REVIEW

Research Required for the Effective Implementation of the Framework Convention on Tobacco Control, Articles 9 and 10

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ABSTRACT

This paper is part of a series of articles intended to set out the research questions that are relevant to the successful implementation of the various provisions of the Framework Convention on Tobacco Control (FCTC). This paper focuses on issues affecting Articles 9 and 10 of the FCTC. This paper focuses on the research that is most important for most countries, rather than on what is desirable in countries with high levels of research capacity.

Articles 9 and 10 of the FCTC address the regulation of contents and emissions of tobacco products and regulation of tobacco product disclosure. Such regulation will be essential if the long-term objective of reducing the danger of tobacco products is to be achieved. There are many components of tobacco and tobacco smoke that are excessively toxic and dangerous to the user. Many of these components are carcinogenic and addictive and can be removed or reduced substantially with current known technology. The fact that these components remain in tobacco and tobacco smoke at levels that are unnecessarily dangerous is precisely the reason why the successful implementation of Articles 9 and 10 of the FCTC is important to tobacco control. This paper discusses the scientific challenges involved in successfully implementing Articles 9 and 10 of the FCTC, which focuses on regulating carcinogens and toxins in tobacco and tobacco smoke, the abuse liability of tobacco products, and the additives and engineering features in tobacco products that make tobacco products appealing to future consumers.

The research issues we focus on are those required to support the early stages of regulation. As regulation proceeds, new and more sophisticated research questions will undoubtedly emerge.

INTRODUCTION

Regulation of tobacco products has lagged behind many other elements of tobacco control. This paper briefly reviews the rationale for tobacco product regulation and then outlines what we know, what we do not know, and what we still need to know in order to effectively regulate the contents and emissions of tobacco products, as required by the Framework Convention on Tobacco Control (FCTC).

Articles 9 and 10 of the FCTC read as follows:

Article 9 (Regulation of the contents of tobacco products): The Conference of the Parties, in consultation with competent international bodies, shall propose guidelines for testing and measuring the contents and emissions of tobacco products, and for the regulation of these contents and emissions. Each Party shall, where approved by competent national authorities, adopt and implement effective legislative, executive, and administrative or other measures for such testing and measuring, and for such regulation.

Article 10 (Regulation of tobacco product disclosures): Each Party shall, in accordance with its national law, adopt and implement effective legislative, executive, administrative or other measures requiring manufacturers and importers of tobacco products to disclose to governmental authorities information about the contents and emissions of tobacco products. Each Party shall further adopt and implement effective measures for public disclosure of information about the toxic constituents of the tobacco products and the emissions that they may produce.

This paper sets out the research questions that are relevant to Articles 9 and 10 of the FCTC. It is slightly different to a range of other papers considering research directions in this field, in that it is not an extensive review of the evidence (e.g., [Scientific Committee on Emerging and Newly Identified Health Risks \[SCENIHR\], 2010](#)), as detailed in the research questions it identifies [cf. Hecht (2011)], has a much broader focus than carcinogens and other toxins (eg, [WHO, 2007](#); Hecht, 2011), and it is not framed as part

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of the broad harm reduction agenda (Zeller, Hatsukami, & the Strategic Dialogue on Tobacco Harm Reduction Group, 2010). This paper has a somewhat different focus in that it covers research that is needed in the early stages of the implementation of effective product regulation under Article 9 of the FCTC and also consideration of research to optimize disclosure that is need to support and evaluate the regulation under Article 10. It takes as its starting point the Conference of the Parties (COP) Partial Guidelines for these two articles (http://www.who.int/fctc/protocol/guidelines/adopted/article_9and10/en/index.html) and focuses on what we believe is the limited amount of research that could facilitate rapid action, and covers the scope of regulatory possibilities from attractiveness, through addictiveness to carcinogenicity/toxicity.

In this paper, we have used the term “additives” to refer to “anything that is added to tobacco.” This definition is necessary as the word “ingredients” is used with different meanings by the tobacco industry. Hecht splits ingredients into “flavors” and “additives.” Flavors impart a specific taste, flavor, or aroma to the product, whereas additives are used for specific technological purposes—they include humectants, preservatives, solvents, binders, strengtheners, and fillers. We have chosen to use additives to apply to both (for simplicity).

CONTEXT BACKGROUND AND HISTORY

Cigarettes are here because of an accident of history. The modern cigarette was developed in the late 19th and early 20th century, and it became the predominant form of tobacco use in many parts of the world by the 1920s (Proctor, 2012). By the time the harms of smoking were recognized, its use had become normalized. Regulators now face the need to regulate it in such a way that harm can be minimized, as prohibition is not deemed possible given the current levels of use and its addictive nature. Progressive reduction of harm is probably the most that can be expected. This can take the form of a gradual reduction in use and, the focus of this paper, regulation to reduce (or if possible eliminate) as many of the carcinogenic and toxic components of tobacco smoke as possible and to lower the abuse liability of tobacco products (i.e., aspects of tobacco product design that lead to prolonged exposures to toxins). This is consistent with the recommendations of the Partial Guidelines. This paper is concerned with the development of a research agenda that can help regulators move the market toward the least harmful possible tobacco products, starting with the products that are currently on the market in any given country. Any effort to regulate tobacco products also needs to be cognizant of the potential for consumers to misconstrue regulation of tobacco products as meaning that the regulation has resulted in greatly reducing the harms (when at most, it will only reduce them a small amount), and thus counteracting the public health message to avoid tobacco use altogether. Tobacco product avoidance (never using or cessation) is the only sure way to prevent the harm caused by tobacco use. Thus, product regulation represents an effort to mitigate the harm caused by tobacco products in those who continue to use tobacco. Product regulation needs to occur within a framework that does not seriously interfere with societal efforts to reduce tobacco use.

With any normal consumer item any regulator would require to know the following:

- What is in it?
- What gets into the body as a result of its use?
- What are the consequences of those exposures?

The first problem with tobacco is that we also have to consider the following:

1. What is in the primary product, for example, the cigarette versus other tobacco, smoked versus smokeless tobacco
2. What is in the smoke (combustion products only)
3. What is absorbed into the body—all products
4. How much of this is harmful or addictive and increases attractiveness

With combusted products, regulation must consider the smoke. Cigarettes are the dominant form of tobacco use, and with other combusted forms such as cigar and pipe smoking, the product that is consumed is the smoke from burning the tobacco. Tobacco smoke consists of a whole range of new carcinogens and toxins created by partial pyrolysis, as well as some that were originally in the tobacco. Smoked tobacco products are not products that could be regulated by simply approving ingredients because smoke is the result of interactions between the tobacco when burnt and any additives or contaminants that are present, plus any other chemicals that are formed by the combustion of the additives.

The challenge of regulation comes down to one of reducing harmfulness, and as harmfulness is related to amount and duration of use, this must include reducing addictiveness and other modifiable factors that potentially increase or prolong usage at a personal and population level. Given the huge variation in the harmfulness of currently available products, there also needs to be consideration of what is an acceptable level of harm. This is not a scientific question, but it can be informed by science.

As we see it, there are three major regulatory possibilities, each requiring a research agenda to assess viability and possible mechanisms.

- **Regulating carcinogens and other toxins:** With tobacco, we face the fact that numerous components of smoke are either carcinogenic or toxic, or both, and the prime objective of regulation is to reduce this. Some of these chemicals come from the tobacco itself and are common to smokeless forms, but most come from the smoke. This is why smoking is inherently more harmful than smokeless tobacco use.
- **Regulating nicotine (addictiveness):** Tobacco products are addictive and addictiveness is positively related to consumer appeal. Cigarettes have the highest abuse liability of tobacco products, with more than 85% of users using on a persistent daily basis. We should be seeking to reduce their addictiveness as far as possible (Benowitz & Henningfield, 1994). In essence, this means regulating nicotine, and the ways nicotine is delivered (Henningfield, Hatsukami, Zeller & Peters, 2011), as nicotine is the drug that is central to tobacco use. Eliminating the nicotine would in effect be prohibition. Unless this is the chosen policy option, the policy can only be about limiting the nicotine in ways likely to reduce addictiveness, most simply by reducing levels of

nicotine but also by regulating the forms of delivery systems (Benowitz & Henningfield, 1994; Hatsukami et al., 2010; Henningfield, Benowitz, Slade, Houston, Davis, & Deitchman, 1998). There are a number of intervention points in the manufacturing process that allow this.

- **Regulating additives and engineering features:** For products as harmful and addictive as cigarettes, a powerful case can be made that it is not acceptable to modify the product in ways that mask some of the unpleasant side effects, such as the natural harshness of nicotine, as these would be a disincentive to use tobacco to start with. Hence, common sense would suggest that additives and engineering features that mask harshness of tobacco smoke could be prohibited as a means of reducing tobacco use. A research agenda is needed to work out what features of modern tobacco products are increasing consumer appeal and of the likely effects of controlling such features on use.

WHAT WE KNOW

We know a lot about the inherent danger and addictiveness of tobacco products. Much of this information has been summarized in the following sources:

- Monographs 37 (1985), 38 (1986), 83 (2004), and 89 (2007) of the International Agency for Research on Cancer (IARC, 1985, 1986, 2004, 2007)
- A series of reports by the U.S. Surgeon General (Shopland, Burns, Benowitz, & Amacher, 2001; U.S. Department of Health and Human Service, 1981)
- Tobacco: Science, policy, and public health (Boyle, Gray, Henningfield, Seffrin, & Zatonski, 2010)
- A series of technical reports by the WHO Study Group on Tobacco Product Regulation (TobReg) (2007; “Mandated lowering of toxicants,” 2008, 2009), which dealt specifically with the issues surrounding regulation
- In addition, there is a large amount of information available to guide regulatory science that has been made public over the last decade as a result of litigation against the tobacco industry (Robertson & Hurt, 2010)

There has been a relatively small research establishment of nonindustry laboratories working on the chemistry of tobacco and that, until recently, most of the work has been of a generic nature focusing primarily on cigarettes, with less on other forms of tobacco (especially forms not common in the west) and very little on specific brands or varieties of any product. Because consumers smoke specific brands of cigarettes, cigars and other forms of tobacco, focusing on brand and product-specific differences is critically important for understanding what is possible with existing technology. Unfortunately, there has been a serious dearth of work published on brands and many of the deficiencies highlighted by this review will focus on brand-specific data. Between-product variability provides much of the justification for regulation of the contents and emissions of tobacco products, of which the cigarette is the most important.

Even parts of the tobacco industry claim to support some limited forms of regulation. For example, the Annual Report of the Philip Morris Company for 2010 (Philip Morris International, 2010) states that the European Commission and some countries are considering regulating “cigarette ingredients” with the

stated objective of reducing “attractiveness” and “palatability.” Philip Morris “opposes regulations that ban ingredients to reduce palatability” but supports a ban on ingredients “that are based on sound scientific test methods and data to significantly increase the inherent toxicity and/or addictiveness of smoke.” Regulators would be unwise to narrow their perspective to one as narrow as this. Reducing the attractiveness of toxic products could potentially do more to reduce harm than reductions in their toxicity. Research is needed to better demonstrate the potential of attractiveness reduction approaches. Regardless of what Philip Morris may or may not support, it is clear that validated scientific methods are needed to help guide regulatory efforts to reduce the harm of tobacco products. For example, there is an immediate need to validate methods that can be used to set upper limits on the nine specific smoke constituents identified by the WHO Study Group on TobReg as likely contributing most to toxicity/carcinogenicity, a set endorsed by the COP Working Group.

EVOLUTION OF THE MODERN CIGARETTE

The cigarette became the dominant form of tobacco use as a result of the discovery of flue curing in the mid-19th century, which encouraged lung inhalation (Proctor, 2012), and the invention of the cigarette-making machine in 1880 (Doll, 2004), which encouraged mass use. The original old-fashioned cigarette or “gasper” that was produced was little more than a simple tube of cut tobacco rolled in paper by a machine, and presumably puffed on much as cigars today. There was also no filter, and the butts were often re-rolled in commercial cigarette paper or newspaper when smokers ran out. For many western nations, the First World War established smoking as a majority behavior among men while women took it up in the late 1920s. The cigarette, as far as we know, did not change much until after the Second World War. The advent of the filter after that war rapidly took over the market, perhaps encouraged by the increasing evidence of the harmfulness of smoking and the hope that filters would reduce the harms. Filters were then promoted as a harm-reduction strategy, even though this has proved to be illusory (U.S. Department of Health and Human Services [USDHHS], 2001). Changes to the tobacco market in the developing world were slower, and in some cases, relatively simple cigarettes are still available at the bottom end of the market in many countries. Indeed, cottage industry production is still an important in countries like India, especially for the cigarette-like bidi.

In the 1960s and 1970s, public health advocates and some health authorities focused their attention on the possibility of reducing the harmfulness of cigarettes. This effort was based on logic that seemed sound at the time. Wynder and Graham (1950) and Doll and Hill (1950) demonstrated a dose response between cigarette consumption and disease. Wynder, Graham, and Croninger (1953) demonstrated a dose response between tobacco tar applied to mouse skin and the tumor response so it was logical to think that a reduction in the number of tar particles applied to the lung would reduce disease potential. Although this view was relatively simple and restricted to the numeric, nobody believed that the tobacco industry would reduce measured tar in ways that

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were unrelated to actual human exposures and may have *increased* the risk of disease.

The main means of achieving this improbable outcome was through the use of filter venting (King, Carter, Borland, Chapman, & Gray, 2003; Kozlowski, Frecker, Khouw, & Pope, 1980). The main effect of this is that it resulted in smokers changing the way they puff on cigarettes to ensure they received their target dose of nicotine. The differences in burn rates and the changes in puffing changed both the mix of carcinogens and toxins and the way they are deposited in the lungs. For example, filter vented American blend cigarettes produce higher levels of tobacco-specific nitrosamines (Gray et al., 2000; Hoffmann, Djordjevic, & Hoffmann, 1997). This and the deeper puffing have been linked to an increase in the incidence of adenocarcinoma that has occurred since their introduction (Burns, Anderson, & Gray, 2011a, 2011b).

From the 1960s, at least there have been a great many changes made to the cigarettes sold in many parts of the world (Hoffmann & Hoffmann, 1994; Hoffmann, Hoffmann, & El-Bayoumy, 2001). Today's modern cigarette is a highly engineered drug delivery device engineered to maximize satisfaction through effective delivery of nicotine and to maximize consumer acceptance through improving the experience of use (i.e., making it taste less harsh; Baker, Pereira da Silva, & Smith, 2004a, 2004b; Bates, Connolly, & Jarvis, 2002; Hoffmann & Hoffmann, 1994; Hoffmann et al., 2001).

The tobacco industry has gone to some trouble to propose that "ingredients," which we have called additives (Baker et al., 2004a, 2004b) are harmless (Wertz, Kyriass, Paranjape, & Glantz, 2011). They have released the results of studies on more than 450 tobacco "ingredients" including over 400 flavors plus flavor/solvents, preservatives, binders, humectants, process aids, and filters and have claimed that these substances have "little effect" on smoke toxicology although they do refer to the exception of formaldehyde, which is a product of combustion of sugars and is carcinogenic. They do not mention acetaldehyde, which is also a product of combustion of sugars, a carcinogen present in microgram quantities in smoke and also recognized as a facilitator of nicotine (Talhout, Opperhuizen, & van Amsterdam, 2007). It is likely that other combustion-produced toxins are also produced. There is a need for independent research to validate the industry research, given the concerns about its limitations.

Other additives (humectants) influence droplet size and hence speed and site of absorption. They may thus play a role in the addictiveness of the product.

From this brief overview, it is clear that the task of product regulation will be challenging and needs to be aided by sound science.

DISCLOSURE—ARTICLE 10

Definition of disclosure: Article 10 requires the disclosure of contents and emissions to government authorities and also the disclosure of toxic content and emissions to the public.

What Is Needed for Disclosure?

- What infrastructure to collect and analyze industry data is required?

- Do we know what to ask for? For example, we can look to Canada but must ask is this viable for low- and middle-income countries (LMIC)?
- How do we develop the capacity for analyzing all the data that is disclosed? Are there critical research questions to ask of this disclosure?

The current situation: Only a small number of countries have legislated to mandate various forms of disclosure from the tobacco industry to provide for the regulation of tobacco products, but to date few have been able to use such legislation to commence any kind of regulatory process. The recent trend to requiring reduced ignition propensity cigarettes is a notable exception. The recent legislation that provides dedicated resources to the U.S. Food and Drug Administration (USFDA) to regulate tobacco products provides the first real possibility of having the resources to build an effective regulatory model, as the United States has the capacity to make extensive use of the information it is collecting. Europe has recently established two systems for collecting tobacco ingredient disclosures (EMTOC; <http://www.rivm.nl/tabakinfo/emtoc/>) and more general regulatory information (PITOC; http://www.fisaonline.de/index.php?act=projects&p_id=5290&lang=en).

What We Might Need to Know

An analysis of what it might be reasonably easy to know usefully can be framed around the process of tobacco production. In the following, we note the aspects where there is or may be sufficient standardization and centralization of decisions to be likely to manifestly affect the end products. Based on our current understanding of factors influencing tobacco toxicity and/or consumer appeal, aspects of tobacco production and manufacturing process that might prove useful for regulators to better understand include the following:

Farm Level

- Tobacco company (or related entity) guides of requirements for growing, including requirements on seed type, cultivation strategy, and use of fertilizers and insecticides, and use of casings.
- Tobacco company guides to curing and on-farm processing.
- Criteria used to influence purchase decisions, including any quantitative test results.

Manufacturing—Tobacco

- Disclosure, by product, of all additives with information as to amount (absolute, or if standardized, what the standardization criteria are).
- Recipes for blends of tobaccos and any standardization of ingredients, for example, nicotine levels and protonation level of the nicotine; cut width; selective use of parts of the leaf or leaves from different positions on the plant.

Manufacturing—To Final Packed Product

- Engineering features of the product where it is not simply the tobacco blend outlined above. This should include use of filters, filter venting (which should certainly be prohibited), packing density, weight, and even needs to include aspects of the packaging that might end up in the product; for example, menthol added to packaging infuses into cigarettes.

Performance

- For smoked tobacco, levels of identified chemicals per brand/variant using standardized testing and reporting criteria (see section on regulating levels of carcinogens and toxicants).

Marketing

- Requirements for disclosure of marketing budgets. This should include agreements with retailers about display of the products and other sales requirements.

Postmarketing

- Volume of sales by brand/variant on a daily/weekly basis (or as collected by the distributor).
- Other aspects of sale, for example, prices are relevant to other aspects of tobacco control, so should be collected concurrently.
- Consumer beliefs, attitudes, and behaviors including brand smoked, consumption, and smoking topography. Much of this survey information will also be relevant to monitoring other aspects of tobacco control.

Research is needed to help regulators determine what needs to be disclosed, in what format, and to whom in an effort to guide regulatory efforts to reduce the harm of tobacco products. Disclosure in Canada, for example, provides the regulator with a comprehensive list of ingredients, production steps, engineering features, and for smoked products the substances in the smoke produced when smoked to a common puffing protocol (Canadian intense). This is needed by each brand and variety within brands. The FDA has established criteria for some testing, as has the Canadian government.

Research Questions Related to Disclosure

- What aspects of the potential mass of information the industry has are likely to be useful for achieving the regulatory aims? Although it might be sensible initially to collect everything the industry knows, this has costs, both for the industry and those who need to fund the analysis of the information. Regulators will require systematic analysis of all that is initially required to be disclosed to see if the disclosure regime can be simplified by not requiring information that is not useful, standardizing the collection of information that is, and if necessary, identifying new things to report on.
- Smoking machines have been used for decades to generate data on smoke constituents of different brands of cigarettes. The data generated can be misleading to consumers and regulators. Research is needed to determine the most useful testing regimes to use as the basis of monitoring? This is an important question given the way the ISO testing regime (the main existing method of testing cigarettes) was misused in the past. The Canadian intense system, a way of testing that overcomes some of the main problems of the ISO system is now widely used (WHO, 2007) and provides a reasonable basis for action, although further research is required to see if even better methods can be found.
- There will need to be capacity to independently validate at least a sample of industry-disclosed characteristics of their products, unless all this testing is done by independent, authorized testing agencies.

RESEARCH TO SUPPORT THE REGULATION OF TOBACCO PRODUCTS—ARTICLE 9

Before considering a policy-oriented research agenda, it is necessary to know what the possible policy options for tobacco regulation are. Based on our earlier analysis, we think that there are three broad strategies that could be taken either alone or in various combinations. These are as follows:

- Acting to *set upper limits on individual carcinogens and toxins* can be used to reduce potential harmfulness.
- Regulating to control addictiveness is rather more complicated. Clearly, nicotine regulation is the basis of this. There may be potential to downregulate levels of nicotine, but more research is needed before this could be readily implemented as policy. Also there is theoretical potential for proscribing additives and/or engineering features where there is evidence that they might be or are designed to affect aspects of addictiveness.
- Regulating to control attractiveness is also difficult but can also be done through strong controls over the reasons why ingredients are allowed to be added to tobacco products.

The purpose of the research agenda is to provide evidence on the practicality and likely effects of regulation in these areas to aid policy makers decide which specific policies to adopt. That is, research is needed to establish more clearly the elements of tobacco product design that increase harm potential in any way.

Capacity

Most LMIC and many high-income countries will lack capacity to do all the regulatory work unassisted. Expansion of international facilities such as the WHO Tobacco Laboratory Network (TobLabNet) may be a partial solution but no solution is in sight for monitoring the number of individual brands currently on markets in developed countries.

At this point, it is relevant to note the enormous difficulties of regulating cottage industry, mainly for smokeless tobacco but which will also apply to bidis and some other forms of smoked tobacco. Solutions for this are beyond the scope of this paper as it seems certain that developed countries will lead the way in developing regulatory models, and they are likely to focus on products that are most prevalent in their markets (cigarettes and perhaps some forms of smokeless tobacco). As capacity develops, the regulation can be extended to other products.

Regulating Carcinogens and Toxins

This section starts with the assessed potential harmfulness of the product, which relates to levels of known carcinogens and toxins in smokeless products and levels of carcinogens and toxins in tobacco smoke for the smoked products.

There is a single research question that applies to every substance known to be dangerous in every brand. It is “How low can we go?” This is the central research question here. In some cases, it can be answered at least in part by disclosures of toxin exposures due to existing products.

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At this time, we do not know just how far we can go in lowering the permitted levels of carcinogens and other toxins. As stated above, the normal policy approach to contaminants in public health is to set them as low as technology allows which, for consumer products, is virtually zero. With tobacco (smoked, at least), this cannot be the case but science needs to show what levels are achievable.

Much of what we already know is to be found in WHO Technical Reports numbers 951 and 955 ([WHO Study Group on Tobacco Product Regulation, 2008a, 2009](#)) for both smoked tobacco and smokeless.

We have examples of analyses from 60 pages of tables, 20 brands per page, to be found in WHO Technical Report number 951 ([WHO Study Group on Tobacco Product Regulation, 2008b](#)) from which a small selection is reproduced in [Table 1](#). For smoked products, TobReg proposed using a metric of amounts per milligram of nicotine, whereas for smokeless tobacco they recommended amounts by weight.

What we see here in a relatively random selection are interesting differences between brands. Even in this small sample, there is more than a 2-fold difference in acetaldehyde levels and more than a 4-fold difference in NNK, whereas benzo[a]pyrene levels are more similar. This clarifies our research agenda and leads us to the central difficulty involved in regulation arriving at a minimal level of each substance that is achievable. It would be convenient if all the minimum levels were in the same brand but they are not.

The WHO Study Group on [TobReg \(2008a\)](#) recommended setting of upper limits on nine specific smoke constituents and the COP Working Group identified the same nine constituents as priorities for which methods of testing should be validated.

The nine substances recommended for regulation are as follows:

- *N*-nitrosonornicotine (NNN)
- NNK
- Acetaldehyde
- Acrolein
- Benzene
- 1,3-butadiene
- Benzo[a]pyrene
- Carbon monoxide
- Formaldehyde

TobReg noted that these substances can be significantly or substantially removed from cigarette smoke by existing technology. TobReg also recommended the following substances for reporting (disclosure):

- Acrylonitrile
- 4-aminobiphenyl
- Cadmium
- Catechol
- Crotonaldehyde
- Hydrogen cyanide
- Hydroquinone
- 2-naphthylamine
- Nitrogen oxides

This list of chemicals is provided as an appropriate starting point for possible regulation as they have been considered by an expert committee and enough is known about them to

Table 1. Yields per Milligram of Nicotine

Brand	Country	Acetaldehyde	Benzo[a]pyrene	NNK
Camel King Size	Canada*	586.34	7.18	100.44
Winston 100	Canada*	544.42	6.96	96.54
Sportsman plain	Canada*	364.48	7.55	25.81
regular size				
Marlboro KSF, sp	USA#	574.67	9.86	111.11
Merit KSF sp	USA#	750.00	7.69	99.68
Winfield filter KSF, sp	Australia@	486.78	7.49	33.70
L&M KSF hp	Europe#	870.00	9.61	59.13

Note. NNK = 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; KSF = king-size filter. Bold figures identify the highest and lowest yields.

*Reported to Health Canada.

#Reported by Counts, Morton, Laffoon, Cox, and [Lipowicz \(2005\)](#).

@Reported to Australian Health Department.

allow certainty that they can be sharply reduced and in some cases eliminated. The research objective is to find the lowest levels of each of these compounds that can be practically achieved.

The diversity of carcinogens/toxins between brands/variants both within and between countries provides clear evidence that there is room to reduce overall exposures by setting limits on carcinogens/toxins.

It should be stressed that there are more chemicals of concern than this. A recently published consolidated list identified 98 chemicals of concern. This highlights the challenge of making tobacco smoke less toxic, as many of these are created by partial pyrolysis.

The Canadian government has sponsored the development of a cigarette-puffing regime that provides a better indication of potential exposures than the current ISO-approved method. TobReg has recommended it to be used as the basis for testing cigarettes. Further, the measures of carcinogens/toxins should be reported per milligram of nicotine delivered.

The rationale for using exposures per milligram of nicotine is that smokers tend to titrate their nicotine intake. There are other advantages of testing per milligram of nicotine as it is a standard that can be applied to just about any tobacco product, including ones like large cigars that are designed to provide multiple doses of nicotine. However, for smokeless tobacco, where there is no combustion and the entire product is put in the mouth, it is reasonable to regulate carcinogens/toxins per gram of tobacco, and this is what TobReg recommended.

In summary, we know enough to start, but over time it should be possible to refine and improve standards. In particular,

- We have the scientific basis for defining objective criteria for defining types of tobacco products that might be subject to different regulatory standards.
- We have identified a set of carcinogens/toxins to regulate and/or monitor.
- We know enough to establish appropriate standardized testing regimes for the carcinogens/toxins that they are intended to regulate and/or monitor.

What We Need to Know Before Any Regulatory Scheme Is Implemented

- Disclosure of the carcinogen/toxin levels for the bulk of the market, but ideally for all products. These need to be measured using standardized procedures.
- Modeling to determine an algorithm to estimate the percentage of the current market (% of variants and/or by sales) that would be prohibited as limits to maximum levels of target chemicals were adjusted. This would enable decisions for the maximum levels to be allowed for any or all of the nine target chemicals. This is needed to allow policy makers to control rate of change, something they are likely to want to achieve.
- What surveillance would be required to ensure no major unintended consequences and to allow early action if signs of such problems occurred? For example, is there risk of increases in other carcinogens/toxins? Is there any evidence of consumers rebelling and seeking illicit forms of products that exceed the standards that are in place at any point in time? To what extent will tobacco companies reengineer cigarettes to meet new standards and what impact will this have on use of such brands; for example, what would be the implications for Marlboro KSF if its NNK levels were reduced to those of Sportsman Plain, that is, only a quarter of what they currently are?

Research Questions That Need to Be Addressed

- What biomarkers do we need to evaluate the potential health impact of reductions in carcinogenicity/toxicity that might be achieved by any given regulatory activity?
- What is the most appropriate way to sample product to test so that it captures the natural variation in yields of a product?
- Is there a better method for testing cigarettes than the Canadian intense standard?
- Should each of the regulated carcinogens/toxicants be treated as equal or should they be weighted in terms of likely harmfulness? How would this be done? This leads to subsidiary questions such as follows: Can we rank carcinogens/toxins in terms of their potential for harm, at any given level of exposure? Is the Fowles and Dybing (2003) ranking a viable basis for more precise regulation? If not, what research is needed to arrive at a better set of criteria?
- To what extent are the levels of carcinogens/toxins correlated and are these relationships causal? Current research indicates that levels of most carcinogens/toxins are not necessarily positively correlated. This makes it more difficult to create products that are lower in total carcinogenicity/toxicity than others, as it limits the capacity to have products simultaneously low in all. If it is not possible to simultaneously reduce levels of them all, then it is important to identify strategies to reduce the most dangerous ones.

Research That Should Not Be Done

We believe that with the exception of the relatively small number of questions that need to be resolved before regulation can

occur, and for the most part this requires being informed by the current science, that enough is known to commence regulation.

The public health establishment has had some unfortunate experiences that have consumed substantial resources and led nowhere. To illustrate the possibilities for avoiding serious mistakes, we make the point that the history of Tobacco Specific Nitrosamines (TSNA) represents a serious public health failure.

The TSNA are powerful carcinogens that occur largely during the curing process. They have been present in high levels in U.S. blended cigarettes for decades (Hoffmann & Hoffmann, 1994) and are still there despite the fact that low nitrosamine tobacco has been developed in Sweden and is now on sale in the form of Snus in the United States by Philip Morris and British American Tobacco. However, it has not been used by Philip Morris or British American Tobacco in their cigarettes.

The conclusion we may draw from this cautionary tale is that there is some research that is not necessary. We already know enough to reduce TSNA to extremely low levels. All that is required is regulation.

Regulating Nicotine (Addictiveness) and the Attractiveness of Tobacco Products

We have combined discussion of these two potential areas for regulation as they overlap somewhat. Some engineering features and additives appear to have both direct (via nicotine absorption) and indirect effects on the addictiveness of tobacco products.

Product Attractiveness

The qualities of a tobacco product can be influenced by everything from the types of tobacco used, growing conditions, things put on the plant (e.g., sprays) during growing, aspects of the drying and curing, through to all aspects of the manufacturing process. The cigarette paper, the filter, and even the packaging (menthol is typically added by allowing it to infuse into cigarettes from the packaging) can all be involved in making changes to the chemistry of the smoke.

Except for the effects of the ground the tobacco is grown in and the climate at the time, virtually everything else about the production of tobacco products is based on purposeful decisions of parts of the tobacco industry. Although some of these will be necessary for producing the particular type of tobacco product and others may be to reduce harm or product spoilage (e.g., mould suppressants), many of the choices affect the attractiveness of the product and some affect nicotine absorption, and thus addictiveness more directly.

Unfortunately, at present, little is known about the rationale for most ingredients and engineering features, including overall recipes of specific tobacco products. This places constraints on regulatory efforts. The need for disclosure of this information was discussed earlier.

What We Know About Nicotine

Nicotine is the main tobacco alkaloid responsible for the development of dependence on tobacco. However, pure nicotine, available as a therapeutic product, currently has less potential for abuse liability than tobacco-delivered nicotine, especially

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smoked forms. Therapeutic nicotine is currently an incomplete substitute for tobacco nicotine, although its use is associated with relief of withdrawal symptoms and cessation of tobacco use in a percentage of tobacco users.

Tobacco is efficiently addictive and its use and maintenance is primarily due to the psychopharmacological effects of nicotine (Henningfield & Benowitz, 2010). Nicotine measured and reported as a single substance by standard methods is the principal alkaloid in tobacco, a basic substance that contains a cyclic nitrogenous nucleus, whereas nornicotine, anabasine, and other minor alkaloids are also of importance (Djordjevic, 2010).

Probably the most important qualities of tobacco nicotine (Hoffmann & Hoffmann, 2010; Wayne & Carpenter, 2010) that have impact on addictiveness and thus the “fix” it provides are as follows:

- The *speed* of absorption that is affected by:
 - The degree of protonation that is affected by,
 - The pH that is also affected by,
 - The ammonia levels and other substances, which are affected by,
 - The level of nitrate in the tobacco, which is affected by,
 - The amount of nitrate in the fertilizer and the method of curing.
- The *site* of absorption—mainly via the alveolar part of the lung, that is affected by:
 - The droplet size that is affected by,
 - Humectants, type of filter, smokers depth of inhalation.

Addictiveness is also affected by a number of *substances* which facilitate the effect of nicotine. These include:

- Acetaldehyde that is dependent on the amount of
- Sugars that produce it on combustion, and
- Levulinic acid that enhances the binding of nicotine in the brain, plus
- Bronchodilators such as cocoa and licorice which allow deeper inhalation, and
- Flavorings that contribute to the attractiveness of the products.

Notably, these are chemicals and are measurable in milligrams.

However, addiction is more than just chemistry. Addiction is a biopsychosocial phenomenon. This means that the addictiveness of a product is affected by the context of use, the experiences associated with use, and the effects of the product on the brain. This complexity is one reason why addiction to one form of a drug does not necessarily translate to alternative forms.

Some of the users’ responses to the sensory characteristics of tobacco use become conditioned to the rewarding effects of the nicotine and thus come to play an important part in nicotine addiction. Other sensory qualities (e.g., sweetness) are there to make the products more appealing to the user, particularly the novice user, independent of their capacity to become conditioned to the nicotine delivery. In this way, they contribute indirectly to increased addictiveness.

All of the above variables contribute to addictiveness. It is apparent that the tobacco industry has delved deeply into behavioral science and has been able to define a number of

these characteristics and measured them by methods such as consumer panel ratings and preference measures. Sensory factors include the following (Wayne & Carpenter, 2010):

- Aroma
- Smoothness
- Harshness
- Mildness
- Palatability
- Aftertaste

These qualities are not measurable in milligrams but are achieved by addition of chemicals that are measured in milligrams. They are produced by a combination of additives and special tobacco blends.

The industry has been able to manipulate sensory qualities in its product designs for individual brands. One purpose is to target specific subpopulations with brands designed to overcome barriers to use associated with the taste of the product. For example, youth and women have been targeted in this way (Carpenter, Wayne, & Connolly, 2005; Carpenter, Wayne, Pauly, Koh, & Connolly, 2005).

Research is needed to unravel these chemical approaches to population targeting. The small amount of evidence we have suggests that there is a lot more to be done in controlling the characteristics of tobacco smoke than merely focusing on carcinogens and toxicants.

As an example, Wayne and Connolly (2002) studied the effects of menthol and linked it to “reduced harshness, increased nicotine-associated impact, greater ease of inhalation, and enhanced bioavailability of nicotine.” The role of menthol is known to be a factor in choice of brand among African-Americans, but the reason for small amounts of menthol in a large number of brands is not clear. Menthol is clearly used to attract smokers (see also Tobacco Control, 2011; U.S. Food and Drug Administration [USFDA], 2011), even though this may not inevitably be successful. Is what we know about menthol enough to justify policy action? If not, what would be enough?

The establishment of Marlboro as the world’s number one brand may be more due to its chemistry than its cowboy (Gordon, 1992).

- What other symbiotic effects on nicotine bioavailability are there?
- What other chemicals contribute to the attractiveness and dependence inducing ability of the cigarette?

One major area where we know enough to act is that of filter ventilation (Benowitz et al., 1983; Kozlowski et al., 1980). Filter ventilation is the means for allowing compensatory smoking and a means by which cigarettes that deliver equivalent levels of tar and nicotine appear to vary in their strength (and thus apparent deliveries). Filter venting is the basis for much of the differentiation of the market in terms of rated strength of flavor. This was originally marketed in terms of light or mild taste and/or variations in tar levels, based on yields from machine-smoking the cigarettes with the venting holes uncovered, but which disappear when smoked as smokers smoke them. The use of the misleading terminology is now prohibited, but the engineering features that create the misperception are still allowed.

These examples suggest that there may have been quite a large number of attempts to capture a particular market and different recipes, coupled with engineering features, used in conjunction with targeted advertising campaigns. On top of this, the industry had the advantage of sales figures available for instant feedback to help them refine their strategy.

However, the large number of additives used and their differential use across a wide variety of products means a potentially huge research effort if the effects of all additives are to be fully understood. Policy makers need to decide how much evidence they need before taking action. Researchers need to be ready to provide the level of evidence required.

In terms of product regulation, there are two important research questions where additional information would help guide policy making:

- Can we standardize the cigarette to deliver a consistent and known maximum nicotine dose?
- Can the national dose be reduced over time?

The objective of regulation is to reduce the intake of carcinogens and toxins. This is dependent on the bioavailability of nicotine taken by the smoker, which we have referred to as “dose.” Nicotine is in itself relatively nontoxic in the amounts delivered by the cigarette, but its powerful addictive capacity is the basis for the damage done by the diverse and complicated mixture that is inhaled in the wake of nicotine.

What we do know from studies of smoking topography is that most addicted smokers take a relatively consistent amount of nicotine over the course of the day (Benowitz, 2001; Benowitz et al., 1983; Djordjevic, Fan, Ferguson, & Hoffmann, 1995; Herning, Jones, Bachman, & Mines, 1981; Kozlowski & O'Connor, 2002). One potential research agenda could be based on additive-free cigarettes with unventilated filters and consistent physical features such as draw resistance and amount of tobacco in the rod. Research studies should be aimed at finding three or four nicotine dosage levels so that there is a cigarette suitable for those with high nicotine need and those with a low need but without the flexibility of the current designs, which facilitate compensatory smoking. Would such modifications reduce tobacco uptake and/or make cessation easier?

There is considerable interest in the potential to reduce overall nicotine levels (Benowitz & Henningfield, 1994; Gray et al., 2005), something that appears to be possible at least in the short term, but which remains controversial. A large research agenda is warranted here.

Research Questions

Central to any regulatory endeavor is addressing the following questions:

- What are legitimate reasons for permitting or mandating an ingredient or an engineering feature in a tobacco product? Can existing additives and engineering features be prohibited based on precautionary principles, or will direct evidence of their adverse effects be required?
- At what levels of likely overall product harmfulness should restrictions on additives that increase attractiveness be implemented?

These questions go beyond conventional science and require consideration by lawyers and ethicists. As the justification

might vary depending on the constitution of the country and other aspects of existing laws, there will need to be consideration of country differences.

Beyond this there is a more conventional research agenda:

- What chemicals, apart from nicotine, contribute to the addictiveness of tobacco?
- What criteria can be used to quantify those features that contribute to addictiveness, directly or indirectly?
- What additives that might be justifiable on grounds of safety or necessity have unwanted effects by increasing consumer appeal?
- When regulations prohibit or restrict additives and/or engineering features, there will be an important evaluation research endeavor to determine the effects, both desired and any possible undesirable effects.
- What effects will any realized restrictions have on the tobacco market? Will they lead to more successful quitting? To less uptake? Will they contribute to a larger illicit market in products that have some of the prohibited features?
- How do behavioral and sensory aspects of tobacco use contribute to the addictiveness of the tobacco product and to what extent do they make the addiction specific to that form of administration?
- To what extent do sensory factors such as aroma, smoothness, harshness, mildness, palatability, and aftertaste actually contribute to both initiating use and to prolonging use?

RESEARCH SPECIFIC TO NICOTINE

At this point, we think more research is needed before population-level attempts to downregulate nicotine will be viable. Some of the questions that need to be answered are as follows:

- Can we standardize the cigarette to deliver a consistent and known maximum nicotine dose?
- Can this be done in a way that constrains the obtained dose of nicotine? This is unlikely to be achieved in a cigarette that uses a ventilated filter as vent blocking facilitates compensatory smoking.
- What would the effects of such changes be on smokers with differing ‘needs’ for nicotine? For example, would those with high needs seek higher yield cigarettes (potentially from illicit sources). Would this cause problems for those with low target thresholds with overdosing?
- One theoretically promising approach would be research based initially on cigarettes with unventilated filters and consistent physical features such as draw resistance and amount of tobacco in the rod. Research studies could be aimed at finding a range of (e.g., three or four) nicotine dosage levels so that there is a cigarette suitable for those with differing needs for nicotine, but which does not have the flexibility of the current designs, which facilitate compensatory smoking.
- Can smokers be trained to reduce their target level of nicotine over time?
- Can the national dose be reduced over time?
- Is nicotine weaning possible?
- Would it work for all smokers?
- How low can we go in reducing maximum nicotine yields from a cigarette?

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- Would a yield reduction strategy need to be done on a whole of population basis (i.e., simultaneously reducing potential yields for all cigarettes) or could it be done as an opt-in strategy that smokers chose?
- If weaning is only possible down to some level before there is consumer resistance, will it be easier for smokers to quit once they have dropped their exposures to these levels?
- Are there any adverse effects of reducing and/or standardizing nicotine dose? For example, could the standard dose be more likely to lead to tolerance and thus larger target doses over time and could this affect the ability of a user to quit?

Communication Issues Arising From Articles 9 and 10

There are two main issues that need to be addressed here:

- Communication about changes in the carcinogen and toxin profile of individual products and thus inferences that might be drawn about reduced harmfulness
- The relative harmfulness of different types of products and possible uses of such products, especially those where there is evidence of reduced harmfulness

These issues are critical as they affect both the likelihood of users moving to less harmful forms and also the risk of increased use of still unacceptably harmful products that are mistakenly construed as somehow “safe enough.” In this paper, we do not have the space to deal with these issues in detail but raise them and identify them as top-level research issues required to complement regulation of the products themselves.

Communicating About Reduced Carcinogenicity/Toxicity

The rationale for reducing levels of carcinogens and toxins is to reduce harm. However, this may not turn out to be right, or the reduction in harm may be small. This reality creates a dilemma, as if the reductions in carcinogenicity and toxicity are taken to mean that smoking is less dangerous, it could be used to justify continuing to use. Based on knowledge of communications, it is clear that these risks are greatest if marketers of tobacco products can promote reductions in toxicity. Governments could prohibit marketers promoting their products in terms of harm reduction unless the outcome was sufficiently demonstrated. It would cause less potential problems if governments were to regulate reductions in carcinogens and toxicants, but not allow this information to be used to market the products. The main argument against this position is that it does not provide an advantage to the least carcinogenic and toxic products in a class, so could slow down any gradual reduction in maximum levels, if the market tends to cluster close to the maximum allowed levels. Depending on the policy maker's act, the size of the research agenda will change markedly. At a minimum, research is needed to document potential effects of consumer awareness of the implementation of harm-reduction strategies.

Communicating About Relative Risk

Low carcinogen and toxin forms of smokeless tobacco are markedly less harmful than smoked tobacco, as are products that provide therapeutic-quality nicotine. Some potentially lower harm products such as Snus are being promoted for use for “...situations where you cannot smoke.” At this point in

time, it is not known how viable a strategy of substitution of less harmful products for those who cannot or will not quit tobacco would be. The substitutability will be a function of the similarity in nicotine delivery and probably the mode of delivery. Wherever there is the possibility of substitution, and especially where public health authorities are prepared to encourage it, research will be needed as to how to do this in ways that minimize risks.

Research Questions

- What communication strategies are required to maximize movement away from the more harmful to less harmful products, without encouraging inappropriate use of these products by those that would not otherwise be using tobacco products?
- To what extent does promotion of cleaner forms of nicotine as strategies to use for when smoking in not possible inhibit movement away from smoked tobacco?
- Is simply mandating, but not publicizing, mandated reductions in yields of carcinogens and toxins enough to prevent misconceptions of safety emerging, or are specific, targeted education campaigns required?
- How can communications about variants of comparably harmful products be managed in ways that do not imply differential harmfulness associated with the variants; for example, taste differences, strength differences (if allowed)?
- How, if at all, are the kinds of communication challenges referred to above affected by such things as strong health warnings on packs or standardized (or plain) packaging? What are the implications for countries with strong laws supporting freedom of expression?

OVERALL RESEARCH PRIORITIES

The research agenda on tobacco products could be almost endless. However, for effective tobacco regulation to commence, we believe the following are the highest priorities:

1. Development of an empirical model on the impacts of various levels of reduction in target carcinogens/toxins, both by consumer market (e.g., country) and overall.
2. Setting up an appropriate monitoring and evaluation mechanism to assess the impacts of regulations when they occur. This should include research to identify better ways of measuring toxin yields; identification of appropriate biomarkers of harm; levels of cessation and uptake; and surveillance of the market, including the illicit sector.
3. If compensatory smoking was to be substantially reduced, would it be possible to reduce average intakes of nicotine? If so, would this make quitting easier?
4. How can governments and regulators best communicate about their efforts to reduce tobacco-related harm in ways that do not lead to unrealistic expectation about reduced harm, or worse still products being perceived as safe enough while still unacceptably harmful. It also involves managing the reality that regulation will show some tobacco products to be far lower in carcinogens/toxins than others, an issue which will vary depending on policy decisions about the desirability of substitution of more for less harmful alternatives.

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