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Review

# Monitoring the tobacco use epidemic II
# The agent: Current and emerging tobacco products

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ABSTRACT

*Objective.* This Agent paper (II of V on monitoring the tobacco use epidemic) summarizes the findings and recommendations of the Agent (product) Working Group of the November, 2002, National Tobacco Monitoring, Research and Evaluation Workshop.

*Methods.* The Agent Working Group evaluated the need to develop new surveillance systems for quantifying ingredients and emissions of tobacco and tobacco smoke and to improve methods to assess uptake and metabolism of these constituents taking into account variability in human smoking behavior.

*Results.* The toxic properties of numerous tobacco and tobacco smoke constituents are well known, yet systematic monitoring of tobacco products has historically been limited to tar, nicotine, and CO in mainstream cigarette smoke using a machine-smoking protocol that does not reflect human smoking behavior. Toxicity of smokeless tobacco products has not been regularly monitored. Tobacco products are constantly changing and untested products are introduced into the marketplace with great frequency, including potential reduced-exposure products (PREPs). The public health impact of new or modified tobacco products is unknown.

*Conclusions.* Systematic surveillance is recommended for mainstream smoke constituents such as polycyclic aromatic hydrocarbons (PAH), tobacco-specific nitrosamines (TSNA), total and free-base nicotine, volatile organic compounds, aromatic amines, and metals; and design attributes including tobacco blend, additives, and filter ventilation. Research on smoking topography is recommended to help define machine-smoking protocols for monitoring emissions reflective of human smoking behavior. Recommendations are made for marketplace product sampling and for population monitoring of smoking topography, emissions of toxic constituents, biomarkers of exposure and, eventually, risk of tobacco-related diseases.



**Contents**



## Introduction

Despite longstanding knowledge of the toxicity and carcinogenicity of many of the thousands of constituents of tobacco and tobacco smoke, systematic monitoring has been historically limited to only three: tar, nicotine, and carbon monoxide in mainstream smoke.

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(Stratton et al., 2001) Even this limited effort is inadequate, as it is based upon a machine-smoking protocol that does not reflect human smoking topography and its variability (Djordjevic et al., 2000). Furthermore, ingredients of smokeless tobacco products have never been monitored. Manufactured cigarettes and other tobacco products are constantly changing and new products are constantly introduced, including potential reduced-exposure products (PREPs). The public health impact of new or substantially altered tobacco products is unknown (Stratton et al., 2001; National Cancer Institute, 2001; Hatsukami et al., 2006; Pankow et al., 2007).

The Agent (product) Working Group of the National Tobacco Monitoring Research and Evaluation Workshop focused on monitoring toxic smoke constituents of cigarettes and the composition of cigarettes and other tobacco products with emphasis on the need to provide measurements which (a) reflect a wide range of toxic compounds relevant to human health, and (b) do so in a manner which reflects human use behavior.

The selection of specific compounds for monitoring is not a simple process. Chemical compounds found in the mainstream smoke of cigarettes number well into the thousands (Hecht and Samet, 2007; IARC, 2004) and belong to a variety of chemical families with distinct toxic, carcinogenic, physiological, and metabolic properties. Even assuming that a reasonable choice of analytes can be made, the measurement procedure itself is a matter of considerable current debate centering on the choice of a protocol for machine-smoking cigarettes. It was the conclusion of the Agent Working Group that no existing protocol could as yet provide a framework for comprehensive product surveillance, and consequently that a program of research in this direction would be an important recommendation, as described below. The Agent Working Group's recommendations are consistent with a set of tobacco product research and testing guidelines which were approved and adopted by the WHO Study Group on Tobacco Product Regulation (TobReg) in Montebello, Canada, in 2004 (WHO Study Group on Tobacco Product Regulation, 2004).

## Methods

### *Existing surveillance and monitoring methods*

The Working Group's starting point was an assessment of current monitoring activity, which is driven to a large extent by legal requirements imposed by the US Federal Trade Commission (FTC). Since 1967 the FTC has reported yields of tar, nicotine, and carbon monoxide in nearly all cigarette brands marketed in the US. Reporting extends to sub-brand varieties (e.g., hard and soft pack, 85 mm and 100 mm, “lights” and “ultra-lights”) which number about 1300 distinct products (Federal Trade Commission, 2000). Since 1987 these data have been assayed and reported to the FTC by laboratories operated by the tobacco industry.

The usefulness of FTC report data for public health monitoring is limited for a number of reasons. First tobacco smoke is a mixture of thousands of chemicals of which many exhibit toxic effects ranging from cancer to cardiovascular disease, respiratory effects, and adverse birth outcomes (IARC, 2004; US Surgeon General, 2004). The three smoke components currently mandated by the FTC do not capture the range of potential toxicity qualitatively associated with cigarette smoking, and therefore cannot provide a rational basis for quantifying or ranking products and associated risks (Fowles and Dybing, 2003). Furthermore, although the Agent Working Group focused on the composition and potential health effects of mainstream tobacco smoke, it has recently been reported that industry-sponsored toxicological studies have shown that sidestream smoke toxicity increases with aging and exposure duration, which may help explain the relatively large biological effects of sidestream smoke compared to equivalent amounts of mainstream smoke (Schick and Glantz, 2006).

Secondly, cigarettes are the only tobacco products whose constituents have been routinely monitored. It was established decades ago that use of snuff and chewing tobacco increases the risk of cancer of the mouth and other organs (National Cancer Institute, 1992; Cogliano et al., 2004) and it has been amply documented that smokeless tobacco contains a wide variety of carcinogenic nitrosamines (Djordjevic et al., 1989; Hoffmann et al., 1991, 1995).

Third, cigarette yields as reported by the FTC are measured using a tobacco industry testing protocol based on machine-smoking of cigarettes which does not reflect human exposure. This is well recognized even within the tobacco industry, which has flatly stated: “The machine results are not necessarily predictive of yields created by individual consumers. Smokers not only smoke different brands differently, but they also smoke the same brand differently depending upon a host of human, social and environmental variables.” (CORESTA, 2005).

Fourth, the practice of surveillance to date has been limited almost entirely to the tobacco product itself and has not made routine use of methods measuring physical human smoking patterns (topography) (Djordjevic et al., 2000; Hammond et al., 2005), the pharmacology of nicotine, (Benowitz, 1999) or use of biomarkers (Shields, 2002). It was the conclusion of the Agent Working Group that a responsible surveillance program should take these factors into consideration.

Finally, manufactured cigarettes and other tobacco products are continuously changing and new products are constantly introduced into the marketplace, such as PREPs. These include products such as Brown & Williamson's Advance, RJ Reynolds's Eclipse and Camel Snus, Philip Morris's Accord and Marlboro Ultrasmooth, Vector's Omni and Quest, and Star Scientific's Ariva. The potential public health impact of several of these products was evaluated by a group of multidisciplinary experts convened by the Institute of Medicine in 1999, which was charged with addressing “the science base for harm reduction” (Stratton et al., 2001). Hatsukami et al. recently summarized the IOM recommendations regarding PREPS, noting that such products accomplish their aims with a variety of techniques, including addition of catalysts to reduce polycyclic aromatic hydrocarbon (PAH)-associated carcinogens, use of genetically modified plants to alter nicotine content and nitrosamine formation, and use of carbon filters to selectively reduce toxicants (Hatsukami et al., 2005). Pankow et al. estimated potential lung cancer risk reduction for four PREP prototypes and four commercial PREP products, and concluded that switching to these products would not reduce risk by more than 2% (Pankow et al., 2007).

Attention was also drawn by Hatsukami et al. to commercial use of modified curing methods to reduce nitrosamines (Hatsukami et al., 2005). For example, tobacco for the Brown & Williamson product is processed by a curing method, patented by Star Scientific, of Petersburg, VA, which produces low-nitrosamine tobacco. The declared corporate mission of Star is “to reduce toxins in tobacco so that adult consumers can have access to products that expose them to

**Table 1**
Short- and long-term recommendations of the Agent Working Group for research and implementation of tobacco constituent surveillance

| Short-term recommendations (within 12- to 24-months) | Long-term recommendations (within 5 years) |
|---|---|
| #1: Begin surveillance of content and composition of unburned or non-combustible tobacco products; support research to identify toxicological assays for subsequent use in monitoring. | #1: Establish a surveillance system of mainstream cigarette smoke composition based upon analytes listed in Table 2 |
| #2: Develop topography-based machine-smoking protocols | #2: Support research to determine a core set of human biomarkers and begin surveillance of the most relevant biomarkers (see Table 2) |

sharply reduced toxin levels." (Star Scientific, 2006) The Agent Working Group was concerned that there is no monitoring system to test the validity of such claims. The public health impact of rapid and drastic changes in tobacco products on a population of millions of smokers is unknown.

## Results

The short- and long-term recommendations of the Agent Working Group are presented in Table 1. As part of its first recommendation, the Agent Working Group enumerated a set of tobacco product characteristics that the industry should report on a regular basis which would alert the public health community and regulators to potential major shifts in product composition. These include the composition of tobacco blend (tobacco type, curing technology, use of reconstituted tobacco sheets and expanded tobacco), cigarette physical design factors (length, circumference, filter type, and percent ventilation; paper porosity; tobacco weight per cigarette), and specific additives. Additionally, this recommendation would cover smokeless products such as moist snuff as well as emerging PREPs. It would cover recent introductions such as low-nitrosamine smokeless and spitless tobacco products, for which limited human risk data are available (Levy et al., 2004).

The second short-term recommendation would lay the groundwork for a future, more comprehensive monitoring system by creating and funding a research program to develop machine-smoking protocols based upon comprehensive assessment of human smoking topography. There is current scientific consensus that yields of tar, nicotine and other smoke constituents derived from machine-smoking using the US Federal Trade Commission (FTC)/International Standardization Organization (ISO) protocols do not provide valid estimates of human exposure or of relative human exposure when smoking different brands of cigarettes (National Cancer Institute, 2001). The limitations of a single machine testing protocol for estimating human exposure are due to both the variation in individual smoking patterns and to systematic differences in smoking patterns that result when cigarettes with different designs are smoked. The difficulty of mimicking human smoking with existing regimens has been discussed by Hammond and colleagues who reviewed four alternative machine-smoking regimens of varying puff frequency and volume, filter blockage, and flow rate (Hammond et al., 2006; Hammond et al., 2007). The protocols included the "intense" Canadian method (puff volume=55 ml, puff frequency=30 s, filter blockage=100%, flow rate=27.5 ml/s). They concluded that none of the methods tested was more representative of human smoking behavior than the FTC/ISO method (35 ml, 60 s, 0% blockage, 27.5 ml/s), and none provided better predictors of human exposure. Machine testing using protocols currently in use should not be used to support claims of reduced risk. New protocols would be useful to characterize cigarette emissions for design and regulatory purposes although communication of machine measurements to smokers can result in misinformation about differences in exposure and risk across brands.

Two longer term recommendations also flow from these proposals. The first is establishment of a program of surveillance of tobacco smoke components based on human smoking parameters. The Agent Working Group recognized that considerable preliminary research is required in order to develop a consensus on the types of instrumentation needed, specific behavioral measurements, and working protocols, which are implicit in this recommendation.

The second long-term recommendation is that surveillance include biomarkers of human exposure in body fluids such as saliva, serum or plasma, and urine (see Table 2). Serum cotinine has long been used routinely to monitor cigarette smoking patterns (O'Connor et al., 2006) as well as exposure to secondhand smoke in defined populations (Pirkle et al., 2006). Other available biomarkers include thiocyanate, metabolites of tobacco-specific nitrosamines (TSNA), glucuronidation products, PAH adducts with DNA and hemoglobin, and genetic markers, as reviewed by Shields (2002) and by Hatsukami et al. (2006). At present, these metabolic products can supplement or replace relatively crude dosage measures such as number of cigarettes per day and FTC tar and nicotine yield. However, despite the widespread and growing use of dosage biomarkers, investigators vary widely in their choice of biomarkers and a consensus on a specific set of compounds has not yet emerged. Furthermore, as Hatsukami et al. pointed out in a recent review, no satisfactory biomarkers are as yet available which are reliably predictive of tobacco-related diseases (Hatsukami et al., 2006).

**Table 2**
Tobacco smoke constituents proposed as targets of surveillance

| Mainstream smoke component | Reason for inclusion | Examples |
|---|---|---|
| Nicotine | Addicting agent | |
| Tar | Carcinogenicity | |
| Carbon monoxide | Anoxic agent; cardiotoxicity | |
| Nicotine protonation factors, pH, free-base nicotine | Uptake facilitation | Free-base nicotine, ammonia, pH (measured using methods described by Pankow et al. (Pankow et al., 2003a,b and Watson et al.(Watson et al., 2004) |
| NOx | Respiratory toxicity | |
| Nitrosamines | Carcinogenicity | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)<br>*N*′-nitrosonornicotine (NNN)<br>Volatile nitrosamines: Dimethylnitrosamine (DMN), *N*-nitrosopyrrolidine (NPYR) |
| Polycyclic aromatic hydrocarbons (PAH) | Carcinogenicity | Benzo(a)pyrene<br>Benz(a)anthracene |
| Benzene | Leukemogen | |
| 1,3-butadiene | Probable carcinogen (IARC class 2A carcinogen: sufficient evidence in animals/limited in humans, IARC, 1999) | |
| Ethylene oxide | Carcinogenicity | |
| Formaldehyde, acetaldehyde | Carcinogenicity | |
| Acrolein | Respiratory toxicity, irritant, ciliatoxic | |
| Metals | Toxicity, neurotoxicity, carcinogenicity | Arsenic, cadmium, chromium, lead, nickel, polonium-210 |
| Aromatic amines | Carcinogenicity | 4-aminobiphenyl |
| Heterocyclic aromatic amines | Carcinogenicity, tumor promotion | 2-amino-3-methylimidazo[4,5f] quinoline (IQ)<br>2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) |
| Phenols, catechols | Cocarcinogens | Phenol, catechol |
| Free radicals | Carcinogen mechanisms | |

## Discussion

### *Methods, challenges, and opportunities*

As noted by Giovino et al. (2009) in their Overview paper, tobacco usage in our society is a complex public health problem that requires a variety of coordinated approaches. As described in this paper, The Agent Working Group focused on the physical, chemical, and biological properties of tobacco products (Stellman and Djordjevic, 2009). Other Working Groups addressed the need to improve population survey methods used to track use of tobacco products (Delnevo and Bauer, 2009), to identify and understand the societal factors that influence tobacco use by individuals (Farrelly, 2009), and to monitor the behavior of the tobacco industry as it adapts to

increasing pressures of social constraints on the marketplace (Cruz, 2009).

The Agent Working Group evaluated the need to develop new surveillance systems, in light of the foregoing limitations of existing knowledge and methods for quantifying critical components of tobacco and tobacco smoke. The evaluation was influenced by several important considerations. First, surveillance of tobacco smoke should be expanded to include classes of chemicals that are found both in particulate matter and the gas/volatile phase, and that are known to play important roles in human illness. Furthermore, surveillance should not be based on the misleading FTC machine-smoking protocol but should take account of the variety and variability of human smoking behavior. The Agent Working Group strongly recommended that the practice of surveillance should be extended beyond tobacco and smoke to include measurement in humans of metabolites and other biomarkers of exposure to tobacco products.

It was recognized that recommendations involving disclosure of tobacco composition require no new technology and could be achieved relatively quickly in a regulated environment. On the other hand, before topography-based surveillance can be implemented, protocols for assessing human smoking behavior must be developed which cover a wide range of tobacco products (e.g., cigarettes whose nicotine yield ranges from very low to high) and must be suitable for large-scale implementation. Therefore, two short-term recommendations address, respectively, an immediate program of tobacco product surveillance and a research program to develop topography-based machine-smoking protocols (Table 1).

Wishing to be as specific as possible the Agent Working Group drew up a list of candidate tobacco smoke constituents based on their potential health effects and the availability of appropriate measurement technology (Table 2) (Hecht and Samet, 2007). These include families of carcinogens such as PAH and nitrosamines, heavy metals, aromatic amines, and compounds which in addition to toxic effects may affect the uptake of toxic agents either pharmacologically (e.g., ammonia content and smoke pH) (Willems et al., 2006; Pankow, 2001; Pankow et al., 2003a,b; Watson et al., 2004) or via physiological action as may be the case with menthol (Wayne and Connolly, 2004). Some research needs regarding measurement of tobacco smoke pH were previously discussed by Henningfield et al., who noted that addition of ammonia and ammonia precursor compounds to tobacco leads to an increase in the amount of nicotine present in both particulate matter and vapor as the unprotonated free base, which may affect human uptake of other smoke components (Henningfield et al., 2004).

## Conclusions

The Agent Working Group of the National Tobacco Monitoring, Research and Evaluation Workshop evaluated the need to develop new surveillance systems for quantifying ingredients and emissions of tobacco and tobacco smoke as well as the need to improve methods to assess uptake and metabolism of these constituents by tobacco users. Constituents of mainstream smoke recommended for surveillance included specific PAH and TSNA, total and free-base nicotine, volatile organic compounds, aromatic amines, and metals. Cigarette design attributes recommended for monitoring included tobacco blend, additives, and filter ventilation. We also recommended research to help define machine-smoking protocols for monitoring emissions reflective of human smoking behavior, marketplace product sampling, and population monitoring of smoking topography, emissions of toxic constituents, biomarkers of exposure and, eventually, risk of tobacco-related diseases.

This research program should be carried out by research groups who are independent of the tobacco industry, which is unfortunately now the major source of data on tobacco and tobacco smoke. Building such research capacity is an expensive, long-term proposition. A coordinated effort will require the support of established health agencies.

It should be noted that while the Agent Working Group was part of a US-based workshop, recommendations along similar lines have also been made by international organizations. The World Health Organization Study Group on Tobacco Product Regulation (TobReg) has recently published a proposal for mandated lowering of specific toxicants in cigarette smoke, as developed by a joint working group of the International Agency for Research on Cancer (IARC) and the WHO (Burns et al., 2008). The TobReg proposal seeks to impose a ceiling on each of nine selected mainstream smoke constituents, including NNK, carbon monoxide, and benzo(a)pyrene. The emissions standards recommended by the WHO working group are based on a single machine-smoking regimen, namely, that of Health Canada. No recommendations were made regarding measurement of biomarkers of exposure or other indicators of disease risk. The WHO working group noted that "[r]esearch is needed to resolve these issues [i.e., variability of human smoking behavior] in order to allow exposure biomarkers to become an effective tool for product regulation." (Burns et al., 2008) Thus, the recommendations of the present Agent Working Group go considerably beyond those of TobReg, in that they prescribe a program of biomarker surveillance and human smoking behavior research which could eventually provide the scientific basis for more extensive regulatory proposals.

**Conflict of interest statement**
The authors declare that there are no conflicts of interest.

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