-free cigarettes are higher, resulting in formation of more NNN during combustion. A comparison of regular cigarettes with non-commercial reduced-nicotine cigarettes provided by Philip Morris for research purposes did not, however, show significant differences in the levels of constituents other than nicotine (82–84).

Several studies addressed the exposure to cigarette smoke constituents of smokers who switched to reduced-nicotine cigarettes. In a small study of 20 smokers who progressively reduced their nicotine level over 10 weeks by changing the type of cigarette smoked, biomarkers of exposure to CO and PAH and markers of cardiovascular end-points were not affected, while urinary excretion of NNAL decreased (83). In a similar study by the same authors but with 135 smokers and progressive nicotine reduction over 6 months (84), the results for smokers who were randomized to reduced-nicotine cigarettes were similar to those in the first trial. In a study by Hatsukami et al. (2010), switching to 0.05-mg nicotine Quest cigarettes for 6 weeks reduced exposure to carcinogens to a greater extent than switching to 0.3-mg nicotine cigarettes, due to the compensatory behaviour associated with smoking 0.3-mg nicotine cigarettes, which was not observed with those containing 0.05 mg nicotine. The reduction in levels of urinary total NNAL and NNN was consistent with the lower levels of TSNA found in Quest cigarettes than in regular cigarettes (13).

Smokers of the 0.05-mg cigarettes also showed reduced exposure to acrolein and benzene, which the authors attributed to the observed reduction in cigarette intake; by the end of the study, the levels of most biomarkers in the 0.05-mg group were not significantly different from those in a group given nicotine lozenges. Hatsukami et al. (87) confirmed significant reductions in nicotine and NNK intake in smokers who switched to reduced-nicotine cigarettes.

Benowitz et al. (82) measured the heart rate and skin temperature (measure of vasoconstriction) of smokers who smoked single cigarettes with different nicotine contents and found a plateau of increased heart rate and decreased skin temperature at about 8 mg nicotine per cigarette, suggesting that there is a cut-off level of nicotine beyond which the effect on cardiovascular risk does not change significantly. Girdhar et al. (88) showed, however, that smoking nicotine-free Quest 3 cigarettes resulted in higher platelet activation (marker of cardiovascular risk) than smoking nicotine-containing Quest 1. They proposed that nicotine modulates platelet activation by non-nicotine smoke components. In mouse embryonic stem cells and normal human bronchial epithelial cells, smoke from Quest cigarettes was as toxic as smoke from regular cigarettes (69, 86, 89). In an animal model of atherosclerosis, mice exposed to smoke from Quest 3 cigarettes developed smaller lesions than those treated with Quest 1 or regular cigarette smoke (85).

Addictive potential; effectiveness in smoking substitution or cessation

A reduction in the nicotine content of cigarettes has been proposed as an approach for reducing their addictiveness (90) (see also Annex 2). While smoking commercial cigarettes in which the reduced nicotine yields are due to smoke dilution is known to cause compensatory behaviour, this may not be true for smoking cigarettes with a reduced nicotine content, or such behaviour may not be effective. Benowitz et al. (82) investigated the intake of nicotine, the degree of compensation and the dose–response relations for various effects of nicotine when people smoked cigarettes made from reduced-nicotine tobacco. Levels of 1, 2, 4, 8 and 12 mg nicotine/cigarette were shown to correlate with systemic exposure to nicotine. Little compensation was made with the lower-nicotine cigarettes (1, 2 and 4 mg), ranging from 0% to 5% in comparison with the usual brand; this was confirmed by the levels of exposure to CO and tar. At higher nicotine levels, however, compensation increased to 34% for 8 mg nicotine and 127% for 12 mg nicotine, supporting the hypothesis that the ease of obtaining nicotine is a determinant of the extent of compensation. Benowitz et al. (83) also studied progressive switching to cigarettes with a gradually decreasing nicotine content over 10 weeks. Five of 20 smokers (25%) spontaneously quit smoking. In a larger, longer trial with the same cigarettes and design, however, only 2 of 53 smokers who switched to lower-nicotine

cigarettes eventually quit (84). Compensation for the lack of nicotine was greater than in the earlier single-cigarette trial (82), ranging from 20% to 60% for the cigarettes with the lowest nicotine content (1, 2 and 4 mg).

Hatsukami et al. (79) suggested that cigarettes with nicotine levels below those tested by Benowitz et al. (82–84) may be effective in eliminating compensatory behaviour and facilitating cessation. Cigarettes containing nicotine at a level of 0.05 mg did not result in compensatory smoking behaviour, in contrast to those containing 0.3 mg, and were associated with reduced nicotine dependence, product withdrawal and a significantly higher rate of cessation. Lack of compensation when smoking high-tar, very low-nicotine cigarettes (0.02 mg) was reported in another study (91). In contrast, Strasser et al. (92) observed behavioural compensation with smoking very low-nicotine cigarettes; the total puff volume was greatest for the 0.05 mg Quest cigarette. The effect of very low-nicotine cigarettes on smoking abstinence was studied in a large randomized controlled trial in New Zealand, in which standard Quitline care alone was compared with Quitline plus an instruction to smoke Quest 3 cigarettes when participants had the urge to smoke (93). In comparison with the group receiving usual Quitline care, participants assigned to Quest 3 had higher abstinence rates at the 6-month follow-up (33% compared with 28%) and higher continuous abstinence rates (23% compared with 15%). Furthermore, the median time to relapse was 2 months for the group assigned to Quest 3 cigarettes and 2 weeks with usual care. These results suggest that adding very low-nicotine cigarettes to standard Quitline smoking cessation support might help some smokers to become abstinent.

Several studies have been conducted of the use of very low-nicotine cigarettes in combination with a nicotine patch. In one small study, participants were assigned to nicotine or a placebo patch in combination with reduced-nicotine cigarettes (94). Participants assigned to the very low-nicotine cigarettes (0.08 mg) and a nicotine patch reported smoking only three cigarettes of their usual brand during the 2 weeks of the study, while those assigned to the same cigarettes but a placebo patch reported smoking 46 cigarettes of their usual brand during the same period. No difference was observed in craving or withdrawal symptoms with addition of the nicotine patch or placebo. In another study, participants were randomly assigned to supplement low-nicotine cigarettes with patches containing various levels of nicotine (95). People assigned to patches with higher doses of nicotine (7 or 21 mg) showed greater decreases in the number of cigarettes smoked, the total volume of cigarette smoke inhaled and the level of CO than those assigned to low-nicotine cigarettes without medicinal nicotine supplement (placebo patch); greater relief of withdrawal symptoms during an abstinence period was also observed. In a recent study, Hatsukami et al. (87) examined the feasibility of using very low-nicotine cigarettes to reduce smoking behaviour significantly and the effect of adding a

nicotine patch with these cigarettes. Both the nicotine patch and the combination of very low-nicotine cigarettes (≤ 0.09 mg/cigarette) plus patch led to a greater increase in nicotine intake than switching to the low-nicotine cigarettes. The combination condition also reduced withdrawal symptoms as compared with an individual patch or low-nicotine cigarettes. No difference in withdrawal symptoms was found with a nicotine patch or low-nicotine cigarettes, and craving did not differ among groups after cessation of the assigned product. The results indicate that combining very low-nicotine cigarettes with a nicotine patch might ameliorate the acute effects that result from switching to either of these products alone.

Regulatory considerations

Reduction of the nicotine content (but not complete elimination) of cigarettes has been discussed in the USA as a potential regulatory approach for making cigarettes non-addictive. This could lead to cessation by smokers who are no longer addicted, with a significant public health benefit. Such a policy measure might include supplementation with nicotine replacement therapy to facilitate tobacco cessation.

Super-slim cigarettes

Super-slim cigarettes have a significantly smaller circumference than regular cigarettes. They have been sold in some countries, such as the USA, for a long time (e.g. Virginia Slims Superslims), but their introduction in other countries is relatively recent. Many such brands were launched from 2007 in Canada (96). The circumference of these cigarettes is 17 mm, while that of regular cigarettes is approximately 25 mm, and they are sold in slimmer packs. These cigarettes are not marketed with explicit health claims; however the “slim” pack profile and the thinner design of super-slim brands are likely to be perceived by consumers as emitting lower levels of toxins and being “less harmful” (96, 97).

Analysis of super-slim cigarettes sold in Canada showed that the yields of many constituents, including CO, carbonyls, volatiles and aromatic amines, were significantly lower due to the reduced circumference and thus lower tobacco weight; however, the yields of other constituents, including formaldehyde and ammonia, were significantly higher. As for regular-size cigarettes, the measured constituent yields depended on the smoking machine regimen used. It was shown that super-slim cigarettes sold in Canada can contain as much nicotine as other Canadian cigarettes, and their addiction potential may be similar. The introduction of these cigarettes in Canada, where virtually all advertising and promotion of tobacco products have been prohibited by law,

represents an attempt by the tobacco industry to use new designs and packaging to promote and market tobacco products to specific audiences (96).

A ban on slim cigarettes was included in the original European Commission proposal for a revision of the European Tobacco Products Directive. The Council and the European Parliament decided, however, to delete this prohibition, and no regulation on slim cigarettes is included in the final version of the Directive, other than the statement that market developments and consumer perceptions of some products, including slim cigarettes, should be monitored (98).

Little cigars and cigarillos

Dramatic increases in the sales of this type of product have been reported in many countries, with the largest increases in China, Germany and the USA (99). Unlike cigarettes, little cigars and cigarillos are wrapped in tobacco leaves or brown tobacco-based paper. Little cigars are similar in size to cigarettes, while cigarillos are intermediate between a cigarette and a large cigar (99, 100). No health claims are made for these products.

The Maxwell Report (101) showed that sales in the USA, the largest market for little cigars and cigarillos, increased by 316% for little cigars and by 255% for cigarillos between 1995 and 2008, and more young adults in the USA have ever smoked little cigars and cigarillos (26%) than the general US population (5.2%) (cited in 99). A study of dual use of cigarettes and cigars showed that approximately 12.5% of cigarette smokers used cigars and that dual users were more likely to be young males, non-Hispanic or black, with lower educational attainment and either unemployed or out of the work force (102). The study also showed that dual users were less likely than cigarette-only smokers to smoke cigarettes daily (odds ratio, 0.57), more likely to have made a recent attempt to quit (odds ratio, 2.39) and more likely to have used at least one other product, such as snus, e-cigarettes, dissolvable products or chewing tobacco (odds ratio, 2.26). A limitation of the study is that little cigars and cigarillos were not differentiated from large cigars in the assessment of current and prior use of cigars; however, smokers of little cigars and cigarillos may not identify these products as cigars, and the questionnaire used in the study cited popular brands, which may have increased self-reported cigar use.

Both the lower prices of little cigars and cigarillos than cigarettes and the variety of flavours may explain their appeal to young people (as for flavoured cigarettes). The Family Smoking Prevention and Tobacco Control Act in the USA (103) provided an unprecedented opportunity to regulate tobacco in the country; however, it contains no restrictions on little cigars, cigarillos or large cigars. After the ban on flavourings in cigarettes by the Food and Drug Administration in 2009, a study among young adults showed that 18.5% currently

used a flavoured tobacco product (104). Almost 50% of little-cigar smokers used a flavoured brand.

The smoke of little cigars, with or without filters, contains the same toxic chemicals that are present in the smoke of cigarettes sold in Canada (105). Furthermore, the smoke of little cigars and cigarillos is inhaled more deeply than that of large cigars, similarly to the smoke of cigarettes (106).

Herbal-tobacco cigarettes

In 2000, several Asian countries started producing cigarettes containing both traditional medicinal herbs and tobacco. Chen et al. (107) collected information on the availability of herbal-tobacco cigarettes between 1999 and 2005 and identified 23 brands. Most were produced in China; after 2000, however, tobacco companies in China (Taiwan), the Republic of Korea and Thailand began producing similar products. These cigarettes are commonly produced by adding herbal extracts to or mixing herbs with tobacco leaves, spraying herbal extracts on shredded tobacco or adding herbal extracts to the cigarette filter material. Most of these cigarettes are claimed to have reduced contents of harmful substances (nicotine, tar, CO, carcinogens and mutagens), and some are claimed to relieve respiratory symptoms, protect internal organs, boost immunity or aid in smoking cessation. Herbal-tobacco cigarette brands in the Republic of Korea have been promoted as reducing the harm of smoking via special filtering of the smoke, addition of green tea catechins, not “hurting smokers’ lungs and throat” or as a smoking cessation aid. In Thailand, a herbal-tobacco cigarette brand, Herbal Krongthip, contained a herbal oil traditionally used to treat cold symptoms; sale of this brand was reportedly stopped in 2002.

These cigarettes are widely available on Asian markets. In 2005, two herbal-tobacco cigarette brands, Jinsheng and Zhongnanhai, were identified by the State Tobacco Monopoly Association of China as two of the “top 36 Chinese cigarette brands” designated for development. While no data on the market share of herbal-tobacco cigarettes in China are available, Jinsheng already had an annual production of 3.5 billion cigarettes in 2003, and the Zhongnanhai brand name had reached “US\$ 244 million in its intangible assets in 2001”. The Chinese herbal-tobacco cigarette brand Wuyeshen was reported also to be sold in San Francisco, California, USA (107).

Some herbal-tobacco cigarette brands available in Asia list a primary herbal ingredient, while others contain a mixture of herbs, which are not necessarily disclosed. Only four of 23 brands identified by Chen et al. (107) contained herbs only. The study showed that 18 medicinal herbs were listed as ingredients in such cigarettes, ginseng being the most common, followed by *Apocynum*

venetum. The effects of herb-derived bioactive compounds in these cigarettes are unknown. For example, datura flower, an anticholinergic herb present in the Chinese YangJinHua brand, is thought to be responsible for most cases of poisoning due to Chinese herbal medicine, while some ginseng preparations might be adulterated with scopolamine.

Tobacco control groups in China (Taiwan), Japan and Thailand have expressed concern about the health claims made for herbal-tobacco products (107).

Bidis

Bidi cigarettes are manufactured primarily in India but are imported in the USA, where a surprisingly high rate of use by young adults has been reported (108–110). Bidis are small, brown, hand-rolled cigarettes consisting of tobacco flakes rolled in a *temburni* (*Diospyros melanoxylon*) or *tendu* (*Diospyros ebenum*) leaf and tied with a small string. As they are hand-rolled, the amount of tobacco in each cigarette varies. Bidis come in unfiltered and filtered varieties, the filter consisting of a small wad of cotton inside the wrapper. Bidis are highly flavoured and sold in brightly coloured packaging almost exclusively for the US market. The flavours include grape, wild cherry, strawberry, clove, vanilla, cinnamon, cardamom, dewberry, black liquorice, lemon–lime, raspberry, mango, menthol and chocolate (109, 110).

The “novelty” aspect of bidi smoking in the USA, particularly for children and young adults, is a concern. Nearly two thirds of US adults who reported current bidi use were under the age of 25. Among young adults, higher rates of any and current bidi use were seen for males, blacks and current cigarette smokers (110). A significant number of consumers reported that bidi cigarettes tasted better and were less expensive, easier to buy (12%) and safer (13%) than regular cigarettes (109).

Analysis of the smoke of bidi cigarettes showed that they deliver substantial amounts of tar, nicotine and CO. In contrast to traditional filtered cigarettes, filters did not reduce the tar, nicotine or CO delivery in smoke. Bidi smokers may be at higher risk than smokers of traditional cigarettes for lung cancer and several other cancers, including of the oral cavity, pharynx and oesophagus (109).

Waterpipes

Waterpipes are used in many cultures in various forms, including *narghile*, hookah, *shisha*, *goza*, hubble-bubble and *arqeela*. They are a traditional method of tobacco use by indigenous peoples of Africa and Asia.

Product description and marketing strategies

A common feature of all types of waterpipe is that smoke passes through water before it reaches the smoker. Very moist flavoured tobacco is often used, which is placed in the “head” of the waterpipe, and charcoal is placed on top. Drawing on the waterpipe creates a vacuum above the water and causes charcoal-heated air to pass through the tobacco, so that the MSS contains evaporated tobacco constituents as well as charcoal combustion products (111). Alternatively, electrical “coals” are used (in products found on several internet sites, e.g. <http://www.hookah-shisha.com/p-15165-blazn-burner-fast-hookah-charcoal-burner.html>). Waterpipe tobacco is often sweet and flavoured (111), making it taste good and smooth, mild and easy to inhale (112, 113). The tobacco for waterpipes is sold at a very low price, often without a health warning and with misleading information about the content. It is frequently designed to look like a harmless product, such as tea, coffee, chewing-gum or sweets. Substances without tobacco are also smoked in waterpipes (112); for example, steam stones, small porous stones containing aroma and no nicotine, are used in some brands (e.g. Starbuzz, Shiazoo, Bigg, Om, Angel, Bump ’n Grind).

Consumer awareness, product use and perceptions

Waterpipe smoking has become increasingly widespread among young people in the Middle East during the past decade and is rapidly spreading elsewhere (114). The prevalence is also high in groups of Middle Eastern descent in Australia and the USA and is high although not specifically in people of Middle Eastern descent in European countries such as Denmark, Estonia, Germany and Sweden (115). According to a European Union survey, waterpipes are regularly used by 1% of European Union citizens (range, 0–2%), occasionally by 4% (range, 0–10%) and were tried once or twice by 11% (range, 3–30%) (116). Many European Union countries reported an increase in waterpipe use on our questionnaire but did not quantify it.

Waterpipe tobacco smoking is particularly popular among school and university students (115). A national survey in the United Kingdom showed that waterpipe smoking was popular among medical students, irrespective of their descent. Students and adults generally stated that waterpipe smoking was less harmful than cigarette smoking (113, 117). The popularity of waterpipe tobacco smoking may reflect a trend of age-specific prevalence, which should be investigated in longitudinal studies (115). Waterpipe smoking fills a social function among young people, most of whom share waterpipes and smoke in company (112, 113).

Constituents, toxicity and disease risk

Constituents are transferred to smoke by absorption in the charcoal-heated air that passes through the tobacco and are the same as those in cigarette smoke, including nicotine, propylene glycol, glycerol, TSNA, CO, PAH (118) and the aldehydes formaldehyde, acetaldehyde and acrolein (119). The levels of CO and PAH are particularly high, due to the charcoal used to heat the air that passes through the tobacco. The CO levels have been reported to be 30 times higher in waterpipe smoke than in cigarette smoke (118), and carboxyhaemoglobin levels in blood, a biomarker of CO exposure, have been reported to be fourfold higher in waterpipe smokers than in cigarette smokers (120). By 2011, six cases of CO poisoning had been reported as a consequence of waterpipe smoking; these patients had carboxyhaemoglobin levels of 20–30% (121). Although nicotine is found at higher levels than in cigarette smoke, the blood levels of nicotine measured over 24 h were lower, probably because smokers consume several cigarettes a day (118). Studies of biomarkers in dual users also showed that waterpipe use was associated with significantly lower intake of nicotine, higher exposure to CO and a different pattern of exposure to carcinogens when compared with cigarette smoking (122). Waterpipe smoking also produces large amounts and high concentrations of harmful particles in environmental smoke, contributing to the risks associated with passive smoking (112).

Waterpipe tobacco smoking is significantly associated with lung cancer, respiratory illness and low birth weight, and associations with cancers of the bladder, throat and mouth have also been suggested (115). The carcinogenic potential of waterpipe tobacco smoke is not surprising, as it contains aldehydes such as formaldehyde, which is a human carcinogen (123) and acetaldehyde, which is possibly carcinogenic to humans (124). The presence of propylene glycol and glycerol in waterpipe tobacco smoke at levels much higher than those that trigger adverse effects in experimental studies is a concern. Their effects include increases in mucus-producing goblet cells in the respiratory tract and throat irritation (118).

Addictive potential

Waterpipe use results in tobacco and nicotine dependence but is often more intermittent than cigarette smoking (113, 125). Although the level of nicotine in waterpipe tobacco smoke is higher than that in cigarette smoke, the blood levels of nicotine measured over 24 h were lower (118).

Regulatory considerations

Waterpipe use appears to be increasing in groups that did not previously smoke this product. Users perceive waterpipe smoking to be relatively harmless and not addictive, whereas in reality they are exposed to the same toxicants as in cigarette smoke, some at dangerously high levels, most notably CO. Their perceptions could be affected by educating them about harm, addiction and exposure to toxicants in waterpipe tobacco (126). Although waterpipe tobacco is usually subject to regulation, waterpipes and their accessories are not (114). In addition, herbal waterpipe tobacco is not subject to laws governing tobacco and clean indoor air, so that in most countries it can be smoked indoors. The exceptions are Canada and Turkey.

Notable alterations to traditional products

Many elements have been introduced into the composition or structure of traditional tobacco products. Thus, while the product itself, for example moist snuff or cigarettes, is not novel, alterations made to a specific brand may present new risks to individual users or to public health. Timely knowledge of emerging modifications can predict any substantial changes in the tobacco product inventory, so that forward-looking strategies can be introduced for tobacco product regulation. Below, we describe some recently introduced modifications of traditional products.

Swedish snus with reduced tobacco content

In our survey, a report was received from Sweden about a new brand of snus called Loonic in forms containing gradually decreasing proportions of tobacco: 75% (Loonic No.1), 50% (Loonic No.2), 25% (Loonic No.3) and 0% (Loonic No.4) tobacco in the total product mass. The product website (<http://www.loonic.se/index.php/en>) indicates that the remainder of the product mass is tea leaves. The decreasing tobacco content in the Loonic series results in gradually decreasing levels of nicotine. Like the Quest series of cigarettes, the Loonic series is advertised for “snus users who want to taper off or quit completely”. The product description states that Loonic No.4, the tobacco-free version, “contains neither tobacco nor nicotine, but guarana, B12, and folic acid have been added”. The product appears to be advertised to current snus users and does not include health claims.

Moist snuff with bioactive additives

Revved Up Energy Dip was introduced in 2008 by the Southern Smokeless tobacco company based in Georgia, USA. According to the description provided

on the product website (<http://www.southernsmokeless.com/Revved-up.html>), Revved Up is a long-cut smokeless tobacco with vitamin B, vitamin C, caffeine, ginseng and taurine added and comes in mint and wintergreen flavours. The blend is claimed to increase alertness, focus and energy. As in the promotion of US snus, Revved Up is described as a discreet way of enjoying smokeless tobacco. The product description states that it is intended for current tobacco users; however, it is promoted mainly for its purported ability to increase focus and energy. The suggested users listed on the product website include military service members, civil servants (police officers, fire-fighters) and athletes. The description claims that the tobacco blend used in Revved Up contains “65% less carcinogens than found in dark fire cured tobaccos”, implying reduced exposure or risk.

Menthol capsules in filters

Cigarettes with a new technology for delivering an additive are available in Japan and the USA and have been marketed in several European Union member states (127). A capsule filled with a flavouring solution is embedded in the cigarette filter, which the smoker can crush to release the flavour into the smoke. The capsule contains menthol, but other additives could be used. The innovation seems to be particularly appealing to young people, and advertising for these products is directed at this target group.

In Turkey, cigarettes with menthol capsules were allowed on the market, as they comply with the technical requirements of the Tobacco and Alcohol Market Regulatory Authority. The scientific commission authorized by the Authority to evaluate the ingredients according to the WHO Framework Convention on Tobacco Control and national legislation is, however, investigating the status of this product.

The National Supervisory Authority for Welfare and Health (Valvira) in Finland reported that cigarette brands that release a fresh taste (menthol and spearmint) by a click-on function were promoted by local retailers who agreed with tobacco companies to offer them as a first choice to consumers.

The new European Union Tobacco Products Directive 2014/40/EU (98) includes a ban on the sale of tobacco products containing flavourings in any of their components, such as filters, papers, packages, capsules or any technical features that allow modification of the smell or taste of the products or their smoke intensity. In addition, filters, papers and capsules shall not contain tobacco or nicotine. The new Directive entered into force in May 2014, and European member Member States have 2 years to bring their national legislation into line with the rules.

No-additive, or organic, cigarettes

In several countries, “natural” tobacco products are being advertised as containing no additives (128).

“Natural American Spirit” (<http://www.von-eicken.com/en/>) and “Manitou” (<https://www.nascigs.com/>), bearing pictures of a tipi and of a native American smoking a peace pipe, respectively, on their packages, have been on the market for many years as cigarettes and fine-cut tobacco. A similar product is Sioux (<http://www.von-eicken.com/en/>). All these brands contain exclusively Virginia tobacco leaves. Flue-cured tobacco leaves, such as Virginia, contain up to 20% of natural sugars, which largely determine consumer acceptance (128–130).

Pueblo tobacco is, according to its website (www.poeschl-tobacco.com), a traditional blend of premium-quality tobaccos. The name Pueblo, like Natural American Spirit, Manitou and Sioux, refers to the native American culture, from which tobacco originated before it became an industrialized product. The names therefore evoke a traditional, authentic, natural feeling. Spain provided data on the sales of Pueblo products, showing that the market share of the cigarettes is only 0.1% (ranking 68 out of 176), whereas the fine cut tobacco Pueblo Burley Blend is more popular, with 9.6% of the market (ranking 3 out of 112). A website (<http://yesmoke.eu/blog/tobacco-shag-natural-organic/>) indicated that this is also the most popular fine-cut tobacco brand in Italy.

Spain also notified a cigarette brand, Yuma Organic, which contains 100% organic tobacco, without pesticides or additives. According to their website (<http://www.yumaorganic.com/>), “by choosing organic products you help to protect the environment”. Yuma supports organic farming. The product is not popular, with 0.0001% of the market (ranking 162 out of 176).

A few years ago, Camel and Lucky Strike also launched brands without additives: Camel natural flavour and Lucky Strike additive-free, in brownish paper packages. The no-additive pure tobacco trend appears to cater for consumers interested in natural products. Some consumers perceive additive-free cigarettes as being “less unhealthy” (see e.g. <http://answers.yahoo.com/question/index?qid=20090212111736AAiemjg>); however, the smoke emitted still contains carcinogens and other toxic compounds from the tobacco (129).

Branding with a brand name

Spain reported two fine-cut tobacco products with brand names: “Roll your own American blend for people who don’t need a brand to tell other people who they are” and “Roll your own Virginia blend for people who don’t need a brand to tell other people who they are”. The commercial name is used as

an advertising and promotional element to attract people pretending to be “self-confident” and independent. As the commercial names were authorized by the European Patent Office, it was difficult for health authorities to refuse their commercialization.

Less-smoke-smell cigarettes

A study of patent records revealed more than 100 patents related to side-stream smoke, including improved smoke odour and reduced visibility (131). One country reported that Japan Tobacco International has requested authorization to place a new tobacco product, Winston XS, on the market, consisting of cigarettes with “less smoke smell” (see <http://www.cigarettestime.com/cigarettes-articles/winston-xs>).

Technologies under development

An increasing number of new tobacco products, especially cigarettes, are being or will be marketed with the claim that they can reduce exposure to harmful chemicals in tobacco smoke. These potential reduced-exposure products (PREPs) include modifications in tobacco processing, filters or design. Many of the studies that support the claims of risk reduction are performed and published by the industry. Independent studies should be conducted to investigate claims that such products can lower the levels of smoke components or toxicants in MSS, can reduce toxicity, can modify biomarkers of human exposure, can modify biomarkers of disease outcome and can pass sensory evaluation such as test panels in controlled clinical studies. In evaluating estimates from smoking machines, account must be taken of human smoking behaviour, which is a complex process involving puff volume, puff duration, inter-puff interval, number of puffs per cigarette and total puff volume (132). Thus, human smoking behaviour can differ from commonly used smoking machine regimes such as the International Organization for Standardization (ISO) and the Canadian Intense protocols. The ISO method involves a puff volume of 35 mL, a puff frequency of 60 s, a total puff volume of 455 mL and open ventilation. The Canadian Intense method involves a puff volume of 55 mL, a puff frequency of 30 s, a total puff volume of 715 mL and 100% blocked ventilation. Standardization of machine-generated yields per milligram of nicotine has been suggested in order to minimize the variation between standardized methods (133).

Below, several PREPs are evaluated to determine whether these products could reduce the levels of harmful toxicants in MSS and whether these reductions might lower disease outcomes. As most of these products are not on the market, they are described, and information is given on their constituents, toxicity

and potential risk. No information was available on the addictive potential of these new products. In regulatory terms, PREPs are tobacco products with modified tobacco processing, filter and/or design and are therefore subject to tobacco product regulation.

Substitution of traditional tobacco burning by heating

Product description: One of the world's largest tobacco companies, Phillip Morris International, plans to market a new type of cigarette by 2017 that allegedly poses lower risks to health (134). According to the company, the toxic components of this new prototype, which heats tobacco rather than burning it, will be reduced by 95%. The company states that "the most promising lower-risk products" heat tobacco or generate an aerosol that consumers inhale, and the new prototype is ready for clinical testing (134). Our survey indicated that Italy, the Netherlands and Romania were soon expecting the release of a new product by Phillip Morris International. The company argues that the 2014 European Tobacco Product Directive regarding pictorial health warnings on packages should not apply to this type of product, and that a textual warning about, for instance, addictive potential will suffice (135).

Cigarettes similar to those that Phillip Morris International plans to place on the market are those sold by Ploom and the Premier and Eclipse cigarettes marketed by RJ Reynolds (see above). Overall, convincing evidence has yet to be provided for the claims of risk reduction and health benefits of products that heat rather than burn tobacco, and better ways are needed to assess the validity of these claims (136). The methods used for conventional cigarettes, such as smoking machine measurements, might have to be adapted or new methods developed, because the puffing behaviour, physical and chemical characteristics (particularly of inhaled aerosols) and longer exposure to these new products are different. Some scientists consider that these new cigarette products are just as harmful as conventional cigarettes (137).

Combination of changed tobacco processing and filter structure

Tobacco substitute sheet with a carbon or cellulose acetate filter

Product description

British American Tobacco has designed several PREP prototypes, one of which is an experimental cigarette with a tobacco substitute sheet (TSS) that releases glycerol on heating. The components of the TSS are calcium carbonate, glycerol, sodium alginate and caramel. It has a dual function: it decreases the amount of tobacco in the overall blend, thus reducing smoke toxicants, and it releases glycerol into MSS to dilute the concentration of particulate constituents,

including toxicants, from tobacco combustion. These experimental cigarettes also have filters that contain a dispersion of activated dual-segment carbon or cellulose acetate. Unlike “light” cigarettes, in which the filter differentiates them from conventional cigarettes, the experimental cigarettes have less tobacco (40–70%), contain 30–60% TSS and filters that vary in design (dual-segment carbon or cellulose acetate filters with 0–55% ventilation) (137).

Constituents, toxicity and disease risk

Studies of smoke chemistry, toxicological investigations and preliminary human studies have been conducted on experimental cigarettes made with TSS (138). British American Tobacco claims that experimental cigarettes with TSS plus dual-segment carbon or cellulose acetate filters have reduced levels of smoke components in MSS and that the filters also reduce the amount of particulate matter: cellulose acetate filters selectively reduce the levels of some phenolic compounds, and dual-segment carbon reduces additional volatile smoke components. No health claims have been made. Analysis of MSS from these experimental cigarettes showed reduced yields of most measured constituents, other than some volatile species. Several studies were conducted of toxicity *in vitro*, including cytotoxicity, mutagenicity and chromosomal damage. In all the studies, Silk Cut King Size filtered cigarettes with the same yield of machine-smoked nicotine-free dry particulate matter were used as controls. The four experimental cigarettes consisted of 60% TSS/cellulose acetate filter, 60% TSS/dual-segment carbon filter, 50% TSS with a tobacco blend containing 2.5% glycerol and a dual-segment carbon filter. Total particulate matter from the four experimental cigarettes induced less cytotoxicity and mutagenicity in bacterial cells and chromosomal damage in mammalian cells than that from the control cigarettes. The greatest reduction in mutagenicity was observed with experimental cigarettes with 60% TSS and a cellulose acetate filter. The total particulate matter used in these tests did not include all compounds, such as volatiles.

Human exposure was evaluated by analysing cigarette filters from smoked commercial cigarettes and an experimental cigarette (60% TSS/cellulose acetate filter) with a similar level of machine smoked nicotine-free dry particulate matter and also analysing biomarkers of exposure in urine 24 h after smoking. Smokers were given 1 day’s supply of either product, a container for collecting a urine sample and a container for collecting smoked cigarette filters. The estimated daily mean exposure of the mouth to nicotine was statistically significantly lower in smokers of the experimental cigarettes. Exposure to nicotine was reduced by a daily mean of 18% as determined from the filters and by 14% as determined from 24-h urinary biomarkers. Exposure to smoke particulates was reduced by a mean of 29% as determined from the filters and

exposure to NNK by a similar degree as determined from the urinary NNAL concentration. Urinary excretion of nicotine metabolites and of NNAL was decreased. These biomarkers of exposure are considered to be representative of each smoke toxicant and are relevant for exposure to tobacco smoke. No biomarkers of effect have been reported. In a sensory evaluation in which participants were allowed to smoke the experimental cigarette or their own brand *ad libitum*, the experimental cigarettes were found to be inferior to the smokers' own brand.

Although reduced in-vitro cytotoxicity and genotoxicity were reported, no method is available to predict whether such reductions would ultimately reduce the risk for disease and whether the observed dilution effect would have any biological relevance to the health risks of smokers. Several models have been proposed, but progress in this area is still necessary (139–141). The results of the biomarker studies suggest that a longer switching period and perhaps more participants would be required to evaluate urinary biomarkers in smokers of experimental cigarettes. The levels of only some smoke toxicants were reduced, and the sensory attributes of the smoke were less acceptable than those of conventional cigarettes.

Tobacco-blend treatment and filters containing functionalized resin or carbon

Product description

British American Tobacco has developed an experimental cigarette prototype based on treatment of the tobacco blend, involving aqueous extraction, treatment with protease, filtration of the extract to remove peptides, amino acids and polyphenols, and recombination of the extract and treated tobacco (142). This treatment is claimed to reduce the levels of toxicants in MSS. Selective filters containing activated carbon and/or resin adsorbents were effective in reducing the yields of volatile toxicants.

Constituents, toxicity and disease risk

In comparison with matched control Silk Cut King Size filtered cigarettes of the same machine smoked nicotine-free dry particulate matter yield, the tobacco-blend treated cigarettes had lower levels of protein nitrogen (59%), polyphenols (33–78%) and nicotine (12%) but 16% more sugars. The ISO yields of 43 toxicants were measured in MSS from cigarettes containing treated tobacco, adjusted per milligram of nicotine. Lower yields of the toxicants ammonia (27%), aromatic amines (34–38%), pyridine (23%), quinolone (21%), hydrogen cyanide (41%), TSNA (10–18%), phenol (42%) and cadmium (21%) were obtained; however, significantly increased yields of formaldehyde (79%),

benzo[*a*]pyrene (13%), acetaldehyde (16%), acetone (12%), acrolein (26%), propionaldehyde (21%), crotonaldehyde (12%), methyl ethyl ketone (16%), isoprene (4%), styrene (19%) and chromium (42%) were found. Reduced side-stream yields of nitrogenous smoke toxicants and increased side-stream yields of several carbonyls, benzo[*a*]pyrene and isoprene were also observed. Tobacco-blend treatment was associated with increased yields of volatile aldehydes (particularly formaldehyde and isoprene), PAH (benzo[*a*]pyrene) and some heavy metals (chromium). Selective filters containing activated carbon and/or resin adsorbents were effective in reducing the yields of these volatile toxicants. Only ISO yields were reported; a comparison with Canadian Intense MSS yields would have been interesting. Toxicity was not tested.

Biomarkers of exposure were evaluated in a 6-week, single-centre, single-blinded, controlled, forced switch clinical study conducted with 1-mg tar cigarettes that had undergone tobacco-blend treatment (143). Smoke yields (MSS under ISO conditions) and biomarkers of exposure were generally reduced, sometimes substantially (> 80%). The reductions in MSS yields and biomarkers of three of the four TSNA were in agreement, with reductions in MSS of 85–96% and reductions in biomarkers of exposure of 81–87%; however, the reduction in NNK in smoke yield of 83% did not correspond to the average reduction in biomarkers of exposure of 49%. This difference is probably due to the long half-life of NNAL and the shorter half-lives of the other, un-metabolized TSNA. No end-points to assess the impact of these findings on long-term health risks (i.e. no biomarkers of effect) were evaluated. In a sensory analysis in terms of acceptability, satisfaction and taste, the treated tobacco-blend, reduced toxicant prototype scored lower than the control in most sensory categories. Acceptability appeared to improve over 4 weeks but was still slightly lower than that of the control cigarette.

The 43 toxicants analysed represent a small fraction of the approximately 5000 chemical constituents identified in MSS. There is no scientific consensus about the relations between smoke toxicants and the health risks associated with smoking. To assess the impact of reduced toxicant prototypes on health risks, comprehensive toxicity testing and clinical studies must be conducted. Wide variations between individuals were observed in the study of biomarkers of exposure, reflecting both differences in individual smoking behaviour and inter-individual variation in metabolism. Biomarkers of exposure to tobacco smoke are needed, as the currently accepted, most widely used biomarkers are specific only for families of compounds. Although significant reductions in some toxicants in MSS and in biomarkers of exposure were reported, the levels of many carcinogens in MSS from the treated tobacco-blend cigarettes were elevated, and there is no convincing evidence for risk reduction with this prototype.

Combination of tobacco substitute sheet and a two-segment carbon filter

Product description

The most promising of the experimental cigarettes developed by British American Tobacco by combining technological applications to reduce machine-measured MSS yields of specific toxicants or groups of toxicants was a combination of 80% US blend tobacco, 20% tobacco substitute sheet and a two-segment filter containing 80 mg polymer-derived carbon (20% TSS/80 mg carbon filter) (144).

Constituents, toxicity and disease risk

ISO and Canadian Intense MSS yields showed overall reductions in toxicant yields from this experimental cigarette when compared with published values for control cigarettes (144). To assess the effects of reduced MSS yields on disease, Fearon et al. (139) used an in vitro model of cardiovascular disease to test the prototype cigarette, which had a 6-mg ISO tar yield. In this assay of endothelial damage repair, endothelial cell migration was inhibited by cigarette smoke particulate matter generated from control cigarettes, with a concentration-dependent decrease in wound recovery, whereas particulate matter from the prototype cigarette had a 22% lower effect on endothelial migration, with better wound recovery (59). Cigarette smoke particulate matter does not include compounds such as volatiles, and only one reduced toxicant prototype was analysed. Because of the complexity of cardiovascular disease, these results cannot be extrapolated to humans, and more studies are needed to determine whether these biological changes seen in vitro reflect disease outcomes in vivo.

Biomarkers of exposure were evaluated in a 6-week, single-centre, single-blinded, controlled, forced-switch clinical study. A 1-mg ISO tar cigarette in which TSS was incorporated into the tobacco blend, combined with a three-stage filter containing carbon, amine functionalized resin and cellulose acetate (TSS1), was compared with a 6-mg ISO tar cigarette prototype with TSS in the tobacco blend combined with a two-stage filter without the amine functionalized resin (TSS6) (143). The yields of all toxicants from the TSS1 were reduced in comparison with the control (Silk Cut King Size filtered cigarettes with the same machine-smoked nicotine-free dry particulate matter), although the extent of the reduction varied by toxicant. The responses in biomarkers of exposure also varied, with some reasonable increases. The changes in MSS yield and in biomarkers of exposure were often not in agreement; for example, the yield of some TSNA, such as NNK, was reduced, while others, such as NNAL, showed an increase. With the TSS6 cigarette, all biomarkers

of exposure showed reductions from baseline levels at the end of study, except for total nicotine equivalents and 4-hydroxyphenanthrene. The reductions were significant except those in 4-aminobiphenyl, 1-hydroxypyrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene and 4-hydroxyphenanthrene. Total nicotine equivalents were significantly higher at end of the study than at baseline, with no significant increase in the number of cigarettes smoked per day. The greatest reductions were seen in volatile compounds, with reductions of 75% for crotonaldehyde, 45% for acrolein and 63% for 1,3-butadiene. Biomarkers of exposure to TSNA were reduced by 10–26%. Thus, biomarkers of exposure generally showed reductions with smoking the TSS1 or the TSS6 prototype, but reductions in MSS yields did not always correspond to reductions in biomarkers of exposure. The measured biomarkers of exposure varied widely among individuals.

Although no biomarkers of effect have been reported, a method has been proposed for assessing toxicant-induced changes in risk associated with smoking PREPs by evaluating changes in the risks for cancer and other diseases related to 1,3-butadiene (130). This compound was chosen because it is one of the toxicants proposed for mandated lowering by WHO TobReg (133). The 20% TSS/80 mg carbon filter prototype resulted in the most significant change in risk for health effects. Although a significant change in risk for cancer (leukaemia) was found, it was not sufficient to make this a “low health concern”. For non-neoplastic effects (ovarian atrophy), the 20% TSS/80 mg carbon filter prototype resulted in 1,3-butadiene levels that would be of no health concern (130).

In a sensory analysis as part of a 6-week, single-centre, single-blinded, controlled, forced switch clinical study, the TSS reduced-toxicant prototype scored lower than the control in terms of acceptability, satisfaction and taste (143). Generally, participants reported equivalent or substantially lower acceptability of the cigarette prototype for most sensory categories. The acceptability appeared to improve over the 4 weeks of the study but was still slightly lower than that of the control cigarette.

Despite the low overall machine yields of toxicants from the TSS1 and TSS6 prototypes, their performance against commercial cigarettes and published data on toxicant yields, much more scientific evidence would be required to determine whether these products are associated with lower health risks. More studies of biomarkers in volunteers smoking PREPs and further refinement of the technologies used in their manufacture are needed. With regard to toxicity *in vitro*, little information is available on the specific cigarette smoke toxicants involved in the pathogenesis of cardiovascular disease and how the results reflect human health risks. In the study of biomarkers, wide variation was seen among individuals, presumably reflecting both smoking behaviour

and inter-individual differences in metabolism. Thus, while the group mean levels of biomarkers of exposure may be reduced, not all the members of the group would experience decreases. As no health end-points were evaluated in this study, the impact on long-term health risks remains unknown.

Modification of filter structure

An amine functionalized ion-exchange resin in filter

Product description: Another experimental prototype developed by British American Tobacco contains an amine functionalized ion-exchange resin in the filter (145). The filter thus contains a macroporous, polystyrene-based ion-exchange resin (Diaion®CR20) with a surface amine group that reacts with aldehydes and hydrogen cyanide in an aerosol stream. The company claims that the resin in the filter reduces the yields of toxicants with high vapour pressure (in particular formaldehyde) in MSS.

Constituents, toxicity and disease risk: In tests with an experimental prototype developed by British American Tobacco containing 60 mg of Diaion®CR20 in a cigarette cavity filter, the yields in ISO and Canadian Intense smoking machine protocols showed a $\geq 50\%$ reduction in formaldehyde (estimated to represent $> 80\%$ of the formaldehyde present in the smoke vapour phase) and removal of substantial proportions of hydrogen cyanide ($> 80\%$) and acetaldehyde ($> 60\%$). The performance of the resin was consistent throughout the 6-month test period. Diaion®CR20 is especially designed to trap smoke toxicants with high vapour pressure at ambient temperature, such as formaldehyde, acetaldehyde and hydrogen cyanide; its ability to remove other compounds is unknown. Although reductions in the levels of some toxicants were reported, those of other toxicants, such as acetone and 2-butanone, were increased in the Canadian Intense smoking machine protocol. The cigarette has not been tested for toxicity, biomarkers of exposure or effect or sensory quality.

Titanate nanosheets, nanotubes and nanowires in filters

The Fujian Tobacco Industrial Corporation in China has evaluated use of titanate nanosheets, titanate nanotubes and titanate nanowires in filters for reducing toxicant levels in MSS (146, 147). Although reductions in the levels of toxicants were reported in both publications, when the yields were standardized per milligram of nicotine, no reduction was found with the nanosheet and the levels of only a few toxicants (ammonia, hydroquinone, catechol and phenol) were reduced with the nanotubes (146). As nicotine levels were not reported in the second paper, the efficiency of nanowires in capturing TSNA cannot be assessed.

No tests of toxicity, biomarkers of exposure or effect or sensory acceptability were performed. More research is needed to determine whether these nanoparticles are transferred to MSS and, if so, the potential health effects of direct exposure to titanate nanoparticles in the lung and other organs.

Charcoal filters

Product description

The US Centers for Disease Control and Prevention evaluated the industry's claim that charcoal-containing filters reduce toxicant levels in MSS (148, 149). The industry claims that, because charcoal has long been used to remove volatile organic compounds from water and air, it should have the same effect in MSS. Cigarettes containing charcoal in their filters at levels of 45–180 mg, either dispersed in the filter material or contained in a small cavity in the filter segment, were evaluated (148).

Constituents, toxicity and disease risk

Tar, nicotine, CO, acetaldehyde, acrolein, benzene, styrene and the sum of 22 volatile organic compounds were measured in MSS. The cigarettes with charcoal filters showed reduced machine-generated MSS delivery (ISO and Canadian Intense protocols) of a wide range of volatile organic compounds as compared with a similar, non-charcoal filtered cigarette. The reduction depended, however, not only on the amount of charcoal present but also on the volume of smoke drawn through the filter. While a brand with 45 mg charcoal reduced the delivery of volatile organic compounds under ISO smoking conditions, charcoal saturation and breakthrough occurred under more intense smoking conditions (Canadian Intense protocol). Overall, the brands with the most charcoal were more effective in reducing the delivery of volatile organic compounds, even under intense smoking conditions. A brand with a 33-mm filter, 43% filter ventilation, 0.5 g tobacco and 120 mg of charcoal yielded consistently lower levels of analytes in both smoking machine regimes. The preliminary results indicated that the levels of other important but less volatile toxic constituents (for example, TSNA and PAH) were not affected or were reduced to a lesser extent than that of volatile organic compounds (148). Hearn et al. (149) showed that, while charcoal-containing filters selectively removed lower molecular mass PAH from MSS, they did not significantly remove the heavier, more toxic PAH studied, such as benzo[*a*]pyrene, a known carcinogen. Likewise, charcoal-containing filters removed phenols and TSNA from MSS to varying degrees, depending on the compound, filter design and smoking regimen. The presence of sufficient charcoal in cigarette filters is known to

remove many volatile compounds and can potentially reduce the deliveries of certain semi-volatile compounds in some machine smoking regimens. Less volatile compounds, with a significant portion in the particulate phase, are less freely available for selective filtration by charcoal-containing filters than the more volatile compounds that reside predominantly in the gas phase. The industry has not reported any toxicity tests with these cigarettes.

The effects of charcoal-filtered cigarettes on biomarkers of exposure were examined in a randomized, crossover, 2-week brand-switching study with 39 smokers (150). Twenty participants smoked cellulose acetate filter-tipped cigarettes, and the other 19 participants smoked charcoal-filtered cigarettes during week 1 of the study. The two types of cigarette had similar smoking machine-derived tar and nicotine yields. In week 2, the participants switched to the brand with the other filter type. Daily cigarette consumption, CO in exhaled breath, salivary cotinine and urinary nicotine equivalents (molar sum of nicotine plus five major metabolites) did not change significantly with switching. The rates of urinary excretion of 3-hydroxy-1-methylpropylmercapturic acid (a metabolite of crotonaldehyde), monohydroxybutenylmercapturic acid (a metabolite of 1,3-butadiene) and S-phenylmercapturic acid (a metabolite of benzene) were significantly lower in samples from participants who smoked charcoal-filtered cigarettes; the reduction in the amount of 3-hydroxypropylmercapturic acid (a metabolite of acrolein) was of borderline significance. The levels of other mercapturic acids and thioethers (the latter being a summary measure of exposure to electrophilic compounds) were not or only slightly reduced in samples from participants smoking charcoal-filtered cigarettes (143). Overall, smoking charcoal-filtered cigarettes did not change the uptake of CO or nicotine from that with cellulose acetate-tipped cigarettes with similar tar and nicotine yields, but it significantly reduced exposure to toxicologically relevant smoke constituents such as acrolein, crotonaldehyde, 1,3-butadiene and benzene (150). The health benefits of reducing the levels of selected compounds in MSS by the addition of charcoal filters are still not clear. The only study of biomarkers (150) was an uncontrolled field study. Acrolein and crotonaldehyde are also products of endogenous lipid peroxidation, and it is not known which smoke components are responsible for increasing their concentrations. Only a limited number of people (39) were evaluated, whereas a large sample size would be required to confirm the results of the biomarker study. The industry has not reported any studies of biomarkers or sensory quality.

Research in progress as presented at the 2013 CORESTA meeting

Research on harm reduction presented at the meeting on smoke science and product technology organized by the Cooperation Centre for Scientific

Research Relative to Tobacco (CORESTA) in Seville, Spain, in 2013 is summarized below. The summaries do not give complete or definitive overviews of the results but signal trends in research on tobacco product technology, including filter materials, TSS and mechanisms of formation of toxicants.

Tobacco additives

The Yunnan Reascend Tobacco Technology (Group) Company in China presented a study on the effect of introducing nanomaterials such as particles of iron oxide into reconstituted tobacco sheet to reduce smoke components such as tar, CO, benzo[*a*]pyrene and NNK (lecture 16, poster 13). The type of cigarette used and whether the reduction was still present after nicotine levels were normalized were not reported.

The Company also reported that the addition of stem granules reduced the delivery of several smoke components but did not affect the sensory quality of the product (lecture 52). Addition of 8% stem granules reduced the levels of tar (32%), nicotine (32%), chromium (28%), nickel (17%), cadmium (53%), lead (28%) and mercury (17%) in MSS. As nicotine was usually reduced to a greater extent than the other toxicants, it could be argued that a smoker titrating a desired amount of nicotine is actually exposed to more toxicants when smoking the product with stem granules.

Filter additives

The Yunnan Reascend Tobacco Technology (Group) Company also made a presentation on polyamidoamine-grafted silica gels in cigarette filters (lecture 17). The absorbent was reported to selectively reduce the levels of phenol, crotonaldehyde and hydrogen cyanide; effects on nicotine were not reported.

The China Tobacco Hunan Industrial Company and the Zhengzhou Tobacco Research Institute reported that common acetate filters selectively reduced the levels of seven phenolic compounds as compared with nicotine (lecture 31).

The China Tobacco Jiangsu Industrial Company showed the results of applying several activated carbon fibres with surfaces modified by metal oxides such as palladium chloride (poster 12). Depending on the product, reductions in tar, phenol, catechol and crotonaldehyde were observed; nicotine levels were not reported.

Precursor studies

The Zhengzhou Tobacco Research Institute presented some results from studies of the main precursors of hydrogen cyanide (mainly proteins) and of

4-aminobiphenyl (lecture 56), and the Japan Tobacco Inc. described the effect of pyrolysis conditions on formation of these compounds (lecture 57). Knowledge of the precursors and mechanisms of pyrolysis could indicate potential harm reduction products.

Summary

A wide spectrum of new tobacco products and technologies has been introduced onto international markets during the past decade. The new products include non-combustible products, such as dissolvable tobacco and novel snus, and modified cigarettes and cigarette-like products that heat rather than burn tobacco.

Non-combustible oral products

Dissolvable tobacco products have undergone significant transformation since they were first introduced onto the US market, with changes in both their packaging and formulations (Figure 1). It is not clear whether these products will persist on the US market or spread internationally. In contrast, novel snus products appear to be gaining popularity in the USA (25). Snus products manufactured in USA and potentially in other countries should, however, be distinguished from traditional Swedish snus. US-manufactured snus differs from Swedish snus in moisture content, pouch size and the content of nicotine and other constituents (15, 34, 151). Furthermore, the higher TSNA levels in the latest versions of Camel snus suggest that either the tobacco type or the tobacco processing method (or both) used in the manufacture of this product are different from those of Swedish snus. Researchers who advocate replication of “Swedish experience” in the USA and other countries should therefore exercise caution. Furthermore, the levels of constituents in novel non-combustible products have been shown to vary widely (15, 33), perhaps as a result of test-marketing experimentation and/or reformulation. This category of products must continue to be monitored as the products are test-marketed and modified and new products are introduced.

The marketing used to promote some novel tobacco products in the USA, such as snus and dissolvable tobacco, includes distribution of free samples, “teaching” new consumers to use the products and messages suggesting that the products will be used only temporarily. These tactics indicate that current snus campaigns are targeting new users and encouraging dual use. Information about consumer research by the tobacco industry in previously secret industry documents strongly supports this hypothesis (152–154). While manufacturers insist that their dissolvable products are neither marketed nor attractive to youth, the research community is concerned that the “candy”-like appearance

of these products and the fact that they can be used discreetly may appeal to children and adolescents, potentially increasing their tobacco use and accidental poisoning (10). The products are also offered in various flavours, and it has been shown that younger adults are more likely to use flavoured tobacco products (104). Product packaging appears to play an important role in the tobacco industry's overall marketing strategy.

In the USA, awareness and use of novel products is more frequent among non-Hispanic, white, male, young smokers (155–158). Young adults apparently tend to perceive some novel snus and dissolvable products as accessible, convenient, attractive, modern, fun, recreational and concealable (159). Both smokers and nonsmokers reported that they would use them when the opportunity arose. Little is known about who uses the dissolvable tobacco products on sale and who will use them if they are widely marketed. For instance, certain demographic groups, such as young people and pregnant women, might be more likely to use dissolvable tobacco than others. If so, it is important to better understand the factors related to product design and marketing that could make these products appealing to certain groups. Limited studies show that, while awareness, testing and interest in dissolvable products are quite low, they were highest among young adults and male smokers (5). Smokers tend to believe in the relative safety of products that are directly or implicitly marketed as less harmful (160–162). Thus, while smokers are generally dissatisfied with the taste of snus and dissolvable products, they may be interested in using these products to reduce their risk (162, 163). The availability of dissolvable tobacco and snus might also attract new users who would have not otherwise have used tobacco. More thorough surveillance of the population response to dissolvable tobacco products and snus in test market areas is essential to obtain the data necessary for tobacco control professionals to formulate policy recommendations (30).

A national assessment of users of both cigarettes and smokeless tobacco in the USA showed that such dual users tend to be young white males—the same category of the population that appears to be interested in such novel products as snus and dissolvable tobacco (164, 165). Most of these dual users were not planning to quit and used smokeless tobacco in places where they could not smoke. Snus advertising actually appears to promote dual use of cigarettes and snus, such as the promotion of smokeless tobacco products as extensions of established cigarette brands. Dual use of cigarettes and smokeless tobacco has unclear consequences for public health but may increase the risks for tobacco-related morbidity and mortality (24).

The initial versions of dissolvable and snus products contained less TSNA than more recent versions (13, 15, 18, 33). Thus, comparison of Ariva and medicinal nicotine lozenges in two small pilot studies showed that the uptake

of tobacco-specific carcinogens was comparable (14). In the rat lip canal model of the mucosal changes induced by chronic daily exposure, all four brands of smokeless tobacco induced dysplasia; however, Stonewall caused less severe dysplasia than conventional moist snuff, consistent with the hypothesis that tobacco with low levels of nitrosamines might induce fewer carcinomas in human users (166). Non-combustible products such as snus and dissolvable tobacco deliver less nicotine than cigarettes and do not expose smokers to CO, implying lower exposure to toxicants (41). The levels of TSNA and other harmful chemicals in dissolvable products, however, were found to range from very low to the levels found in traditional smokeless tobacco products (13, 15–17).

The frequency of use of alternative tobacco products, including snus and dissolvables, and the association of use with attempts and intention to quit was studied in a nationally representative probability-based sample of 1836 current or recently former smokers in the USA. No indication was found that these products promote cessation (167). Novel snus and dissolvable products are generally not particularly effective in suppressing symptoms of abstinence (41, 43), although oral tobacco products containing more nicotine are more effective in suppressing cigarette smoking and leading to abstinence than those with lower nicotine levels. Studies should be conducted to determine whether use of snus products containing higher nicotine levels leads to dependence on the product, as in Scandinavian smokers who use snus to quit smoking (168). Many studies have shown that use of such products results in lower nicotine concentrations and equivalent or smaller reductions in subjective measures, such as craving and withdrawal symptoms, than medicinal nicotine (42). Until the health effects of such products are better understood, medicinal nicotine should be recommended for smokers who are willing to quit or to switch to lower-risk products.

In Europe, the sale of snus is prohibited by the Tobacco Product Directive, except in Sweden. New products have appeared on the market that resemble snus but are advertised as chewing tobacco, which is allowed in Europe. Several Member States are discussing the regulatory status of this product type.

Most researchers in the field of tobacco control agree that use of low-nitrosamine, non-combustible tobacco products such as snus could reduce the harm to individual smokers who switched entirely to these products (169). For instance, epidemiological evidence suggests that exclusive use of Swedish snus is associated with a relatively low risk for cancer (37, 38). A panel of experts reviewed the risk for mortality associated with use of low-nitrosamine smokeless tobacco marketed for oral use and concluded that the median relative risk for mortality of individual users was 5–9%, depending on the age of the smoker (169). The median risks associated with smoking were estimated to be 2–3% for lung cancer, 10% for heart disease and 15–30% for oral cancer.

The experts estimated a reduction of at least 90% in the relative risk of users of low-nicotine smokeless tobacco products in comparison with smoking. An expert evaluation of the potential impact of low-nitrosamine smokeless tobacco products on the prevalence of cigarette smoking concluded that introduction of a well-regulated smokeless tobacco product might reduce smoking and increase smokeless tobacco use in the USA only modestly (170). The effects of such products may, however, be modified by factors such as the willingness of smokers to switch, the potential for recruiting new tobacco users and the robust regulation of product chemistry. Smokeless tobacco products around the world vary in carcinogenic potential, and promotion of smokeless tobacco for reducing harm in countries where the locally marketed products have high contents of cancer-causing chemicals would be inappropriate (171–173). The results of epidemiological studies of smokeless tobacco use and disease risk depend on the product and the population studied (174). Furthermore, the effects of harm reduction strategies may differ according to cultural, social and economic differences among countries, especially between low- and middle-income countries and wealthier countries (173).

Cigarettes and cigarette-like devices

The tobacco industry has developed a number of PREP cigarettes and cigarette-like devices, such as those that heat rather than burn tobacco. Although use of some of these products results in reduced levels of biomarkers, they have not been shown to reduce the disease burden or addictive potential significantly in comparison with usual cigarettes. Overall, these products have been market failures, with little public awareness of them (175). Nevertheless, marketing of “reduced exposure” cigarettes in the USA raised substantial interest among smokers, indicating that “health conscious” smokers and heavy smokers who are not planning to quit may be especially vulnerable to the industry’s marketing messages that such products are an alternative to smoking cessation (176).

The peer-reviewed literature on “potential reduced exposure” cigarettes that involve heating of tobacco instead of burning shows that these products are not effective in reducing exposure. Exposure to CO from some of these cigarettes may be higher than from regular smoking. Furthermore, as tobacco smoke has over 4000 constituents, 60 of which are known carcinogens, decreasing the content of a limited number of carcinogens may not decrease the overall health risk and could affect the concentrations of other carcinogens in the smoke (175). Introduction of new materials into cigarette fillers and filters raises similar concern, potentially adding risks from new chemicals with unknown consequences for smokers’ health.

The spread of the “low-tar” cigarette market in some regions is another concern. The levels of exposure to tar are similar from cigarettes with different yields, and no health benefit has been found of smoking cigarettes with lower yields. Nevertheless, the tar reduction strategy is still being promoted in some countries, such as China.

Reduced-nicotine cigarettes are considered a promising approach for reducing the addictive properties of cigarettes and thus reducing exposure to the harmful constituents of smoke. Switching to cigarettes with a very low nicotine content (< 0.05 mg) may be accompanied by minimal compensatory behaviour, reduce cigarette consumption, decrease dependence and facilitate abstinence by smokers (87). It is not clear, however, whether accustomed smokers would compensate for the lack of nicotine, as all the available evidence is from small trials of switching. In addition, reference to cigarettes as “low-nicotine” may be misinterpreted by consumers as indicating “low-risk” or “healthier”. Perusal of tobacco industry documents shows that such consumer misconceptions were the basis for the development of reduced-nicotine cigarettes (80). Apparently, the tobacco companies sought to define and lead a new market for “healthier” cigarettes that might appeal to “quitters”. Few brands of low-nicotine cigarettes are available, but the market may expand in the near future.

The introduction of super-slim cigarettes to new markets is a concern, because the design appears to be tailored specifically for female users and because the slimmer design may be interpreted as that of a less harmful cigarette (96). Tobacco industry documents on the effect of cigarette pack shape, size and openings on consumer perceptions show that packaging not only communicates such attributes as premium quality and smooth taste but also influences perceptions of reduced harm. Furthermore, slim, rounded, oval, booklet and generally novel packs were found to be particularly appealing to young adults (177).

Herbal cigarettes are an issue of concern, particularly in Asia, where medicinal plants have been used for centuries, making the population more vulnerable to misleading claims of health benefits than in countries where herbal medicine is less widely accepted; furthermore, unconfirmed scientific evidence is being widely cited in the Asian media to support the health claims. Adequate research and strict control of such claims are essential.

Young urban males, particularly students, are more likely to use alternative products such as bidis (108, 178). The rates of bidi use among young adults may be a consequence of experimentation during adolescence; therefore, bidis may serve as a gateway to regular cigarette smoking. Tobacco prevention and control programmes must be aware of such emerging products.

A waterpipe delivers charcoal-heated smoke that is first passed through sweet, flavoured tobacco and then through water before being inhaled by the smoker.

Waterpipe tobacco smoking is increasingly widespread; it is traditionally popular in Africa and the Middle East and is now spreading globally. It is particularly popular among school and university students. Longitudinal studies should be conducted to investigate whether the popularity of waterpipe tobacco smoking is a trend of age-specific prevalence. Waterpipe tobacco smoke contains numerous toxicants and carcinogens that are also found in cigarette smoke; therefore, it is not harmless but is significantly associated with various diseases, including cancer. A particular concern is the high level of CO inhaled when smoking waterpipes with or without tobacco, as the exposure is due mainly to charcoal combustion. Cases of CO poisoning after waterpipe smoking have been reported. The First International Conference on Waterpipe Tobacco Smoking held in October 2013 (179) made several recommendations to stop the global spread of waterpipe tobacco smoking: education and communication on the dangers of waterpipe smoking and misperceptions; support and evaluation of programmes to prevent initiation of young people and encourage smoking cessation; banning of flavoured waterpipe products; inclusion of waterpipe smoking in clean indoor air regulations; more effective warning labels, increased taxes, restricted access of young people and elimination of advertising and marketing of waterpipe tobacco products.

Notable changes in cigarette design and marketing have been observed in Europe. Cigarettes and fine-cut tobacco brands that are advertised as containing only natural tobacco and no additives have been on the market for years. Recently, large brands such as Camel and Lucky Strike have also launched no-additive variants. This trend may be due to increasing social interest in natural, organic products, the fact that cigarette additives are associated with product manipulation and the expectation that tobacco additives will be regulated more strictly in the future. Cigarettes are available with capsules in their filters that release a flavour, usually menthol-like, to smoke; however, additives may no longer be allowed in filters, including capsules, in the tobacco product directive that is being negotiated. Cigarettes with “less smoke smell” are being marketed, which may increase the acceptability of smoking by bystanders.

An increasing number of new tobacco products are being or will be marketed with the claim that they can reduce exposure to harmful chemicals in tobacco smoke. These PREPs include modifications in tobacco processing, filters and design. Many of the studies that support claims of risk reduction are performed and published by the industry. There is some evidence that adaptations in product design, such as TSS and the tobacco-blend treatment in conjunction with various filters (Diaion®CR20, carbon, cellulose acetate, CR20L and polymer-derived carbon), reduce toxicant levels in MSS and biomarkers of exposure. The most promising PREP was a combination of 20% TSS with an 80-mg carbon filter, which significantly reduced biomarkers of exposure; generally, participants reported equivalent or substantially poorer

acceptability of the experimental cigarette for most sensory categories. The acceptability appeared to improve over 4 weeks but was still slightly lower than for the control cigarette. No effect on MSS toxicant levels was observed when titanate nanoparticles were added to the filters of cigarettes. Charcoal filters specifically remove compounds present in the gas phase, such as volatile organic compounds, phenols and TSNA, but are less efficient in removing less volatile compounds in the particulate phase. In general, smoking charcoal-tipped cigarettes did not reduce the uptake of CO or nicotine when compared with cellulose acetate filter-tipped cigarettes with similar tar and nicotine yields, but it significantly reduced exposure to toxicologically relevant smoke constituents such as acrolein, crotonaldehyde, 1,3-butadiene and benzene. Biomarkers of exposure were measured in only a few studies, and only a limited number of biomarkers were measured. As tobacco smoke has over 5000 compounds, measurement of only a few biomarkers of exposure is insufficient to capture exposure to all the toxicants in MSS. Biomarkers of effect may provide a better indication of whether reductions in the levels of a few toxicants in MSS reduces tobacco-related diseases. A limitation of this approach is that it is not known whether reduced toxicant levels in MSS and biomarkers of exposure result in reduced disease outcomes. Although lower machine yields of toxicants in MSS were found with PREPs than with conventional cigarettes, substantial scientific data would be required to conclude that such products are associated with lower health risks. When evaluating the efficacy of PREPs in reducing human risk, consideration must be given to how people smoke, in terms of the level of toxicity and whether a design change actually results in reduced exposure or only a false sense of safety.

The evidence that the PREPs evaluated can reduce risk is insufficient. Reductions in smoking machine-measured toxicant levels in MSS are not consistently reflected in reduced biomarkers of exposure, and the relations between biomarkers of exposure and disease outcomes should be investigated further.

To date, there is insufficient evidence that any of the currently marketed modified cigarettes or alternative tobacco-burning or -heating devices can be used as “harm reduction” products. Pankow et al. (51), using risk assessment modelling, estimated that switching to a PREP cigarette would reduce the risk for lung cancer by < 2% as compared with conventional cigarettes. Smokers have accepted none of the tobacco-containing alternative cigarettes, and their market life has generally been short, so that it is impossible to assess any effect of these products on smoking-attributable morbidity and mortality. The general public, policy-makers and health professionals must be educated. For example, a study of harm reduction perceptions among US nurses revealed a widespread belief in the relative safety of “light” or additive-free cigarettes and other misperceptions about tobacco, which may have led them to make inaccurate recommendations during medical encounters (180).

Reductions in both exposure to toxic compounds and the addictive potential of tobacco products are important for harm reduction strategies. It must be remembered, however, that exposure reduction may encourage cigarette consumption by promoting a safer image, and reducing addictiveness may encourage compensatory smoking. Research indicates that cigarettes with a very low nicotine content do not lead to compensatory smoking and may be a viable approach for reducing exposure. In a study of the health impact of reductions in product addictiveness and toxicity, estimated in a computer model of changes in age- and gender-specific smoking behaviour in the US population over time, it was found that such reductions would produce net gains in population health and cumulative quality-adjusted life-years (181).

Conclusions

Novel tobacco product types and technologies that have entered worldwide markets during the past decade vary substantially. Tobacco industry research indicates that more products may be introduced in the near future. A better approach is required for monitoring these novel tobacco products, with systematic collection of data to guide tobacco control and to understand the implications for public health.

The impact of most novel tobacco products on public health is not clear. The major concerns include their potential unrecognized toxicity; increased or sustained prevalence of tobacco use by recruitment of new users, relapse of ex-smokers and maintenance of tobacco use by current smokers who might otherwise have quit; dual use of novel tobacco products and cigarettes; and initiation with a novel “gateway” product and eventual switching to cigarette smoking.

Future research should focus on issues such as the toxicity of novel products (by analysis of the products and measurement of biomarkers of tobacco-related exposure and toxicity), their addictive potential and how they are perceived and used. Such information will help to determine whether they reduce or induce harm in individuals and at a population level.

Acknowledgements

We thank Dr Anne Kienhuis (Centre for Health Protection, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands) for her contribution to the paragraph on waterpipes.

We thank Mr Robert Carlson (University of Minnesota, Minneapolis, USA) for editorial assistance.

The following people are acknowledged for their contributions to the background paper by sharing valuable information on new products in their countries in response to our questionnaire:

Michael Anderegg, Federal Department of Home Affairs, Federal Office of Public Health, Consumer Protection Directorate, Bern, Switzerland

Teresa Cepeda, Secretariat General for the Promotion of Health and Epidemiology, Directorate General of Public Health, Quality and Innovation, Ministry of Health, Social Services and Equality, Madrid, Spain

Nuan Ping Cheah, Cigarette Testing Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore.

Magda Ciobanu, Ministry of Health, Bucharest, Romania.

Dr Daniela Galeone, Ministry of Health, Department of Public Health and Innovation, Rome, Italy

Dorianne Grech, Environmental Health Policy Co-ordination Unit, Environmental Health Directorate, Valletta, Malta

Prakash C. Gupta, Healis Sekhsaria Institute for Public Health, Mumbai, India

Jürgen Hahn, Chemical and Veterinary Investigation Office, Sigmaringen, Germany

Tiiu Härm, National Institute for Health Development, Tallinn, Estonia

Dr Antero Heloma, National Institute for Health and Welfare, Helsinki, Finland

Herodotos Herodotou, Medical and Public Health Services, Ministry of Health, Nicosia, Cyprus

Lenka Kostelecka, Ministry of Health, Department of Health Services, Prague, Czech Republic

Sofia Kuitunen and Linda-Maria Viitala, National Supervisory Authority for Welfare and Health (Valvira), Helsinki, Finland

Rita Lindbak, Norwegian Directorate of Health, Oslo, Norway

Lee McGill, Department of Health, London, United Kingdom

Karin Molander Gregory, Swedish National Institute of Public Health, Department of Supervision, Östersund, Sweden

Dr Ljiljana Muslić, Croatian National Institute of Public Health, Zagreb, Croatia

Emília Nunes, National Programme for the Prevention and Control of Tobacco Use, Directorate General for Health, Lisbon, Portugal

Helen O'Brien, Health Promotion Unit, Department of Health, Dublin, Ireland

Andre Luiz Oliveira da Silva, National Health Surveillance Agency, Brasilia, Brazil

Stela Ondrušová, Department of European Union Affairs and International Relations, Ministry of Health, Bratislava, Slovak Republic

Dr Helga Osiander-Fuchs, Bavarian State Office for Health and Food Safety, Erlangen, Germany

Nuray Akan Yaltirakli, Tobacco and Alcohol Market Regulatory Authority, Ankara, Turkey

References

1. Zeller M, Hatsukami D, Strategic Dialogue on Tobacco Harm Reduction Group. The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US. *Tob Control* 2009;18:324–32.
2. Colilla S. An epidemiologic review of smokeless tobacco health effects and harm reduction potential. *Regul Toxicol Pharmacol* 2010;56:197–211.
3. Hatsukami DK, Henningfield JE, Kotlyar M. Harm reduction approaches to reducing tobacco-related mortality. *Annu Rev Public Health* 2004;25:377–95.
4. Statement of principles guiding the evaluation of new or modified tobacco products. Geneva: Scientific Advisory Committee on Tobacco Product Regulation, World Health Organization; 2003 (<http://apps.who.int/iris/handle/10665/42648>, accessed October 2014).
5. Southwell BG, Kim AE, Tessman GK, MacMonegle AJ, Choiniere CJ, Evans SE, et al. The marketing of dissolvable tobacco: social science and public policy research needs. *Am J Health Promot* 2012;26:331–2.
6. Rainey CL, Conder PA, Goodpaster JV. Chemical characterization of dissolvable tobacco products promoted to reduce harm. *J Agric Food Chem* 2011;59:2745–51.
7. Rainey CL, Berry JJ, Goodpaster JV. Monitoring changes in the chemical composition of dissolvable tobacco products. *Anal Methods* 2013;5:3216–21.
8. Seidenberg AB, Rees VW, Connolly GN. RJ Reynolds goes international with new dissolvable tobacco products. *Tob Control* 2012;21:368–9.
9. Centers for Disease Control and Prevention. State-specific secondhand smoke exposure and current cigarette smoking among adults—United States, 2008. *Morbid Mortal Wkly Rep* 2009;58(44).
10. Romito LM, Saxton MK, Coan LL, Christen AG. Retail promotions and perceptions of RJ Reynolds' novel dissolvable tobacco in a US test market. *Harm Reduction J* 2011;8:10.
11. Caraballo RS, Pederson LL, Gupta N. New tobacco products: do smokers like them? *Tob Control* 2006;15:39–44.
12. Connolly GN, Richter P, Aleguas A, Pechachek TF, Stanfill SB, Alpert HR. Unintentional child poisonings through ingestion of conventional and novel

- tobacco products. *Pediatrics* 2010;125:896–9.
13. Stepanov I, Jensen J, Hatsukami D, Hecht SS. Tobacco-specific nitrosamines in new tobacco products. *Nicotine Tob Res* 2006;8:309–13.
 14. Mendoza-Baumgart MI, Tulunay OE, Hecht SS, Zhang Y, Murphy SE, Le CT, et al. Pilot study on lower nitrosamine smokeless tobacco products compared to medicinal nicotine. *Nicotine Tob Res* 2007;9:1309–23.
 15. Stepanov I, Biener L, Knezevich A, Nyman AL, Bliss R, Jensen J, et al. Monitoring tobacco-specific N-nitrosamines and nicotine in novel Marlboro and Camel smokeless tobacco products: findings from round I of the New Product Watch. *Nicotine Tob Res* 2012;14:274–81.
 16. Watson C. Quantitative and qualitative analysis of dissolvable tobacco products. Report to the Food and Drug Administration Tobacco Scientific Advisory Committee, 18–22 January 2012. Rockville, Maryland: Food and Drug Administration; 2012.
 17. Stepanov I. Toxic and carcinogenic constituents in dissolvable tobacco products. Report to the Food and Drug Administration Tobacco Scientific Advisory Committee, 18–22 January 2012. Rockville, Maryland: Food and Drug Administration; 2012.
 18. Lawler TS, Stanfill SB, Zhang L, Ashley DL, Watson CH. Chemical characterization of domestic oral tobacco products: total nicotine, pH, unprotonated nicotine and tobacco-specific N-nitrosamines. *Food Chem Toxicol* 2013;57:380–6.
 19. Hatsukami DK, Jensen J, Anderson A, Broadbent B, Allen S, Zhang Y et al. Oral tobacco products: preference and effects among smokers. *Drug Alcohol Depend* 2011;118:230–6.
 20. Kotlyar M, Hertsgaard LA, Lindgren BR, Jensen JA, Carmella SG, Stepanov I, et al. Effect of oral snus and medicinal nicotine in smokers on toxicant exposure and withdrawal symptoms: a feasibility study. *Cancer Epidemiol Biomarkers Prev* 2011;20:91–100.
 21. Connolly GN. The marketing of nicotine addiction by one oral snuff manufacturer. *Tob Control* 1995;4:73–9.
 22. Summary: TPSAC Report on Dissolvable Tobacco Products (Rep. No. March 1, 2012). Silver Spring, Maryland: Food and Drug Administration, Tobacco Scientific Advisory Committee; 2012.
 23. Biener L, Bogen K. Receptivity to Taboka and Camel Snus in a US test market. *Nicotine Tob Res* 2009;11:1154–9.
 24. Bahreinifar S, Sheon NM, Ling PM. Is snus the same as dip? Smokers' perceptions of new smokeless tobacco advertising. *Tob Control* 2013;22:84–90.
 25. Delnevo CD, Wackowski OA, Giovenco DP, Bover Manderski MT, Hrywna M, Ling PM. Examining market trends in the United States smokeless tobacco use: 2005–2011. *Tob Control* 2013;22:266–73.
 26. Timberlake DS, Pechmann C, Tran SY, Au V. A content analysis of Camel Snus advertisements in print media. *Nicotine Tob Res* 2011;13:431–9.

27. Gany F, Rastogi N, Suri A, Hass C, Bari S, Leng J. Smokeless tobacco: how exposed are our children? *J Community Health* 2013;38:750–2.
28. Wackowski OA, Lewis MJ, Delnevo CD. Qualitative analysis of Camel Snus' website message board—users' product perceptions, insights and online interactions. *Tob Control* 2011;20:e1.
29. Choi K, Forster J. Awareness, perceptions, and use of snus among young adults from the upper Midwest region of the USA. *Tob Control* 2012;102:208893.
30. Biener L, McCausland K, Curry L, Cullen J. Prevalence of trial of snus products among adult smokers. *Am J Public Health* 2011;101:1874–6.
31. Loukas A, Batanova MD, Velazquez CE, Lang WJ, Sneden GG, Pasch KE, et al. Who uses snus? A study of Texas adolescents. *Nicotine Tob Res* 2012;14:626–30.
32. Caraway JW, Chen PX. Assessment of mouth-level exposure to tobacco constituents in US snus consumers. *Nicotine Tob Res* 2013;15:670–7.
33. Stepanov I, Jensen J, Biener L, Bliss RL, Hecht SS, Hatsukami DK. Increased pouch sizes and resulting changes in the amounts of nicotine and tobacco-specific N-nitrosamines in single pouches of Camel Snus and Marlboro Snus. *Nicotine Tob Res* 2012;14:1241–5.
34. Stepanov I, Jensen J, Hatsukami D, Hecht SS. New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels. *Nicotine Tob Res* 2008;10:1773–82.
35. Digard H, Gale N, Errington G, Peters N, McAdam K. Multi-analyte approach for determining the extraction of tobacco constituents from pouched snus by consumers during use. *Chem Central J* 2013;7:55.
36. Sarkar M, Liu J, Koval T, Wang J, Feng S, Serafin R, et al. Evaluation of biomarkers of exposure in adult cigarette smokers using Marlboro Snus. *Nicotine Tob Res* 2010;12:105–16.
37. Foulds J, Ramstrom L, Burke M, Fagerstrom K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob Control* 2003;12:349–59.
38. Luo J, Ye W, Zandehdel K, Adami J, Adami HO, Boffetta P, et al. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 2007;369:2015–20.
39. Greer RO Jr. Oral manifestations of smokeless tobacco use. *Otolaryngol Clin N Am* 2011;44:31–56.
40. Health effects of smokeless tobacco products. Brussels: European Commission, Scientific Committee on Emerging and Newly Identified Health Risks; 2008.
41. Cobb CO, Weaver MF, Eissenberg T. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tob Control* 2010;19:367–373.
42. Kotlyar M, Mendoza-Baumgart MI, Li Z, Pentel PR, Barnett BC, Feuer RM, et al. Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge. *Tob Control* 2007;16:138–42.

43. Blank MD, Eissenberg T. Evaluating oral noncombustible potential-reduced exposure products for smokers. *Nicotine Tob Res* 2010;12:336–43.
44. European Commission. Directive 2001/37/EC of the European Parliament and of the Council of 5 June 2001 on the approximation of the laws, regulations and administrative provisions of the Member States, concerning the manufacture, presentation and sale of tobacco products. *Off J L* 2013;194:26.
45. Hughes JR, Keely JP, Callas PW. Ever users versus never users of a “less risky” cigarette. *Psychol Addictive Behav* 2005;19:439–42.
46. Breland AB, Evans SE, Buchhalter AR, Eissenberg T. Acute effects of Advance: a potential reduced exposure product for smokers. *Tob Control* 2002;11:376–8.
47. Brown B, Kolesar J, Lindberg K, Meckley D, Mosberg A, Doolittle D. Comparative studies of DNA adduct formation in mice following dermal application of smoke condensates from cigarettes that burn or primarily heat tobacco. *Mutat Res* 1998;414:21–30.
48. Buchhalter AR, Schrinel L, Eissenberg T. Withdrawal-suppressing effects of a novel smoking system: comparison with own brand, not own brand, and denicotinized cigarettes. *Nicotine Tob Res* 2001;3:111–8.
49. Tarantola A. Ploom modelTwo E-Cig review: welcome to flavor country. *Gizmodocom*;2013 (<http://gizmodo.com/ploom-modeltwo-e-cig-review-welcome-to-flavor-country-586563052>, accessed October 2014).
50. Breland AB, Acosta MC, Eissenberg T. Tobacco specific nitrosamines and potential reduced exposure products for smokers: a preliminary evaluation of Advance™. *Tob Control* 2003;12:317–21.
51. Pankow JF, Watanabe KH, Toccalino PL, Luo W, Austin DF. Calculated cancer risks for conventional and “potentially reduced exposure product” cigarettes. *Cancer Epidemiol Biomarkers Prev* 2007;16:584–592.
52. Hughes JR, Hecht SS, Carmella SG, Murphy SE, Callas P. Smoking behavior and toxin exposure during six weeks use of a “less risky” cigarette—Omni. *Tob Control* 2004;13:175–9.
53. Rees VW, Wayne GF, Connolly GN. Puffing style and human exposure minimally altered by switching to a carbon-filtered cigarette. *Cancer Epidemiol Biomarkers Prev* 2008;17:2995–3003.
54. Shiffman S, Pillitteri JL, Burton SL, DiMarino ME. Smoker and ex-smoker reactions to cigarettes claiming reduced risk. *Tob Control* 2004;13:78–84.
55. Shiffman S, Jarvis MJ, Pillitteri JL, DiMarino ME, Gitchell JG, Kemper KE. UK smokers’ and ex-smokers’ reactions to cigarettes promising reduced risk. *Addiction* 2007;102:156–60.
56. Lee EM, Malson JL, Moolchan ET, Pickworth WB. Quantitative comparisons between a nicotine delivery device (Eclipse) and conventional cigarette smoking. *Nicotine Tob Res* 2004;6:95–102.
57. Stabbert R, Voncken P, Rustemeier K, Hausmann HJ, Roemer E, Schaffernicht H, et al. Toxicological evaluation of an electrically heated cigarette. Part 2: Chemical composition of mainstream smoke. *J Appl Toxicol* 2003;23:329–39.

58. Fowles J. Novel tobacco products: health risk implications and international concerns (Client report FW0175). Auckland: Ministry of Health; 2001 (www.moh.govt.nz/moh.nsf/.../noveltobaccoproductshealthrisk.doc, accessed October 2014).
59. Breland AB, Kleykamp BA, Eissenberg T. Clinical laboratory evaluation of potential reduced exposure products for smokers. *Nicotine Tob Res* 2006;8:738.
60. Ayres PH, Hayes JR, Higuchi MA, Mosberg AT, Sagartz JW. Subchronic inhalation by rats of mainstream smoke from a cigarette that primarily heats tobacco compared to a cigarette that burns tobacco. *Inhal Toxicol* 2001;13:149–86.
61. Bowman DL, Smith CJ, Bombick BR, Avalos JT, Davis RA, Morgan WT, et al. Relationship between FTC “tar” and urine mutagenicity in smokers of tobacco-burning or Eclipse cigarettes. *Mutat Res* 2002;521:137–49.
62. Slade J, Connolly GN, Lymperis D. Eclipse: does it live up to its health claims? *Tob Control* 2002;11(Suppl 2):ii64–70.
63. Fagerstrom KO, Hughes JR, Callas PW. Long-term effects of the Eclipse cigarette substitute and the nicotine inhaler in smokers not interested in quitting. *Nicotine Tob Res* 2002;4(Suppl 2):S141–5.
64. Fagerstrom KO, Hughes JR, Rasmussen T, Callas PW. Randomised trial investigating effect of a novel nicotine delivery device (Eclipse) and a nicotine oral inhaler on smoking behaviour, nicotine and carbon monoxide exposure, and motivation to quit. *Tob Control* 2000;9:327–33.
65. Rennard SI, Umino T, Millatmal T, Daughton DM, Manouilova LS, Ullrich FA, et al. Evaluation of subclinical respiratory tract inflammation in heavy smokers who switch to a cigarette-like nicotine delivery device that primarily heats tobacco. *Nicotine Tob Res* 2002;4:467–76.
66. Stewart JC, Hyde RW, Boscia J, Chow MY, O’Mara RE, Perillo I, et al. Changes in markers of epithelial permeability and inflammation in chronic smokers switching to a nonburning tobacco device (Eclipse). *Nicotine Tob Res* 2006;8:773–83.
67. Breland AB, Buchhalter AR, Evans SE, Eissenberg T. Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. *Nicotine Tob Res* 2002;4(Suppl 2):S131–40.
68. Hatsukami DK, Lemmonds C, Zhang Y, Murphy SE, Le C, Carmella SG et al. Evaluation of carcinogen exposure in people who used “reduced exposure” tobacco products. *J Natl Cancer Inst* 2004;96:844–52.
69. Lin S, Tran V, Talbot P. Comparison of toxicity of smoke from traditional and harm-reduction cigarettes using mouse embryonic stem cells as a novel model for preimplantation development. *Hum Reprod* 2009;24:386–97.
70. Riveles K, Tran V, Roza R, Kwan D, Talbot P. Smoke from traditional commercial, harm reduction and research brand cigarettes impairs oviductal functioning in hamsters (*Mesocricetus auratus*) in vitro. *Hum Reprod* 2007;22:346–55.
71. Benowitz NL. Compensatory smoking of low-yield cigarettes. In: *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, 2001:1–10.

Health, National Cancer Institute; 2001:39–63.

72. Harris JE, Thun MJ, Mondul AM, Calle EE. Cigarette tar yields in relation to mortality from lung cancer in the Cancer Prevention Study II prospective cohort, 1982–8. *BMJ* 2004;328:72–9.
73. Hecht SS, Murphy SE, Carmella SG, Li S, Jensen J, Le C, et al. Similar uptake of lung carcinogens by smokers of regular, light, and ultra-light cigarettes. *Cancer Epidemiol Biomarkers Prev* 2005;14:693–8.
74. Yang G Marketing “less harmful, low-tar” cigarettes is a key strategy of the industry to counter tobacco control in China. *Tob Control* 2013;23:167–72.
75. Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *J Natl Cancer Inst* 2000;92:106–11.
76. Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. *Clin Pharmacol Ther* 2008;83:531–41.
77. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol* 2009;49:57–71.
78. Strasser AA, Ashare RL, Kozlowski LT, Pickworth WB. The effect of filter vent blocking and smoking topography on carbon monoxide levels in smokers. *Pharmacol Biochem Behav* 2005;82:320–9.
79. Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA et al. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction* 2010;105:343–55.
80. Dunsby J, Bero L. A nicotine delivery device without the nicotine? Tobacco industry development of low nicotine cigarettes. *Tob Control* 2004;13:362–9.
81. Shadel WG, Lerman C, Cappella J, Strasser AA, Pinto A, Hornik R. Evaluating smokers’ reactions to advertizing for new lower nicotine Quest cigarettes. *Psychol Addict Behav* 2006;20:80–4.
84. Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, et al. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomarkers Prev* 2012;21:761–9.
82. BenowitzNL, JacobPIII, HerreraB. Nicotineintakeanddose responsewhensmoking reduced-nicotine content cigarettes. *Clin Pharmacol Ther* 2006;80:703–14.
90. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction—the implications for tobacco regulation. *N Engl J Med* 1994;331:123–5.
85. Catanzaro DF, Zhou Y, Chen R, Yu F, Catanzaro SE, DeLorenzo MS et al. Potentially reduced exposure cigarettes accelerate atherosclerosis: evidence for the role of nicotine. *Cardiovasc Toxicol* 2007;7:192–201.
86. Chen J, Higby R, Tian D, Tan D, Johnson MD, Xiao Y et al. Toxicological analysis of low-nicotine and nicotine-free cigarettes. *Toxicology* 2008;249:194–203.
87. Hatsukami DK, Hertsgaard LA, Vogel RI, Jensen JA, Murphy SE, Hecht SS et al. Reduced nicotine content cigarettes and nicotine patch. *Cancer Epidemiol Biomarkers Prev* 2013;22:1015–24.

88. Girdhar G, Xu S, Bluestein D, Jesty J. Reduced-nicotine cigarettes increase platelet activation in smokers in vivo: a dilemma in harm reduction. *Nicotine Tob Res* 2008;10:1737–44.
83. Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P III. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomarkers Prev* 2007;16:2479–85.
89. Lin S, Fonteno S, Weng JH, Talbot P. Comparison of the toxicity of smoke from conventional and harm reduction cigarettes using human embryonic stem cells. *Toxicol Sci* 2010;118:202–12.
91. Rose JE, Behm FM. Effects of low nicotine content cigarettes on smoke intake. *Nicotine Tob Res* 2004;6:309–19.
92. Strasser AA, Lerman C, Sanborn PM, Pickworth WB, Feldman EA. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug Alcohol Depend* 2007;86:294–300.
93. Walker N, Howe C, Bullen C, Grigg M, Glover M, McRobbie H, et al. The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial. *Addiction* 2012;107:1857–67.
94. Rose JE, Behm FM, Westman EC, Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. *Nicotine Tob Res* 2006;8:89–101.
95. Donny EC, Jones M. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. *Drug Alcohol Depend* 2009;104:23–33.
96. Siu M, Mladjenovic N, Soo E. The analysis of mainstream smoke emissions of Canadian “super slim” cigarettes. *Tob Control* 2012;22:e10.
97. Hammond D, Doxey J, Daniel S, Bansal-Travers M. Impact of female-oriented cigarette packaging in the United States. *Nicotine Tob Res* 2011;13:579–88.
98. European Commission. Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC Text with EEA relevance. *Off J L* 2014;127:1–38.
99. Richardson A, Vallone DM. YouTube: a promotional vehicle for little cigars and cigarillos? *Tob Control* 2012;23:21–6.
100. Kozlowski LT, Dollar KM, Giovino GA. Cigar/cigarillo surveillance: limitations of the US Department of Agriculture system. *Am J Prev Med* 2008;34:424–6.
101. Maxwell JC. The Maxwell report. Cigar industry in 2008. Richmond, Virginia; 2008.
102. Richardson A, Xiao H, Vallone DM. Primary and dual users of cigars and cigarettes: profiles, tobacco use patterns, and relevance to policy. *Nicotine Tob Res* 2012;14:927–32.
103. Family Smoking Prevention and Tobacco Control Act (7-22-2009). Public Law 11-31, H.R. 1256. Washington DC: Government Printing Office, US Congress; 2009

(<http://www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf>, accessed October 2014).

104. Villanti AC, Richardson A, Vallone DM, Rath JM. Flavored tobacco product use among US young adults. *Am J Prev Med* 2013;44:388–91.
105. Little cigars—big concerns. Ottawa: Health Canada; 2011.
106. Henningfield JE, Fant RV, Radzius A, Frost S. Nicotine concentration, smoke pH and whole tobacco aqueous pH of some cigar brands and types popular in the United States. *Nicotine Tob Res* 1999;1:163–8.
107. Chen A, Glantz S, Tong E. Asian herbal-tobacco cigarettes: “not medicine but less harmful”? *Tob Control* 2007;16:e3.
108. Soldz S, Huyser DJ, Dorsey E. Characteristics of users of cigars, bidis, and kreteks and the relationship to cigarette use. *Prev Med* 2003;37:250–8.
109. Watson CH, Polzin GM, Calafat AM, Ashley DL. Determination of tar, nicotine, and carbon monoxide yields in the smoke of bidi cigarettes. *Nicotine Tob Res* 2003;5:747–53.
110. Delnevo CD, Pevzner ES, Hrywna M, Lewis MJ. Bidi cigarette use among young adults in 15 states. *Prev Med* 2004;39:207–11.
111. Waterpipe tobacco smoking: health effects, research needs and recommended actions by regulators. Geneva: World Health Organization; 2005.
112. Vattenpipa—rök utan risk? Hälsoeffekter, vanor, attityder och tillsyn [Hookah—smoke without risk? Health effects, habits, attitudes and supervision]. Östersund: Statens Folkhälsoinstitut; 2010.
113. Morton J, Song Y, Fouad H, Awa FE, Abou El Naga R, Zhao L, et al. Cross-country comparison of waterpipe use: nationally representative data from 13 low and middle-income countries from the Global Adult Tobacco Survey (GATS). *Tob Control* 2013;23:419–27.
114. Maziak W. The global epidemic of waterpipe smoking. *Addict Behav* 2011;36:1–5.
115. Akl EA, Gunukula SK, Aleem S, Obeid R, Abou Jaoude P, Honeine R, et al. The prevalence of waterpipe tobacco smoking among the general and specific populations: a systemic review. *BMC Public Health* 2011;11:244.
116. Attitudes of Europeans towards tobacco (Special Eurobarometer 385, Wave EB77.1). Brussels: European Commission; 2012.
117. Jawad M, Abass J, Hariri A, Rajasooriar KG, Salmasi H, Millett C, et al. Waterpipe smoking: prevalence and attitudes among medical students in London. *Int J Tuberc Lung Dis* 2013;17:137–40.
118. Schubert J, Hahn J, Dettbarn G, Seidel A, Luch A, Schulz TG. Mainstream smoke of the waterpipe: does this environmental matrix reveal as significant source of toxic compounds? *Toxicol Lett* 2011;205:279–84.
119. Al Rashidi M, Shihadeh A, Saliba NA. Volatile aldehydes in the mainstream smoke of the narghile waterpipe. *Food Chem Toxicol* 2008;46:3546–9.
120. Cobb CO, Shihadeh A, Weaver MF, Eissenberg T. Waterpipe tobacco smoking and cigarette smoking: a direct comparison of toxicant exposure and subjective

- effects. *Nicotine Tob Res* 2011;11:78–87.
121. La Fauci G, Weiser G, Steiner IP, Shavit I. Carbon monoxide poisoning in naghile (water pipe) tobacco smokers. *Can J Emerg Med* 2012;14:57–9.
 122. Jacob P III, Abu Raddaha AH, Dempsey D, Havel C, Peng M, Yu L, et al. Comparison of nicotine and carcinogen exposure with water pipe and cigarette smoking. *Cancer Epidemiol Biomarkers Prev* 2013;22:765–72.
 123. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 71, Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. Lyon: International Agency for Research on Cancer; 1999.
 124. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 88, Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. Lyon: International Agency for Research on Cancer; 2006.
 125. Maziak W, Eissenberg T, Ward KD. Patterns of waterpipe use and dependence: implications for intervention development. *Pharmacol Biochem Behav* 2005;80:173–9.
 126. Lipkus IM, Eissenberg T, Schwartz-Bloom RD, Prokhorov AV, Levy J. Affecting perceptions of harm and addiction among college waterpipe tobacco smokers. *Nicotine Tob Res* 2011;13:599–610.
 127. Menthol capsules in cigarette filters—increasing the attractiveness of a harmful product. Heidelberg: German Cancer Research Center; 2012.
 128. Addictiveness and Attractiveness of Tobacco Additives. Brussels: European Commission, Scientific Committee on Emerging and Newly Identified Health Risks; 2010.
 129. Tobacco additives. Bilthoven: National Institute for Public Health and the Environment; 2012.
 130. Soeteman-Hernandez LG, Bos PM, Talhout R. Tobacco smoke-related health effects induced by 1,3-butadiene and strategies for reduction. *Toxicol Sci* 2013;136:566–80.
 131. Kennedy RD, Millstein RA, Rees VW, Connolly GN. Tobacco industry strategies to minimize or mask cigarette smoke: opportunities for tobacco product regulation. *Nicotine Tob Res* 2013;15:596–602.
 132. Marian C, O'Connor RJ, Djordjevic MV, Rees VW, Hatsukami DK, Shields PG. Reconciling human smoking behavior and machine smoking patterns: implications for understanding smoking behavior and the impact on laboratory studies. *Cancer Epidemiol Biomarkers Prev* 2009;18:3305–20.
 133. Burns DM, Dybing E, Gray N, Hecht S, Anderson C, Sanner T et al. Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization TobReg proposal. *Tob Control* 2008;17:132–41.
 134. Mulier T. Philip Morris to introduce lower-risk cigarette by 2017. Bloombergcom; 2013 (<http://www.bloomberg.com/news/2012-06-21/philip-morris-to-introduce-next-generation-cigarette-by-7.html>, accessed October 2014).
 135. Smeltsigaret op komst [Melt cigarette arriving]. SP!TS; 2013 (<http://www>.

spitsnieuws.nl/archives/binnenland/2013/10/smeltsigaret-op-komst, accessed 5 October 2013).

136. Rees VW, Kreslake JM, O'Connor RJ, Cummings KM, Parascandola M, Hatsukami D, et al. Methods used in internal industry clinical trials to assess tobacco risk reduction. *Cancer Epidemiol Biomarkers Prev* 2009;18:3196–208.
137. Kleinstreuer C, Feng Y. Lung deposition analyses of inhaled toxic aerosols in conventional and less harmful cigarette smoke: a review. *Int J Environ Res Public Health* 2013;10:4454–85.
138. McAdam KG, Gregg EO, Liu C, Dittrich DJ, Duke MG, Proctor CJ. The use of a novel tobacco-substitute sheet and smoke dilution to reduce toxicant yields in cigarette smoke. *Food Chem Toxicol* 2011;49:1684–96.
139. Fearon IM, Acheampong DO, Bishop E. Modification of smoke toxicant yields alters the effects of cigarette smoke extracts on endothelial migration: an in vitro study using a cardiovascular disease model. *Int J Toxicol* 2012;31:572–83.
140. Fearon IM, Gaca MD, Nordskog BK. In vitro models for assessing the potential cardiovascular disease risk associated with cigarette smoking. *Toxicol in Vitro* 2013;27:513–22.
141. St Charles FK, McAughey J, Shepperd CJ. Methodologies for the quantitative estimation of toxicant dose to cigarette smokers using physical, chemical, and bioanalytical data. *Inhal Toxicol* 2013;25:363–72.
142. Liu C, DeGrandpre Y, Porter A, Griffiths A, McAdam K, Voisine R, et al. The use of a novel tobacco treatment process to reduce toxicant yields in cigarette smoke. *Food Chem Toxicol* 2011;49:1904–17.
143. Shepperd CJ, Eldridge A, Camacho OM, McAdam K, Proctor CJ, Meyer I. Changes in levels of biomarkers of exposure observed in a controlled study of smokers switched from conventional to reduced toxicant prototype cigarettes. *Regul Toxicol Pharmacol* 2013;66:147–62.
144. McAdam KG, Gregg EO, Bevan M, Dittrich DJ, Hemsley S, Liu C, et al. Design and chemical evaluation of reduced machine-yield cigarettes. *Regul Toxicol Pharmacol* 2012;62:138–50.
145. Branton PJ, McAdam KG, Winter DB, Liu C, Duke MG, Proctor CJ. Reduction of aldehydes and hydrogen cyanide yields in mainstream smoke using an amine functionalised ion exchange resin. *Chem Central J* 2011;5:15.
146. Deng Q, Huang C, Xie W, Xu H, Wei M. Significant reduction of harmful compounds in tobacco smoke by the use of titanite nanosheets and nanotubes. *Chem Commun (Camb)* 2011;47:6153–5.
147. Deng Q, Huang C, Zhang J, Xie W, Xu H, Wei M. Selectively reduction of tobacco specific nitrosamines in cigarette smoke by use of nanostructural titanates. *Nanoscale* 2013;5:5519–23.
148. Polzin GM, Zhang L, Hearn BA, Tavakoli AD, Vaughan C, Ding YS, et al. Effect of charcoal-containing cigarette filters on gas phase volatile organic compounds in mainstream cigarette smoke. *Tob Control* 2008;17(Suppl 1):i10–6.
149. Hearn BA, Ding YS, Vaughan C, Zhang LQ, Polzin G, Caudill SP, et al. Semi-

- volatiles in mainstream smoke delivery from select charcoal-filtered cigarette brand variants. *Tob Control* 2010;19:223–30.
150. Scherer G, Urban M, Engl J, Hagedorn HW, Riedel K. Influence of smoking charcoal filter tipped cigarettes on various biomarkers of exposure. *Inhal Toxicol* 2006;18:821–9.
 151. Foulds J, Furberg H. Is low-nicotine Marlboro snus really snus? *Harm Reduction J* 2008;5:9.
 152. Carpenter CM, Connolly GN, Ayo-Yusuf OA, Wayne GF. Developing smokeless tobacco products for smokers: an examination of tobacco industry documents. *Tob Control* 2009;18:54–9.
 153. Rees VW, Kreslake JM, Cummings KM, O'Connor RJ, Hatsukami DK, Parascandola M, et al. Assessing consumer responses to potential reduced-exposure tobacco products: a review of tobacco industry and independent research methods. *Cancer Epidemiol Biomarkers Prev* 2009;18:3225–40.
 154. Mejia AB, Ling PM. Tobacco industry consumer research on smokeless tobacco users and product development. *Am J Public Health* 2010;100:78–87.
 155. Parascandola M, Augustson E, Rose A. Characteristics of current and recent former smokers associated with the use of new potential reduced-exposure tobacco products. *Nicotine Tob Res* 2009;11:1431–8.
 156. Regan AK, Dube SR, Arzola R. Smokeless and flavored tobacco products in the US 2009 Styles survey results. *Am J Prev Med* 2012;42:29–36.
 157. Wray RJ, Jupka K, Berman S, Zellin S, Vijaykumar S. Young adults' perceptions about established and emerging tobacco products: results from eight focus groups. *Nicotine Tob Res* 2012;14:184–90.
 158. Shaikh RA, Siahpush M, Singh GK. Socioeconomic, demographic and smoking-related correlates of the use of potentially reduced exposure to tobacco products in a national sample. *Tob Control* 2013;23:353–8.
 159. Choi K, Fabian L, Mottey N, Corbett A, Forster J. Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: findings from a focus group study. *Am J Public Health* 2012;102:2088–93.
 160. O'Connor RJ, Hyland A, Giovino GA, Fong GT, Cummings KM. Smoker awareness of and beliefs about supposedly less-harmful tobacco products. *Am J Prev Med* 2005;29:85–90.
 161. O'Connor RJ, McNeill A, Borland R, Hammond D, King B, Boudreau C, et al. Smokers' beliefs about the relative safety of other tobacco products: findings from the ITC Collaboration. *Nicotine Tob Res* 2007;9:1033–42.
 162. Pederson LL, Nelson DE. Literature review and summary of perceptions, attitudes, beliefs, and marketing of potentially reduced exposure products: communication implications. *Nicotine Tob Res* 2007;9:525–34.
 163. O'Connor RJ, Norton KJ, Bansal-Traves M, Mahoney MC, Cummings KM, Borland R. US smokers' reactions to a brief trial of oral nicotine products. *Harm Reduction J* 2011;8:1.

164. Tomar SL, Alpert HR, Connolly GN. Patterns of dual use of cigarettes and smokeless tobacco among US males: findings from national surveys. *Tob Control* 2010;19:104–9.
165. McClave-Regan AK, Berkowitz J. Smokers who are also using smokeless tobacco products in the US: a national assessment of characteristics, behaviours and beliefs of “dual users”. *Tob Control* 2011;20:239–42.
166. Schwartz JL, Brunnemann KD, Adami AJ, Panda S, Gordon SC, Hoffmann D, et al. Brand specific responses to smokeless tobacco in a rat lip canal model. *J Oral Pathol Med* 2010;39:453–9.
167. Popova L, Ling PM. Alternative tobacco product use and smoking cessation: a national study. *Am J Public Health* 2013;103:923–30.
168. Lund KE, McNeill A, Scheffels J. The use of snus for quitting smoking compared with medicinal products. *Nicotine Tob Res* 2010;12:817–22.
169. Levy DT, Mumford EA, Cummings KM, Gilpin EA, Giovino G, Hyland A, et al. The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: estimates of a panel of experts. *Cancer Epidemiol Biomarkers Prev* 2004;13:2035–42.
170. Levy DT, Mumford EA, Cummings KM, Gilpin EA, Giovino GA, Hyland A, et al. The potential impact of a low-nitrosamine smokeless tobacco product on cigarette smoking in the United States: Estimates of a panel of experts. *Addict Behav* 2006;31:1190–200.
171. Hatsukami DK, Lemmonds C, Tomar SL. Smokeless tobacco use: harm reduction or induction approach? *Prev Med* 2004;38:309–17.
172. Bedi R, Scully C. Tobacco control—debate on harm reduction enters new phase as India implements public smoking ban. *Lancet Oncol* 2008;9:1122–3.
173. Ayo-Yusuf OA, Burns DM. The complexity of “harm reduction” with smokeless tobacco as an approach to tobacco control in low-income and middle-income countries. *Tob Control* 2012;21:245–51.
174. Benowitz NL. Smokeless tobacco as a nicotine delivery device: harm or harm reduction? *Clin Pharmacol Ther* 2011;90:491–3.
175. McNeill A, Hammond D, Gartner C. Whither tobacco product regulation? *Tob Control* 2012;21:221–6.
176. Parascandola M, Augustson E, O’Connell ME, Marcus S. Consumer awareness and attitudes related to new potential reduced-exposure tobacco product brands. *Nicotine Tob Res* 2009;11:886–95.
177. Kotnowski K, Hammond D. The impact of cigarette pack shape, size and opening: evidence from tobacco company documents. *Addiction* 2013;108:1658–68.
178. Tomar SL. Trends and patterns of tobacco use in the United States. *Am J Med Sci* 2003;326:248–54.
179. Declaration. First International Conference on Waterpipe Tobacco Smoking: Building Evidence for Intervention and Policy. Abu Dhabi: American University of Beirut, NYU Abu Dhabi; 2013.

180. Borrelli B, Novak SP. Nurses' knowledge about the risk of light cigarettes and other tobacco "harm reduction" strategies. *Nicotine Tob Res* 2007;9:653–61.
181. Ahmad S, Billimek J. Estimating the health impacts of tobacco harm reduction policies: a simulation modeling approach. *Risk Anal* 2005;24:801–12.

Appendix. Questionnaire on new tobacco products, including products with potentially "modified risk"

This questionnaire has been prepared in the context of a background paper for the 7th Meeting of WHO TobReg, entitled "Research and monitoring the evolution of new tobacco products, including products with potentially "modified risks". This assignment has been commissioned by WHO Tobacco Free Initiative. One of the objectives of the paper is to provide an update on regional and country level activity including, but not limited to, availability, policy and regulation of contents, sale, advertisement and promotion. To this purpose, we kindly ask you to complete the questionnaire below. Any information you provide will be helpful for our inventory, and enable evidence-based future regulation of these products where necessary.

If you cannot or do not want to answer all these questions, leave them open. Please indicate if you want (part of) your information to be treated confidentially. We welcome any other information regarding these issues that is not covered by the questions asked.

We are looking for information on products that contain *tobacco* and meet one or more of the following criteria:

- Product is NOT just another variation or flavor of a traditional/regular cigarette, cigar, pipe tobacco, roll-your-own, or oral tobacco
- Product contains new technology and/or is marketed as a reduced harm product
- Product type has been on the market for less than fifteen years (for example dissolvable tobacco), with an emphasis on the last few years.
- Product type has been on the market for a longer time, but market share increases in areas where it was not used traditionally (for example water-pipe and snus)

Examples of products we are interested in:

- Chewing tobacco called “Thunder”. It is a strongly flavoured tobacco paste filled into round plastic tins, manufactured by V2 Tobacco, Denmark.
- “Dutch Magic”. This is a cigarette that contains virtually no nicotine in tobacco, but average level of tar (not a “light” cigarette).
- Dissolvable tobacco.
- Products considered/promoted as “reduced harm”, for example low-nitrosamine cigarettes.

Questionnaire:**General**

Country

Contact person

Contact information (phone or email)

Which new or modified tobacco products have come to your attention in the last few years, in shops, via internet, news, request for license, or otherwise?

Per product, please answer the following questions.

Kindly provide references to sources that document this information, if available. E.g. Internet sources with examples of advertisements or discussions, reports on market shares.

Product description:

1. Brand name (e.g. “Thunder”)
2. Manufacturer (e.g. V2 Tobacco, Denmark)
3. Product type as indicated by manufacturer (e.g. “chewing tobacco”)
4. Description (e.g. a strongly flavoured tobacco paste)
5. Package (e.g. filled into round plastic tins, containing 37g)
6. Contents and emissions as indicated on package or from other sources (e.g. ingredient lists, chemical analysis)

7. Pictures of product, if available, or link to internet site
8. Any other information

Policy and regulation in your country

9. How are these products regulated in your country?
10. Are there regulations on contents and emissions of this specific product?
11. Any other information

Market

12. Are they popular?
13. Do you know their market share?
14. Do specific groups use them? E.g. young people, women?
15. Any other information

Promotion

16. What is the promotion strategy?
17. Are there specific target groups?
18. How is the product advertised? Do you have examples from e.g. internet?
19. Any other information

Any other remarks

Annex 2

Role of ammonia in delivery of free nicotine: recent work and analytical challenges

C.V. Watson, Research Chemist, Tobacco Products Laboratory, Tobacco & Volatiles Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

Introduction

Recent publications on nicotine transfer to smoke

Recent publications on nicotine uptake

Current role of ammonia technology

References

Introduction

While ammonia occurs naturally at relatively low levels in tobacco leaves, the tobacco industry often adds ammonia for various reasons. From a public health perspective, the most significant reason for adding ammonia is to increase the rate of delivery of nicotine to the brain. Unprotonated, “free-base” nicotine is more lipophilic than protonated nicotine and can therefore be absorbed more quickly. It has been reported that ammonia is responsible for the pH shift required to deprotonate a portion of the nicotine molecule, which can then be perceived more quickly by smokers, a phenomenon known as “impact” (1). Publically, the tobacco industry denies this, although numerous internal documents refer to the “impact”, “strength” and “kick” of smoke.

The Tobacco Master Settlement Agreement of 1998 provided the public health community with a rich source of information on the history of ammonia technology from the tobacco industry’s internal documents. A simple search of these documents brought to light dozens of references to the “discovery” of ammonia technology and how it was extensively researched and tested on panels of smokers to derive subjective feedback on sensory elements such as taste and “impact.” Philip Morris appears to have “discovered” ammonia technology in the 1960s while attempting to engineer a better reconstituted tobacco sheet. At the time, Philip Morris was the smallest of the four largest cigarette manufacturers and was struggling to reduce costs. They seized on the idea of using 100% of the tobacco lamina (rather than the normal 80%) by taking

the scraps, ribs, stems and “fines” and making a tobacco sheet with band cast technology (similar to older paper making techniques). To add mechanical strength to the sheet, diammonium phosphate was added to break down the calcium ion bridges found in protopectins in the leaf and to bind the calcium to phosphate so that the bridges could not immediately re-form (2). The free pectin then became available to re-link, giving strength to the new sheet, or to form complexes with other molecules, like nicotine. Philip Morris scientists also discovered that the addition of diammonium hydrogen phosphate to reconstituted tobacco sheets gave the final product much better sensory “impact” and taste. At the time, Philip Morris did not know exactly why the impact was improved, but they quickly realized its importance and capitalized on this technology. The new, improved smoke flavour, the higher impact and a massive marketing campaign centred on the “Marlboro Man” quickly made Marlboro the top selling cigarette brand in the USA (3). Competing manufacturers scrambled to reverse-engineer the Marlboro cigarette in order to understand its sudden rise in popularity. In 1973, RJ Reynolds concluded that the free nicotine content correlates most closely with share performance (4). After extensive research, British American Tobacco concluded that the band-cast reconstituted tobacco sheet produced with ammonia technology was the “heart and soul” of the Marlboro cigarette (3, 5).

Continued use of a product known to be responsible for hundreds of thousands of deaths annually is a major concern for the public health community. The main explanation for the habitual use of cigarettes is the addictive potential of nicotine. As reported by Ashley et al. (6), two steps are involved in nicotine delivery: transfer of nicotine from the filler to smoke and uptake of nicotine from the smoke by the user. The role of ammonia in these steps has been addressed in a number of studies, some funded by Philip Morris. The following text discusses concern about the analysis of these studies and a discussion of the difficulty for researchers of elucidating the role of ammonia in pH manipulation and the subsequent impact on the delivery of free nicotine.

Recent publications on nicotine transfer to smoke

Although nicotine is a natural component of tobacco plants, the levels in the leaves, the amount transferred to cigarette smoke and the amount available as the free base can be closely controlled, as indicated in most of the industry documents cited. In tobacco leaves and cured tobacco filler, most nicotine is in the non-volatile, protonated salt form; however, a slight shift in pH can cause deprotonation of a large portion, making it more volatile. The volatile form is thought to be more readily bioavailable because it is lipophilic, allowing more rapid penetration into lung membranes, and because it is more rapidly available than nicotine diffusing from the particulate phase (7, 8). Industry

documents indicate that only a small amount of free nicotine is needed to have a favourable sensory effect; too much free nicotine due to a higher pH would make the smoke “harsher” and difficult to inhale (9, 10). During production of reconstituted sheets, pectins can be freed from protopectins by diammonium phosphate and can form a complex with nicotine that decomposes at temperatures more favourable to smoking, thereby increasing the efficiency with which nicotine is transferred to smoke. Increasing the temperature also increases the free nicotine levels in smoke, as hydrolysis of nicotine is temperature-dependent (11, 12). Seeman and Carchman (13) reported that the temperature in a burning cigarette is more than enough to volatilize nicotine and its salts. If nicotine present in the reconstituted tobacco sheets forms stable complexes with pectins, thus increasing the heat required to evaporate nicotine, these complexes remain on the sheet longer and are thereby exposed to much higher temperatures as the burning zone approaches, which could increase the fraction of free-base nicotine in the smoke.

Callicutt et al. (14) studied nicotine transfer efficiency in test cigarettes containing various levels of ammonia. An interesting aspect of this study is the ability of the investigators to design and manufacture cigarettes that differed only in their ammonia content; however, there are questions about the test cigarettes analysed. Of the four test cigarettes produced, one that was supposedly additive-free still contained about 1.7 mg/g of “soluble ammonia”; this was acknowledged but not adequately explained by the authors. Although tobacco type, agricultural practices and processing differences can result in differences in ammonia content, this concentration appears to be high for an “additive-free” cigarette. No information was provided about use of a reconstituted tobacco sheet in making the additive-free cigarette; only the lack of ammonia-forming ingredients was mentioned. Reconstituted tobacco sheets can be made without these chemicals, although industry research indicates that they are more difficult to produce and less pleasant for smokers (15). As research cigarettes are not meant for human consumption, this would not be a concern. The presence of a reconstituted tobacco sheet potentially containing nicotine–pectin complexes could shift the amount of free-base nicotine to the levels smokers perceive as “strength” or “impact”. Callicutt et al. (14) found no significant difference in nicotine transfer among the cigarettes analysed. They stated that the main goal of the study was to examine the rate of total nicotine transfer according to ammonia level; however, the total nicotine content can remain constant while free nicotine delivery changes (14, 16). A greater concern is physical or chemical changes made to cigarettes that can change the level of free nicotine by changing the ratio of free to total nicotine. A limitation of this study is lack of data on free nicotine concentrations, although industry methods for analysing free nicotine have been available since the 1930s (17). A more meaningful question that could have been answered in this study is

the extent to which use of ammonia technology in the manufacture of reconstituted tobacco sheets alters the amount of free nicotine in smoke.

Recent publications on nicotine uptake

A study, funded by Philip Morris, was conducted on the pharmacokinetics of nicotine in relation to ammonia in mainstream smoke, which provides information on the usefulness of measuring ammonia in smoke. McKinney et al. (18) concluded that differences in ammonia levels in mainstream smoke do not affect the pharmacokinetics of nicotine. The procedure involved rapid arterial blood sampling from smokers receiving puffs of smoke through an inhalation device from one of two cigarettes, delivering 10 or 19 μg /cigarette of ammonia to the smoke. Unpublished data from the US Centers for Disease Control and Prevention on measures of ammonia in mainstream smoke particulate and vapour phases suggest that the difference between brands containing 10 and 19 μg /cigarette is insignificant; a difference of 10 μg was even found between two brands of “light”, unmentholated cigarettes made by different manufacturers. Therefore, a statistically significant difference in the plasma nicotine concentration–time curve would not be expected between cigarettes delivering similar ammonia levels in smoke. The cigarettes designated as “low ammonia” also contained higher percentages of Burley tobacco and stems, which can increase the pH of smoke and therefore compensate for the slightly lower ammonia level (19, 20). Information on the levels of ammonia in the fillers would have been helpful for determining whether there were true differences between the two brands. The complex smoke inhalation system was not adequately described in terms of delivery to the smoker. Smoke can be diluted in a number of ways. First, there is no mention that ventilation holes were blocked, whereas unblocked ventilation holes do not accurately mimic human smoking. Secondly, according to the diagram, more clean air could have been introduced through the transducer, although the mechanics and requirement for this are not explained. Finally, loss of free-base nicotine and ammonia due to moisture accumulation in the tubing is not addressed.

There has been some discussion of the significance of puff count. In the study of McKinney et al. (18), only the fourth puff from each cigarette was sampled, so that subjects may have been exposed to lower concentrations of free-base nicotine than those in the initial puffs (21). Industry documents indicate that excess ammonia imparts negative sensory effects to smokers, and most of the added ammonia is intended to react in various ways before or in the first few milliseconds of smoking (22–24). According to the *Handbook for leaf blenders and product developers* (16), ammonia reacts with known irritants, immediately reducing their effects. This ameliorating activity might also liberate more free nicotine by binding acids that could form salts with nicotine (25). The

cellulose acetate filter also effectively traps ammonia during smoking, and another large percentage is lost to side-stream smoke (26). Further, ammonia reacts immediately with irritants such as aldehydes in smoke, thereby reducing its harshness (23–25). Ammonia detected in smoke is probably the pyrolysis product of nitrogenous compounds such as amino acids and nicotine rather than the result of direct migration of added ammonia from the filler to smoke. Little free ammonia is available for analysis, as indicated by the low values for ammonia in smoke; therefore, ammonia in mainstream smoke is a poor indicator of smoke pH and of the delivery of free nicotine. This study would have been more informative if the rate of change in nicotine concentration in arterial blood had been compared with the levels of free nicotine and smoke pH.

The total amount of nicotine absorbed is less pertinent than the rate of nicotine absorption, as the human body effectively absorbs most of the nicotine introduced by smoking. A study of nicotine absorption by van Amsterdam et al. (27) illustrates this point. Venous blood samples were taken from subjects who smoked two test cigarettes with different measured levels of ammonia in the filler (0.89 and 3.43 mg/g). The first sample was taken 2.5 min after the last puff. As expected, no difference was seen between the two brands in “nicotine exposure”, as a sample drawn 2.5 min after smoking would not reflect the rate of absorption of free-base nicotine. Rose et al. (28), in a study of nicotine accumulation in the brain, found that nicotine can reach the brain as little as 7 s after entry into the mouth. Henningfield et al. (29) emphasized that the most important parameter in reinforcing nicotine dependence is the uptake rate and the concentration spike within 10–15 s of the first puff, not the total nicotine absorbed. Furthermore, while there was a large difference in the ammonia content of the two brands used in the study of van Amsterdam et al., levels of 1 mg/g are found in “full-flavour” mentholated cigarettes, which is still considered a significant amount of detectable ammonia. As in the study by Callicutt et al. (14), the level of ammonia in the test cigarettes does not appear to have been below 0.9 mg/g, which is about that found in some mentholated cigarettes. The significance of this amount of ammonia in filler is currently unknown. In the paper by van Amsterdam et al. (27), there was no mention of the presence of reconstituted tobacco sheet in the blend, although this is one of the main sources of ammonia and could affect the efficiency of transfer of free nicotine. A major limitation for independent researchers wishing to compare different cigarettes is the inability to produce test cigarettes that differ only in the ammonia content of the tobacco. A more interesting comparison would be between a fully ammoniated cigarette containing reconstituted sheets and an “additive-free” brand with a low Burley tobacco content, slightly acidic smoke and no reconstituted tobacco sheet.

Current role of ammonia technology

The timeline of ammonia technology is well known. What was once considered one of the “greatest triumphs in the history of modern drug design” (3) can now be considered a legacy technology. The question of the current role of ammonia technology in cigarette design remains. The available industry research on ammonia is at least 20 years old and does not reflect chemical and biotechnological advances for manipulating and controlling smoke pH and free nicotine delivery. Further, the smoke aerosol is a complex mixture of chemicals in a dynamic state. Thus, attempting to correlate ammonia in filler or smoke directly with smoke pH or free nicotine delivery, while a logical, necessary start, vastly oversimplifies the smoke matrix. Ammonia is only one of many compounds that could deprotonate nicotine and form Maillard reaction products, and the industry has had ample time to devise, refine and test alternative technologies and approaches. Aside from ammonia–diammonium phosphate alternatives, a myriad of bases are present in smoke that can create an alkaline environment favourable to the formation of free nicotine. Many other means of manipulation are also possible: the levels of certain constituents in leaves can be altered by biotechnological methods; additives and changes in the design of cigarette filters can be used to create an alkaline smoke or to change the particle size to enhance “off-gassing” of free-base nicotine from the particle; bronchodilators and menthol can be used to enhance nicotine uptake by smokers; and physical characteristics like paper porosity and filter ventilation can be altered to change smoke chemistry.

By the late 1980s, a ban on use of diammonium phosphate in some countries led the tobacco industry to investigate alternative means of making diammonium phosphate-free sheets that still delivered the sugar–diammonium phosphate reaction products to smoke. Brown & Williamson investigated use of solid pineapple extract, caramel and high-maltose corn syrup as substitutes for diammonium phosphate in reconstituted sheets. They found that use of sheets without diammonium phosphate “yielded cigarettes with less irritation, more body, and better tobacco taste” than control samples (15, 30). Industry documents also make reference to the urea–urease system, indicating that urea can dramatically increase smoke pH and the extractable nicotine content and has the added benefit of remaining chemically inert until the cigarette is smoked (31). Urea is, however, difficult to analyse, and urease breaks down urea into ammonia and carbon dioxide in the presence of water. If water-based extraction is used during analysis, urea in filler is analysed as ammonia. In another industry document, Johnson (2) stated “you will never find all the urea you added to tobacco”; this was not explained but might indicate that urea reacts fully once in the system and is therefore not found.

In 1977, the Lorillard Tobacco Company investigated whether addition of inorganic cations, such as potassium and calcium, would raise the smoke pH and increase impact (32). The report stated that, as these compounds occur naturally in tobacco, extensive toxicity studies would not be necessary. Another industry study showed that treating tobacco with potassium carbonate raised the smoke pH without increasing the level of total volatile bases, as ammonia does (33). The potassium ion is a stronger base than ammonia, and potassium and calcium are present in popular brands in the USA. In Germany, where diammonium phosphate is banned, organic or inorganic compounds that can decompose thermally to bases, like calcium carbonate, are used to enhance nicotine delivery (34). Alkali metals like potassium and calcium do not have to be added to tobacco blends, as the levels in leaves can be easily manipulated with fertilizers or by curing practices. Naturally occurring compounds that are used as additives are difficult to analyse, as the levels present in untreated, unmodified tobacco are unknown, and there is no reliable way to differentiate between natural and added levels without a blank tobacco matrix.

In a discussion of nicotine delivery at RJ Reynolds (35), industry scientists expressed concern about a potential “severe ingredients issue for the cigarette industry” and discussed achieving the same smoothness of Philip Morris cigarettes by using chemicals that occur naturally in tobacco in order to avoid having to reformulate products in order to meet possible future regulations. One way of obtaining desirable elements in a blend without additives (particularly those that are banned in some countries) is manipulating the tobacco leaf. References to genetic modification in industry documents include production of a high-nicotine Burley tobacco by somaclonal variation and hybrid sorting (36) and a high-nicotine flue-cured tobacco (37–39). A genetically modified, virtually nicotine-free tobacco species was engineered for use in the Quest cigarette (40). A “worldwide biotech assessment” by Philip Morris (41) identified several areas of interest, including improving flavour and quality, but there was no discussion of whether the improvements were meant to replace additives such as ammonia by increasing the basic properties of leaves. A report from the Philip Morris Tobacco Biotechnology Working Group in 1999 addressed the possibility of increasing the level of reducing sugars in tobacco by enzymatic modification (42). In 2003, Philip Morris provided significant financial support to researchers at North Carolina State University for mapping the tobacco genome. In response to a media inquiry, they claimed that the purpose of the research was to reduce harmful constituents of tobacco (43). It stands to reason that, through either genetic engineering or enzymatic modification, novel tobaccos could be engineered to achieve target deliveries and ensure the delicate balance of taste and “impact” necessary to keep smokers using the product without the use of additives that might be problematic in a regulated market.

The chemistry of cigarette smoke is complex. The low level of ammonia present in the smoke of most modern brands sold in the USA could not alone bring about the pH shift necessary to create the alkaline environment most favourable to free-nicotine formation. Hundreds of bases have been identified in tobacco smoke, many of which are nitrogen heterocyclic compounds, which could be responsible for tobacco flavours (44, 45). In older industry documents, ammonia in smoke was measured separately and included in a measure of total volatile bases. These bases are listed as free ammonia, nicotine, pyridine, alkaloids, pyrazines, pyrrole derivatives and volatile amines that may form Schiff bases with aldehydes present in smoke, which are then further pyrolysed to “basic nitrogen compounds which contribute to the alkalinity of the smoke” (46). The documents state that a measure of total volatile bases gives the most “linear plot with smoke pH, with total alkaloid and total nitrogen also showing strong correlations” (47). Interestingly, pyrolysis of deoxyfructazines formed in the diammonium phosphate–sugar reaction produces several of the pyridines and pyrazines present in smoke (2, 48). Amino acids, which are present at high levels in Burley tobacco, can also react with sugars to create similar, weakly basic compounds (49, 50). Nicotine, one of the most abundant compounds in tobacco leaves, can decompose thermally to ammonia, amines and pyridines. In a review from Philip Morris (51) of the effects of filters on smoke chemistry, smoke was characterized in terms of the total basic fraction (pyrazines, pyridines and alkaloids) and the total acidic fraction (organic acids, phenyl acids, phenolic acids and fatty acids), the larger fraction being basic. Sufficient compounds are therefore present, in addition to ammonia, to create an alkaline smoke, and ammonia should not be considered the sole contributor to smoke alkalinity. Ammonia technology is nevertheless still largely responsible, albeit indirectly, for a large portion of the weak bases present in tobacco smoke.

Several other ways of manipulating free nicotine delivery and uptake are described in industry documents. Cocoa and menthol, two common cigarette additives, have been implicated as potential bronchodilators, thereby increasing inhalation depth and volume and allowing better nicotine absorption (52). Filter additives such as calcium carbonate and sodium carbonate can increase the pH of smoke, possibly eliminating the need to add bases to tobacco filler (53). Increased paper porosity and filter ventilation could also influence smoke particle size or raise the smoke pH. Highly ventilated cigarettes could have a lower aerosol particle density so that their normal coalescence rate is slower (the particles stay smaller longer, with more surface area to facilitate “off-gassing”). Another potential mechanism by which filter ventilation plays an important role is that the air drawn through filter ventilation holes acts as a “drying gas”. A reduction in the water content of aerosol particles effectively increases pH, thereby favouring formation of free-base nicotine in the gas

phase. Differences in blends, the use of expanded tobaccos and the position of the tobacco leaf on the stalk can all alter smoke pH and chemistry, without chemical additives (19, 46).

While ammonia technology may have shown the tobacco industry that nicotine delivery can be manipulated, the industry has had 50 years to study, design and perfect other techniques for controlling the dose of nicotine while maintaining a product “pleasing” to the “dedicated” smoker while still appealing to the novice smoker. Ammonia addition can be viewed as an older technology, still used in some products and in the manufacture of reconstituted sheet, but it does not appear to be a necessary design factor in modern US blend-ed cigarettes. Many variables affect free nicotine delivery, obviating a direct correlation between ammonia and free nicotine. Questions remain regarding the role of ammonia and ammonia alternatives in free nicotine delivery, the most important being whether ammonia affects the alkalinity of the smoke, thereby affecting free nicotine delivery. Does the presence of the reconstituted tobacco sheet without use of ammonia technology affect free nicotine delivery? And do differences in the rate of nicotine uptake within the first 5–20 s reflect differences in free nicotine delivery? We consider these to be some of the most important questions, and none of the studies conducted to date has adequately addressed these critical research gaps.

References

1. Schori TR. Free nicotine: its implications on smoke impact. Bates: 542001986–96; 1979 (<http://legacy.library.ucsf.edu/tid/rlk46b00>).
2. Johnson R. Ammonia technology conference minutes. Bates: 508104012–164; 1989 (<http://legacy.library.ucsf.edu/tid/cfl36b00>).
3. Stevenson T, Proctor RN. The secret and soul of Marlboro: Phillip Morris and the origins, spread, and denial of nicotine freebasing. *Am J Public Health* 2008;98:1184–94.
4. Blevins RA. Letter: Free nicotine. Bates: 500917503; 1973 (<http://legacy.library.ucsf.edu/tid/gnq46b00>).
5. Backhurst JD. A relation between “strength” of a cigarette and the “extractable nicotine” in the smoke. Bates: 620364222; 1965 (<http://legacy.library.ucsf.edu/tid/kgf83f00>).
6. Ashley DL, Pankow JF, Tavakoli AD, Watson CH. Approaches, challenges, and experience in assessing free nicotine. In: Henningfield JE, London ED, Pogun S, editors. *Nicotine psychopharmacology (Handbook of Experimental Pharmacology, No. 192)*. Berlin: Springer-Verlag; 2009:437–56.
7. RJ Reynolds. Nicotine toxicity. Bates: 511194087–114; 1977 (<http://legacy.library.ucsf.edu/tid/ggg53d00>).

8. Reininghaus W. Bioavailability of nicotine. Bates: 3990473388–93; 1994 (<http://legacy.library.ucsf.edu/tid/jgn13j00>).
9. Ireland MS. Research proposal—development of assay for free nicotine. Bates: 00044522–3; 1976 (<http://legacy.library.ucsf.edu/tid/nts76b00>).
10. Larson TM, Morgan JP. Application of free nicotine to cigarette tobacco and the delivery of that nicotine in the cigarette smoke. Bates: 00781406; 1976 (<http://legacy.library.ucsf.edu/tid/pts76b00>).
11. Riehl TF. Project SHIP main technical conclusions 840400–841100. Bates: 650554484–8; 1984 (<http://legacy.library.ucsf.edu/tid/gxq23f00>).
12. Philip Morris. Bates: 2060554039; 1999 (<http://legacy.library.ucsf.edu/tid/iqf13e00>).
13. Seeman JI, Carchman RA. The possible role of ammonia toxicity on the exposure, deposition, retention, and the bioavailability of nicotine during smoking. *Food Chem Toxicol* 2008;46:1863–81.
14. Callicutt CH, Cox RH, Hsu F, Kinser RD, Laffoon SW, Lee PN, et al. The role of ammonia in the transfer of nicotine from tobacco to mainstream smoke. *Regul Toxicol Pharmacol* 2006;46: 1–17.
15. Tang JY. DAP-free recon development update. Bates: 508102219–224; 1991 (<http://legacy.library.ucsf.edu/tid/dtm51f00>).
16. Aulbach PL, Black RR, Chakraborty BB, Diesing AC, Gonterman RA, Johnson RR, et al. Root technology: a handbook for leaf blenders and product developers. Louisville, Kentucky: Brown & Williamson. Bates: USX47046–105; 1991 (<http://legacy.library.ucsf.edu/tid/nqz36b00>).
17. Vickery HB, Pucher GW. The determination of “free nicotine” in tobacco: the apparent dissociation constants of nicotine. *J Biol Chem* 1929;84(1): 233–41.
18. McKinney DL, Gogova M, Davies BD, Ramakrishnan V, Fisher K, Carter WH. Evaluation of the effect of ammonia on nicotine pharmacokinetics using rapid arterial sampling. *Nicotine Tob Res* 2012;14:586–95.
19. Hellams RD. pH determination of mainstream cigarette smoke. Bates: 2050871031; 1984 (<http://legacy.library.ucsf.edu/tid/jgu46b00>).
20. British American Tobacco. How does pH affect transfer of nicotine to smoke? Bates: 566630379–83; 1995 (<http://legacy.library.ucsf.edu/tid/ajs46b00>).
21. Pankow JF, Tavakoli AD, Luo W, Isabelle LM. Percent free base nicotine in the tobacco smoke particulate matter of selected commercial and reference cigarettes. *Chem Res Toxicol* 2003;16(8): 1014–8.
22. Routh WE. Ammonia treatment of tobacco. Bates: 00044858–79; 1977 (<http://legacy.library.ucsf.edu/tid/jtm99d00>).
23. Johnson R (1984) The unique differences of Phillip Morris cigarette brands—R&D-B016-84. Bates: 103281081–112; 1984 (<http://legacy.library.ucsf.edu/tid/ton66b00>).
24. Crellin RA (1985) Project Ship (examination of branded and experimental products from the USA). Bates: 570316962 (<http://legacy.library.ucsf.edu/tid/pls46b00>).

25. Christopher FH Jr (1978) Free nicotine/ammonia treatment of tobacco. Bates: 505197081 (<http://legacy.library.ucsf.edu/tid/cru46b00>).
26. Kusama M, Matsuki T, Sakuma H, Sugawara S, Yamaguchi K. The distribution of cigarette smoke components between mainstream and sidestream smoke II. Bases. Bates: 501523990–4006; 1983 (<http://legacy.library.ucsf.edu/tid/kpm77c00>).
27. van Amsterdam J, Sleijffers A, van Spiegel P, Blom R, Witte M, van de Kassteele J, et al. Effect of ammonia in cigarette tobacco on nicotine absorption in human smokers. *Food Chem Toxicol* 2011;49:3025–30.
28. Rose JE, Mukhin AG, Lokitz SJ, Turkington TG, Herskovic J, Behm FM, et al. Kinetics of brain nicotine accumulation in dependent and nondependent smokers assessed with PET and cigarettes containing 11C-nicotine. *Proc Natl Acad Sci U S A* 2010;107:5190–5.
29. Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug Alcohol Depend* 1993;33(1): 23–9.
30. Alford ED, Hsieh TC. A major sugar/ammonia reaction product in Marlboro 85's. Bates: 510001069–79; 1983 (<http://legacy.library.ucsf.edu/tid/yh23f00>).
31. Newton P, Johnson R. Urea development. Bates: 620136145–9; 1971 (<http://legacy.library.ucsf.edu/tid/gmd43f00>).
32. Ihrig AM. Inorganic additives for the improvement of tobacco. Bates: 00382055–62; 1977 (<http://legacy.library.ucsf.edu/tid/fku61e00>).
33. Glock E. Leaf services monthly report for June: increasing nicotine transfer in smoke. Bates: 514804804–9; 1980 (<http://legacy.library.ucsf.edu/tid/tja87h00>).
34. Wigand JS. Additives, cigarette design and tobacco product regulation. A report to World Health Organization Tobacco Free Initiative Tobacco Product Regulation Group. Bates: 3990512671–715; 2006 (<http://legacy.library.ucsf.edu/tid/ccj13j00>).
35. RJ Reynolds. Regarding means to achieve nicotine balance and deliveries. Bates: 508408649–770; 1992 (<http://legacy.library.ucsf.edu/tid/ikv46b00>).
36. Brown & Williamson. High nicotine Burley flavor development. Bates: 589100515–9; 1996 (<http://legacy.library.ucsf.edu/tid/ewm41f00>).
37. Brown & Williamson. Y1 product. Bates: 661071395A–6 (<http://legacy.library.ucsf.edu/tid/uql66b00>).
38. Brown & Williamson. The Y1 story. Bates: 682727985–90 (<http://legacy.library.ucsf.edu/tid/eqv70f00>).
39. Fisher PR. Y1 product development. Bates: 620017189–91; 1990 (<http://legacy.library.ucsf.edu/tid/chf93f00>).
40. Lightner JG. Cigarette information highlights: Quest Menthol Lights. Bates: 3039591093; 2004 (<http://legacy.library.ucsf.edu/tid/uko91g00>).
41. Gadani F, Rossi L. Worldwide biotechnology assessment: inventory of research activities. Bates: 2073337017–9; 1997 (<http://legacy.library.ucsf.edu/tid/wyz27d00>).

42. Philip Morris. Final report tobacco biotechnology: a worldwide technology assessment. Bates: 2065359566–9631; 1999 (<http://legacy.library.ucsf.edu/tid/itb29h00>).
43. Philip Morris. Response to media inquiry—genome technology 2.271 RWL.doc. Bates: 3008849132–4; 2004 (<http://legacy.library.ucsf.edu/tid/vde30i00>).
44. Schmeltz I, Stedman RL, Chamberlain WJ, Burdick B. Composition studies on tobacco. XX. Bases of cigarette smoke. *Tob Sci* 1964;8:82–91.
45. Heckman RA, Best FW. An investigation of the lipophilic bases of cigarette smoke condensate. Bates: 620398463–70; 1981 (<http://legacy.library.ucsf.edu/tid/xvz90c00>).
46. Ihrig AM. pH of particulate phase. Bates: 87644270–81; 1973 (<http://legacy.library.ucsf.edu/tid/iwr46b00>).
47. Creighton DE. The significance of pH in tobacco and tobacco smoke. Bates: 500104402; 1988 (<http://legacy.library.ucsf.edu/tid/edk86b00>).
48. Anonymous. Ammonia process comparisons fructose conversion vs. tobacco temperature. Bates: 681915855 (<http://legacy.library.ucsf.edu/tid/pek46b00>).
49. Wang MX. Analytical results of the experimental flavor samples. Bates: 583150454–5; 1986 (<http://legacy.library.ucsf.edu/tid/qar03f00>).
50. Evans RJ, Nimlos MR. Kinetics and mechanisms of the pyrolysis of amino acids. Bates: 3003669136; 2002 (<http://legacy.library.ucsf.edu/tid/fnh95g00>).
51. Lin SS. Basic flavor investigation low tar / high flavor literature review. Bates: 2050878148–90; 1990 (<http://legacy.library.ucsf.edu/tid/wgu46b00>).
52. Ferris Wayne G, Connolly GN. Application, function, and effects of menthol in cigarettes: a survey of tobacco industry documents. *Nicotine Tob Res* 2004;6(Suppl 1):S43–54.
53. Irwin WDE. Comment by W.D.E. Irwin on Handbook for leaf blenders and product developers. Bates: 400820196–7; 1983 (<http://legacy.library.ucsf.edu/tid/ogc54a99>).

Annex 3

Reducing the dependence potential of manufactured cigarettes by reducing their nicotine content to levels that cannot cause or sustain addiction

G. Ferris Wayne, WHO Consultant

Introduction

Tobacco addictiveness model

- Nicotine addiction

- Individual variation in response to nicotine

- Delivery of nicotine from tobacco

- Dual reinforcement model of addiction

- Drug expectancy

- Social and contextual factors

- Summary

Establishing a threshold for addiction

- Nicotine self-administration

- Acquisition of nicotine dependence

- Reinforcing effects of low-nicotine cigarettes

- Addiction threshold versus reinforcement threshold

- Threshold for conditioned stimulus

- Summary

Feasibility of reducing nicotine

- Cigarette nicotine delivery

- Methods for reducing nicotine in tobacco

- Denicotinized or reduced-nicotine cigarettes

- Free-base nicotine in low-delivery cigarettes

- Products that lead to compensatory smoking

- Product formulation and approaches to nicotine reduction

- Summary

Potential behavioural and population outcomes

- Potential effects on cigarette consumption

- Potential effects on topography and smoking behaviour

- Potential effects on abstinence and quitting

- Potential effects on acquisition of cigarette use

- Potential unintended behavioural consequences

- Potential population differences

- Potential health effects

- Potential illicit sales of nicotine-containing cigarettes

- Models of population effects

- Summary
- Policy approaches to nicotine reduction
 - Comprehensive regulation of nicotine
 - Performance standards
 - Gradual versus sudden reduction
 - Alternative forms of nicotine
 - Cessation and behavioural treatment
 - Surveillance
 - Consumer education and beliefs
 - Public support for a reduced nicotine policy
 - Unintended market consequences
- Summary
- Conclusions
- Recommendations
- References

Introduction

Nearly two decades ago, Benowitz and Henningfield (1) proposed a gradual reduction of the nicotine content of cigarettes as a strategy for harm reduction. A number of health scientists have since concluded that such an approach could have a significant positive impact on public health (2–8). The goals of a nicotine reduction policy are to reduce the pharmacological addiction of smokers, making it easier for them to quit or encouraging them to change to less harmful sources of nicotine, and also to prevent novice smokers from moving from experimental or occasional smoking to cigarette addiction (2, 6). This strategy is consistent with Article 9 of the WHO Framework Convention on Tobacco Control (WHO FCTC), which calls for guidelines for regulating the contents and emissions of tobacco products (9, 10).

A nicotine reduction strategy is based on the assumption that it is nicotine that is primarily responsible for cigarette use and that a threshold level of nicotine can be identified, below which the acquisition and maintenance of cigarette dependence will be substantially reduced (2). Both theoretical and practical questions must be addressed in evaluating the probable outcomes of this approach: the role of nicotine in initiating and sustaining tobacco addiction, the amount of nicotine necessary for addiction, differences associated with the chemical form or mechanism of delivery of nicotine, variation in the response to nicotine among individuals or vulnerable populations such as children and people with mental illness, processes for reducing nicotine in tobacco and their potential effects, behavioural responses to reduced-nicotine cigarettes (such as compensatory or increased smoking by nicotine-addicted smokers) and the relative toxicity of reduced-nicotine cigarettes.

An early obstacle to evaluating the potential outcomes of a nicotine reduction strategy was the lack of a scientific basis. For example, an initial concern was that reduced-nicotine products might increase the harmful effects of cigarette use as a result of more intense or more frequent smoking (11, 12). Recent clinical studies appear to address this concern, demonstrating substantial reductions in smoking and less exposure to toxins, with little compensation, even at very low doses of nicotine (13–15). In this annex, I review the state of the science with respect to tobacco and nicotine addiction, the concept of a threshold for nicotine addiction and the practical feasibility of reducing nicotine in cigarettes below the threshold for addiction.

Environmental factors are also known to affect the adoption and use of tobacco products and would be likely to play a role in the effectiveness of a nicotine reduction strategy. The factors to be considered include the availability of alternative sources of nicotine, the extent of regulation of alternative products, the potential growth of illicit sales of high-nicotine cigarettes, the availability of treatment for dependence, education of smokers and potential smokers about use, withdrawal and treatment, and public support for regulation of nicotine. For example, barriers to access to less toxic nicotine delivery systems and treatment medications are likely to spur illicit sales or drive smokers to other potentially harmful tobacco products (16). In this annex, I review the anticipated population outcomes of a nicotine reduction strategy and policy approaches for supporting such a strategy and for minimizing any unintended or negative health consequences of nicotine reduction.

The report by the Institute of Medicine in the USA, *Clearing the smoke* (17), provides a useful framework for assessing the harm of tobacco products due to both their toxicity and the factors that encourage experimentation and use (see also 5, 18). Cigarettes and other burnt tobacco are not only much more toxic than alternatives such as medicinal nicotine but also have unmatched potential for harm due to their greater availability, addictiveness and appeal. A nicotine reduction strategy could substantially reduce population harm, even if it did not reduce toxicity, by removing incentives to begin or continue use of these deadly products (5). In this annex, I assess the likelihood of such an outcome on the basis of the available scientific evidence and identify areas in which additional research is needed.

Tobacco addictiveness model

Early attempts to reduce the disease burden associated with tobacco smoking were based on reducing the smoke delivery from cigarette products, mainly by the introduction of filter ventilation to dilute the smoke and use of expanded tobacco and other product changes (19). However, smokers simply compensated for the reduced delivery by altering their smoking behaviour: puffing longer

and more frequently or increasing the number of cigarettes they smoked per day, maintaining their exposure to both nicotine and toxins (20, 21).

Parascandola (22) observed that the failure of past attempts to reduce the harm of tobacco use was due to incomplete understanding by the public health community of the factors that control smoking behaviour and in particular the role of nicotine in driving that behaviour. A nicotine reduction strategy is based directly on the assumption that nicotine is the primary psychoactive drug in tobacco and is the key to continuing tobacco use. Scientific understanding of both nicotine addiction and tobacco use is evolving. Anticipating the consequences—both intended and unintended—of product regulation requires clear, complete understanding of dependence on nicotine and tobacco.

Nicotine addiction

Nicotine is a highly addictive, potent drug, which has psychoactive rewarding effects at an acutely administered dose of < 1 mg (23). Low doses of nicotine stimulate the central and peripheral nervous systems and cause arousal, mood enhancement and increased heart rate or blood pressure; high doses may cause bradycardia, hypotension and depressed mental status. Nicotine improves motor reflexes and cognitive performance, including attention and memory (24). Tolerance to the behavioural and cardiovascular effects of nicotine develops rapidly with repeated exposure. Thus, the pharmacological basis of nicotine addiction is a combination of positive reinforcement (arousal, mood, performance) and avoidance of the withdrawal symptoms that occur in the absence of nicotine (23, 25).

The addictive potential of a nicotine delivery system depends on its dosing mechanism, including the speed with which it delivers nicotine and the ease with which nicotine can be extracted (26, 27). Cigarettes are a particularly effective form of delivery. When an individual inhales smoke from a cigarette, nicotine from the tobacco is carried in smoke particles into the lungs, where it is rapidly absorbed and carried to the brain. Nicotine diffuses readily into brain tissue, where it binds to nicotinic cholinergic receptors. The gradual absence of nicotine after smoking results in subnormal release of dopamine and other neurotransmitters, which is experienced as malaise and inability to experience pleasure. Other symptoms of nicotine withdrawal include irritability, restlessness, anxiety, difficulty in concentrating, decreased heart rate, increased appetite and inability to sleep (23).

Cigarette addiction is maintained by repeated behaviour. The first cigarette of the day produces a substantial pharmacological effect and enhanced mood; the next cigarettes cause accumulation of nicotine in the body, resulting in greater tolerance, and withdrawal symptoms become more pronounced between

successive cigarettes. Most smokers tend to absorb the same amount of nicotine each day and to adjust their smoking behaviour to compensate for changes in the availability of nicotine or in the rate of its elimination from the body in order to regulate their level of nicotine (23).

Compulsion is a core feature of tobacco addiction; it is characterized by a craving to smoke that recurs after each cigarette (28). When compulsion is defined as including withdrawal symptoms, it has a sensitivity of 99% for identifying which novice smokers will progress to established smoking (29–31).

Individual variation in response to nicotine

Most tobacco use begins in adolescence. While many young people try cigarette smoking, only 20–25% of those who try cigarettes become addicted adult smokers (32). Genetic vulnerability to nicotine dependence may explain tobacco use by some people. Studies of twins indicate > 50% heritability in the prevalence of cigarette smoking, the number of cigarettes smoked per day, the ability to quit smoking and the nature of the withdrawal symptoms experienced on quitting (33). Other risk factors for smoking include peer and parental influences, individual personality traits and conditions such as depression and anxiety (32).

Early exposure to nicotine is associated with more severe dependence and increased smoking among adult smokers (1, 34–37). These results are corroborated by studies in animal models, in which exposure during the period corresponding to human adolescence resulted in higher levels of self-administration (38–44). These findings suggest that the developing brain is more susceptible to permanent changes due to nicotine that support addiction (23, 45).

An approximately fourfold individual variation in the rate of metabolism of nicotine has been observed (45, 46). Women metabolize nicotine faster than men (23, 47), which may contribute to greater addiction. Women are also more sensitive to nicotine than men (48) and have more difficulty in quitting smoking (49–53). The smoking behaviour of women is more strongly influenced by conditioned cues and by negative affect, while men are more likely to smoke in response to pharmacological cues and to regulate their nicotine intake (54–57).

Individuals with psychiatric and/or substance abuse disorders have much higher rates of nicotine dependence, smoke more cigarettes per day and have more difficulty in quitting (58–62). Nicotine may be used as a form of self-medication for some disorders (63), particularly schizophrenia, as nicotine can improve deficient sensory gating (64, 65), and depression, as nicotine may desensitize nicotinic receptors in a manner functionally similar to many

antidepressant drugs (66, 67). In addition, smoking (but not nicotine) inhibits brain monoamine oxidase, which could contribute to antidepressant activity (68). Smokers with mental illness constitute more than a third of all smokers and more than half of nicotine-dependent smokers (58, 69, 70).

A subset of light or occasional smokers consume five or fewer cigarettes per day or non-daily and appear to smoke primarily for the positive reinforcing effects of nicotine (23). They often use cigarettes in association with specific activities, such as after meals or with alcohol, and less in response to negative affect; they may be more reactive to smoking cues (71). Although they experience minimal or no withdrawal symptoms, many of these occasional smokers have difficulty in quitting, suggesting a form of dependence distinct from that of daily smokers.

Delivery of nicotine from tobacco

Tobacco smoke is a complex mixture of several thousand compounds (19, 26) that may contribute to a cigarette's addictive properties either independently (72) or in combination with nicotine (73, 74).

Nicotine in its unprotonated or free-base form is readily absorbed through the oral mucosa and upper respiratory tract, as occurs from smokeless tobacco products or cigars. When taken in this form, nicotine gives a stinging sensation or "bite" in the upper respiratory tract, which may be considered irritating or unpalatable. In cigarette smoke, however, a large percentage of nicotine remains in the protonated or bound form, in which it is more easily inhaled and carried deep into the respiratory tract. Bound nicotine is not absorbed as quickly or readily as unprotonated nicotine and does not provide the same sensory stimulus (26, 75). The aim of modern cigarette construction is to provide an ideal balance between the efficiency and palatability of nicotine delivery. For example, a high ammonia content can increase the proportion of unprotonated nicotine in cigarette smoke, allowing more rapid or efficient absorption of nicotine (76). Sugars and other additives may then be added to offset the harshness of unprotonated nicotine and facilitate deeper inhalation (26).

The sensory characteristics (taste, aroma, tracheobronchial sensations) of tobacco smoke provide direct cues to the smoker, guiding smoking behaviour at the level of the individual puff (77, 78). The motor aspects of cigarette use (handling, puffing, inhaling) do not elicit significant satisfaction in smokers in the absence of sensory components, as indicated in studies with unlit cigarettes (79). Variations in sensory components, such as taste and impact, may, however, have significant effects on measures of smoking reward (77, 80). For example, attenuation of olfactory and taste cues diminishes both the

enjoyment and behaviourally reinforcing effects of cigarette smoke, particularly among female smokers (77, 81).

Nicotine plays a central role in the sensory composition of cigarette smoke. Nicotine-containing cigarettes are consistently rated as stronger than denicotinized cigarettes in terms of perceived respiratory tract sensations (81, 82). Inhalation of nicotine aerosol has strong irritant effects (83), and even intravenous nicotine infusions can elicit respiratory tract sensations (27, 84).

A balance of smoke constituents is necessary to offset the excessive harshness of nicotine and make tobacco smoke palatable. "Tar" is a common measure of the total particulates in smoke except nicotine, and the ratio of tar : nicotine has been found to be a key determinant of the overall harshness of smoke (77, 85). Other tobacco constituents may provide additional stimuli, either with or in place of nicotine (26). Menthol, which has strong sensory stimulant properties, is a common tobacco additive and has been used to compensate for reduced nicotine in products with extremely low delivery (86, 87). Menthol may also attenuate some of the irritant effects of nicotine by virtue of its local anaesthetic properties (88) and increase the permeability of biological membranes (89), which could influence nicotine absorption.

Smoke components other than nicotine may have direct pharmacological effects on the brain or interact with the reinforcing effects of nicotine. Brody et al. (90) found significant occupancy of $\alpha 4\beta 2$ nicotinic cholinergic receptors in individuals smoking denicotinized cigarettes, suggesting that, even in the absence of nicotine, tobacco smoke may have measurable pharmacological effects. Various minor tobacco alkaloids are reinforcing on their own (non-nicotine) or by potentiating the effects of nicotine (anabasine, nornicotine, anatabine, cotinine and myosmine) (91, 92). Acetaldehyde is self-administered in animal models (72) and has been shown to potentiate the reinforcing effects of nicotine, especially in adolescent animals (73, 93–95).

Harman and salsolinol are condensation products of acetaldehyde that inhibit monoamine oxidase (73), and they increase self-administration of nicotine substantially when given to rats (74, 96, 97), possibly by exerting antidepressant effects or by potentiating the reinforcing effects of nicotine by increasing the lifetime of neurotransmitters such as dopamine after their release by nicotine (98).

Dual reinforcement model of addiction

Although the addictive properties of tobacco are often attributed exclusively to nicotine (99), nicotine alone, in the absence of tobacco, has not been shown conclusively to have reinforcing effects in studies with blinded protocols (100,

101). Like other psychostimulants, nicotine has unconditioned effects that increase conditioned reinforcing by non-drug stimuli, independently of a direct association between nicotine administration and presentation of the stimulus (102–108).

The critical role of non-drug stimuli has been demonstrated in studies in rodents, in which discontinuation of environmental stimuli associated with intravenous nicotine injection decreased self-administration almost as effectively as removal of nicotine (102, 109). In experiments in rats (110) and squirrel monkeys (111), the response rate maintained by light stimuli associated with nicotine was equivalent to that maintained by nicotine. Behavioural interventions without environmental stimuli paired directly with nicotine delivery resulted in very little self-administration (112).

A new hypothesis is that nicotine addiction, seen as high rates of self-administration by laboratory animals or as cigarette smoking by humans, is supported by the reinforcing stimuli that accompany nicotine intake and the capacity of nicotine to enhance the reinforcing effects of such stimuli. In this dual-reinforcement model, nicotine acts first as a primary reinforcer, establishing a concurrent neutral stimulus as a conditioned reinforcer by association, and then as a reinforcement enhancer, magnifying the incentive of the nicotine-associated conditioned reinforcement (113). As the effects of nicotine become associated with various non-nicotine stimuli, the stimuli acquire conditional value or serve as cues for future nicotine delivery. As a result, the conditional stimuli for tobacco can alter behaviour in a manner to maintain smoking or result in lapse or relapse after sustained abstinence. Thus, proximal stimuli usually associated with smoking, such as a lit cigarette, can induce craving in smokers but not in non-smokers (114). This hypothesis explains the importance of sensory stimuli relative to nicotine in determining subjective responses to tobacco smoke (77, 84) and the reduction in subjective reports of craving for tobacco, desire to smoke and tobacco withdrawal symptoms of people given placebo cigarettes (115).

Rees et al. (116) observed that sensory cues may be highly characteristic of individual tobacco products and suggested that such brand-specific cues acquire incentive salience, reinforcing use on the basis of brand characteristics. They suggested that the limited commercial appeal of denicotinized cigarettes such as Quest is due in part to disruption of the established chemosensory cue–nicotine dose contingency. While nicotine administration increases the salience of sensory cues, it does not alter palatability (117). Thus, the incentive-amplifying effect of nicotine may be most effective for familiar sensory stimuli that already have positive associations, such as flavours like cocoa or menthol.

Drug expectancy

Drug expectancy plays an important role in smokers' responses (118–121), particularly in women (56). According to expectancy theory, a smoker's urge is reduced when smoking a placebo cigarette if he or she has the stimulus (or dose) expectancy of smoking an active-nicotine cigarette and has the response expectancy that nicotine reduces the urge to smoke (122, 123). The expectation of receiving nicotine increases the "likeability" and clinical efficacy of nicotine replacement products, and this expectation interacts with pharmacological factors to produce overall subjective and behavioural responses (120, 124, 125).

In a study with a balanced placebo design, smokers who expected smoking to relieve the negative affect of an anxious mood induction had improved mood even when they smoked a placebo cigarette (126). Telling smokers that they are smoking nicotine attenuates their urge to smoke a placebo cigarette but has little effect in the context of nicotine administration, indicating that either nicotine or the belief that one is smoking a nicotine-containing cigarette is sufficient to attenuate the urge to smoke but that dose expectancy is not additive with the effects of nicotine (121).

Drug expectancy may be informed by sensory stimuli that indicate to a smoker the likelihood of a given nicotine dose due to conditioned associations. Such cues may be expressed by a smoker as the "strength" of the cigarette and reflect some combination of nicotine-derived impact and other smoke compounds that interact with oral, trigeminal or other receptors (26, 127, 128).

Expectancy can also be separated from non-pharmacological stimuli. For example, the same denicotinized cigarette smoked with a different dose expectancy has different effects (129). Information on nicotine content plays a role in smokers' subjective response to nicotine inhalers, particularly with respect to the craving associated with positive reinforcement (i.e. intention to smoke) but not to the craving associated with negative reinforcement (i.e. withdrawal relief) (120, 130). Although smokers expect pleasurable effects from smoking, they show less expectancy of positive effects from less familiar formulations (123).

Social and contextual factors

Dependence is not limited to physiological experience, but is also shaped by behavioural practices and by the environmental factors that support them. The social context of tobacco use is clearly relevant to understanding the patterns of use of various tobacco products, as is the extent of external pressure to abstain or quit. De Leon et al. (131) called for measures of tobacco use that account for contextual factors in determining smoking behaviour and dependence. These would include where it is permissible to use tobacco products (both legally

and in terms of social norms); the cost of tobacco use, both individually and to families; and the degree of stigmatization of tobacco use with respect for example to gender, religious affiliation and social status. Knowledge of these factors might be useful for understanding experimentation with tobacco before tobacco dependence, the processes that lead to the choice to quit and quitting outcomes.

Summary

- Tobacco addiction is maintained by nicotine. Cigarettes that do not deliver nicotine do not sustain addiction.
- Nicotine addiction is supported both by positive reinforcement (e.g. mood, performance) and avoidance of withdrawal symptoms.
- There is considerable individual variation in the response to nicotine. Women differ from men in metabolizing nicotine and are more responsive to conditioned cues.
- Nicotine dependence initiated in adolescence has implications for dependence in adulthood.
- Nicotine delivered by tobacco smoke is distinct from other forms of nicotine.
- Key determinants of the addictiveness of tobacco-delivered nicotine include the form of nicotine, ease of inhalation, related sensory stimulus and the addictive or reinforcing effects of other smoke constituents.
- Denicotinized tobacco more effectively reduces craving and produces pleasure in smokers than nicotine without tobacco.
- Evidence supports the validity of the dual-reinforcement model of addiction, in which the conditioned stimulus (tobacco smoke) strengthens dependence beyond that produced by unconditioned nicotine.
- Drug expectancy alters responses to nicotine and non-nicotine cigarettes. Expectancy may reflect cues within the delivery mechanism (sensory stimuli) as well as information received from advertising, packaging or other forms of communication.
- Development of dependence is associated with social context and environmental factors that determine product access and appeal.

Establishing a threshold for addiction

The concept of a threshold for nicotine addiction implies that a minimum intake of nicotine is required for acquisition and maintenance of addiction. In their original proposal, Benowitz and Henningfield (1) estimated that the threshold for addiction to nicotine was 5 mg/day, associated with a plasma cotinine level of 50–70 ng/mL per day. The estimate was based on observation of experienced smokers rather than on empirical studies in which exposure to nicotine was manipulated. It was intended for use as a starting-point for critical research and discussion.

Since that initial proposal, the widespread availability of denicotinized cigarettes has led to a significant body of research on the effects of reduced exposure to nicotine on smoking behaviour and subjective measures (45, 132). Self-administration of nicotine and the related behaviour have also been studied in experimental animals (8, 113, 133, 134). Together, these studies provide insight into the potential reinforcing effects of cigarettes with extremely low levels of nicotine.

Nicotine self-administration

Henningfield and colleagues (27, 135) studied intravenous self-administration of nicotine in smokers. The overall response rates for nicotine did not reliably exceed those for saline, although responses for nicotine tended to be more regularly spaced. Harvey et al. (136) gave abstinent male cigarette smokers access to both nicotine (0.75, 1.5 and 3 mg/injection) and saline by intravenous injection during a 3-h session. Smokers preferred the nicotine injections at all three doses. These doses are higher than the usual nicotine intake of smokers, which is 1–4 mg/h from an average of one or two cigarettes per hour (21).

Self-administration of nicotine at doses within the range of the average intake by smokers was studied in male and female smokers who were asked to choose an intravenous dose of 0.1, 0.4 or 0.7 mg nicotine or saline (137). The 0.1-mg dose represents approximately half the amount of nicotine inhaled in a typical cigarette puff. The 0.4- and 0.7-mg doses were preferred to the placebo, indicating that the reinforcing threshold dose of nicotine for smokers is between 0.1 and 0.4 mg. The findings are consistent with research on nicotine discrimination, which indicates that the threshold for nicotine discrimination is well below the typical level of nicotine delivered by most cigarette brands. No difference was found between smokers and non-smokers, with median thresholds of 3 and 2 µg/kg, respectively (about 0.23 and 0.15 mg nicotine) (80). As noted by Hatsukami et al. (45), however, more than 100-fold individual variation in nicotine discrimination has been reported.

More studies of nicotine self-administration have been conducted in animal models than in humans, with similar conclusions for the nicotine threshold. Smith et al. (8) reported significantly decreased nicotine self-administration by rats when the nicotine dose was reduced to $\leq 3.75 \mu\text{g}/\text{kg}$ per infusion, while doses $\geq 7.5 \mu\text{g}/\text{kg}$ per infusion resulted in similar or higher rates of self-administration relative to maintenance at $60 \mu\text{g}/\text{kg}$. In this study, nicotine was administered with a cocktail of other tobacco constituents in order to mirror the effects of tobacco use.

Donny et al. (133) examined the dose–response curves from a number of studies of both acquisition and maintenance of nicotine self-administration. They placed the peak of the acquisition curve at $20\text{--}30 \mu\text{g}/\text{kg}$. Similar results were obtained in rats, dogs, monkeys and humans (136, 138). At lower unit doses ($3.75\text{--}10 \mu\text{g}/\text{kg}$), the mean response rate increased with dose but with considerable individual variation; few participants acquired nicotine self-administration when compared with saline controls (139, 140). During maintenance of nicotine self-administration, the peak of the dose–response curve was typically between 10 and $30 \mu\text{g}/\text{kg}$ (141–146). Again, nicotine self-administration decreased and variation increased when unit doses $< 10 \mu\text{g}/\text{kg}$ were substituted. The threshold reinforcing dose at the low end of the dose range has rarely been determined; however, doses as low as $3 \mu\text{g}/\text{kg}$ maintain nicotine self-administration rates above those for saline in studies of both limited and extended access. The findings suggest that a reinforcement threshold for maintenance of nicotine self-administration in adult animals might lie between 3 and $7.5 \mu\text{g}/\text{kg}$ nicotine (0.23 and 0.56 mg), consistent with (although marginally higher than) those indicated by studies in humans. In most studies, however, the number and range of doses were small, limiting their accuracy. Moreover, in some studies, manipulated doses were given to participants. This would not reflect the change in dose for individual smokers that would follow implementation of a nicotine reduction policy (132)

Most research on nicotine self-administration involved rapid infusions of high unit doses of nicotine ($15\text{--}30 \mu\text{g}/\text{kg}$ per infusion). Sorge and Clarke (147) compared self-administration of nicotine in rats at a duration of infusion of $3, 30, 60$ or 120 s and found that slow infusion was preferred to fast infusion; self-administration was seen at doses as low as $3 \mu\text{g}/\text{kg}$. Their findings indicate that slower self-administration differs pharmacologically from the usual procedure and suggest that the time course of dose delivery plays a role in determining a nicotine reinforcement threshold.

Acquisition of nicotine dependence

The dose of nicotine necessary for maintaining smoking may differ from that for acquisition of dependence (7). Despite the lack of data directly relevant to the question, Donny et al. (133) concluded from a comparison of studies that the threshold for maintenance is probably lower than that for acquisition. This conclusion would be consistent with the observation that pre-exposure to nicotine can increase acquisition of nicotine self-administration (42, 143, 148).

Acquisition of dependence among adolescents may be different from acquisition among adults. As noted previously, adolescent rats and mice appear to be more vulnerable than adults to the reinforcing effects of nicotine (41, 44, 149), with faster acquisition of nicotine self-administration and higher baseline rates than adults (40, 43, 150, 151). Evidence that adult male rats are more likely than rats in early adolescence to acquire nicotine self-administration at a low dose of nicotine conflicts, however, with this conclusion (140, 152, 153). Cross-sectional and longitudinal studies indicate that young people who smoke less than daily report the onset of dependence symptoms (31, 154–158). Adolescent smokers self-administer physiologically active doses of nicotine despite taking smaller puffs than adults (159–162).

Expectancy plays a significant role in the smoking behaviour and motivation to smoke of adolescents. Specifically, a stronger expectancy of the ability of cigarettes to reduce negative affect predicts escalation of smoking, although, as expectancy becomes stronger with increased smoking experience, its effect stabilizes (163, 164). In a study among adolescent smokers of high-yield and denicotinized cigarettes, smoking resulted in reduced negative affect regardless of the nicotine content of the cigarette smoked. This effect was moderated by affect-related expectancy; thus, participants who smoked a high-yield cigarette and held a strong expectancy that smoking would alleviate negative affect experienced the greatest reduction in negative affect. No change in affect was found among non-smoking adolescents (165). The onset of smoking and subsequent exposure to nicotine during adolescence, even at levels below that for daily reinforcement, may lower the threshold for nicotine dependence in adulthood, despite highly attenuated rewarding or reinforcing effects (35, 37, 151).

Reinforcing effects of low-nicotine cigarettes

Evidence from clinical studies indicates that denicotinized tobacco can provide significant subjective satisfaction and an immediate reduction in craving (84, 115, 166–172), although ratings may rely on the level of dependence of the smokers (173). Suppression of craving appears to be a particularly robust effect that is less sensitive to extinction procedures (115). Nicotine-containing and denicotinized smoke suppress craving and ad-libitum smoking equally,

but intravenous nicotine has only a small effect in suppressing ad-libitum smoking (174, 175).

Cigarettes with very low levels of nicotine may be sufficient to maintain smoking behaviour. Brain imaging showed that smoking a single very low-nicotine cigarette resulted in significant (23%) occupancy of $\alpha 4\beta 2$ nicotinic receptors, which are considered the primary receptor subtype that mediates the reinforcing and other behavioural effects of nicotine (90). The effects of low levels of nicotine may be further reinforced by non-nicotine elements of tobacco. Use of denicotinized tobacco was associated with a greater feeling of relaxation than use of a nicotine inhaler, suggesting that non-nicotine factors are partially or even largely responsible for the calming effect of tobacco smoking (172).

Dependence on cigarettes could be generated in other ways, even with an extremely low intake of nicotine, for example through desensitization of receptors, which can occur with chronic exposure to even very low levels of nicotine (176). Desensitization of receptors mediates the acute reinforcing effect of nicotine (177, 178).

Environment is also likely to play a role in the behaviour of smokers. For example, Donny and Jones (179) found that denicotinized cigarettes maintained their reinforcing properties throughout a 9-day outpatient assessment, whereas in a similar study of inpatients (115) both motivation to smoke and the number of denicotinized cigarettes smoked decreased somewhat over time. It was hypothesized that extinction may proceed more slowly in a natural setting, possibly because of the presence of numerous stimuli associated with smoking (180).

Addiction threshold versus reinforcement threshold

There is no universally accepted definition of nicotine or tobacco addiction. WHO (181) defined drug dependence in terms of compulsion, that is, a behavioural pattern in which use of a drug is given priority over other behaviour to an extent that is considered detrimental to the individual or to others. The US Surgeon General's report on nicotine addiction (99)EC also required that the drug produce psychoactive effects and that drug-taking behaviour be clearly reinforced by the effects of the drug. Although most cigarette smokers meet these criteria, not all do so (23).

The diagnostic criteria widely used to identify nicotine addiction include those of the fourth edition of the *Diagnostic and statistical manual of mental disorders* (DSM-IV), published by the American Psychiatric Association, for assessing general drug dependence, and the Fagerström test of nicotine dependence, used to assess tolerance and the severity of dependence. Concern has been

raised about the validity of these instruments for measuring addiction. They correlate poorly with each other, and neither consistently predicts other indices of smoking behaviour or the outcome of treatment of smokers (182–185). They may also not be sensitive for assessing addiction in smokers who are in the early stages of nicotine use, as they were developed and validated for evaluating adult end-stage smokers (186, 187).

DiFranza et al. (25) argued that the diagnostic criteria for addiction should, at the very least, differentiate between individuals who can and cannot abstain when they decide to do so. They proposed that self-assessment of addiction should be the gold standard, as it correlates strongly with self-rated difficulty in quitting ($r = 0.89$) and correlates better than the DSM-IV with the number of cigarettes smoked per day and the time to the first morning cigarette (183). Self-assessment may also better identify emerging dependence in children than other measures. In one study (188), self-assessment of addiction by adolescents predicted neurophysiological responses to smoking more successfully than the Fagerström test.

Sofuoglu and LeSage (189) found that the lack of a consensus about valid methods for assessing nicotine addiction is a significant challenge to nicotine reduction strategies. They noted that the concept of a reinforcement threshold is not synonymous with an addiction threshold, although the terms are sometimes used interchangeably, and might be a preferable basis for establishing a threshold level of nicotine. The reinforcement threshold would be defined as the lowest dose of nicotine that increases or maintains nicotine self-administration (i.e. tobacco use). A nicotine reinforcement threshold would have a number of practical advantages. First, it is more clearly defined and would be easier to measure than an addiction threshold, as a drug is considered to be reinforcing if it is self-administered to a greater extent than a vehicle or placebo (190). Secondly, because dependence does not occur if a drug is not reinforcing, a nicotine reinforcement threshold is likely to be lower than a nicotine addiction threshold and may be a more sensitive index for predicting tobacco use below the threshold for addiction (190, 191). Thirdly, a reinforcement threshold could be measured in short-term studies of self-administration in either humans or experimental animals and could easily be adapted to assessment of individual differences (in e.g. age, gender, genetic factors) and of environmental factors (e.g. stress, peer influence) (192).

Threshold for conditioned stimulus

Given the importance of conditioned stimuli in reinforcing smoking behaviour and the primary role of nicotine in enhancing salience, consideration should be given to whether there is a separate nicotine threshold for the acquisition of reinforcing properties in non-nicotine stimuli.

Rats trained on a dose of 0.4 mg/kg nicotine readily acquire conditioned response to an unconditioned reward (193–195). Groups assigned to a training dose of 0.1, 0.2 or 0.4 mg/kg nicotine showed similar acquisition of conditioned response, but the groups given the two higher doses showed greater resistance to extinction (196). The similarity of the acquisition rate among groups might suggest that 0.1 mg/kg nicotine is as salient as the higher doses. A non-salience explanation involves the rich schedule of sucrose delivery in nicotine sessions; that is, less nicotine was necessary to prompt conditioned responding because of the large number of nicotine–sucrose pairings (193, 195).

Palmatier et al. (197) compared the effects of a lower (0.03 mg/kg) and a higher nicotine dose (0.09 mg/kg), reasoning that the new conditioned properties of an associated stimulus should be based in part on the strength or intensity of the primary reinforcer. They concluded that the conditional reinforcing properties acquired by the stimulus are a direct function of increased dose.

These findings imply that stimulus control of tobacco-seeking behaviour will be most potent in people exposed to high levels of nicotine and is likely to be greatly reduced with exposure to very low-nicotine products. The strength of conditional stimuli is also driven, however, by the frequency with which the stimulus is paired with nicotine, how closely it is correlated with nicotine and how closely related it is in time and space. Thus, as suggested by Murray and Bevins (196), if there are enough pairings, even a nicotine dose that would otherwise have been a weaker conditional stimulus could become a strong conditioned exciter.

Summary

- Threshold reinforcement studies in experimental animals and in humans show strong agreement. These studies allow a preliminary estimate of the reinforcing threshold for nicotine at 0.1–0.5 mg.
- The threshold for reinforcement is lower when a self-administration mechanism that more accurately models cigarette nicotine delivery is used.
- The threshold for discrimination of nicotine in humans is approximately 0.2 mg, although there is wide individual variation.
- In adults, the threshold for maintenance appears to be lower than that for acquisition of reinforcing behaviour.
- Acquisition of nicotine use by adolescents may differ from that by adults. Adolescent smokers have low daily rates of cigarette use but appear to self-administer physiologically active doses of nicotine. Expectation of reduced negative affect is a primary motivation for smoking among adolescents.

- Cigarettes with nicotine yields of 0.05–0.1 mg can provide significant subjective satisfaction and an immediate reduction in craving.
- The low levels of nicotine present in denicotinized cigarettes may be sufficient to maintain smoking behaviour. Alternatively, responses to denicotinized cigarettes may reflect conditioned reinforcing effects or imply that some non-nicotine constituents have primary effects.
- The goal of reducing nicotine levels below the threshold for addiction requires a reliable measure of addiction. No readily accepted measure of addiction is applicable to establishing a nicotine threshold. Common measures of dependence do not apply to all smokers and may fail to capture adolescent smoking.
- The alternative definitions proposed are self-assessment of addiction (25) and a reinforcement threshold (189).
- A high nicotine dose has a stronger conditioned reinforcing effect than a low dose; however, even a low nicotine dose may be sufficient for conditioned reinforcement, particularly in the context of many highly correlated pairings (as in the case of long-term smoking).

Feasibility of reducing nicotine

Most studies of the behavioural effects of nicotine reduction have been conducted with commercially available low-nicotine products, including so-called denicotinized cigarettes such as Quest. These studies provide valuable insight into the behavioural responses of smokers, but they do not necessarily reflect the commercial products that are likely to become available with mandated nicotine reduction. Internal tobacco industry documents, although potentially less reliable than published clinical studies, may provide insight into the commercial manipulation of cigarette-delivered nicotine and the range of product approaches that are likely to be used by tobacco product manufacturers (26, 198).

Cigarette nicotine delivery

Tobacco manufacturers have used brain imaging to determine the effective ranges of nicotine delivery from cigarettes under controlled smoking conditions (198). A comparison of cigarettes delivering no nicotine, low nicotine (0.14 mg) or high nicotine (1.34 mg) showed a statistically significant decrease in the amplitude of evoked potentials only with the high-nicotine cigarette ($p < 0.05$) (199). In a similar comparison of six cigarettes delivering 0.12–1.1 mg nicotine, the electrophysiological effect of smoking the 0.12-mg delivery cigarette was indistinguishable from that of a nicotine-free cigarette, while cigarettes delivering ≥ 0.21 mg had measurable effects (200).

A theoretical best-fit curve relating the latency of the measured brain response to cigarette-delivered nicotine showed that the decrease in latency as a function of nicotine was greatest up to 0.4 mg delivered nicotine per cigarette, with no further shift beyond approximately 1.4 mg per cigarette. This implies that reductions in smoke nicotine to ≤ 0.4 mg are likely to have the greatest overall effect on smoking behaviour (201). In a comparison of latency effects during controlled and ad-libitum smoking of commercial cigarettes delivering 0.11–1.04 mg nicotine per cigarette, smokers showed central nervous system effects comparable to that elicited by full-flavour cigarettes, due to compensation, even with the lowest nicotine delivery (201). In a study to determine whether the effects of a cigarette with high nicotine delivery (0.9 mg) could be replicated by smoking three cigarettes with lower delivery (0.3 mg), latency effects were successfully mimicked, whereas the amplitude effects required a single, relatively large intake of nicotine over a short interval. When the effect of three 0.1-mg nicotine cigarettes was compared with that of a single 0.3-mg cigarette, the latency was no longer similar ($p < 0.05$). The author concluded that the neurophysiological effects of nicotine exhibit “a threshold [...] somewhere between 0.1 and 0.3 mg” (201)—a result consistent with the findings described under “Nicotine self-administration”, above.

Methods for reducing nicotine in tobacco

The concentration of nicotine in tobacco is significantly correlated with the nicotine yield of smoke (202) and can readily be altered and controlled by manufacturers (26, 203–205). Type, grade and the position of leaves on the stalk can significantly affect the nicotine concentration of tobacco. By blending different tobaccos, manufacturers can balance tobacco characteristics and adjust for natural variations in nicotine content in order to meet production standards for specific brands and styles (206). Differences of a factor of 10 are found in tobacco types, and factors of 5 and 6 are common; e.g. oriental tobacco has a 1% nicotine content by weight, while Burley tobaccos have 5% by weight (207). Differences in products achieved by tobacco selection are not limited to nicotine but include sugar and ammonia content, aroma and taste characteristics and relative harshness and irritation (207, 208).

Strains of tobacco with extremely high and low nicotine were developed for research purposes with the assistance of public research agencies in both Canada and the USA (209–212). For example, Brown & Williamson compared three strains of Burley tobacco containing approximately 1/20, 1/2 and 9/10 of the normal levels of nicotine and showed that the level of nicotine in smoke was proportional to that in the tobacco (213). In other cases, bacteria were used to degrade nicotine while leaving other components of the leaf intact (214, 215). Tobacco derived by this process was as acceptable as untreated tobacco (216).

The earliest tobacco processing included steam extraction of Burley tobacco and stems in order to reduce the irritation commonly associated with their high nicotine content. Later, ammonia and similar compounds were incorporated during extraction (217, 218). Treatment of tobacco disassociates the naturally occurring nicotine salts into free nicotine and free acid. In heat or steam treatment, free nicotine is driven from the tobacco (219). Other treatments, such as use of a solvent (e.g. freon) allow easier extraction of free nicotine, after which the denicotinized extract may or may not be added back. Extraction processes can result in significant reductions in smoke nicotine delivery and have significant effects on the subjective or sensory characteristics of smoke (220).

Research conducted by Philip Morris on nicotine reduction, before development of the denicotinized brand Next, included genetic modification, enzymatic processes and nicotine-extracted tobacco (205). While none of these methods completely eliminated nicotine, reductions of 80–98% were achieved. Quest cigarettes, produced by Vector Tobacco in 2003, were made from genetically modified tobacco.

Denicotinized or reduced-nicotine cigarettes

Although in principle it should be possible to make cigarettes with tobacco completely free of nicotine, in most cases the term “denicotinized” indicates tobacco with a concentration of ≤ 1 mg nicotine. When they are smoked on a standard smoking machine, they produce nicotine yields of 0.05–0.1 mg, equivalent to 5–10% of the nicotine yield of standard commercial brands (6).

The main technical challenge of producing denicotinized cigarettes is not reducing the nicotine content but maintaining the sensory characteristics and appeal of the smoke. The earliest nicotine-extracted tobaccos, derived by techniques such as solvent or steam extraction, were perceived as “stinging” and “numbing” and had extremely low acceptability, regardless of tobacco type and despite use of flavourings (221). The differences were not due simply to lack of nicotine, as adding extracted nicotine back to test cigarettes did not restore the taste of unextracted cigarettes. Other tobacco materials were removed incidentally during extraction, including waxes, heavy hydrocarbons and essential oils, which, when added back after extraction, improved the subjective acceptability. Thus, elements other than nicotine determine product acceptance (221, 222).

For the brand Next, Philip Morris used the supercritical extraction technique that is used to decaffeinate coffee to remove nicotine from tobacco (205). Despite attempts to improve selectivity and limit the underlying effects of extraction, the process altered the taste characteristics of the tobacco. Many

post-extraction flavouring and casing systems were tested (223); the most successful were menthol-based prototypes, which covered much of the unusual taste while providing some of the impact lost by removal of nicotine (86, 224).

An extended test of the Next prototype conducted by an internal expert panel showed that, although the extracted cigarettes were appealing initially, continued smoking of a pack of the cigarettes led to increasingly poor acceptability ratings. When nicotine was added back to the extracted cigarette, the level of acceptability did not decrease over time (225). In a study conducted with highly motivated smokers, “liking” ratings for the extracted cigarettes improved over time, indicating that smokers may adjust their expectations under some conditions (222).

Free-base nicotine in low-delivery cigarettes

Pankow (75) and others (76, 226) identified the fraction of free-base nicotine in tobacco smoke as critical to the rate of transfer of nicotine from both tobacco to smoke and smoke to nicotine receptors in the back of the throat and lungs. Standard measures of smoke nicotine delivery do not differentiate between forms of nicotine (227); however, internal industry documents suggest that comparisons of free-base nicotine delivery may provide a more accurate measure of subjective response to products, particularly in low-yield brands (26, 226).

Products that appear to differ significantly in total smoke nicotine can resemble each other in terms of free nicotine delivery. Brown & Williamson compared the smoke yields of Marlboro (1.15 mg nicotine) and the high-impact, low-yield product Merit (0.64 mg) and found essentially the same free nicotine (about 0.3 mg) in each brand. The authors concluded that a person would have difficulty in differentiating the two brands physiologically (228). Similarly, although smoke from a Marlboro had less nicotine than that from a Winston, it had higher levels of weaker bases, such as pyrazines. These bases “accounted for the pH being slightly higher” of Marlboro, indicating equivalent levels of volatile or “free” nicotine, despite the fact that the level of nicotine was not as high (229).

Limited published measures of free-base nicotine in cigarette smoke suggest that differences between commercial brands are not identified in standard smoking protocols (230, 231). The concentrations of free-base nicotine are similar within but differ between nicotine delivery categories of full-flavoured, light and ultralight cigarette brands. The degree of filter ventilation increases the proportion of free-base nicotine in mainstream smoke, suggesting that, even without compensatory behaviour, a ventilated cigarette delivers a greater proportion of total nicotine in free-base form (231).

Products that lead to compensatory smoking

Smokers adjust their smoking behaviour when they switch from regular to light (or low-yield) cigarettes in order to maintain their desired nicotine intake (20, 166, 232). Unlike conventional low-yield cigarettes, reduced-nicotine cigarettes do not require ventilation for reduced smoke yields and do not appear to lead to compensation as readily (13, 14, 83). Rose and Behm (82) compared smoking a cigarette with a smoke yield of 0.2 mg nicotine and 14 mg tar with smoking a commercial, highly ventilated low-yield cigarette (0.2 mg nicotine and 1 mg tar) in a single-session ad-libitum crossover study and found substantial compensation for the commercial low-nicotine cigarette but no appreciable compensation for the low-nicotine cigarette with 14 mg of tar.

Benowitz et al. (233) compared smoking behaviour with the smoker's usual brand of cigarette with that of a cigarette with an adjusted nicotine content of 1–12 mg. Strong compensatory behaviour was seen with cigarettes with moderate levels of nicotine but minimal compensation and a significant reduction in exposure to nicotine for cigarettes with 1, 2 or 4 mg nicotine (0.1, 0.2, 0.3 mg nicotine yields). The lowest-nicotine cigarette resulted in an average nicotine intake of 0.26 mg, while the usual brand delivered 1.47 mg. A longer study of cigarettes with the same range of nicotine levels (1–12 mg), which was decreased at monthly intervals over 6 months, gave similar results, with a high level of compensation for the 12-mg cigarette but little compensation for the cigarette with lowest nicotine content (15).

Hatsukami et al. (14) assigned smokers to cigarettes with either 0.3 or 0.05 mg nicotine yield or to 4-mg nicotine lozenges in a 6-week switching study. For participants who smoked the 0.3-mg cigarettes, the number of cigarettes smoked per day increased significantly in each of the first 5 weeks of treatment over that of the usual brand, while for participants assigned the 0.05-mg cigarettes, the number of cigarettes smoked per day (relative to baseline) decreased significantly.

These studies suggest that, for cigarettes with a reduced nicotine content, there may be a threshold below which compensation is less likely. This threshold appears to be 0.05–0.1 mg smoke nicotine yield. At less extreme levels of reduced nicotine (0.2–0.3 mg), compensatory behaviour is significantly increased.

A similar threshold may exist for commercial, ventilated low-yield cigarettes. In a 10-week study of commercially available cigarettes, Benowitz et al. (234) found that forced switching from regular cigarettes to popular low-yield cigarettes with machine-determined yields of ≥ 0.6 mg nicotine resulted in complete or nearly complete compensation, with no reduction in exposure to nicotine or tobacco smoke toxins. When participants switched to ultralow-yield

cigarettes delivering 0.1–0.2 mg nicotine, exposure to nicotine and tobacco smoke toxins was substantially although not entirely decreased (by about 40%, with a 90% reduction in nominal yields).

Product formulation and approaches to nicotine reduction

Differences in formulation play a key role in the likelihood that a product will be abused and in determining the threshold for reinforcement. For example, the risk for addiction to oral smokeless tobacco products appears to be somewhat lower than that to cigarettes (235, 236), and the risk for becoming addicted to nicotine replacement medication appears to be small (99, 237), even though the absolute nicotine delivery may be similar. Currently, most manufactured cigarettes contain 10–15 mg of nicotine per cigarette, of which approximately 10% is delivered in smoke. This leads to a typical systemic intake of 1–2 mg nicotine per cigarette (6). Setting a threshold for nicotine at 0.1–0.2 mg per cigarette would result in an overall reduction in nicotine intake of about 90%.

Various approaches can be considered to achieve such a reduction. The nicotine concentration in tobacco could be reduced such that the total content per cigarette remained at or below the intake threshold. This would ensure that the nicotine consumption per cigarette remained below the threshold regardless of behavioural changes by the smoker (i.e. increased frequency or volume of puffs) or manipulation of the form of nicotine delivery, although it would not prevent the smoker from increasing the number of cigarettes smoked to obtain more nicotine. For construction of such a cigarette, the nicotine concentration in tobacco would have to be reduced approximately 10 times more than that in the commercial denicotinized brands Next and Quest. The reduction would probably result in significant changes in the sensory or taste characteristics of the tobacco. No studies have been conducted on the probable behavioural responses to cigarettes with this range of nicotine.

The reduction in the nicotine concentration of tobacco could alternatively be such that the machine-measured smoke yield is likely to be at or below the nicotine threshold. This is the approach of the commercial products Next and Quest, which have a smoke nicotine yield of < 0.1 mg and a total nicotine content of tobacco of < 1 mg. The existence of saleable brands containing this level of nicotine provides strong evidence that the approach is technically feasible. Most research on behavioural responses to nicotine reduction has been conducted with cigarettes containing such levels of nicotine.

A third alternative to meeting a threshold for smoke nicotine intake would be to alter product parameters other than nicotine concentration of the tobacco or in combination with reduced-nicotine tobacco. This approach could include

extreme filter ventilation, high levels of expanded tobacco and lower tobacco content. The technical feasibility of this approach has also been demonstrated commercially, in cigarettes at the extreme end of the ultralight category, i.e. those yielding approximately 0.1 mg nicotine and 1 mg tar under machine smoking conditions. Cigarettes manufactured by this approach would probably maintain nicotine : tar ratios that are similar to or greater than those in current commercial cigarettes, while cigarettes with a reduced nicotine concentration would produce smoke with extremely low nicotine : tar ratios. They might lead to more frequent compensatory behaviour, such as covering vent holes and altering puffing behaviour.

Manufacturers could manipulate the physical or chemical parameters of cigarette construction to alter the characteristics of smoke and offset reductions in nicotine delivery. For example, new filters could be added to alter the form of nicotine (by addition of an acid or base) or to change the size distribution of the aerosol particles that determine deposition and absorption of nicotine and other constituents (26, 127, 238). Changes in tobacco processing, use of additives and physical construction parameters, including length, width, moisture and packing density, could alter the combustion or pyrolysis conditions of the cigarette and change the composition and sensory characteristics of smoke; or new compounds could be introduced with unique behavioural or sensory effects or that interact with or alter nicotine (26, 78, 128). Thus, regulators must be attentive to other product factors in addition to nicotine delivery.

Summary

- Cigarettes may be pharmacologically active above a certain threshold of smoke nicotine yield, whereas below this threshold (somewhere between 0.1 and 0.3 mg) they are no longer as effective.
- A single intake of nicotine from a single cigarette over a short time is more effective than a series of smaller intakes from many cigarettes, particularly when they have a lower level of nicotine.
- Reduction of the total nicotine concentration of tobacco is a common practice in the tobacco industry. A wide range of techniques has been used, including selection and processing of tobacco, genetic selection, microbial or enzymatic treatment and selective extraction of nicotine.
- Both selective extraction and genetic modification have been shown to produce tobaccos in which the nicotine content is reduced by 80–95%.
- Reduced-nicotine tobacco has different sensory characteristics from unmodified tobacco, due in part to the absence of nicotine but also to the loss of incidental compounds such as waxes, hydrocarbons and essential oils.

- Total nicotine intake is only one measure of the overall sensory and pharmacological effects of nicotine and does not differentiate between forms of nicotine. Free-base nicotine is primarily responsible for the sensory impact of nicotine, and the level of free-base nicotine might be a more accurate measure of subjective or physiological effects, particularly from low- or reduced-nicotine products.
- For cigarettes with a reduced nicotine content, there may be a threshold below which compensation is less likely. This threshold appears to be in the range of 0.05–0.1 mg nicotine yield. At a less extreme level of reduced nicotine (0.2–0.3 mg), compensatory behaviour is significantly increased.
- Similar findings are reported from studies of switching to denicotinized cigarettes (0.05 mg nicotine) or conventional cigarettes with extremely low nicotine levels (0.1–0.2 mg), despite differences in construction and the greater available nicotine in the rod.
- Reduction of the nicotine content in cigarettes below the 0.1 mg threshold would require a reduction 10-fold greater than that of current denicotinized products. The feasibility of and behavioural responses to such a product are unknown.
- Most research on behavioural responses has been conducted with cigarettes made with reduced-nicotine tobacco that have machine-measured smoke yields of nicotine near the 0.1 mg threshold.
- The physical and chemical parameters of cigarettes can be manipulated, including the introduction of new compounds, to alter basic characteristics such as the size distribution of particles, combustion and pyrolysis. Attention must be paid to product factors other than nicotine delivery.

Potential behavioural and population outcomes

Smoking denicotinized cigarettes can reduce smoking of conventional cigarettes by providing a temporary behavioural substitute and by removing the primary reinforcing effects of nicotine, resulting in less craving over time (239). The evidence presented above indicates that, while smokers prefer nicotine-containing cigarettes, reduced-nicotine cigarettes can provide subjective satisfaction and reduce immediate craving. Some individuals may continue to smoke after mandated nicotine reduction, either because of the strong substitution effects reported above or because the nicotine content of cigarettes remains greater than their individual threshold for reinforcement (45, 240).

In behavioural models, evidence on the effects of reduced-nicotine cigarettes in individuals is used to predict population outcomes. There are, however, few studies on the acquisition of reduced-nicotine cigarette use in non-smoking populations and on the long-term effects of reduced-nicotine cigarette use.

Potential effects on cigarette consumption

Research in behavioural economics provides information on smokers' consumption. For example, DeGrandpre et al. (241) conducted a "demand curve" meta-analysis of 17 studies of the effects of nicotine yield on smoking behaviour. They found a strong relation between consumption and nicotine yield, suggesting that decreasing smokers' usual nicotine yield increased their smoking behaviour.

Studies of the use of nicotine-containing and denicotinized cigarettes indicate a similar elasticity, as an increase in unit price resulted in a similar reduction in self-administration. When the two cigarette types were available at the same range of unit prices, however, the nicotine-containing cigarettes were reliably preferred. The study showed that the act of smoking has reinforcing value in regular smokers, regardless of the nicotine content of cigarettes, and that denicotinized cigarettes serve as an effective behavioural economic substitute for nicotine-containing cigarettes (242, 243).

Increasing the unit price of nicotine-containing cigarettes while holding the price of denicotinized cigarettes or nicotine chewing-gum constant increases consumption of the latter (244). When both alternatives are available, however, consumption of nicotine chewing-gum diminishes but that of denicotinized cigarettes does not (245). Increasing the price of both denicotinized and nicotine-containing cigarettes results in increased chewing-gum consumption. These findings suggest that the availability of nicotine substitutes such as medications, oral tobacco or nicotine-containing electronic cigarettes may directly affect self-administration of cigarettes, regardless of the cigarette nicotine content.

Potential effects on topography and smoking behaviour

Switching to cigarettes with a reduced nicotine content can elicit modest withdrawal symptoms (13, 14, 234, 246, 247), suggesting that withdrawal symptoms might motivate an increase in smoking. There is little evidence, however, that cigarettes yielding 0.05–0.1 mg nicotine lead to compensatory smoking, as indicated under "Products that lead to compensatory smoking", above. Strasser et al. (248) found that participants who smoked reduced-nicotine cigarettes (Quest 3, with 0.05 mg yield) increased their total puff volume. The response

of the participants was, however, evaluated only at first use of the study cigarettes. Studies of use of reduced-nicotine cigarettes over several days or weeks consistently found no increase in compensatory smoking and in fact showed a tendency to decreased smoking over time, as would be expected during behavioural extinction. Measurement of smoking behaviour over 9 days showed initial differences in puff volume, which dissipated as the study progressed, suggesting that puffing behaviour may be disrupted only temporarily by a switch to reduced-nicotine cigarettes (179). In an 11-day assessment, participants smoking reduced-nicotine cigarettes showed less ad-libitum smoking than those smoking nicotine-containing cigarettes (115). Hatsukami et al. (14) found a similar reduction over a 6-week treatment period. In a 26-week study of stepped reduction in nicotine content from 12 mg to 1 mg (15), cigarette consumption remained unchanged between baseline and week 14, when the nicotine content had reached 4 mg; from this point to the end of the study, cigarette consumption decreased significantly by four cigarettes per day, and the nicotine intake, as measured by plasma cotinine, decreased to 30% of the baseline level.

In a study of self-administration in rats, dose reduction did not elicit withdrawal symptoms for the group as a whole; however, it elicited symptoms in some individuals, the severity of which did not determine differences in compensation (249). These results complement a report that a large partial reduction in brain nicotine levels induced by administration of nicotine-specific antibodies was not sufficient to elicit withdrawal in rats that were dependent on a chronic nicotine infusion (250). These findings suggest that withdrawal is not a prominent adverse consequence of reduced nicotine intake for most individuals and that significant compensatory smoking behaviour in the form of greater intensity of smoking or smoking more cigarettes per day is not a likely outcome at very low (0.1 mg) levels of nicotine.

Potential effects on abstinence and quitting

Studies in both laboratory and outpatient research settings demonstrate that use of reduced-nicotine cigarettes over 1–2 weeks weakens the reinforcing effects of smoking (82, 115). In clinical trials conducted over 6 weeks or more (14, 15, 234), smokers consistently reported less dependence after use of reduced-nicotine cigarettes.

Reduced-nicotine cigarettes may serve as a coping mechanism for the initial stages of abstinence by replacing some of the conditioned rituals associated with smoking, such as the hand-to-mouth action, the tactile action of puffing on a cigarette and the sensation of smoke in the mouth and throat (251). Among smokers seeking to quit, continuous abstinence at week 6 was 13.5%

for smokers who switched to a 0.3-mg cigarette and 30.2% for those assigned to a 0.05-mg cigarette. This suggests that a nicotine reduction policy would be more likely to help smokers to achieve abstinence when they are making an active attempt to quit (14).

Reduced-nicotine cigarettes may, however, support quitting not only in smokers seeking treatment but also in those who have not previously expressed an interest in quitting. Benowitz et al. (13) found that 25% of participants had stopped smoking 4 weeks after the end of a progressive 6-week reduction in the nicotine content of their cigarettes. In a similarly designed study, 10% of participants who had not previously expressed an interest in quitting had quit smoking after progressive reduction of the nicotine content of their cigarettes (234). After progressive reduction in nicotine over 6 months, a quit rate of 4% was found at completion (15).

The effects of reduced-nicotine cigarettes on quitting may be increased by nicotine-based treatment. When smokers were switched to reduced-nicotine cigarettes (0.05–0.09 mg nicotine yield) with or without nicotine patches for 6 weeks, the group without patches smoked significantly more cigarettes per day than those assigned patches and had more withdrawal symptoms, although the scores for craving were similar in the two groups. At follow-up at 36 weeks, continued abstinence was achieved by 18% of smokers who had used the reduced-nicotine cigarettes alone and 20% of those who had used the combination of reduced nicotine and patches (252). In another study, smokers assigned a nicotine patch with reduced-nicotine cigarettes smoked fewer cigarettes, inhaled a smaller total volume of cigarette smoke and had greater relief of withdrawal symptoms than those without a patch (179).

Walker et al. (251) conducted a randomized controlled trial of use of denicotinized cigarettes with or without usual Quitline care (nicotine replacement therapy and behavioural support). The quit rates were higher with the combination, with a shorter time to relapse and good acceptability. The trial provides strong evidence that the combination of reduced-nicotine cigarettes with nicotine replacement therapy and behavioural support is an effective smoking cessation strategy.

Potential effects on acquisition of cigarette use

The impact of a reduced-nicotine policy on smoking initiation has not been quantified. Studies cited under “Acquisition of nicotine dependence”, above, suggest that the expectancy that cigarettes can reduce negative affect plays a primary role in acquisition of smoking by adolescents (163, 164) and that the reduction in negative affect with denicotinized cigarettes is comparable to that with a nicotine-containing cigarette among adolescent smokers. No change

in affect was found, however, among non-smoking adolescents who used a reduced-nicotine cigarette (165). This suggests that non-smoking adolescents are unlikely to escalate their smoking behaviour in the absence of acute effects of nicotine. Establishment of a threshold for reducing negative affect in non-smoking adolescents would confirm this hypothesis.

The effect of a reduced-nicotine policy on the acquisition of reduced-nicotine cigarette use by adult non-smokers has not been studied separately. Self-administration of a nicotine nasal spray was similar in dependent and non-dependent smokers and was more frequent in both groups than in ex-smokers or non-smokers. In non-smokers, self-administration is related directly to pleasurable effects but inversely to aversive effects (253). Expectancy of both positive and negative reinforcement changed significantly after initiation of smoking (254). Exposure to reduced nicotine in adolescence is likely to reduce their vulnerability to nicotine dependence in adulthood (see “Individual variation in response to nicotine”, above). More research should be conducted on the effects of reduced-nicotine cigarette use among non-smokers and non-dependent smokers.

Potential unintended behavioural consequences

Experimentation with reduced-nicotine cigarettes by adolescents might increase their risk for addiction to other drugs of abuse (45). In experimental animals, very brief intravenous exposure of adolescent rats to nicotine (two infusions of 0.03 mg/kg daily for 4 days) sensitized them to the reinforcing effects of cocaine (255). This daily dose is comparable to the nicotine intake from four standard cigarettes (4.2 mg) or approximately 40 reduced-nicotine cigarettes.

Reduced-nicotine cigarettes might serve as starter products for higher-nicotine products, in a manner similar to that demonstrated for smokeless tobacco products with low levels of free-base nicotine (254). Dual use of reduced-nicotine cigarettes and tobacco products with higher nicotine contents, such as oral tobacco or small cigars, could also result in greater exposure to toxicants (45).

Potential population differences

As observed under “Individual variation in response to nicotine”, above, factors other than nicotine may determine tobacco dependence in women. Women are less responsive than men to manipulations of nicotine exposure and more responsive than men to manipulation of non-nicotine components of cigarette smoking, such as sensory cues (52, 56, 125). At least some of the difference precedes the onset of dependence caused by chronic exposure to nicotine from

smoking (125). Reduced-nicotine cigarettes relieve craving to a greater extent (172), have more positive subjective effects (satisfaction, relaxation, reduced anxiety) and result in a greater reduction in the intention to smoke in women than in men (257). These observations suggest that women are at greater risk for maintaining long-term use of reduced-nicotine tobacco than men; however, in a study of cessation, tapered reduction of nicotine in combination with nicotine replacement therapy had a greater effect on continuous abstinence at 4 weeks for women than for men (239). Walker et al. (251) observed no difference by gender in the effect of the paired Quitline intervention.

The potential adverse effects of nicotine reduction in people with severe psychiatric disorders remain a concern. Tidey et al. (258) studied the effects of reduced-nicotine cigarettes among smokers with schizophrenia. Denicotinized cigarettes reduced craving for cigarettes, nicotine withdrawal symptoms, smoking withdrawal symptoms and smoking of usual brands and were well tolerated; there was no indication that the reduction in nicotine affected psychiatric symptoms. Nevertheless, denicotinized cigarettes substituted less effectively for nicotine-containing cigarettes in smokers with schizophrenia than in control smokers, suggesting that long-term use of reduced-nicotine cigarettes by patients with schizophrenia would be less likely if nicotine-containing alternatives were available. Further studies of reduced nicotine should be conducted among people with depression or other serious mental health disorders.

Potential health effects

Hatsukami et al. (14) reported significant reductions in the exposure to toxicants of smokers who switched to reduced-nicotine cigarettes, including tobacco-specific nitrosamines, acrolein and benzene, although no measured reduction in exposure to polycyclic aromatic hydrocarbons was found. The reductions in nitrosamines were consistent with the reduced levels measured in the tobacco, while the differences in other toxicants were considered to reflect reductions in smoking. These findings indicate that a reduced-nicotine policy might reduce health risks not only among people who quit or do not acquire tobacco dependence but also among people who continue to use tobacco products despite the lower nicotine (259).

The probable reduction in nicotine intake is another potential health benefit (82, 259). Although components of tobacco other than nicotine are the main causes of tobacco-related disease, nicotine may contribute to the development of cardiovascular disease by causing vasoconstriction, promoting thrombosis and atherosclerosis and impairing sensitivity to insulin (260, 261). Nicotine may also promote arteriogenesis (262), which could increase the blood supply

to tumours and inhibit apoptosis (263), promoting carcinogenesis. Girdhar et al. (264) postulated that nicotine moderates the risk for cardiovascular disease caused by other smoke components by reducing platelet activation. A reduction in cigarette nicotine content would therefore increase the risk for cardiovascular disease; however, use of pure nicotine as a tobacco substitute has not been reported to be harmful, suggesting that the direct health effects of nicotine use are minimal.

No significant difference in adverse health events was identified between people assigned to a reduced-nicotine cigarette and those assigned to nicotine replacement therapy only in the Quitline intervention conducted in New Zealand (251). The weight of the evidence suggests that the health risks associated with switching to reduced-nicotine cigarettes are similar to or lower than those associated with conventional cigarettes, but more studies are needed.

Potential illicit sales of nicotine-containing cigarettes

A number of studies have shown the importance of smuggling to cigarette manufacturers as a means of promoting their products in low- and middle-income countries (265, 266). Most illicit cigarette sales are supply-driven and remain commonplace even when prices and excise taxes remain low (267). The rate of smuggling may be represent as much as 10–15% of all sales (268, 269, 270).

There have been no published studies of the likelihood of illicit sales of higher-nicotine cigarettes in a reduced-nicotine market. Givel (271) described the outcome of a sales ban enacted in 2004 to end tobacco consumption in Bhutan, which allowed only small quantities of tobacco to be imported for personal consumption. Smuggling and black market sales increased in the years following the ban, sufficient to support a smoking rate of 10% among Bhutanese men.

In the event of a nicotine reduction policy, both the appeal of reduced-nicotine cigarettes and the availability and appeal of alternative forms of nicotine are likely to affect the extent of illicit tobacco sales (272). In Canada, contraband cigarettes were rated by young people as less appealing than leading brands, suggesting that the availability of contraband cigarettes might have greater appeal for addicted smokers than for novice or experimenting users (273). The availability of contraband cigarettes has also, however, been associated with a reduced likelihood of cessation and fewer attempts to quit (274–276).

Models of population effects

Tengs et al. (4) simulated the population effects of a reduced-nicotine mandate in the USA over 6 years. Assuming an 80% decrease in smoking prevalence,

a 10% increase in mortality among current smokers due to compensatory behaviour and entry of 10% of smokers into the black market annually, they estimated a cumulative gain of 157 million quality-adjusted life years over 50 years. They then varied the model parameters in several ways and concluded that, as long as smoking cessation increased by 10% or more, relapse and initiation of smoking decreased by 10% or more and compensatory behaviour increased the mortality rates of smokers by no more than 80%, there would still be a net gain in quality-adjusted life years. Significantly, over a range of plausible estimates (0–50% of all smokers), quality-adjusted life years were uniformly gained rather than lost, regardless of the extent of entry into the black market.

In another simulated model, health outcomes were estimated on the assumption that a reduction in nicotine would reduce the probability of initiating smoking for people of every age and gender, that the probability of cessation would increase and that former smokers would be less likely to relapse (277). The authors also simulated the possibility that promotion of reduced-nicotine cigarettes as “safer” would worsen all three outcomes. Outcome estimates were created for the probability of behaviour change in increments of 10% from –80% to +80%. They concluded that a 60% reduction in smoking (initiation, use, relapse) would offset any plausible increase ($\leq 50\%$) in harm resulting from compensatory smoking or other unintended health consequences among people who continued to smoke. A modest 20% reduction in initiation, use and relapse, with a 20% reduction in disease risk among continuing smokers, would result in a cumulative gain of 165 million quality-adjusted life years, while a significant 80% reduction in initiation, use and relapse, with no change in disease risk for people who continued to smoke, would result in an estimated gain of 281 million quality-adjusted life years.

A study was commissioned by Health Canada to model the potential effects in Canada of a nicotine-reduction policy for all tobacco products (278). The study was based on a literature review and on interviews with health experts. The outcomes considered were smoking initiation and cessation, increased black market sales, substitution of other tobacco products for cigarettes and potential compensatory behaviour. It was estimated that the impact of such a policy on initiation and cessation, in the absence of effects on black market sales, substitution and compensation, would reduce the cost of treating tobacco-related illness by 19% after 30 years. Assumption of an increase in the black market share from 15% to 50% would decrease the benefit by 40%. The benefits of a reduced-nicotine standard for mortality were due mainly to the effect on cessation, while the benefits for morbidity were due mainly to the effect on initiation.

Summary

- The act of smoking has a reinforcing effect in addicted smokers, regardless of the nicotine content. Denicotinized cigarettes can serve as an effective behavioural economic substitute for nicotine-containing cigarettes.
- The availability of alternative nicotine substitutes, such as nicotine medication, oral tobacco and nicotine-containing electronic cigarettes, may directly affect self-administration of cigarettes, whether or not the cigarettes themselves contain nicotine.
- Withdrawal symptoms are not a prominent adverse consequence of a reduction in nicotine intake for most individuals, and significant compensatory smoking behaviour in the form of greater intensity of smoking or smoking more cigarettes per day is not a likely outcome at very low (< 0.1 mg) levels of nicotine.
- A nicotine reduction policy may be more likely to help smokers achieve abstinence when they make an active attempt to quit. Use of reduced-nicotine cigarettes improved quit rates in a number of studies.
- Non-smoking adolescents are unlikely to escalate their smoking behaviour in the absence of acute effects of nicotine. Identification of a threshold for reducing negative affect in non-smoking adolescents would confirm this hypothesis.
- The use and effects of reduced-nicotine cigarettes in non-smokers and non-dependent smokers have not been studied adequately. In non-smokers, self-administration of reduced-nicotine cigarettes is related directly to pleasurable effects and inversely to aversive effects.
- Exposure of adolescents to low levels of nicotine could increase their risk for addiction to other drugs of abuse. Low-nicotine products could also serve as starter products for other forms of tobacco or other forms of nicotine delivery.
- Women may be more likely than men to sustain long-term use of reduced-nicotine tobacco. Nicotine reduction had no aversive effects on mental health symptoms in patients with schizophrenia; more studies should be conducted in other populations at risk.
- Reduced nicotine may reduce health risks not only in people who quit or do not acquire tobacco dependence but also in people who continue to use tobacco products despite reduced nicotine. More studies are needed.
- Illicit tobacco sales may undermine the health goals of a nicotine reduction policy. Although no formal estimates have been made, both the appeal of reduced-nicotine cigarettes and the availability and appeal of

alternative forms of nicotine are likely to affect the extent of illicit tobacco sales significantly.

- Various models have been designed to estimate the likely effects of a nicotine reduction policy. All indicate a significant positive effect on health outcomes.

Policy approaches to nicotine reduction

A number of authors have proposed reducing the nicotine content of cigarettes in the context of a harm reduction model in which safer products are made more appealing than more toxic products (272, 279–284). A regulatory framework is essential to support a nicotine reduction policy, both with respect to the resulting commercial marketplace in which smokers and non-smokers develop and sustain use of tobacco or nicotine and the social environment that influences and supports this behaviour.

Comprehensive regulation of nicotine

The effects of a policy to reduce the nicotine content of cigarettes would depend significantly on the availability, toxicity and appeal of alternative nicotine delivery systems, including other forms of (combustible or incombustible) tobacco, medicinal nicotine and commercial non-tobacco nicotine products (45). Therefore, a successful nicotine reduction policy must be part of comprehensive regulation of all tobacco- and nicotine-containing products (3, 5, 7, 280, 281).

A single institution with authority for tobacco and nicotine regulation would allow coordination of approaches for different products (280). This institution would be responsible for deciding how tobacco and nicotine products are regulated, setting performance standards, authorizing health or other claims for products, evaluating products on the market and evaluating their population effects. A comprehensive surveillance system would be essential for responding quickly to any unanticipated change in nicotine use or health outcomes (7, 280).

The main goals of comprehensive regulation of nicotine would be to minimize use of the most toxic nicotine-containing products, to encourage the development of new, improved nicotine delivery systems as alternatives to more toxic products and to continue to monitor and regulate less toxic products for health effects (3, 6, 280). Policy approaches could be considered to incentivize smokers to adopt less hazardous forms of tobacco or nicotine use, including restrictions on access, marketing and use, as well as differential taxation, such

that taxes on cigarettes and combusted tobacco are much higher than those on cleaner nicotine-delivery products (6, 281, 285).

Performance standards

Performance standards are necessary to ensure implementation of a reduced-nicotine policy (284, 285). A number of approaches could be considered for determining standards for nicotine products, such as restricting delivered or inhaled nicotine or restricting individual doses of nicotine defined at the level of a single puff. The most promising approach, however, is to focus on the total nicotine available in an unburnt cigarette, because it is more easily measured and less subject to behavioural manipulation and individual variation (see “Product formulation and approaches to nicotine reduction”, above).

The evidence presented in this annex suggests that a reduction of the nicotine content of cigarettes to < 1 mg would be sufficient to reduce dependence in a proportion of the smoking population, with minimal adverse effects. This evidence comes from studies of cigarettes constructed with very low-nicotine tobacco and design parameters similar to those of standard conventional cigarettes. It is possible and even likely that performance standards exclusively for the nicotine content of tobacco would encourage development of cigarettes that contain little tobacco nicotine but that are otherwise quite different in form and function from conventional cigarettes. Examples might include products that release nicotine in a more readily available (free-base) form, that alter the particle formation or deposition of nicotine, that release the full amount of nicotine in a single dose, that encourage and enable use of many cigarettes to maintain nicotine dose or that contain nicotine analogues and other pharmacologically active compounds to enhance or replace the effects of nicotine.

Performance standards must respond to the changing marketplace (7, 18, 22, 285). Initial standards should require that products resemble conventional cigarettes in various basic physical characteristics, including tobacco weight, length, circumference, filter, paper and ventilation (286). New products and technologies must be carefully evaluated and their commercial introduction permitted only once their reduced risk, addictiveness and appeal have been sufficiently demonstrated (7, 18, 287, 288).

Global standards for addiction and harm should ultimately be set through the WHO FCTC (281). Such global standards could include further product standards, such as restrictions on toxicants (e.g. nitrosamines), on physical design parameters that lead to or support compensatory behaviour (e.g. ventilation) and on flavourings and other factors that increase product appeal (e.g. menthol). The effects of each of these standards would have to be carefully evaluated (18, 281, 284, 285).

Gradual versus sudden reduction

In their original proposal, Benowitz and Henningfield (1) called for a reduction in nicotine levels over 10–15 years, in order to minimize potential withdrawal symptoms, among other practical concerns. A gradual reduction in nicotine could, however, have negative health consequences (45). First, individuals would be exposed for an extended period to doses of nicotine that maintained their smoking behaviour. Secondly, a gradual market-wide shift in nicotine levels might alter smokers' relation to nicotine in unanticipated ways, potentially adjusting the threshold for addiction (8); for example, in early work on nicotine self-administration, addiction in rats that were switched to saline extinguished more slowly if they received an intermediate dose reduction before saline substitution (139).

There is no model of the effects of reducing nicotine over the course of years. Studies of progressive reduction in nicotine over weeks or months, however, showed that nicotine consumption can be decreased gradually without significant compensation. Further, once tapering is completed, the nicotine intake remains below the baseline level, suggesting reduced nicotine dependence (13, 15, 234). A strong association was found between the extent of reduction of daily smoking and nicotine dependence, supporting the idea that a gradual reduction in intake may reduce nicotine dependence (289). After reviewing the literature, Walker et al. (290) concluded that a progressive reduction in the level of nicotine in cigarette tobacco could reduce nicotine dependence in smokers, with minimal compensatory smoking (at a smoke nicotine level < 0.1 mg) and no adverse effects.

Even immediate reductions in nicotine may be successful in decreasing both smoking rates and dependence. Smokers who switched abruptly from their own cigarettes to reduced-nicotine cigarettes for 6 weeks showed reduced exposure, decreased consumption and higher rates of cessation (14). Similarly, in an 11-day switching study, cigarette consumption declined immediately and motivation to smoke decreased (115).

Gradual and immediate reductions in the dose of nicotine resulted in similar self-administration behaviour in rats, with no compensation in either group (8). A meta-analysis of the effect on quit rates of an intermediate reduction in consumption before quitting showed no difference between reducing the number of cigarettes smoked before “quit day” and quitting abruptly with no prior reduction (291). Taken together, the results of these studies suggest that the dose of nicotine from cigarettes could be reduced quickly with no significant adverse effects among smokers.

Alternative forms of nicotine

Some cigarette smokers faced with reduced-nicotine products are likely to switch to products that contain more nicotine. The appeal of alternative tobacco products, such as oral and smokeless tobacco, waterpipes, pipes and cigars, may increase if they can substitute for conventional cigarettes more effectively than reduced-nicotine cigarettes (see “Potential effects on cigarette consumption”, above). Combusted tobacco is significantly more harmful than un-combusted tobacco, which is itself more harmful than clean nicotine products such as patches and chewing-gum (17). In view of this continuum of harm, it might be advisable to mandate nicotine reduction not only in cigarettes but in all combusted tobacco products, thus minimizing the risks associated with switching to the most harmful products (285).

Pharmaceutical products for dispensing nicotine, while much safer than tobacco products, are designed to be unappealing in order to avoid abuse and are not intended for long-term use (287, 288). Although these products may help smokers through withdrawal, they do not produce sufficient positive reward (particularly fast, effective nicotine delivery) to be reasonable alternatives to tobacco products (292).

Electronic cigarettes were designed with the express purpose of replicating the act of smoking, without tobacco (285, 293). These and similar products may be more viable alternatives to cigarettes (294), and evidence is rapidly accumulating on their use and acceptance (293, 295–297). Electronic cigarettes produce a vapour of nicotine and other constituents, usually including glycerine or propylene glycol. Currently, they are used primarily for smoking cessation, although for longer than nicotine replacement therapy (297). Users believe them to be safer than smoking (297).

Electronic cigarettes deliver nicotine more effectively and more rapidly than a nicotine inhaler (298) but somewhat less effectively than a conventional cigarette (293, 298). They significantly reduce craving, due at least in part to the physical sensory characteristics of the cigarette, independently of nicotine delivery (293, 299). At least some electronic cigarettes deliver reliable blood levels of nicotine (mean, 6.77 ng/mL 10 min after 10 puffs; mean maximum, 13.91 ng/mL by the end of the ad-libitum puffing period). They reduce tobacco-related withdrawal symptoms and the urge to smoke, provide direct positive effects and have few adverse effects (295).

Cessation and behavioural treatment

As nicotine is reduced to non-addictive levels, there will probably be a sharp increase in the number of smokers who want to quit (2, 6). Many smokers will visit physicians seeking nicotine replacement or behavioural therapy to

aid cessation or relief from withdrawal symptoms. The availability of effective, affordable treatment offered by health care professionals will be invaluable in ensuring the success of the policy (5, 6, 285). Coverage by insurance programmes is critical, as are individualized services for populations who may have greater adverse effects, such as people with co-morbid psychiatric disorders (2). The widespread availability of pharmacological treatment might not only limit the discomfort associated with reduced nicotine in cigarettes but also substantially reduce cigarette smoking and possibly lead to cessation of all tobacco and nicotine products by some or many current smokers.

Surveillance

The public health community has been slow to recognize the potential limitations of regulatory or harm-reduction approaches, despite early evidence of their ineffectiveness (22, 281). An adequate surveillance system will permit regulators to monitor the effects of tobacco products on the prevalence and initiation of their use and the associated harm and to address unintended outcomes (7). Mandatory reporting regulations for all nicotine and tobacco products, as adopted in Canada and described in Articles 9 and 10 of the WHO FCTC, are a necessary condition of adequate surveillance. Reporting should include physical design components (tobacco weight, nicotine concentration, filter ventilation), tobacco and added constituents, emissions (for combustible products) and measures of the likelihood of abuse (7, 18, 281, 287).

Hatsukami et al. (7) and Stratton et al. (17) described a comprehensive approach for evaluating tobacco products that could be effective for continuous evaluation of reduced-nicotine cigarettes. The approach includes: preclinical tests in experimental animals to assess the likelihood of abuse, acquisition of nicotine self-administration by both adolescent and adult animals and neurophysiological changes that affect function; imaging, laboratory tests and clinical trials in humans to determine the likelihood of abuse, tobacco use patterns, exposure to toxicants and potential health risks in general and vulnerable populations; and assessment of moderating factors, including how the consumer perceives the product and its appeal, its packaging, price and promotion (7).

Although testing for biomarkers in large studies of smokers is a promising method for evaluating disease risk, it may not be feasible in countries with few resources (281). The complexity of tobacco products and the expertise required to assess toxicological results, the likelihood of abuse or other outcome measures, may prove to be additional barriers. McNeill et al. (281) called for a global data repository to facilitate implementation of tobacco product regulations and surveillance worldwide. The repository would ease the burden

of regulators for collecting and analysing data, allow global comparisons and make information and recommendations available to national regulators in a readily understandable form.

Consumer education and beliefs

The effects of a reduced nicotine policy will depend in part on how effectively risks are communicated and on the relative appeal of reduced-nicotine and of other tobacco or nicotine products. Beliefs about the greater safety of reduced-nicotine products could reduce the likelihood of quitting or switching to safer alternatives and could encourage greater experimentation with cigarettes.

Limited evidence suggests that smokers believe that reduced-nicotine cigarettes are less harmful. Shadel et al. (300) evaluated beliefs after exposure to a single print advertisement for a nicotine-free product (Quest). Smokers made a number of false inferences about the product: that it had a lower tar content and was “healthier” and less likely to cause cancer. The denicotinized Philip Morris brand Next was developed in response to interest in no-nicotine products in focus groups that perceived the product as healthier and as potentially facilitating quitting (205).

Despite interest in reduced-exposure products, smokers express doubt about health claims for reduced-exposure products, about whether they would actually switch to such a product and whether the product would taste as good as conventional cigarettes (301). These and other responses are likely to be affected by marketing and communication by manufacturers, public health communication strategies in support of nicotine reduction and the availability and public knowledge of other tobacco or nicotine products. Both smokers and non-smokers must be educated about the health risks of tobacco without nicotine, the relative harm of the available products and opportunities for treatment. Marketing of tobacco and nicotine products must be strongly regulated (7, 281)

Public support for a reduced nicotine policy

Studies in the USA showed strong public support for mandated nicotine reduction. In a survey of 511 non-smokers and 510 smokers, 65% supported a reduction in nicotine in cigarettes to non-addictive levels; these comprised 73% of the non-smokers and 58% of the smokers. More than three in four participants (77%), including 81% of non-smokers and 74% of smokers, said that they would support a reduction in nicotine if it resulted in fewer children becoming addicted to cigarettes. Non-smokers were significantly more likely

than smokers to support a reduction of nicotine levels in cigarettes (302). In another survey, 67% of smokers said they would support a Food and Drug Administration regulation that made cigarettes less addictive if “nicotine was made easily available in non-cigarette form” (303). In a cross-sectional survey of 2649 adults, nearly half supported a reduction in nicotine, comprising 46% of people who had never smoked, 49% of former smokers and 46% of current smokers. Among smokers, support was greatest among those who intended to quit within the next 6 months (304). This survey was the only one of the three that included a neutral response option, and nearly 27% of respondents chose this option, which might explain the closer agreement in the other surveys.

Unintended market consequences

Reduced access to nicotine-containing cigarettes might increase the demand for contraband cigarettes among addicted smokers (6). Minimizing illicit cigarette sales will require effective surveillance strategies (7) and policies to limit the contraband market (268). Most worldwide smuggling is on a large scale and well organized, in which containers of cigarettes are exported by tobacco manufacturers to countries in which they have no legal market (267, 268). Successful attempts to control smuggling have involved making manufacturers liable for the safe transport of cigarettes to legitimate markets.

Chain-of-custody markings would require manufacturers to print legibly, on all packages of tobacco products, a unique serial number to identify the manufacturer and the date and location of manufacture and another identifier to show the chain of custody—wholesaler, exporter, distributor and end market. Other successful anti-smuggling measures include scanners for detecting containers, prominent fiscal marks on packs, stronger punishment, more customs officers and parliamentary hearings to expose tobacco industry export practices. These approaches have resulted in reductions in cigarette smuggling from around 15% to 1–2% in Italy and Spain and significant reductions in the United Kingdom (268). Voluntary approaches have had no measurable effect.

Besides large-scale, organized smuggling, illegal trade also includes bootlegged or counterfeit products. These products could contain extremely low-grade tobaccos with high levels of toxins or present other, unanticipated risks for the subset of smokers who use them. As noted by Benowitz and Henningfield (6), however, it is difficult to imagine growth of a bootlegged cigarette industry operating outside of regulatory control that would be sufficient in scale to rival the present cigarette market.

Unregulated combustible tobacco, such as roll-your-own, could become a substitute for manufactured cigarettes. Other possibilities include significant dual use of reduced-nicotine cigarettes in conjunction with nicotine delivery

devices, pH modification or additives to increase the pharmacological effect of manufactured products and significant unanticipated behavioural changes in use of reduced-nicotine products as a result of long-term use. The availability of more appealing alternative nicotine products would be likely to function as a check on these unintended market outcomes (6, 7).

Summary

- Comprehensive, coordinated regulation of all tobacco- and nicotine-containing products is necessary for successful implementation of a nicotine reduction policy.
- Regulating the total nicotine available in unburnt cigarettes is the most promising approach to nicotine reduction, as it is both more easily measured and less subject to behavioural manipulation and variation.
- Performance standards exclusively for the nicotine content of tobacco would be likely to encourage the development of cigarettes that contain relatively little tobacco nicotine but are quite different in form and function from conventional cigarettes.
- New products and technologies must be carefully evaluated and their commercial introduction permitted only once the reduced risk, addictiveness and appeal of the products have been sufficiently demonstrated.
- A gradual reduction in nicotine over a course of years might have unintended consequences, which have yet to be studied. Neither progressive reduction over months nor immediate reduction had adverse effects or led to compensatory smoking.
- Smokers are likely to switch to alternative products. The most promising of these are electronic cigarettes and other devices that both provide nicotine and have the sensory characteristics of cigarettes, in the absence of tobacco.
- Behavioural counselling and pharmacotherapy to assist smokers with significant withdrawal symptoms and those who wish to quit should be made more widely available to support nicotine reduction.
- An adequate surveillance system is necessary to enable regulators to monitor the impact of reduced-nicotine cigarettes on the prevalence and initiation of use, and to assess the associated harm and unintended outcomes. Countries that cannot support a large-scale surveillance system might require assistance.
- Beliefs about the greater safety of reduced-nicotine products might reduce the likelihood of quitting or switching to safer alternatives. Public health

communication strategies and regulation of marketing are critical.

- Public support for reducing nicotine in cigarettes is high among both smokers and non-smokers in the USA, particularly if other forms of nicotine were made available.
- Successful attempts to control smuggling have involved making manufacturers liable for the safe transport of cigarettes to their legitimate markets.
- Health might be threatened by contraband cigarettes sold on a smaller scale, unregulated forms of tobacco, dual use and modifications made to reduced-nicotine cigarettes to increase or replace the effectiveness of nicotine.

Conclusions

Although scientific research on nicotine reduction and the use of reduced-nicotine cigarettes remains limited, the agreement among the available studies is striking. The findings of studies in experimental animals and humans are broadly comparable: they show similar thresholds for self-administration, effects of both sensory stimuli and broad classes of tobacco compounds (monoamine oxidases, alkaloids) on nicotine reinforcement, the importance of acquisition of dependence in adolescence rather than adulthood and a relative lack of withdrawal or adverse effects with a progressive reduction in nicotine.

On the basis of the weight of the evidence presented above, the most likely consequences of mandated nicotine reduction include:

- a reduction in the acquisition of smoking and progression to addiction among novice smokers;
- a reduction in smoking by some proportion of addicted smokers as a result of behavioural extinction;
- an increase in the rate of quitting and a reduction in the number of quitters who relapse;
- increased use and availability of alternative forms of nicotine, including oral or smokeless tobacco products, nicotine aerosol or vapour products and medicinal nicotine; and
- a reduction in the health risks of most smokers, reflecting reduced consumption, reduced exposure to tobacco smoke and reduced levels of toxicants in tobacco (e.g. tobacco-specific nitrosamines, nicotine).

Possible consequences of mandated nicotine reduction, for which there is currently too little information to make judgements, include:

- an increased proportion of smokers using black market cigarettes with a high nicotine content;
- an increased proportion of some smokers using both nicotine-containing products and reduced-nicotine cigarettes;
- changes in the design or construction of reduced-nicotine products, by manufacturers or by smokers, that alter the delivery characteristics of the product, with unanticipated effects on toxicity, addiction and appeal;
- increased use of nicotine-containing products by non-smokers and people who would not have smoked, because of their greater availability and appeal and the lower perceived risk of disease; and
- greater long-term use of reduced-nicotine cigarettes by women than men.

Other potential but less likely outcomes of a mandated nicotine reduction include:

- increased smoke intake (more puffing or more cigarettes per day) by some proportion of smokers as a compensatory response to lack of nicotine;
- an increased risk for cardiovascular disease among continuing smokers as a result of exposure to tobacco smoke in the absence of nicotine;
- increased use of other drugs of abuse potentiated by exposure to reduced-nicotine cigarettes; and
- a significant black market for high-nicotine cigarettes replacing or supplanting the regulated cigarette market.

Recommendations

A nicotine reduction policy is technically feasible, is supported by smokers and non-smokers and is likely to have a significant positive impact on population health. It should therefore be supported by comprehensive regulation of all nicotine- and tobacco-containing products.

Comprehensive regulation should encourage the use of products that are less toxic, such as medicinal nicotine and nicotine delivery devices, and should reduce the availability and appeal of more toxic products.

There is strong evidence that the threshold level of nicotine in cigarettes required for reinforcement is 0.1–0.2 mg of delivered nicotine. This level is at or below the level of nicotine self-administered by smokers (0.1–0.4 mg) and animal models (0.2–0.5 mg) and at or below the threshold for discrimination of nicotine by both smokers and non-smokers. It is consistent with studies of the threshold for latency effects of cigarette nicotine yield conducted by manufacturers (0.1–0.3 mg).

Mandated nicotine reduction over a relatively short time had few adverse withdrawal or behavioural effects. A more gradual reduction might have unintended behavioural and health consequences. The availability of effective, affordable treatment and of alternative forms of nicotine will help dependent smokers who experience adverse effects.

Population outcomes in a number of areas have not been predicted. Research should be conducted to determine the likelihood of use and the effects of reduced-nicotine cigarettes by non-smoking adolescents, non-smoking adults and non-dependent smokers. Further studies should be done among populations at risk, such as people with moderate or severe depression, and on the relative health effects of reduced-nicotine and nicotine-containing cigarettes. Studies should also be performed on long-term use of reduced-nicotine cigarettes.

References

1. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *N Engl J Med* 1994;331:123–5.
2. Henningfield JE, Benowitz NL, Slade J, Houston TP, Davis RM, Deitchman SD. Reducing the addictiveness of cigarettes. Council on Scientific Affairs, American Medical Association. *Tob Control* 1998;7:281–93.
3. Gray N, Henningfield JE, Benowitz NL, Connolly GN, Dresler G, Fagerstrom K, et al. Toward a comprehensive long term nicotine policy. *Tob Control* 2005;14:161–5.
4. Tengs TO, Ahmad S, Savage JM, Moore R, Gage E. The AMA proposal to mandate nicotine reduction in cigarettes: a simulation of the population health impacts. *Prev Med* 2005;40:170–80.
5. Zeller M, Hatsukami D, Strategic Dialogue on Tobacco Harm Reduction G. The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US. *Tob Control* 2009;18:324–32.
6. Benowitz NL, Henningfield JE. Reducing the nicotine content to make cigarettes less addictive. *Tob Control* 2013;22(Suppl 1):i14–7.
7. Hatsukami DK, Benowitz NL, Donny E, Henningfield J, Zeller M. Nicotine reduction: strategic research plan. *Nicotine Tob Res* 2013;15:1003–13.
8. Smith TT, Levin ME, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Gradual and immediate nicotine reduction result in similar low-dose nicotine self-administration. *Nicotine Tob Res* 2013;15:1918–25.
9. Framework Convention on Tobacco Control. Geneva: World Health Organization; 2013 (<http://www.who.int/fctc/en/>).
10. Report on the Scientific Basis of Tobacco Product Regulation: Fourth Report of

- a WHO Study Group (WHO Technical Report Series, No. 967). Geneva: World Health Organization; 2012 (http://www.who.int/tobacco/publications/prod_regulation/trs_967/en/index.html).
11. Jarvis MJ, Bates C. Eliminating nicotine in cigarettes. *Tob Control* 1999;8:106–7; author reply 107–9.
 12. Shatenstein S. Eliminating nicotine in cigarettes. *Tob Control* 1999;8:106; author reply 107–9.
 13. Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiol Biomarkers Prev* 2007;16:2479–85.
 14. Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA, et al. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction* 2010;105:343–55.
 15. Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, et al. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomarkers Prev* 2012;21:761–9.
 16. Henningfield JE, Benowitz N, Connolly G, Davis R, Gray N, Myers M, et al. Reducing tobacco addiction through tobacco product regulation. *Tob Control* 2004;13:132–5.
 17. Stratton K, Shetty P, Wallace R, Bondurant S. Clearing the smoke: the science base for tobacco harm reduction—executive summary. *Tob Control* 2001;10:189–95.
 18. Hatsukami DK, Biener L, Leischow SJ, Zeller MR. Tobacco and nicotine product testing. *Nicotine Tob Res* 2012;14:7–17.
 19. Hoffmann D, Hoffmann I. The changing cigarette, 1950–1995. *J Toxicol Environ Health* 1997;50:307–64.
 20. Risks associated with smoking cigarettes with low tar machine-measured yields of tar and nicotine (Monograph 13). Bethesda, Maryland: National Cancer Institute; 2001.
 21. Benowitz NL, Jacob P 3rd. Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. *J Pharmacol Exp Ther* 1990;254:1000–5.
 22. Parascandola M. Tobacco harm reduction and the evolution of nicotine dependence. *Am J Public Health* 2011;101:632–41.
 23. Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. *Clin Pharmacol Ther* 2008;83:531–41.
 24. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology* 2010;210:453–69.
 25. DiFranza J, Ursprung WW, Lauzon B, Bancej C, Wellman RJ, Ziedonis D, et al. A systematic review of the Diagnostic and Statistical Manual diagnostic criteria for nicotine dependence. *Addict Behav* 2010;35:373–82.

26. Wayne GF, Carpenter CM. Tobacco industry manipulation of nicotine dosing. *Handb Exp Pharmacol* 2009;192:457–85.
27. Henningfield JE, Goldberg SR. Control of behavior by intravenous nicotine injections in human subjects. *Pharmacol Biochem Behav* 1983;19:1021–6.
28. DiFranza JR, Ursprung WW, Carson A. New insights into the compulsion to use tobacco from an adolescent case-series. *J Adolesc* 2010;33:209–14.
29. Wellman RJ, DiFranza JR, Savageau JA, Dussault GF. Short term patterns of early smoking acquisition. *Tob Control* 2004;13:251–7.
30. DiFranza JR, Savageau JA, Fletcher K, O'Loughlin JE, Pbert L, Ockene JK, et al. Symptoms of tobacco dependence after brief intermittent use: the Development and Assessment of Nicotine Dependence in Youth-2 study. *Arch Pediatr Adolesc Med* 2007;161:704–10.
31. DiFranza JR, Savageau JA, Fletcher K, Pbert L, O'Loughlin J, McNeill AD, et al. Susceptibility to nicotine dependence: the Development and Assessment of Nicotine Dependence in Youth 2 study. *Pediatrics* 2007;120:e974–83.
32. Lynch BS, Bonnie RJ, editors. Growing up tobacco free—preventing nicotine addiction in children and youths. Washington DC: Institute of Medicine, The National Academies; 1994:28–68.
33. Lessov-Schlaggar CN, Pergadia ML, Khroyan TV, Swan GE. Genetics of nicotine dependence and pharmacotherapy. *Biochem Pharmacol* 2008;75:178–95.
34. Taioli E, Wynder EL. Effect of the age at which smoking begins on frequency of smoking in adulthood. *N Engl J Med* 1991;325:968–9.
35. Breslau N, Peterson EL. Smoking cessation in young adults: age at initiation of cigarette smoking and other suspected influences. *Am J Public Health* 1996;86:214–20.
36. Lando HA, Thai DT, Murray DM, Robinson LA, Jeffery RW, Sherwood NE, et al. Age of initiation, smoking patterns, and risk in a population of working adults. *Prev Med* 1999;29:590–8.
37. Cui Y, Wen W, Moriarty CJ, Levine RS. Risk factors and their effects on the dynamic process of smoking relapse among veteran smokers. *Behav Res Ther* 2006;44:967–81.
38. Trauth JA, Seidler FJ, McCook EC, Slotkin TA. Adolescent nicotine exposure causes persistent upregulation of nicotinic cholinergic receptors in rat brain regions. *Brain Res* 1999;851:9–19.
39. Trauth JA, Seidler FJ, Slotkin TA. Persistent and delayed behavioral changes after nicotine treatment in adolescent rats. *Brain Res* 2000;880:167–72.
40. Adriani W, Macri S, Pacifici R, Laviola G. Peculiar vulnerability to nicotine oral self-administration in mice during early adolescence. *Neuropsychopharmacology* 2002;27:212–24.
41. Vastola BJ, Douglas LA, Varlinskaya EI, Spear LP. Nicotine-induced conditioned place preference in adolescent and adult rats. *Physiol Behav* 2002;77:107–14.
42. Adriani W, Spijker S, Deroche-Gamonet V, Laviola G, Le Moal M, Smit AB,

- et al. Evidence for enhanced neurobehavioral vulnerability to nicotine during periadolescence in rats. *J Neurosci* 2003;23:4712–6.
43. Levin ED, Lawrence S, Petro A, Horton K, Rezvani AH, Seidler FJ, et al. Adolescent vs adult-onset nicotine self-administration in male rats: duration of effect and differential nicotinic receptor correlates. *Neurotoxicol Teratol* 2007;29:458–65.
 44. Kota D, Martin BR, Damaj MI. Age-dependent differences in nicotine reward and withdrawal in female mice. *Psychopharmacology* 2008;198:201–10.
 45. Hatsukami DK, Perkins KA, LeSage MG, Ashley DL, Henningfield JE, Benowitz NL, et al. Nicotine reduction revisited: science and future directions. *Tob Control* 2010;19:e1–10.
 46. Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev* 2005;57:79–115.
 47. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin Pharmacol Ther* 2006;79:480–8.
 48. Sofuoglu M, Mooney M. Subjective responses to intravenous nicotine: greater sensitivity in women than in men. *Exp Clin Psychopharmacol* 2009;17:63–9.
 49. Fant RV, Everson D, Dayton G, Pickworth WB, Henningfield JE. Nicotine dependence in women. *J Am Med Womens Assoc* 1996;51:19–20, 22–4, 28.
 50. Gritz ER, Nielsen IR, Brooks LA. Smoking cessation and gender: the influence of physiological, psychological, and behavioral factors. *J Am Med Womens Assoc* 1996;51:35–42.
 51. Eissenberg T, Adams C, Riggins EC 3rd, Likness M. Smokers' sex and the effects of tobacco cigarettes: subject-rated and physiological measures. *Nicotine Tob Res* 1999;1:317–24
 52. Perkins KA, Donny E, Caggiula AR. Sex differences in nicotine effects and self-administration: review of human and animal evidence. *Nicotine Tob Res* 1999;1:301–15.
 53. Wetter DW, Kenford SL, Smith SS, Fiore MC, Jorenby DE, Baker TB. Gender differences in smoking cessation. *J Consult Clin Psychol* 1999;67:555–62.
 54. Perkins KA, Sanders M, D'Amico D, Wilson A. Nicotine discrimination and self-administration in humans as a function of smoking status. *Psychopharmacology* 1997;131:361–70.
 55. Carpenter CM, Wayne GF, Connolly GN. Designing cigarettes for women: new findings from the tobacco industry documents. *Addiction* 2005;100:837–51.
 56. Perkins KA, Doyle T, Ciccocioppo M, Conklin C, Sayette M, Caggiula A. Sex differences in the influence of nicotine dose instructions on the reinforcing and self-reported rewarding effects of smoking. *Psychopharmacology* 2006;184:600–7.
 57. Bevins RA, Caggiula AR. Nicotine, tobacco use, and the 55th Nebraska Symposium on Motivation. *Nebr Symp Motiv* 2009;55:1–3.
 58. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH.

- Smoking and mental illness: a population-based prevalence study. *JAMA* 2000;284:2606–10.
59. Williams JM, Ziedonis D. Addressing tobacco among individuals with a mental illness or an addiction. *Addict Behav* 2004;29:1067–83.
 60. Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine Tob Res* 2008;10:1691–715.
 61. Lawrence D, Considine J, Mitrou F, Zubrick SR. Anxiety disorders and cigarette smoking: results from the Australian Survey of Mental Health and Wellbeing. *Aust N Z J Psychiatry* 2010;44:520–7.
 62. McClave AK, McKnight-Eilly LR, Davis SP, Dube SR. Smoking characteristics of adults with selected lifetime mental illnesses: results from the 2007 National Health Interview Survey. *Am J Public Health* 2010;100:2464–72.
 63. Schroeder SA, Morris CD. Confronting a neglected epidemic: tobacco cessation for persons with mental illnesses and substance abuse problems. *Annu Rev Public Health* 2010;31:297–314 1p following 314.
 64. Leonard S, Adler LE, Benhammou K, Berger R, Breese CR, Drebing C, et al. Smoking and mental illness. *Pharmacol Biochem Behav* 2001;70:561–70.
 65. Leonard S, Adams CE. Smoking cessation and schizophrenia. *Am J Psychiatry* 2006;163:1877.
 66. Mineur YS, Picciotto MR. Biological basis for the co-morbidity between smoking and mood disorders. *J Dual Diagn* 2009;5:122–30.
 67. Mineur YS, Picciotto MR. Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis. *Trends Pharmacol Sci* 2010;31:580–6.
 68. Lewis A, Miller JH, Lea RA. Monoamine oxidase and tobacco dependence. *Neurotoxicology* 2007;28:182–95.
 69. Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry* 2004;61:1107–15.
 70. Lawrence D, Mitrou F. One-third of adult smokers have a mental illness. *Aust N Z J Psychiatry* 2009;43:177–8.
 71. Watson NL, Carpenter MJ, Saladin ME, Gray KM, Upadhyaya HP. Evidence for greater cue reactivity among low-dependent vs. high-dependent smokers. *Addict Behav* 2010;35:673–7.
 72. Plescia F, Brancato A, Marino RA, Cannizzaro C. Acetaldehyde as a drug of abuse: insight into AM281 administration on operant-conflict paradigm in rats. *Front Behav Neurosci* 2013;7:64.
 73. Talhout R, Opperhuizen A, van Amsterdam JG (2007) Role of acetaldehyde in tobacco smoke addiction. *Eur Neuropsychopharmacol* 17:627–36.
 74. Villégier AS, Lotfipour S, McQuown SC, Belluzzi JD, Leslie FM. Tranylcypromine enhancement of nicotine self-administration. *Neuropharmacology* 2007;52:1415–25.

75. Pankow JF. A consideration of the role of gas/particle partitioning in the deposition of nicotine and other tobacco smoke compounds in the respiratory tract. *Chem Res Toxicol* 2001;14:1465–81.
76. Henningfield J, Pankow J, Garrett B. Ammonia and other chemical base tobacco additives and cigarette nicotine delivery: issues and research needs. *Nicotine Tob Res* 2004;6:199–205.
77. Rose JE. Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology* 2006;184:274–85.
78. Carpenter CM, Wayne GF, Connolly GN. The role of sensory perception in the development and targeting of tobacco products. *Addiction* 2007;102:136–47.
79. Breland AB, Buchhalter AR, Evans SE, Eissenberg T. Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. *Nicotine Tob Res* 2002;4(Suppl 2):S131-40.
80. Perkins KA, Gerlach D, Broge M, Grobe JE, Sanders M, Fonte C, et al. Dissociation of nicotine tolerance from tobacco dependence in humans. *J Pharmacol Exp Ther* 2001;296:849–56.
81. Rose JE, Behm FM. Extinguishing the rewarding value of smoke cues: pharmacological and behavioral treatments. *Nicotine Tob Res* 2004;6:523–32.
82. Rose J, Behm F. Effects of low nicotine content cigarettes on smoke intake. *Nicotine Tob Res* 2004;6:309–19.
83. Lee LY, Gerhardstein DC, Wang AL, Burki NK. Nicotine is responsible for airway irritation evoked by cigarette smoke inhalation in men. *J Appl Physiol* 1993;75:1955–61.
84. Rose JE, Behm FM, Westman EC, Johnson M. Dissociating nicotine and nonnicotine components of cigarette smoking. *Pharmacol Biochem Behav* 2000;67:71–81.
85. Rose JE, Behm FM, Westman EC, Coleman RE. Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: implications for addiction. *Drug Alcohol Depend* 1999;56:99–107.
86. Ferris Wayne G, Connolly GN. Application, function, and effects of menthol in cigarettes: a survey of tobacco industry documents. *Nicotine Tob Res* 2004;6(Suppl 1):S43–54.
87. Celebucki CC, Wayne GF, Connolly GN, Pankow JF, Chang EI. Characterization of measured menthol in 48 US cigarette sub-brands. *Nicotine Tob Res* 2005;7:523–31.
88. Galeotti N, Ghelardini C, Mannelli L, Mazzanti G, Baghiroli L, Bartolini A. Local anaesthetic activity of (+)- and (–)-menthol. *Planta Med* 2001;67:174–6.
89. Shojaei AH, Khan M, Lim G, Khosravan R. Transbuccal permeation of a nucleoside analog, dideoxycytidine: effects of menthol as a permeation enhancer. *Int J Pharm* 1999;192:139–46.
90. Brody AL, Mandelkern M, Costello MR, Abrams AL, Scheibal D, Farahi J, et al. Brain nicotinic acetylcholine receptor occupancy: effect of smoking a

- denicotinized cigarette. *Int J Neuropsychopharmacol* 2009;12:305–16.
91. Bardo MT, Green TA, Crooks PA, Dwoskin LP. Nicotine is self-administered intravenously by rats. *Psychopharmacology* 1999;146:290–6.
 92. Clemens KJ, Caille S, Stinus L, Cador M. The addition of five minor tobacco alkaloids increases nicotine-induced hyperactivity, sensitization and intravenous self-administration in rats. *Int J Neuropsychopharmacology* 2009;12:1355–66.
 93. Rodd-Henricks ZA, Melendez RI, Zaffaroni A, Goldstein A, McBride WJ, Li TK. The reinforcing effects of acetaldehyde in the posterior ventral tegmental area of alcohol-preferring rats. *Pharmacol Biochem Behav* 2002;72:55–64.
 94. Belluzzi JD, Wang R, Leslie FM. Acetaldehyde enhances acquisition of nicotine self-administration in adolescent rats. *Neuropsychopharmacology* 2005;30:705–12.
 95. Cao J, Belluzzi JD, Loughlin SE, Keyler DE, Pentel PR, Leslie FM. Acetaldehyde, a major constituent of tobacco smoke, enhances behavioral, endocrine, and neuronal responses to nicotine in adolescent and adult rats. *Neuropsychopharmacology* 2007;32:2025–35.
 96. Guillem K, Vouillac C, Koob JF, Cador M, Stinus L. Monoamine oxidase inhibition dramatically increases the motivation to self-administer nicotine in rats. *J Neurosci* 2005;25:8593–600.
 97. Guillem K, Vouillac C, Koob GF, Cador M, Stinus L. Monoamine oxidase inhibition dramatically prolongs the duration of nicotine withdrawal-induced place aversion. *Biol Psychiatry* 2008;63:158–63.
 98. Rose JE, Behm FM, Ramsey C, Ritchie JC Jr. Platelet monoamine oxidase, smoking cessation, and tobacco withdrawal symptoms. *Nicotine Tob Res* 2001;3:383–90.
 99. The health consequences of smoking: nicotine addiction. A report of the Surgeon General. Rockville, Maryland: Department of Health and Human Services, Public Health Service, Centers for Disease Control, Office on Smoking and Health; 1988.
 100. Dar R, Frenk H. Do smokers self-administer pure nicotine? A review of the evidence. *Psychopharmacology* 2004;173:18–26.
 101. Fulton HG, Barrett SP. A demonstration of intravenous nicotine self-administration in humans? *Neuropsychopharmacology* 2008;33:2042–3; author reply 2044.
 102. Caggiula AR, Donny EC, Chaudhri N, Perkins KA, Evans-Martin FF, Sved AF. Importance of nonpharmacological factors in nicotine self-administration. *Physiol Behav* 2002;77:683–7.
 103. Olausson P, Jentsch JD, Taylor JR. Repeated nicotine exposure enhances reward-related learning in the rat. *Neuropsychopharmacology* 2003;28:1264–71.
 104. Olausson P, Jentsch JD, Taylor JR. Nicotine enhances responding with conditioned reinforcement. *Psychopharmacology* 2004;171:173–8.
 105. Chaudhri N, Caggiula AR, Donny EC, Palmatier MI, Liu X, Sved AF. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology* 2006;184:353–66.

106. Chaudhri N, Caggiula AR, Donny EC, Booth S, Gharib M, Craven L, et al. Self-administered and noncontingent nicotine enhance reinforced operant responding in rats: impact of nicotine dose and reinforcement schedule. *Psychopharmacology* 2007;190:353–62.
107. Palmatier MI, Liu X, Caggiula AR, Donny EC, Sved AF. The role of nicotinic acetylcholine receptors in the primary reinforcing and reinforcement-enhancing effects of nicotine. *Neuropsychopharmacology* 2007;32:1098–108.
108. Palmatier MI, Liu X, Matteson GL, Donny EC, Caggiula AR, Sved AF. Conditioned reinforcement in rats established with self-administered nicotine and enhanced by noncontingent nicotine. *Psychopharmacology* 2007;195:235–43.
109. Le Foll B, Goldberg SR. Control of the reinforcing effects of nicotine by associated environmental stimuli in animals and humans. *Trends Pharmacol Sci* 2005;26:287–93.
110. Cohen C, Perrault G, Griebel G, Soubrie P. Nicotine-associated cues maintain nicotine-seeking behavior in rats several weeks after nicotine withdrawal: reversal by the cannabinoid (CB1) receptor antagonist, rimonabant (SR141716). *Neuropsychopharmacology* 2005;30:145–55.
111. Le Foll B, Wertheim C, Goldberg SR. High reinforcing efficacy of nicotine in non-human primates. *PLoS One* 2007;2:e230.
112. Donny EC, Chaudhri N, Caggiula AR, Evans-Martin FF, Booth S, Gharib MA, et al. Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: implications for nicotine self-administration and reinforcement. *Psychopharmacology* 2003;169:68–76.
113. Caggiula AR, Donny EC, Palmatier MI, Liu X, Chaudhri N, Sved AF. The role of nicotine in smoking: a dual-reinforcement model. *Nebr Symp Motiv* 2009;55:91–109.
114. Carter BL, Tiffany ST. Cue-reactivity and the future of addiction research. *Addiction* 1999;94:349–51.
115. Donny EC, Houtsmuller E, Stitzer ML. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. *Addiction* 2007;102:324–34.
116. Rees VW, Kreslake JM, Wayne GF, O'Connor RJ, Cummings KM, Connolly GN. Role of cigarette sensory cues in modifying puffing topography. *Drug Alcohol Depend* 2012;124:1–10.
117. Palmatier MI, Lantz JE, O'Brien LC, Metz SP. Effects of nicotine on olfactogustatory incentives: preference, palatability, and operant choice tests. *Nicotine Tob Res* 2013;15:1545–54.
118. Perkins KA, Jacobs L, Ciccocioppo M, Conklin C, Sayette M, Caggiula A. The influence of instructions and nicotine dose on the subjective and reinforcing effects of smoking. *Exp Clin Psychopharmacol* 2004;12:91–101.
119. Perkins KA, Ciccocioppo M, Conklin CA, Milanak ME, Grottenthaler A, Sayette MA. Mood influences on acute smoking responses are independent of nicotine intake and dose expectancy. *J Abnorm Psychol* 2008;117:79–93.

120. Darredeau C, Barrett SP. The role of nicotine content information in smokers' subjective responses to nicotine and placebo inhalers. *Hum Psychopharmacol* 2010;25:577–81.
121. Juliano LM, Fucito LM, Harrell PT. The influence of nicotine dose and nicotine dose expectancy on the cognitive and subjective effects of cigarette smoking. *Exp Clin Psychopharmacology* 2011;19:105–15.
122. Kirsch I, Lynn SJ. Automaticity in clinical psychology. *Am Psychol* 1999;54:504–15
123. Perkins K, Sayette M, Conklin C, Caggiula A. Placebo effects of tobacco smoking and other nicotine intake. *Nicotine Tob Res* 2003;5:695–709.
124. Hughes JR, Gulliver SB, Amori G, Mireault GC, Fenwick JF. Effect of instructions and nicotine on smoking cessation, withdrawal symptoms and self-administration of nicotine gum. *Psychopharmacology* 1989;99:486–91.
125. Perkins KA, Coddington SB, Karelitz JL, Jetton C, Scott JA, Wilson AS, et al. Variability in initial nicotine sensitivity due to sex, history of other drug use, and parental smoking. *Drug Alcohol Depend* 2009;99:47–57.
126. Juliano LM, Brandon TH. Effects of nicotine dose, instructional set, and outcome expectancies on the subjective effects of smoking in the presence of a stressor. *J Abnorm Psychol* 2002;111:88–97.
127. Wayne GF, Connolly GN, Henningfield JE. Assessing internal tobacco industry knowledge of the neurobiology of tobacco dependence. *Nicotine Tob Res* 2004;6:927–40.
128. Megerdichian CL, Rees VW, Wayne GF, Connolly GN. Internal tobacco industry research on olfactory and trigeminal nerve response to nicotine and other smoke components. *Nicotine Tob Res* 2007;9:1119–29.
129. Darredeau C, Stewart SH, Barrett SP. The effects of nicotine content information on subjective and behavioural responses to nicotine-containing and denicotinized cigarettes. *Behav Pharmacol* 2013;24:291–7.
130. Perkins KA, Grottenthaler A, Ciccocioppo MM, Conklin CA, Sayette MA, Wilson AS. Mood, nicotine, and dose expectancy effects on acute responses to nicotine spray. *Nicotine Tob Res* 2009;11:540–6.
131. De Leon E, Smith KC, Cohen JE. Dependence measures for non-cigarette tobacco products within the context of the global epidemic: a systematic review. *Tob Control* 2013;23:197–203.
132. Hatsukami DK, Joseph AM, LeSage M, Jensen J, Murphy SE, Pentel PR, et al. Developing the science base for reducing tobacco harm. *Nicotine Tob Res* 2007;9(Suppl 4):S537–53.
133. Donny EC, Taylor TG, LeSage MG, Levin M, Buffalari DM, Joel D, et al. Impact of tobacco regulation on animal research: new perspectives and opportunities. *Nicotine Tob Res* 2012;14:1319–38.
134. Palmatier MI, O'Brien LC, Hall MJ. The role of conditioning history and reinforcer strength in the reinforcement enhancing effects of nicotine in rats. *Psychopharmacology* 2012;219:1119–31.

135. Henningfield JE, Miyasato K, Jasinski DR Cigarette smokers self-administer intravenous nicotine. *Pharmacol Biochem Behav* 1983;19:887–90.
136. Harvey DM, Yasar S, Heishman SJ, Panlilio LV, Henningfield JE, Goldberg SR. Nicotine serves as an effective reinforcer of intravenous drug-taking behavior in human cigarette smokers. *Psychopharmacology* 2004;175:134–42.
137. Sofuoglu M, Yoo S, Hill KP, Mooney M. Self-administration of intravenous nicotine in male and female cigarette smokers. *Neuropsychopharmacology* 2008;33:715–20.
138. Matta SG, Balfour DJ, Benowitz NL, Boyd RT, Buccafusco JJ, Caggiula AR, et al. Guidelines on nicotine dose selection for in vivo research. *Psychopharmacology* 2007;190:269–319.
139. Cox BM, Goldstein A, Nelson WT. Nicotine self-administration in rats. *Br J Pharmacol* 1984;83:49–55
140. Shram MJ, Li Z, Le AD. Age differences in the spontaneous acquisition of nicotine self-administration in male Wistar and Long-Evans rats. *Psychopharmacology* 2008;197:45–58.
141. Corrigan WA, Coen KM. Nicotine maintains robust self-administration in rats on a limited-access schedule. *Psychopharmacology* 1989;99:473–8
142. Donny EC, Caggiula AR, Knopf S, Brown C. Nicotine self-administration in rats. *Psychopharmacology* 1995;122:390–4
143. Shoaib M, Schindler CW, Goldberg SR. Nicotine self-administration in rats: strain and nicotine pre-exposure effects on acquisition. *Psychopharmacology* 1997;129:35–43.
144. Watkins SS, Epping-Jordan MP, Koob GF, Markou A. Blockade of nicotine self-administration with nicotinic antagonists in rats. *Pharmacol Biochem Behav* 1999;62:743–51.
145. Brower VG, Fu Y, Matta SG, Sharp BM. Rat strain differences in nicotine self-administration using an unlimited access paradigm. *Brain Res* 2002;930:12–20.
146. DeNoble VJ, Mele PC. Intravenous nicotine self-administration in rats: effects of mecamylamine, hexamethonium and naloxone. *Psychopharmacology* 2006;184:266–72.
147. Sorge RE, Clarke PB. Rats self-administer intravenous nicotine delivered in a novel smoking-relevant procedure: effects of dopamine antagonists. *J Pharmacol Exp Ther* 2009;330:633–40.
148. Hanson HM, Ivester CA, Morton BR. Nicotine self-administration in rats. In: Krasnegor NA, editor. *Cigarette smoking as a dependence process* (NIDA Research Monograph 23). Washington DC: National Institute on Drug Abuse; 1979:70–90.
149. Kota D, Martin BR, Robinson SE, Damaj MI. Nicotine dependence and reward differ between adolescent and adult male mice. *J Pharmacol Exp Ther* 2007;322:399–407.
150. Levin ED, Rezvani AH, Montoya D, Rose JE, Swartzwelder HS. Adolescent-

- onset nicotine self-administration modeled in female rats. *Psychopharmacology* 2003;169:141–9.
151. Chen H, Matta SG, Sharp BM. Acquisition of nicotine self-administration in adolescent rats given prolonged access to the drug. *Neuropsychopharmacology* 2007;32:700–9.
 152. Shram MJ, Funk D, Li Z, Le AD. Nicotine self-administration, extinction responding and reinstatement in adolescent and adult male rats: evidence against a biological vulnerability to nicotine addiction during adolescence. *Neuropsychopharmacology* 2008;33:739–48.
 153. Shram MJ, Siu EC, Li Z, Tyndale RF, Le AD. Interactions between age and the aversive effects of nicotine withdrawal under mecamylamine-precipitated and spontaneous conditions in male Wistar rats. *Psychopharmacology* 2008;198:181–90.
 154. DiFranza JR, Savageau JA, Rigotti NA, Fletcher K, Ockene JK, McNeill AD, et al. Development of symptoms of tobacco dependence in youths: 30 month follow up data from the DANDY study. *Tob Control* 2002;11:228–35.
 155. O’Loughlin J, Gervais A, Dugas E, Meshefedjian G. Nicotine-dependence symptoms are associated with smoking frequency in adolescents. *Am J Prev Med* 2003;25:219–25.
 156. Gervais A, O’Loughlin J, Meshefedjian G, Bancej C, Tremblay M. Milestones in the natural course of onset of cigarette use among adolescents. *Can Med Assoc J* 2006;175:255–61.
 157. Kandel DB, Hu MC, Griesler PC, Schaffran C. On the development of nicotine dependence in adolescence. *Drug Alcohol Depend* 2007;91:26–39.
 158. Caraballo RS, Novak SP, Asman K. Linking quantity and frequency profiles of cigarette smoking to the presence of nicotine dependence symptoms among adolescent smokers: findings from the 2004 National Youth Tobacco Survey. *Nicotine Tob Res* 2009;11:49–57.
 159. Corrigan WA, Zack M, Eissenberg T, Belsito L, Scher R. Acute subjective and physiological responses to smoking in adolescents. *Addiction* 2001;96:1409–17.
 160. Aung AT, Pickworth WB, Moolchan ET. History of marijuana use and tobacco smoking topography in tobacco-dependent adolescents. *Addict Behav* 2004;29:699–706.
 161. Wood T, Wewers ME, Groner J, Ahijevych K. Smoke constituent exposure and smoking topography of adolescent daily cigarette smokers. *Nicotine Tob Res* 2004;6:853–62.
 162. Kassel JD, Greenstein JE, Evatt DP, Wardle MC, Yates MC, Veilleux JC, et al. Smoking topography in response to denicotinized and high-yield nicotine cigarettes in adolescent smokers. *J Adolesc Health* 2007;40:54–60.
 163. Wahl SK, Turner LR, Mermelstein RJ, Flay BR. Adolescents’ smoking expectancies: psychometric properties and prediction of behavior change. *Nicotine Tob Res* 2005;7:613–23.

164. Heinz AJ, Kassel JD, Berbaum M, Mermelstein R. Adolescents' expectancies for smoking to regulate affect predict smoking behavior and nicotine dependence over time. *Drug Alcohol Depend* 2010;111:128–35.
165. Kassel JD, Evatt DP, Greenstein JE, Wardle MC, Yates MC, Veilleux JC. The acute effects of nicotine on positive and negative affect in adolescent smokers. *J Abnorm Psychol* 2007;116:543–53.
166. Baldinger B, Hasenfratz M, Battig K. Switching to ultralow nicotine cigarettes: effects of different tar yields and blocking of olfactory cues. *Pharmacol Biochem Behav* 1995;50:233–9.
167. Butschky MF, Bailey D, Henningfield JE, Pickworth WB. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacol Biochem Behav* 1995;50:91–6.
168. Westman EC, Behm FM, Rose JE. Dissociating the nicotine and airway sensory effects of smoking. *Pharmacol Biochem Behav* 1996;53:309–15.
169. Gross J, Lee J, Stitzer ML. Nicotine-containing versus de-nicotinized cigarettes: effects on craving and withdrawal. *Pharmacol Biochem Behav* 1997;57:159–65.
170. Pickworth WB, Fant RV, Nelson RA, Rohrer MS, Henningfield JE. Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine Tob Res* 1999;1:357–64.
171. Buchhalter AR, Schrinel L, Eissenberg T. Withdrawal-suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes. *Nicotine Tob Res* 2001;3:111–8.
172. Barrett SP. The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behav Pharmacol* 2010;21:144–52.
173. Brauer LH, Behm FM, Lane JD, Westman EC, Perkins C, Rose JE. Individual differences in smoking reward from de-nicotinized cigarettes. *Nicotine Tob Res* 2001;3(2):101–9.
174. Dallery J, Houtsmuller EJ, Pickworth WB, Stitzer ML. Effects of cigarette nicotine content and smoking pace on subsequent craving and smoking. *Psychopharmacology* 2003;165:172–80.
175. Rose JE, Behm FM, Westman EC, Bates JE, Salley A. Pharmacologic and sensorimotor components of satiation in cigarette smoking. *Pharmacol Biochem Behav* 2003;76:243–50.
176. Grady SR, Marks MJ, Collins AC. Desensitization of nicotine-stimulated [3H]dopamine release from mouse striatal synaptosomes. *J Neurochem* 1994;62:1390–8.
177. Lu Y, Marks MJ, Collins AC. Desensitization of nicotinic agonist-induced [3H]gamma-aminobutyric acid release from mouse brain synaptosomes is produced by subactivating concentrations of agonists. *J Pharmacol Exp Ther* 1999;291:1127–34.
178. Picciotto MR, Addy NA, Mineur YS, Brunzell DH. It is not “either/or”: activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors

- related to nicotine addiction and mood. *Prog Neurobiol* 2008;84:329–42.
179. Donny EC, Jones M. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. *Drug Alcohol Depend* 2009;104:23–33.
180. Bouton ME. Context and behavioral processes in extinction. *Learn Mem* 2004;11:485–94.
181. International statistical classification of diseases and related health problems, 10th revision. Geneva: World Health Organization; 1992.
182. Moolchan ET, Radzius A, Epstein DH, Uhl G, Gorelick DA, Cadet JL, et al. The Fagerstrom test for nicotine dependence and the Diagnostic Interview Schedule: do they diagnose the same smokers? *Addict Behav* 2002;27:101–13.
183. Hughes JR, Oliveto AH, Riggs R, Kenny M, Liguori A, Pillitteri JL, et al. Concordance of different measures of nicotine dependence: two pilot studies. *Addict Behav* 2004;29:1527–39.
184. Hendricks PS, Prochaska JJ, Humfleet GL, Hall SM. Evaluating the validities of different DSM-IV-based conceptual constructs of tobacco dependence. *Addiction* 2008;103:1215–23.
185. Hughes JR, Baker T, Breslau N, Covey L, Shiffman S. Applicability of DSM criteria to nicotine dependence. *Addiction* 2011;106:894–5; discussion 895–7.
186. Colby SM, Tiffany ST, Shiffman S, Niaura RS. Measuring nicotine dependence among youth: a review of available approaches and instruments. *Drug Alcohol Depend* 2000;59(Suppl 1):S23–39.
187. Rose JS, Dierker LC. DSM-IV nicotine dependence symptom characteristics for recent-onset smokers. *Nicotine Tob Res* 2010;12:278–86.
188. Rubinstein ML, Luks TL, Moscicki AB, Dryden W, Rait MA, Simpson GV. Smoking-related cue-induced brain activation in adolescent light smokers. *J Adolesc Health* 2011;48:7–12.
189. Sofuoglu M, LeSage MG. The reinforcement threshold for nicotine as a target for tobacco control. *Drug Alcohol Depend* 2012;125:1–7.
190. Audrain-McGovern J, Rodriguez D, Epstein LH, Rodgers K, Cuevas J, Wileyto EP. Young adult smoking: what factors differentiate ex-smokers, smoking cessation treatment seekers and nontreatment seekers? *Addict Behav* 2009;34:1036–41.
191. Glautier S. Measures and models of nicotine dependence: positive reinforcement. *Addiction* 2004;99(Suppl 1):30–50.
192. Comer SD, Ashworth JB, Foltin RW, Johanson CE, Zacny JP, Walsh SL. The role of human drug self-administration procedures in the development of medications. *Drug Alcohol Depend* 2008;96:1–15.
193. Besheer J, Palmatier MI, Metschke DM, Bevins RA. Nicotine as a signal for the presence or absence of sucrose reward: a Pavlovian drug appetitive conditioning preparation in rats. *Psychopharmacology* 2004;172:108–17.
194. Bevins RA, Palmatier MI. Extending the role of associative learning processes in nicotine addiction. *Behav Cogn Neurosci Rev* 2004;3(3):143–58.
195. Wilkinson JL, Murray JE, Li C, Wiltgen SM, Penrod RD, Berg SA, Bevins RA.

- Interoceptive Pavlovian conditioning with nicotine as the conditional stimulus varies as a function of the number of conditioning trials and unpaired sucrose deliveries. *Behav Pharmacol* 2006;17:161–72.
196. Murray JE, Bevins RA. Behavioral and neuropharmacological characterization of nicotine as a conditional stimulus. *Eur J Pharmacol* 2007;561:91–104.
 197. Palmatier MI, Coddington SB, Liu X, Donny EC, Caggiola AR, Sved AF. The motivation to obtain nicotine-conditioned reinforcers depends on nicotine dose. *Neuropharmacology* 2008;55:1425–30.
 198. Panzano VC, Wayne GF, Pickworth WB, Connolly GN. Human electroencephalography and the tobacco industry: a review of internal documents. *Tob Control* 2010;19:153–9.
 199. Gullotta FP, Hayes C. The effects of cigarette smoking on pattern reversal evoked potentials (preps). Philip Morris. Bates No. 2028817734–40; 1981 (<http://legacy.library.ucsf.edu/tid/rfp12e00>).
 200. Gullotta FP, Hayes CS, Martin BR. Electrophysiological and subjective effect of cigarettes delivering varying amounts of nicotine. Philip Morris. Bates No. 2062374615–22; 1990 (<http://legacy.library.ucsf.edu/tid/izy26c00>).
 201. Charles JL, Gullotta FP, Schultz CJ. Electrophysiological studies—820000 annual report. Philip Morris. Bates No. 2056128455–504; 1982 (<http://legacy.library.ucsf.edu/tid/bra52e00>).
 202. Connolly GN, Alpert HR, Wayne GF, Koh H. Trends in nicotine yield in smoke and its relationship with design characteristics among popular US cigarette brands, 1997–2005. *Tob Control* 2007;16(5):e5.
 203. Slade J, Bero LA, Hanauer P, Barnes DE, Glantz SA. Nicotine and addiction. The Brown and Williamson documents. *J Am Med Assoc* 1995;274:225–33.
 204. Hurt RD, Robertson CR. Prying open the door to the tobacco industry's secrets about nicotine: the Minnesota Tobacco Trial. *J Am Med Assoc* 1998;280:1173–81.
 205. Dunsby J, Bero L. A nicotine delivery device without the nicotine? Tobacco industry development of low nicotine cigarettes. *Tob Control* 2004;13:362–9.
 206. British American Tobacco. Research and Development Department: Progress in 1972—Plans for 1973. Bates No. 402409855–89; 1972 (<http://legacy.library.ucsf.edu/tid/qdb84a99/>).
 207. British American Tobacco. Introductory notes on leaf blending. Bates No. 102638105–66; 1969 (<http://legacy.library.ucsf.edu/tid/qmy36a99/>).
 208. Browne CL. The design of cigarettes. Charlotte, North Carolina: Hoechst Celanese; 1990.
 209. Cohen N. Minutes of meeting on May 6 1971. British American Tobacco. Bates No. 103551202–4; 1971 (<http://legacy.library.ucsf.edu/tid/rng84a99/>).
 210. Gibb RM. [Memo from RM Gibb to EP Gage regarding low nicotine]. Bates No. 103408473–4; 1974 (<http://legacy.library.ucsf.edu/tid/kly06a99/>).
 211. Johnson DP. Low nicotine tobacco. RJ Reynolds. Bates No. 511040740; 1977 (<http://legacy.library.ucsf.edu/tid/xsk53d00/>).

212. Kentucky Tobacco Research Board. 1977 annual review. Bates No. 9809; 1977 (<http://legacy.library.ucsf.edu/tid/omd76b00>).
213. Smith TE. Tobacco and smoke characteristics of low nicotine strains of Burley. British American Tobacco. Bates No. 402379156–69; 1972 (<http://legacy.library.ucsf.edu/tid/dly54a99/>).
214. Geiss VL. Bw process. I Reductions of tobacco nicotine using selected bacteria. British American Tobacco. Bates No. 402350891–915; 1972 (<http://legacy.library.ucsf.edu/tid/jlw84a99/>).
215. Geiss VL. Bw process. VI Metabolism of nicotine and other biochemistry of the Bw process. British American Tobacco. Bates No. 107474767–70; 1975 (<http://legacy.library.ucsf.edu/tid/gpx86a99/>).
216. Gravely LE, Newton RP, Geiss VL. Bw process: IV Evaluation of low nicotine cigarettes used for consumer product testing. British American Tobacco. Bates No. 402371546–59; 1973 (<http://legacy.library.ucsf.edu/tid/zso05a99/>).
217. York JE. Control of nicotine in tobacco and cigarette smoke. American Tobacco. Bates No. 950796661–6; 1977 (<http://legacy.library.ucsf.edu/tid/ywy90a00/>).
218. Rickett FL, Pedersen PM. A review of methods for reduction of nicotine in tobacco. American Tobacco. Bates No. 950643646–55; 1980 (<http://legacy.library.ucsf.edu/tid/rgd90a00/>).
219. Ashburn G. Vapor-phase removal of nicotine from smoke. RJ Reynolds. Bates No. 500937661–714; 1961 (<http://legacy.library.ucsf.edu/tid/cyo59d00/>).
220. Green CR. Denicotinization of low nicotine, high sugar flue cured tobacco. RJ Reynolds. Bates No. 504804962–3; 1979 (<http://legacy.library.ucsf.edu/tid/jwm55d00/>).
221. Kassman AJ, Knudson DB, Lilly AC, Sherwood JF. Alkaloid reduced Tobacco (ART) Program Current Status and Plans for 1987. Philip Morris. Bates No. 2051841630–44; 1986 (<http://legacy.library.ucsf.edu/tid/xth52e00/>).
222. Philip Morris. Alkaloid reduced tobacco (ART) program. Philip Morris. Bates No. 2063096617–51; 1995 (<http://legacy.library.ucsf.edu/tid/xus47d00/>).
223. Houghton KS. Monthly development summary—May, 1990. Philip Morris. Bates No. 2022156219–42; 1990 (<http://legacy.library.ucsf.edu/tid/ggx44e00/>).
224. Gullotta F, Hayes C, Martin B. The effects of nicotine and menthol on electrophysiological and subjective responses. Philip Morris. Bates No. 2029213006–18; 1991 (<http://legacy.library.ucsf.edu/tid/ezc69e00/>).
225. Philip Morris. Study concept: the electrophysiological and subjective effects of smoking cigarettes with constant nicotine but varying tar levels. Philip Morris. Bates No. 2025988473–5; 1995 (<http://legacy.library.ucsf.edu/tid/vlo46b00/>).
226. Ferris Wayne G, Connolly GN, Henningfield JE. Brand differences of free-base nicotine delivery in cigarette smoke: the view of the tobacco industry documents. *Tob Control* 2006;15:189–98.
227. Ashley DL, Pankow JF, Tavakoli AD, Watson CH. Approaches, challenges, and experience in assessing free nicotine. *Handb Exp Pharmacol* 2009;192:437–56.

228. Gregory CF. Observation of free nicotine changes in tobacco smoke/528. Brown & Williamson. Bates No. 510000667-70; 1980 (<http://legacy.library.ucsf.edu/tid/zds24f00>).
229. Shannon D, Walker RJ, Smith NA, Perfetti T, Ingebrethsen B, Saintsing B, et al. We Are Looking at Smoothness from a Different Perspective. RJ Reynolds. Bates No. 508408649-770; 1992 (<http://legacy.library.ucsf.edu/tid/mcq93d00>).
230. Pankow JF, Tavakoli AD, Luo W, Isabelle LM. Percent free base nicotine in the tobacco smoke particulate matter of selected commercial and reference cigarettes. *Chem Res Toxicol* 2003;16:1014-8.
231. Watson CH, Trommel JS, Ashley DL. Solid-phase microextraction-based approach to determine free-base nicotine in trapped mainstream cigarette smoke total particulate matter. *J Agric Food Chem* 2004;52:7240-5.
232. Benowitz NL, Jacob P III, Bernert JT, Wilson M, Wang L, Allen F, et al. Carcinogen exposure during short-term switching from regular to "light" cigarettes. *Cancer Epidemiol Biomarkers Prev* 2005;14:1376-83.
233. Benowitz NL, Jacob P 3rd, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clin Pharmacol Ther* 2006;80:703-14.
234. Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, et al. Progressive commercial cigarette yield reduction: biochemical exposure and behavioral assessment. *Cancer Epidemiol Biomarkers Prev* 2009;18:876-83.
235. Henningfield JE, Fant RV, Tomar SL. Smokeless tobacco: an addicting drug. *Adv Dental Res* 1997;11:330-5.
236. Hatsukami DK, Lemmonds C, Tomar SL. Smokeless tobacco use: harm reduction or induction approach? *Prev Med* 2004;38:309-17.
237. Henningfield JE, Shiffman S, Ferguson SG, Gritz ER. Tobacco dependence and withdrawal: science base, challenges and opportunities for pharmacotherapy. *Pharmacol Ther* 2009;123:1-16.
238. Wayne GF, Connolly GN, Henningfield JE, Farone WA. Tobacco industry research and efforts to manipulate smoke particle size: implications for product regulation. *Nicotine Tob Res* 2008;10:613-25.
239. Becker KM, Rose JE, Albino AP. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. *Nicotine Tob Res* 2008;10:1139-48.
240. Rose JE. Disrupting nicotine reinforcement: from cigarette to brain. *Ann N Y Acad Sci* 2008;1141:233-56.
241. DeGrandpre RJ, Bickel WK, Hughes JR, Higgins ST. Behavioral economics of drug self-administration. III. A reanalysis of the nicotine regulation hypothesis. *Psychopharmacology* 1992;108:1-10
242. Shahan TA, Bickel WK, Madden GJ, Badger GJ. Comparing the reinforcing efficacy of nicotine containing and de-nicotinized cigarettes: a behavioral economic analysis. *Psychopharmacology* 1999;147:210-6.

243. Shahan TA, Bickel WK, Badger GJ, Giordano LA. Sensitivity of nicotine-containing and de-nicotinized cigarette consumption to alternative non-drug reinforcement: a behavioral economic analysis. *Behav Pharmacol* 2001;12:277–84.
244. Shahan TA, Odum AL, Bickel WK. Nicotine gum as a substitute for cigarettes: a behavioral economic analysis. *Behav Pharmacol* 2000;11:71–9.
245. Johnson MW, Bickel WK, Kirshenbaum AP. Substitutes for tobacco smoking: a behavioral economic analysis of nicotine gum, denicotinized cigarettes, and nicotine-containing cigarettes. *Drug Alcohol Depend* 2004;74:253–64.
246. West RJ, Jarvis MJ, Russell MA, Carruthers ME, Feyerabend C. Effect of nicotine replacement on the cigarette withdrawal syndrome. *Br J Addict* 1984;79:215–9.
247. Zacny JP, Stitzer ML. Cigarette brand-switching: effects on smoke exposure and smoking behavior. *J Pharmacol Exp Ther* 1988;246:619–27.
248. Strasser AA, Lerman C, Sanborn PM, Pickworth WB, Feldman EA. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug Alcohol Depend* 2007;86:294–300.
249. Harris AC, Pentel PR, Burroughs D, Staley MD, Lesage MG. A lack of association between severity of nicotine withdrawal and individual differences in compensatory nicotine self-administration in rats. *Psychopharmacology* 2011;217:153–66.
250. Roiko SA, Harris AC, LeSage MG, Keyler DE, Pentel PR. Passive immunization with a nicotine-specific monoclonal antibody decreases brain nicotine levels but does not precipitate withdrawal in nicotine-dependent rats. *Pharmacol Biochem Behav* 2009;93:105–11.
251. Walker N, Howe C, Bullen C, Grigg M, Glover M, McRobbie H, et al. The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial. *Addiction* 2012;107:1857–67.
252. Hatsukami DK, Hertsgaard LA, Vogel RI, Jensen JA, Murphy SE, Hecht SS, et al. Reduced nicotine content cigarettes and nicotine patch. *Cancer Epidemiol Biomarkers Prev* 2013;22:1015–24.
253. Perkins KA, Gerlach D, Broge M, Fonte C, Wilson A. Reinforcing effects of nicotine as a function of smoking status. *Exp Clin Psychopharmacol* 2001;9:243–50.
254. Doran N, Schweizer CA, Myers MG. Do expectancies for reinforcement from smoking change after smoking initiation? *Psychol Addict Behav* 2011;25:101–7.
255. McQuown SC, Belluzzi JD, Leslie FM. Low dose nicotine treatment during early adolescence increases subsequent cocaine reward. *Neurotoxicol Teratol* 2007;29:66–73.
256. Connolly GN. The marketing of nicotine addiction by one oral snuff manufacturer. *Tob Control* 1995;4: 73–9.
257. Barrett SP, Darredeau C. The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent smokers. *Behav Pharmacol* 2012;23:221–7.

258. Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM, Ahnallen CG. Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schizophrenia and controls. *Nicotine Tob Res* 2013;15:121–9.
259. Joel DL, Denlinger RL, Dermody SS, Hatsukami DK, Benowitz NL, Donny EC. Very low nicotine content cigarettes and potential consequences on cardiovascular disease. *Curr Cardiovasc Risk Rep* 2012;6:534–41.
260. Benowitz NL. Toxicity of nicotine: implications with regard to nicotine replacement therapy. *Prog Clin Biol Res* 1988;261:187–217.
261. Assali AR, Beigel Y, Schreiber R, Shafer Z, Fainaru M. Weight gain and insulin resistance during nicotine replacement therapy. *Clin Cardiol* 1999;22:357–60.
262. Heeschen C, Weis M, Cooke JP. Nicotine promotes arteriogenesis. *J Am Coll Cardiol* 2003;41:489–96
263. Suzuki J, Bayna E, Dalle Molle E, Lew WY. Nicotine inhibits cardiac apoptosis induced by lipopolysaccharide in rats. *J Am Coll Cardiol* 2003;41:482–8.
264. Girdhar G, Xu S, Bluestein D, Jesty J. Reduced-nicotine cigarettes increase platelet activation in smokers in vivo: a dilemma in harm reduction. *Nicotine Tob Res* 2008;10:1737–44.
265. Legresley E, Lee K, Muggli ME, Patel P, Collin J, Hurt RD. British American Tobacco and the “insidious impact of illicit trade” in cigarettes across Africa. *Tob Control* 2008;17:339–46.
266. Lee S, Ling PM, Glantz SA. The vector of the tobacco epidemic: tobacco industry practices in low and middle-income countries. *Cancer Causes Control* 2012;23(Suppl 1):117–29.
267. Joossens L, Raw M. Turning off the tap: the real solution to cigarette smuggling. *Int J Tuberc Lung Dis* 2003;7:214–22.
268. Joossens L, Raw M. Progress in combating cigarette smuggling: controlling the supply chain. *Tob Control* 2008;17:399–404.
269. Pavananunt P. Illicit cigarette trade in Thailand. *Southeast Asian J Trop Med Public Health* 2011;42:1531–9.
270. Mecredy GC, Diemert LM, Callaghan RC, Cohen JE. Association between use of contraband tobacco and smoking cessation outcomes: a population-based cohort study. *Can Med Assoc J* 2013;185:E287–94.
271. Givel MS. History of Bhutan’s prohibition of cigarettes: implications for neo-prohibitionists and their critics. *Int J Drug Policy* 2011;22:306–10.
272. Borland R. Minimising the harm from nicotine use: finding the right regulatory framework. *Tob Control* 2013;22(Suppl 1):i6–9.
273. Czoli CD, Hammond D. Cigarette packaging: youth perceptions of “natural” cigarettes, filter references, and contraband tobacco. *J Adolesc Health* 2013;54:33–9.
274. Hyland A, Higbee C, Li Q, Bauer JE, Giovino GA, Alford T, et al. Access to low-taxed cigarettes deters smoking cessation attempts. *Am J Public Health* 2005;95:994–5.

275. Hyland A, Laux FL, Higbee C, Hastings G, Ross H, Chaloupka FJ, et al. Cigarette purchase patterns in four countries and the relationship with cessation: findings from the International Tobacco Control (ITC) Four Country Survey. *Tob Control* 2006;15(Suppl 3):iii59–64.
276. Licht AS, Hyland AJ, O'Connor RJ, Caloupka FJ, Borland R, Fong GT. How do price minimizing behaviors impact smoking cessation? Findings from the International Tobacco Control (ITC) Four Country Survey. *Int J Environ Res Public Health* 2011;8:1671–91.
277. Ahmad S, Billimek J. Estimating the health impacts of tobacco harm reduction policies: a simulation modeling approach. *Risk Anal* 2005;25:801–12.
278. Modeling the health benefits of a nicotine standard for tobacco products sold in Canada. Cambridge, Massachusetts: Industrial Economics Inc.; 2013.
279. Hall W, West R. Thinking about the unthinkable: a de facto prohibition on smoked tobacco products. *Addiction* 2008;103:873–4.
280. Le Houezec J, McNeill A, Britton J. Tobacco, nicotine and harm reduction. *Drug Alcohol Rev* 2011;30:119–23.
281. McNeill A, Hammond D, Gartner C. Whither tobacco product regulation? *Tob Control* 2012;21:221–6.
282. Arnott D. There's no single endgame. *Tob Control* 2013;22(Suppl 1):i38–9.
283. Britton J, McNeil A. Nicotine regulation and tobacco harm reduction in the UK. *Lancet* 2013;381:1879–80.
284. Hatsukami DK. Ending tobacco-caused mortality and morbidity: the case for performance standards for tobacco products. *Tob Control* 2013;22(Suppl 1):i36–7.
285. O'Connor RJ. Non-cigarette tobacco products: what have we learnt and where are we headed? *Tob Control* 2012;21:181–90.
286. Wayne GF, Connolly GN. Regulatory assessment of brand changes in the commercial tobacco product market. *Tob Control* 2009;18:302–9.
287. Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK. Abuse liability assessment of tobacco products including potential reduced exposure products. *Cancer Epidemiol Biomarkers Prev* 2009;18:3241–62.
288. Henningfield JE, Hatsukami DK, Zeller M, Peters E. Conference on abuse liability and appeal of tobacco products: conclusions and recommendations. *Drug Alcohol Depend* 2011;116:1–7.
289. Mooney ME, Johnson EO, Breslau N, Bierut LJ, Hatsukami DK. Cigarette smoking reduction and changes in nicotine dependence. *Nicotine Tob Res* 2011;13:426–30.
290. Walker N, Bullen C, McRobbie H. Reduced-nicotine content cigarettes: Is there potential to aid smoking cessation? *Nicotine Tob Res* 2009;11:1274–9.
291. Lindson-Hawley N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. *Cochrane Database Syst Rev* 2012;11:CD008033.
292. Rooke C, McNeill A, Arnott D. Regulatory issues concerning the development and circulation of nicotine-containing products: a qualitative study. *Nicotine Tob*

Res 2013;15(6):1052–9.

293. Cahn Z, Siegel M. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? *J Public Health Policy* 2011;32:16–31.
294. Le Houezec J, Aubin HJ. Pharmacotherapies and harm-reduction options for the treatment of tobacco dependence. *Expert Opin Pharmacother* 2013;14:1959–67.
295. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology* 2013;231:401–7.
296. Dawkins L, Turner J, Crowe E. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. *Psychopharmacology* 2013;227:377–84.
297. Dawkins L, Turner J, Roberts A, Soar K “Vaping” profiles and preferences: an online survey of electronic cigarette users. *Addiction* 2013;108:1115–25.
298. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control* 2010;19:87–8.
299. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010;19:98–103.
300. Shadel WG, Lerman C, Cappella J, Strasser AA, Pinto A, Hornik R. Evaluating smokers’ reactions to advertising for new lower nicotine quest cigarettes. *Psychol Addict Behav* 2006;20:80–4.
301. Parascandola M, Augustson E, O’Connell ME, Marcus S. Consumer awareness and attitudes related to new potential reduced-exposure tobacco product brands. *Nicotine Tob Res* 2009;11:886–95.
302. Connolly GN, Behm I, Heaton CG, Alpert HR. Public attitudes regarding banning of cigarettes and regulation of nicotine. *Am J Public Health* 2012;102:e1–2.
303. Fix BV, O’Connor RJ, Fong GT, Borland R, Cummings KM, Hyland A. Smokers’ reactions to FDA regulation of tobacco products: findings from the 2009 ITC United States survey. *BMC Public Health* 2011;11:941.
304. Pearson JL, Abrams DB, Niaura RS, Richardson A, Vallone DM. Public support for mandated nicotine reduction in cigarettes. *Am J Public Health* 2013;103:562–7.

This report presents the conclusions reached and recommendations made by the members of the WHO Study Group on Tobacco Product Regulation (TobReg) at its seventh meeting, in December 2013, during which it reviewed background papers specially commissioned for the meeting, which dealt, respectively, with the following four themes:

1. Novel tobacco products, including potential reduced exposure products
2. Smokeless tobacco products: research needs and regulatory recommendations
3. Reduced ignition propensity cigarettes: research needs and regulatory recommendations
4. Non-exhaustive priority list of toxic contents and emissions of tobacco products

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 Chapter 6.

