FDA Tobacco Regulation and Novel Tobacco Products

Robert L. Balster
Co-Director, Center for the Study of Tobacco Products
Virginia Commonwealth University

Family Smoking Prevention and Tobacco Control Act (the Tobacco Control Act) (Public Law 111–31)

• Signed into Law June 22, 2009
• Resulted in establishment of the Center for Tobacco Products in the FDA
  – Mitch Zeller, Director
  – David Ashley, Director, Office of Science
Stated Goals of the Tobacco Control Act

- Prevent youth tobacco use
- Help adults who use tobacco to quit
- Promote public understanding of contents and consequences of use of tobacco products
- Develop science base and begin meaningful product regulation to reduce the toll of tobacco–related disease, disability, and death

Scope of the Tobacco Control Act

- The Act gives FDA authority to regulate tobacco products, which are products made or derived from tobacco intended for human consumption (cigarettes and smokeless tobacco products, but not cigars or pipe tobacco).
- Tobacco products do not include drugs or devices which are regulated under different provisions of the Food, Drug, and Cosmetic Act (not NRTs).
- Status of e–cigarettes is controversial
Some Authorities Under the TCA

- Premarket applications for new and modified risk tobacco products
- Reduce nicotine, ban certain ingredients, and ban certain new products
- Conduct post market surveillance
- Development performance standards
- Require testing and reporting of ingredients
- Require adverse event reporting
- Impose new warning labels
- Advertising and promotion restrictions
- User fees

FDA Authorities (cont.)

- The FDA may not:
  - Ban a class of tobacco products on the market before the passage of the law
  - Reduce nicotine yields to zero
Evidence-based Policy and Regulation

- CTP Office of Science
- Being set up similar to Center for Drug Evaluation in FDA that regulates medications
- Tobacco Products Scientific Advisory committee (TPSAC)
- Uses a “Public Health Standard”
  - Based not just on effects in users, but in nonusers, former users and never users as well

Tobacco Products Scientific Advisory Committee (TPSAC)

- Federal register notice chartering the committee issued August 26, 2009
- 9 voting members with overlapping 4-year terms having mostly scientific backgrounds
- 3 nonvoting members representing industry

-[http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/default.htm](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/default.htm)
Tobacco Products Scientific Regulatory Committee Voting Members

Jonathan M. Samet, M.D., M.S. (Chair)
Professor and Flora L. Thornton Chair
Department of Preventive Medicine
Keck School of Medicine, UCLA

Warren Bickel, Ph.D
Professor
Director, Addiction Recovery Center
Virginia Tech

Mark Stuart Clanton, M.D., M.P.H.
(former) Chief Medical Officer
American Cancer Society

Phillip Huang, M.D., M.P.H.
(Employee of a state or local government or of the Federal Government)
Austin/Travis County Health Department

Thomas Eisenberg, Ph.D
Professor and Co-Director
Center for the Study of Tobacco Products
Virginia Commonwealth University

Patricia Nez Henderson, M.P.H., M.D.
(Representative of the general public)
Vice President
Black Hills Center for American Indian Health

Suchitra Krishnan-Sarin, Ph.D.
Department of Psychiatry
Yale University

Kurt Ribisi, Ph.D
School of Public Health
UNC Chapel Hill

Joanna Cohen, Ph.D
Director, Institute for Global Tobacco Control
Johns Hopkins

Tobacco Products Scientific Regulatory Committee Nonvoting Members

Hampton Henton
(Representative of the interests of tobacco growers)
Versailles, KY

Jonathan Daniel Heck, Ph.D., DABT
(Representative of the tobacco manufacturing industry)
Lorillard Tobacco Company
A.W. Spears Research Center
Greensboro, North Carolina
Significant work already done by TPSAC

- **Menthol Report**
  - Advised that menthol has adverse public health impact, not because of toxic effects of menthol but because it attracts vulnerable populations of users

- **Dissolvables Report**
  - Very little data exists on dissolvables
  - Swedish snus example may not have implications for US
  - We need to understand the risks and benefits of dissolvable tobacco products to the population as a whole, including users and nonusers of tobacco products
  - Will availability of dissolvables increase or decrease likelihood that current tobacco users will stop smoking
  - Will dissolvables increase or decrease the likelihood that those who don’t currently use tobacco products will start using such products.

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**Figure 1. Conceptual Framework: From Experimentation to Disease**

Hypothesized mechanisms by which dissolvable tobacco products could have impact on public health. The pathways include: 1) increased experimentation and initiation of cigarette smoking as a consequence of access to an oral, nicotine-containing product; 2) experimental use leading to an established pattern of mixed use of tobacco products (e.g., dissolvable products, other smokeless products, and/or cigarettes); 3) decreased likelihood of smoking cessation, given a nicotine-delivering product that can be used where smoking is not permitted; and 4) differing risk profile for tobacco-caused diseases and premature mortality.
FDA Research Agenda

- HUGE need for data to inform FDA regulatory decisions ("regulatory science")
- FDA developed several mechanisms to fund research
  - Contracts
    - PATH Study
  - NIH Grants
    - Tobacco Regulatory Science Program

Tobacco Center for Regulatory Science (TCORS)

- Virginia Commonwealth University, Richmond
- American Heart Association, Dallas
- University of Maryland, College Park
- Georgia State University, Atlanta
- University of California–San Francisco
- University of Vermont, Burlington
- University of Pennsylvania, Philadelphia
- Yale University, New Haven
- Penn State College of Medicine, Hershey
- University of Southern California, Los Angeles
- University of Texas Health Sciences Center, Houston
- University of North Carolina at Chapel Hill (risk communication)
- University of North Carolina at Chapel Hill, School of Medicine
  - Lung disease
- Ohio State University, Columbus
VCU Center for the Study of Tobacco Products

- September 2013–2018
- $18.3 million
- Tomas Eissenberg and Robert Balster, Co-Directors
- Grew out of the research program of the Virginia Foundation for Healthy Youth Virginia Tobacco Youth Tobacco Project
- Multidisciplinary and Multi-institutional
  - American University of Beirut
  - Penn State University

VCU CSTP Goals

- Develop a multidisciplinary research approach for the assessment of Modified Risk Tobacco Products (MRTPs) that may come to be regulated by the FDA
- Using e-cigarettes as the exemplar but which can be applied to many other forms of MRTPs
- Based on considerable amount of research already conducted at VCU on MRTPs, including e-cigarettes
CSTP Components

- Engineering (Alan Shihadeh, AUB)
  - How are products made and how do methods of use influence what chemicals are delivered by the product?
- Human Lab Studies (Alison Breland, VCU)
  - Smoking topography, physiological effects, nictone and toxicant exposures, dependence potential
- Naturalistic Randomized Controlled Trial (Tom Eissenberg and Jonathon Foulds, VCU and Penn State)
  - How are products used under naturalistic conditions?
  - What happens with other forms of tobacco use?
  - What adverse effects are produced?
- Attitudes and beliefs (Aashir Nasim, VCU)
  - How are products perceived using such sources as internet, chat rooms, questionnaires, etc?
  - Unintended use patterns

CSTP Components (cont)

- Research Core (Tom Eissenberg and Bob Balster, VCU)
  - Informatics (Center for Clinical and Translational Research, VCU)
  - Biostatistics (School of Medicine, VCU)
  - Facilitate interdisciplinary science (link to Massey Cancer Center)
- Training (Robert Balster, VCU)
  - Train next generation of tobacco regulatory scientists (pre- and post-doctoral)
- Pilot Projects (J Randy Koch, VCU)
  - Will use VFHY scientists for RFA
The ultimate goal of the CSTP is to help the FDA with science-based implementation of the 911 provisions of the TCA concerning Modified Risk Tobacco Products
• Achieved by the FD by issuing “Orders” concerning MRTP products in response to product applications

Overview of Section 911: Modified Risk Tobacco Products (MRTPs)
• Generally, an applicant must demonstrate that the product will significantly reduce harm and the risk of tobacco-related disease to tobacco users, and benefit the health of a population as a whole before a product may be commercially marketed as an MRTP.
  • “Risk Modification Order”
• Special rules and standards for review apply for MRTPs which solely claim to reduce or eliminate harmful substances.
  • “Exposure Modification Order”
• FDA will refer any MRTP application received to the TPSAC for recommendations.
Alternative tobacco use methods: What are they and what do they do?

Thomas Eissenberg, Ph.D.
Virginia Commonwealth University, Richmond, Virginia, USA
and
Syrian Center for Tobacco Studies, Aleppo, Syria

Supported by U.S. NIH grants TW008371, CA120142, CA103827, and DA0

Acknowledgments.

• Colleagues:
  - Wasim Maziak, M.D., Ph.D.
  - Alan Shihadeh, Sc.D.
  - Ken Ward, Ph.D.

• VCU students and staff.

• U.S. National Institutes of Health:
  - Fogarty International Center (R03 TW008371).
  - National Cancer Institute (R01 CA120142, R01 CA103827).
  - National Institute on Drug Abuse (R01 DA 024876).
Questions to answer.

- What are alternative tobacco use methods that are on the U.S. market today?
- How can we find out what alternative tobacco use methods do?
- What do we know now about alternative tobacco use methods?

Conclusion: We need to know a lot more about alternative tobacco use methods if we are to craft and gain support for science-based regulation that protects the public health.

What are alternative tobacco use methods?

- moist snuff
- reduced emission cigarettes
- little cigars
- waterpipe/hookah
- chewable
- dissolvable
- vaporizer
e-cigarettes
Waterpipe tobacco smoking.

- Hookah
- Narghile
- Arghile
- Shisha or shisha-pipe
- Goza
- Hubble-bubble

Figure courtesy Dr. Alan Shihadeh, American University of Beirut

Why would we care about waterpipe use?

- Among 105,000 U.S. university students surveyed in 2008, 30% reported “ever use” of a waterpipe to smoke tobacco, and WTS was the second most commonly reported tobacco use method (cigarettes were first; Primack et al., 2013).

- Of 3,770 students from 8 N.C. universities surveyed in 2008, 40% reported ever and 17% reported current use (Sutfin et al., 2011).

- WTS among U.S. adolescents is also common (e.g., Primack et al., 2009; Barnett et al., 2009; Sterling & Mermelstein, 2011).

- In a nationwide sample of U.S. 12th graders past-year WTS was:
  - 17.1% in 2010 (N = 15,100; Johnston et al., 2011).
Cigarettes and waterpipes are smoked differently

- Waterpipe smokers are exposed to both the toxicants in the tobacco PLUS the toxicants in the charcoal and whatever flavorings have been added to the tobacco.
- Water filtration does NOT remove toxicants from the smoke since tars and most others are not water soluble.
- Waterpipe smoking topography is different from cigarette smoking.
  - Typical cigarette results in 10-12 puffs consumed over 5 minutes whereas waterpipe smoking bouts typically last 45 minutes or more with much higher smoke exposure.
  - About 1 liter of cigarette smoke
  - About 48 liters of waterpipe smoke

Human toxicant exposure: CO and nicotine

Data from Eissenberg & Shihadeh, 2010 (see also Cobb et al., 2011).
Mean smoke toxicant content for waterpipe and cigarette.

<table>
<thead>
<tr>
<th>Toxicant (mg)</th>
<th>Waterpipe $^1$</th>
<th>Cigarette $^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tar</td>
<td>802</td>
<td>22.3</td>
</tr>
<tr>
<td>Nicotine</td>
<td>2.96</td>
<td>1.74</td>
</tr>
<tr>
<td>CO</td>
<td>145</td>
<td>17.3</td>
</tr>
</tbody>
</table>

$^1$Shihadeh and Saleh 2005; $^2$Djordjevic et al., 2000

1.7 times the nicotine, 8.4 times the CO, 36 times the tar!

Product emissions: Many times the polycyclic Aromatic hydrocarbon yield

<table>
<thead>
<tr>
<th>Known/suspected carcinogen</th>
<th>WP (ng/session)</th>
<th>Cig (ng/cig)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naphthalene</td>
<td>2130</td>
<td>236</td>
<td>9.0</td>
</tr>
<tr>
<td>Acenaphthylene</td>
<td>180</td>
<td>50.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Acenaphthene</td>
<td>487</td>
<td>25.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Fluorene</td>
<td>437</td>
<td>119</td>
<td>3.7</td>
</tr>
<tr>
<td>Phenanthrene</td>
<td>2650</td>
<td>110</td>
<td>24.1</td>
</tr>
<tr>
<td>Anthracene</td>
<td>493</td>
<td>38.1</td>
<td>12.9</td>
</tr>
<tr>
<td>Fluoranthen(e)</td>
<td>2380</td>
<td>46.2</td>
<td>51.5</td>
</tr>
<tr>
<td>Pyren</td>
<td>2510</td>
<td>33.2</td>
<td>75.6</td>
</tr>
<tr>
<td>Chrysene + Benz[a]anthracene</td>
<td>677</td>
<td>35</td>
<td>19.3</td>
</tr>
<tr>
<td>Benzo fluoranthenes</td>
<td>370</td>
<td>10.1</td>
<td>36.6</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>307</td>
<td>7.9</td>
<td>38.9</td>
</tr>
<tr>
<td>Benzo[g,h,i]perylene</td>
<td>140</td>
<td>2.5</td>
<td>56.0</td>
</tr>
<tr>
<td>Di-benzo[a,h]anthracene</td>
<td>147</td>
<td>0.6</td>
<td>245.0</td>
</tr>
<tr>
<td>Indeno[1,2,3-cd]pyrene</td>
<td>183</td>
<td>3.5</td>
<td>52.3</td>
</tr>
</tbody>
</table>

$^1$Waterpipe data from Sepetdjian et al., 2008; cigarette data from Gmeiner et al., 1977.
Note that waterpipe smoke is produced using “standard” topography method: 171 puffs, 0.53 l, 17 sec ipi.
Product emissions: Many times the aldehyde yield

<table>
<thead>
<tr>
<th>Compound</th>
<th>Waterpipe µg/episode</th>
<th>Cigarette µg/cigarette</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>630</td>
<td>23</td>
<td>27.4</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>2520</td>
<td>619</td>
<td>4.1</td>
</tr>
<tr>
<td>Acrolein</td>
<td>892</td>
<td>47</td>
<td>19.0</td>
</tr>
<tr>
<td>Propionaldehyde</td>
<td>403</td>
<td>46.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Methacrolein</td>
<td>106</td>
<td>24</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Data from Al Rashidi et al., 2008: Note that waterpipe smoke is produced using "standard" topography method: 171 puffs, 0.53 l, 17 sec ipi.

Dependence in humans? Waterpipe smoking reduces nicotine withdrawal

Data from Maziak et al., 2009 (61 Syrian waterpipe smokers, overnight abstinence; CO increased 31.5 ppm)
What are the messages paired with the product?
Labels mislead about nicotine content

Data from Vansickle et al., 2011.

Waterpipes and indoor air quality.

Indoor air quality in Virginia waterpipe cafés

Cordine Oates Cobb,1 Andrea Roe Vansickle,2 Melissa D Blank,3 Kade Jentink,3 Mark J Travers,2 Thomas Eisenberg1,5

Methods Indoor air quality in 28 venues (17 waterpipe cafés, five cigarette smoking-permitted restaurants and six smoke-free restaurants (five with valid data)) in Virginia was assessed during 4 March to 27 May 2011. Real-time measurements of particulate matter (PM) with 2.5 μm aerodynamic diameter or smaller (PM$_{2.5}$) were obtained and occupant behaviour/venue characteristics were assessed.
What does it do? Indoor air quality.

**Indoor air quality in Virginia waterpipe cafés**

Cordine Oates Cobb, Andrea Rae Varsickel, Melissa D Blank, Kade Jentink, Mark J Travers, Thomas Eisenberg

<p>| Table 2 Summary statistics (mean±SD) for each venue/category |<br />
|---|---|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>N</th>
<th>Venue type</th>
<th>Room measured</th>
<th>Mean volume (m³)</th>
<th>Mean active smoker density*</th>
<th>Mean PM₁₀ (μg/m³)</th>
<th>Median PM₁₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Waterpipe café</td>
<td>Smoking</td>
<td>288±80</td>
<td>355±1.89</td>
<td>384±270</td>
<td>315</td>
</tr>
<tr>
<td>11</td>
<td>Waterpipe café</td>
<td>Smoking</td>
<td>256±110</td>
<td>432±3.87</td>
<td>369±500</td>
<td>124</td>
</tr>
<tr>
<td>5</td>
<td>Waterpipe café</td>
<td>Non-smoking</td>
<td>375±273</td>
<td>3.0±0.70</td>
<td>173±274</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>Cigarette</td>
<td>Smoking</td>
<td>335±144</td>
<td>0.8±0.79</td>
<td>119±95</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>Cigarette</td>
<td>Non-smoking</td>
<td>405±241</td>
<td>0.00±0.00</td>
<td>26±31</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>Smoke-free</td>
<td>Non-smoking</td>
<td>466±642</td>
<td>0.00±0.00</td>
<td>9±2</td>
<td>8</td>
</tr>
</tbody>
</table>

*Running cigarettes—waterpipe per 100 cm²

PM = Particulate Matter

What does it do? Other long-term health effects

- Lung cancer: OR 2.12 (1.08-4.18; Akl et al., 2010).
- Maternal WP use and newborn pulmonary problems: OR = 3.65 (1.52-8.75; Akl et al., 2010).
- Perennial rhinitis (cough, wheezing, runny nose, nasal congestion): OR=2.3 (1.1-5.10; Tamim et al., 2003).
- Coronary heart disease: OR (ever WP use) = 2.2 (0.9-5.4; Jabbour et al., 2003).
- Male Infertility: OR=2.5 (1.0-6.3; Inhorn et al., 1994).
Conclusions: What we know about waterpipe.

- Lots of people here and abroad are using waterpipes to smoke tobacco.
- Looking at smoke toxicant content or user toxicant exposure, there is absolutely no evidence that waterpipe tobacco smoking is less lethal than cigarette smoking.
- Marketing messages are clearly misleading.
- Very preliminary data suggest that waterpipe tobacco smoking is associated with cancer, heart disease, lung disease, and other adverse health consequences.
- There are significant indoor air quality concerns in “hookah bars.”
- These results are enough to support immediate waterpipe-specific regulatory action (no flavors; accurate marketing; product labeling; public information)

Electronic cigarettes: what are they?

The coil heats the ECIG solution-containing wick, causing solution to vaporize. The rate of vaporization is a function of the electrical power flowing through the coil, which is equal to the square of the battery voltage divided by the coil resistance (here, 2.4 Watts). The air drawn over the wick entrains and cools the vapors. As they cool, they condense and form a dense visible mist or aerosol. The polyester wool surrounding the wick-heater assembly is soaked in the nicotine-containing liquid, and acts as a reservoir, constantly replenishing the wick.
Electronic cigarettes: what are they?

Individual use vials (15ml) of nicotine “juice” may contain up to 540mg of nicotine or more.

Mix you own can have 3000 mg.

Fatal dose around 60 mg in adults, 10 mg in children.

From Farsalinos et al., 2013
Why does engineering matter?

Mean ECIG vapor yield of nicotine (left) and total particulate matter (TPM; right) from repeated trials where device voltage was varied and puff parameters held constant. Error bars indicate standard deviation. Emissions from ECIG cartridges were investigated by connecting the ECIG (V4L™ 555, 24 mg/ml nicotine) to a smoking machine programmed to execute 15 puff cycles. Each puff cycle consisted of a puff of 1.8 s duration with a puff velocity of 36 ml/s, and an interpuff interval (IPI) of 10 s. These parameters are based on values reported by Goniewicz et al. (2013) for ECIG users.

From Shihadeh et al., 2013

Toxicant exposure depends on numbers of puffs

Particulate matter, volatile aldehyde, and formaldehyde emissions from two drops (54 mg) of e-liquid when one, two, three, or four puffs are drawn from the atomizer. (ECIG formaldehyde for 1.8s, 3.7V case <0.1 μg)

Adapted from Shihadeh et al., 2013
Electronic cigarettes: what are they?

What are ECIGs?

- A variety of products that can have widely varying design characteristics (e.g., voltage, heater coil configuration, liquid reservoir).
- Design characteristics can influence nicotine and other toxicant yield.
- Dripping and other unorthodox use can alter the nicotine and toxicant yield of ECIG vapor.
What does it do?: Some focused questions.

- What is in the product's emissions and do they have biological action?
- What does the product do to people, including toxicant exposure and short-term health effects?
- What are the messages paired with the product?
- What are the long-term effects of product use?

Product emissions: lower toxicant levels?

<table>
<thead>
<tr>
<th>Toxic compound</th>
<th>Conventional cigarette (µg in mainstream smoke)</th>
<th>Electronic cigarette (µg per 15 puffs)</th>
<th>Average ratio TCig:ECIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>1.6–52</td>
<td>0.20–5.61</td>
<td>9</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>52–140</td>
<td>0.11–1.36</td>
<td>450</td>
</tr>
<tr>
<td>Acrolein</td>
<td>2.4–62</td>
<td>0.07–4.19</td>
<td>15</td>
</tr>
<tr>
<td>Toluene</td>
<td>8.3–70</td>
<td>0.02–0.63</td>
<td>120</td>
</tr>
<tr>
<td>NNN</td>
<td>0.005–0.19</td>
<td>0.00008–0.00043</td>
<td>380</td>
</tr>
<tr>
<td>NNK</td>
<td>0.012–0.11</td>
<td>0.00011–0.000283</td>
<td>40</td>
</tr>
</tbody>
</table>

Notes:
- Puffing parameters uncertain.
- without regulation these values could change…anytime.
- no in vitro or in vivo preclinical data available.

Data from Goniewicz et al., 2013:
Note that ECIG data are from 15 puffs of 70 ml each and conventional cigarette data are from three different smoking regimens.
Early ECIGs: no nicotine, heart rate, CO increase

Note: ECIG naïve cigarette smokers; 2, 10 puff bouts

Vansickel et al., 2010

E-Cigs increase plasma nicotine.

"Chuck"
24 mg Cartomizer

Vansickel et al., 2011
Human nicotine exposure: Individual data.

From Dawkins and Corcoran, 2013 (with thanks to the authors for sharing individual data).

Marketing messages: Health.
What do ECIGs do?

- They deliver widely varying amounts of nicotine.
- Nicotine delivery to the user can be rapid (pulmonary?) and can lead to plasma nicotine concentrations equivalent to or higher that seen in cigarette smokers.
- ECIGS generally produce less toxicant exposures
- ECIGs also have the capacity, under certain conditions, to expose users to high levels of volatile aldehydes.
- ECIGS are being marketed as safe and healthy and for use by people who smoke.