

HOW SCIENCE INFORMS FDA REGULATORY DECISIONS ON TOBACCO PRODUCTS

David L. Ashley, Ph.D.
Director, Office of Science,
FDA Center for Tobacco Products

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dissemination of information by FDA and does not
represent agency position or policy*

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PRESENTER DISCLOSURE

**RADM David Ashley, PhD
Office of Science
Center for Tobacco Products
US Food and Drug Administration**

No relationships to disclose

THE SCIENCE OF TOBACCO REGULATION



■Product

- Chemistry
- Engineering
- Microbiology

■Tobacco Product User

- Toxicology
- Pharmacology
- Clinical medicine
- Addiction
- Product use behavior

■Population as a Whole

- Environmental assessment
- Epidemiology
- Consumer perception
- Statistical analysis
- Evaluation

SCIENTIFIC EVIDENCE HAS A DIRECT IMPACT ON FDA REGULATORY ACTIONS

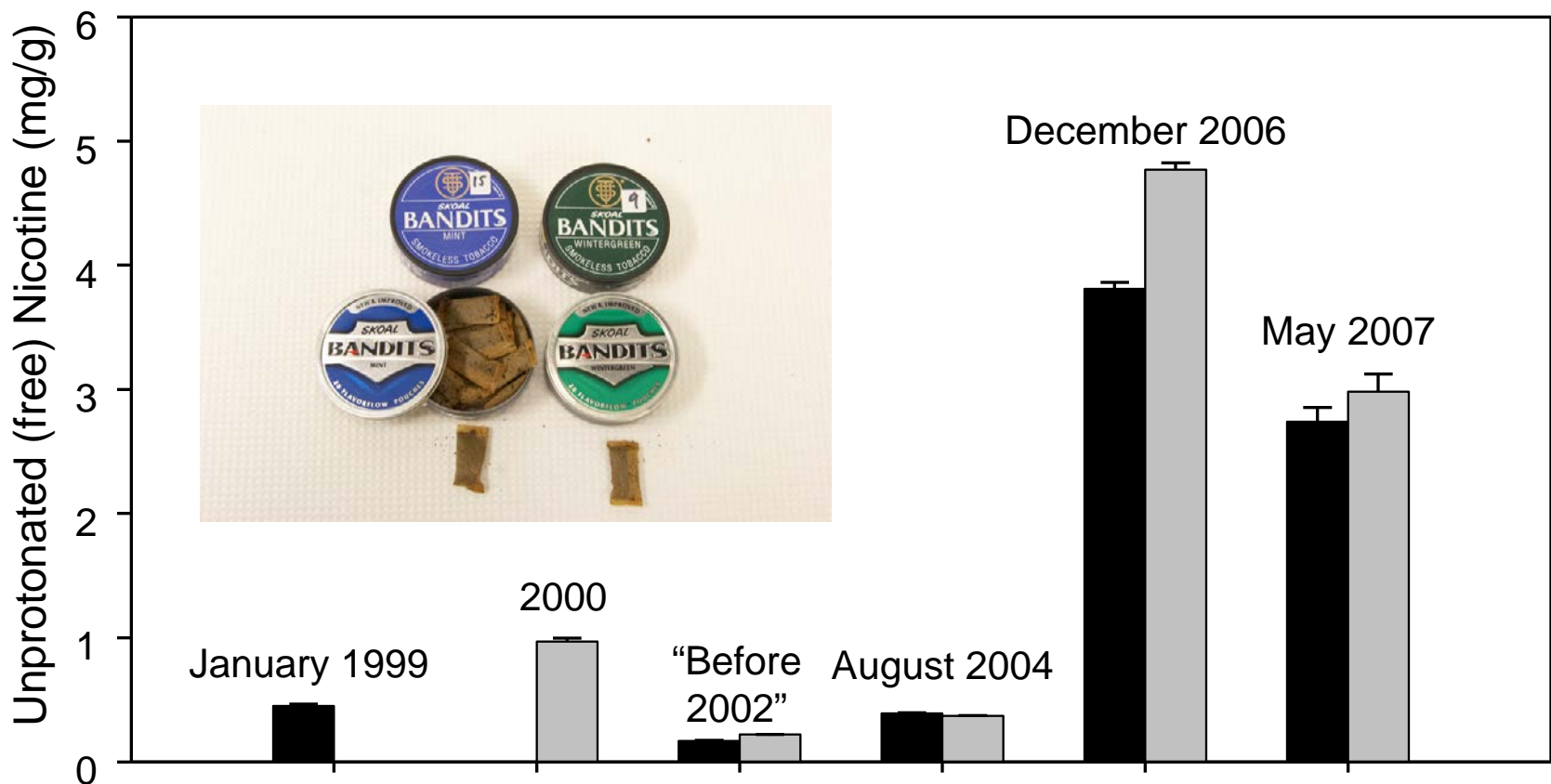
- Restrict product changes to protect public health
- Prohibit modified risk claims that state/imply reduced exposure or risk without an order
- Decrease the harms of tobacco products



RESTRICT PRODUCT CHANGES TO PROTECT PUBLIC HEALTH

- Tobacco Products are changed by the manufacturer to:
 - Increase product share
 - Attract new users
 - Adjust to supply issues
 - Retain current users as their preferences change

MANUFACTURERS HAVE CHANGED PRODUCT CHARACTERISTICS



PATHWAYS TO MARKET

- No regulated tobacco product can be changed or first introduced to market after March 21, 2011 without FDA evaluating the science and issuing a marketing order.
- Products changed or introduced between February 15, 2007 and March 20, 2011, may be marketed in a provisional status awaiting FDA review of their SE reports submitted before March 23, 2011.
- **New tobacco product applications:**
 - The primary statutory pathway to market
 - Premarket review
 - Permitting the product to be marketed would be appropriate for the protection of public health.



PATHWAYS TO MARKET

Substantial equivalence (SE)

- An alternative to new product applications; characteristics are the same as grandfathered products or characteristics are different but the product does not raise different questions of public health.
- Substantive scientific review has begun on all regular SE Reports
- FDA has fully resolved 45% of regular SE reports received to date either through an SE/NSE decision or by the report being withdrawn (most after receiving a deficiency letter).
- FDA is also actively reviewing provisional SE reports (prioritized according to their potential to raise different questions of public health)

PATHWAYS TO MARKET

Substantial equivalence exemption

- An alternative to substantial equivalence in which the only change is to an additive, the product change is minor and a full substantial equivalence report is not necessary to ensure that permitting the tobacco products to be marketed is appropriate for the protection of public health.



DESIGN CHARACTERISTICS CAN ALTER CONSTITUENT DELIVERY OR PRODUCT USE

Paper

- Porosity
- Diffusivity
- Low ignition propensity
- Salt content
- Burn rate

Tipping paper

- Pressure drop
- Tip ventilation



Tobacco filler

- Blend
- Additives/acidity
- Cut Size
- Moisture

Cellulose acetate filter

- Denier (fiber density)
- Efficiency
- Resistance to draw
- Additives

TOBACCO BLEND IMPACTS THE DELIVERY OF CARCINOGENIC EMISSIONS

Table 1. Levels of different tobacco

	Smoke nicotine (mg/g tobacco)	Smoke TSNA (ng/g tobacco)		from
		NNN	NNK	
Burley	5.40 ± 0.09	1,970.27 ± 81.87	174.12 ± 3.84	7.34
Bright	3.97 ± 0.10	35.30 ± 3.16	35.94 ± 4.00	1.46
Oriental	1.53 ± 0.03	84.23 ± 5.42	25.12 ± 2.32	5.11
Reconstituted Blend I	0.48 ± 0.02	241.70 ± 7.13	326.92 ± 7.38	15.41
Blend II	3.14 ± 0.07	486.68 ± 22.39	143.69 ± 7.51	9.33
Blend I	2.42 ± 0.06	534.92 ± 23.58	179.70 ± 5.82	8.49
Blend II				is were

Ding YS, et al. Levels of Tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons in mainstream smoke from different tobacco varieties. *Cancer Epidemiol Biomarkers Prev* 2008;17:3366-71.

PROHIBIT MODIFIED RISK CLAIMS THAT STATE/IMPLY REDUCED EXPOSURE OR RISK WITHOUT AN ORDER

Modified risk tobacco product” means any tobacco product that is *sold or distributed* for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products.

The term “sold or distributed” includes labeling and advertising, as well as any communication actions “directed to consumers through the media or otherwise.”


THE STATUTE REQUIRES EVALUATION OF BOTH MODIFIED RISK AND MODIFIED EXPOSURE CLAIMS



VEKTOR TOBACCO

AN OPEN LETTER TO AMERICAN SMOKERS:

**OMNI. THE FIRST REDUCED
CARCINOGEN CIGARETTE.**



When You Can't Smoke™

Whether you're at work, in a restaurant or on an airplane, Ariva™ can help you satisfy your craving for a smoke — in any place or situation where smoking isn't an option!

Ariva™ is a refreshing mint-flavored cigarett™ made from tobacco designed to melt in your mouth.

Ariva™ is a discrete tobacco alternative.
No smoke. No ash.

Ariva™ does not contain the hundreds of toxic substances found in cigarette smoke.

Ariva™ provides real tobacco satisfaction in all the places you can't smoke: workplace, restaurants, airports, sporting events.

Ariva™ is the satisfying alternative when you can't smoke™

Simply place one cigarett™ piece in mouth between cheek and gum, and allow to dissolve.
Do not chew or swallow whole.

There are no safe tobacco products.
Quitting or not starting is your best option.
THIS PRODUCT IS FOR ADULT TOBACCO USERS ONLY.

WARNING:
THIS PRODUCT MAY CAUSE GUM DISEASE AND TOOTH LOSS

For more information, call 1-866-GOARIVA.
Or visit www.goariva.com.

EVALUATION OF MODIFIED RISK CLAIMS MUST ADDRESS IMPACT ON THE POPULATION AS A WHOLE

Increased Harm

Product is more toxic to the user

Instead of quitting, smokers become dual users

Products are used in a way that makes them more harmful

Youth/Adults initiate more

Former smokers relapse more

Reduced Harm

Product is less toxic to the user

Smokers switch completely to less toxic products

Products are used in a way that makes them less harmful

Initiation is reduced

Former smokers relapse less

DECREASE THE HARMS OF TOBACCO PRODUCTS

“Use of tobacco products is driven by their appeal or attractiveness to potential consumers and sustained by their pharmacological addiction or dependence potential.”



Henningfield JE, et al. Conference on abuse liability and appeal of tobacco products: Conclusions and recommendations. *Drug and Alcohol Dependence* 2011;116:1-7.

STATUTORY BASIS FOR TOBACCO PRODUCT STANDARDS

Through rulemaking, the Tobacco Control Act allows adoption of “...tobacco product standards... appropriate for the protection of public health.” Sec 907.

- Nicotine yields
- Reduction or elimination of constituents, including smoke constituents
- Construction, components, ingredients, additives, constituents, and properties of the tobacco product
- Provisions for testing or measuring product characteristics
- Restrictions on sale and distribution
- Form and content of labeling

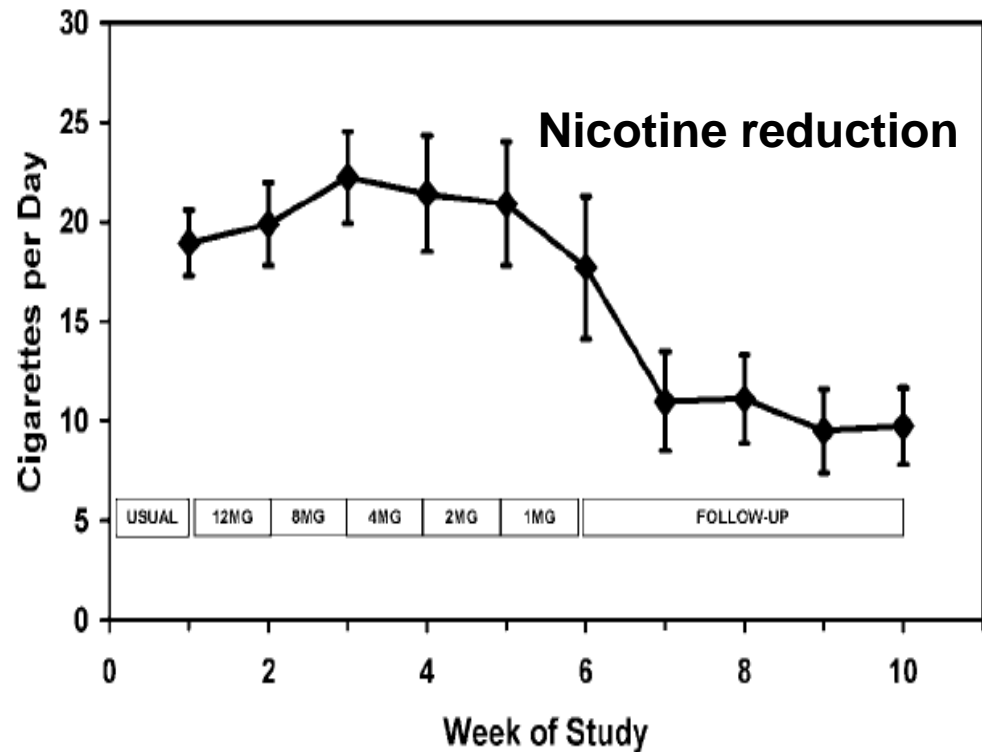
SMOKING CESSATION LEADS TO BETTER HEALTH OUTCOMES

Age at time of quitting smoking	Additional life expectancy due to quitting
30 years old	Almost 10 years
40 years old	9 years
50 years old	6 years
60 years old	3 years

Doll R, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. British Medical Journal 2004;328:1519-28.

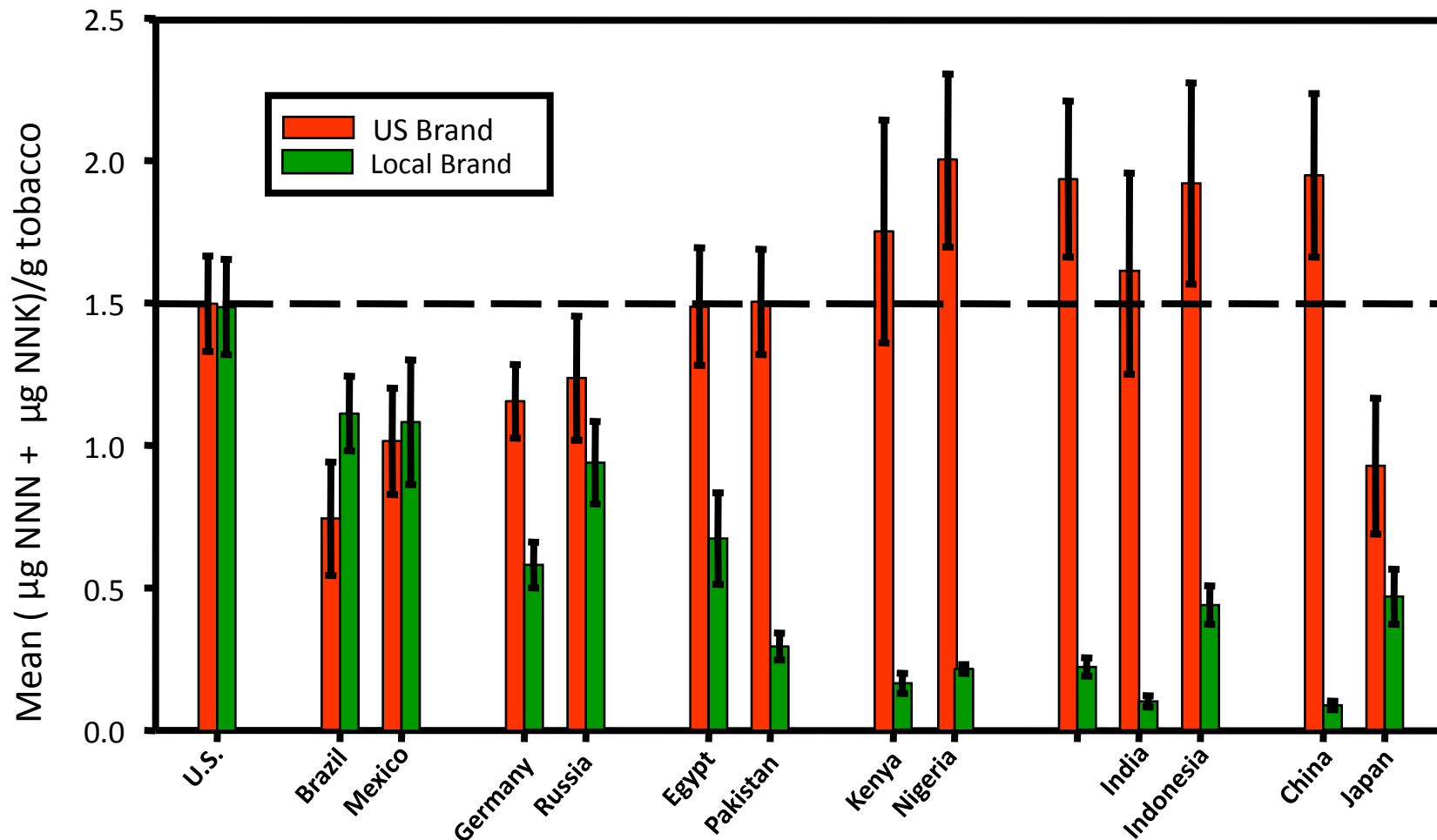
REDUCED NICOTINE PRODUCTS MAY ENCOURAGE QUITTING

25% of participants who were originally not interested in quitting spontaneously quit smoking 4 weeks after completing the study



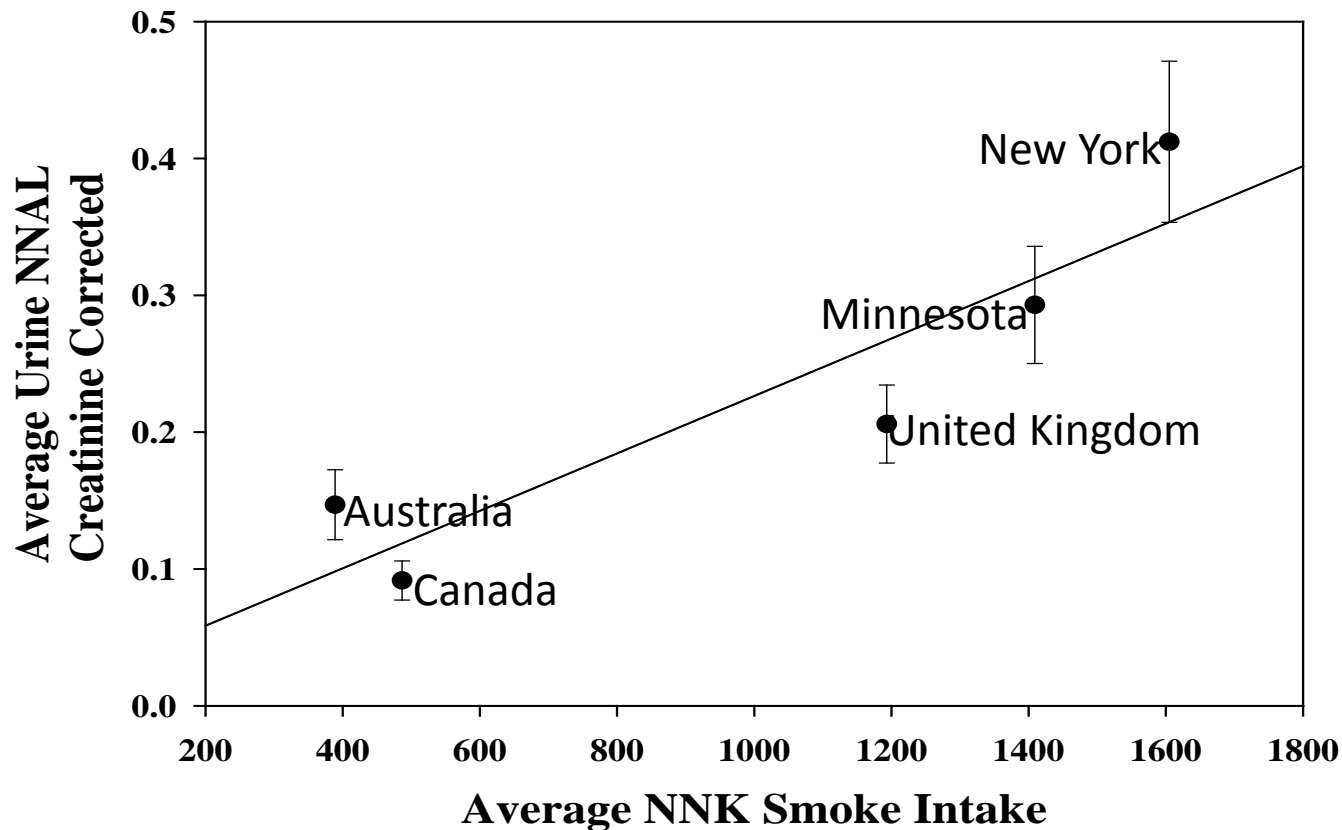
Benowitz NL, Hall SM, et al. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarettes. *CEBP* 2007;16(11):2479-85.

SOME TOXIC AND CARCINOGENIC CONSTITUENTS VARY WIDELY IN PRODUCTS



Ashley DL, Beeson MD, et al. Tobacco-specific nitrosamines in U.S brand and non-U.S. brand cigarettes. *Nicotine & Tobacco Research* 2003;5:323-31.

HIGHER TOBACCO-SPECIFIC NITROSAMINES IN U.S. CIGARETTES INCREASE THE LEVEL OF EXPOSURE



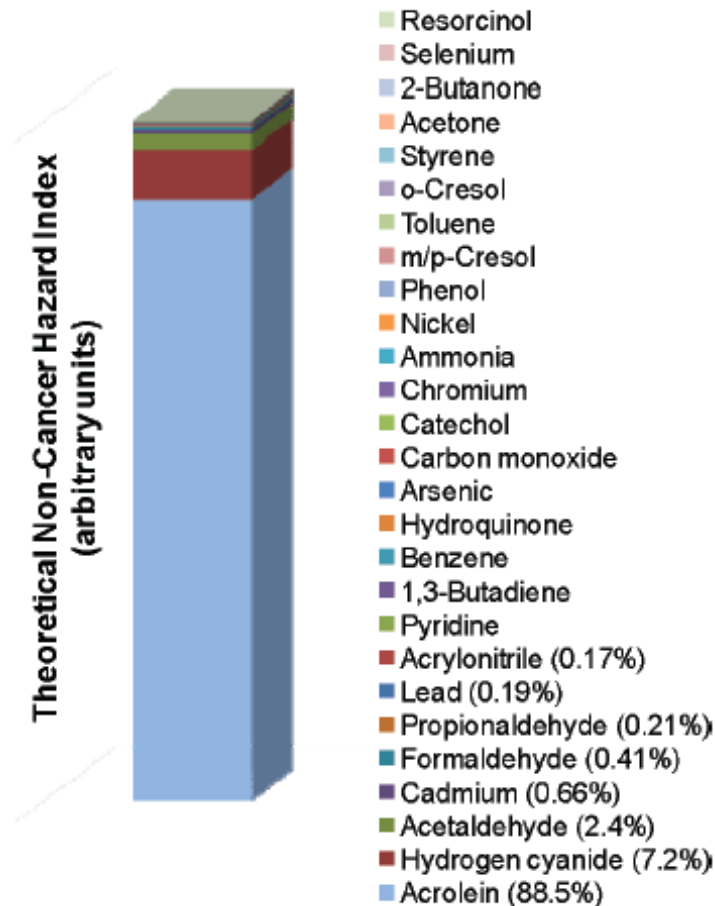
Ashley DL, O'Connor RJ, et al. Effect of differing levels of tobacco-specific nitrosamines in cigarette smoke on the levels of biomarkers in smokers. *CEBP* 2010;19(6):1389-98.

CIGARETTE DESIGN INFLUENCES TOXICITY

Rates for squamous cell carcinoma are similar for men in the United States and Canada [2]. However, Canadian male adenocarcinoma incidence rates remain lower than those for squamous cell and are well below the adenocarcinoma incidence for White men in the United States [2].

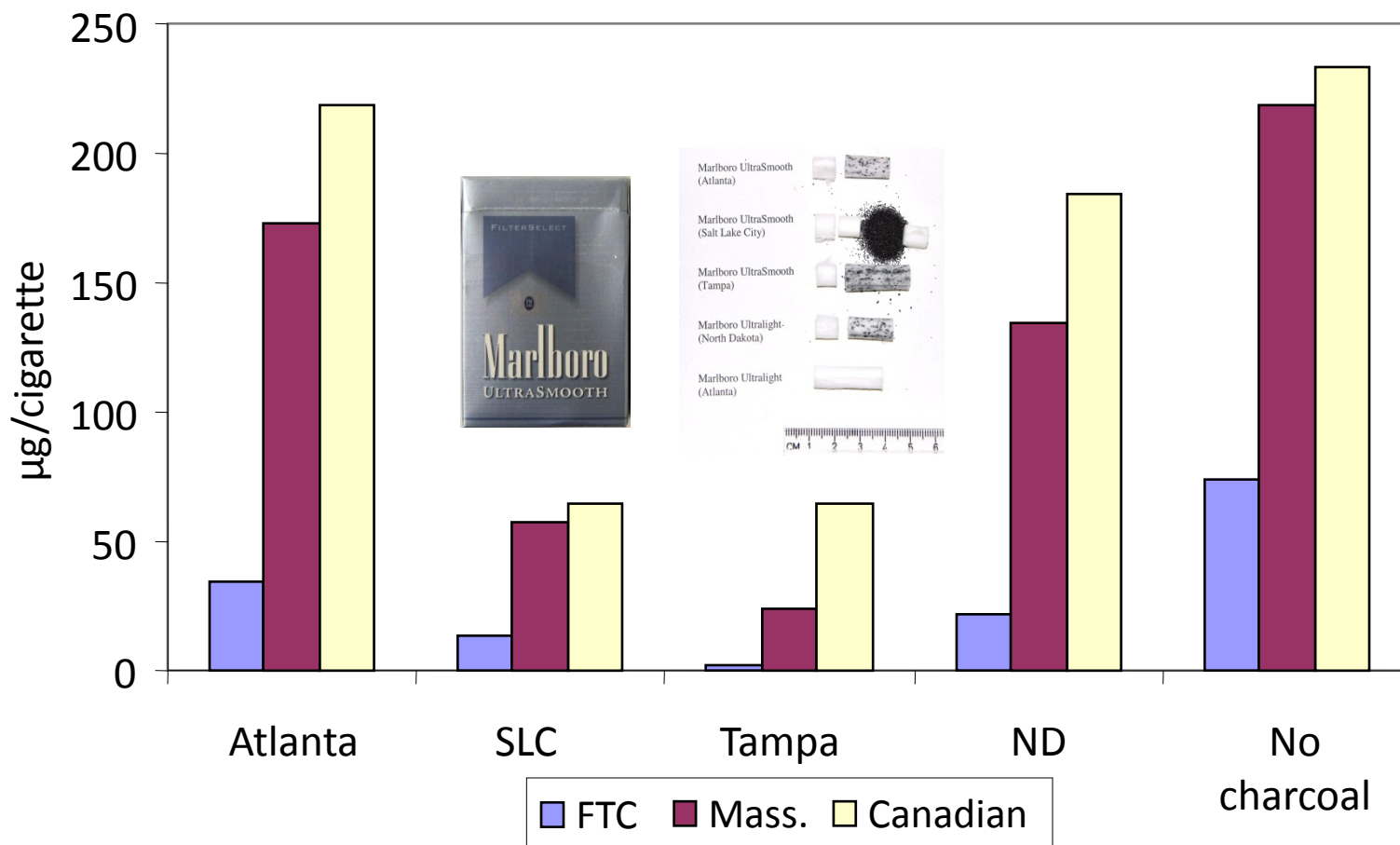
Burns DM, et al. Do changes in cigarette design influence the rise in adenocarcinoma of the lung? *Cancer Causes Control* 2011;22:13-22.

THEORETICAL NONCANCER HAZARD INDEX



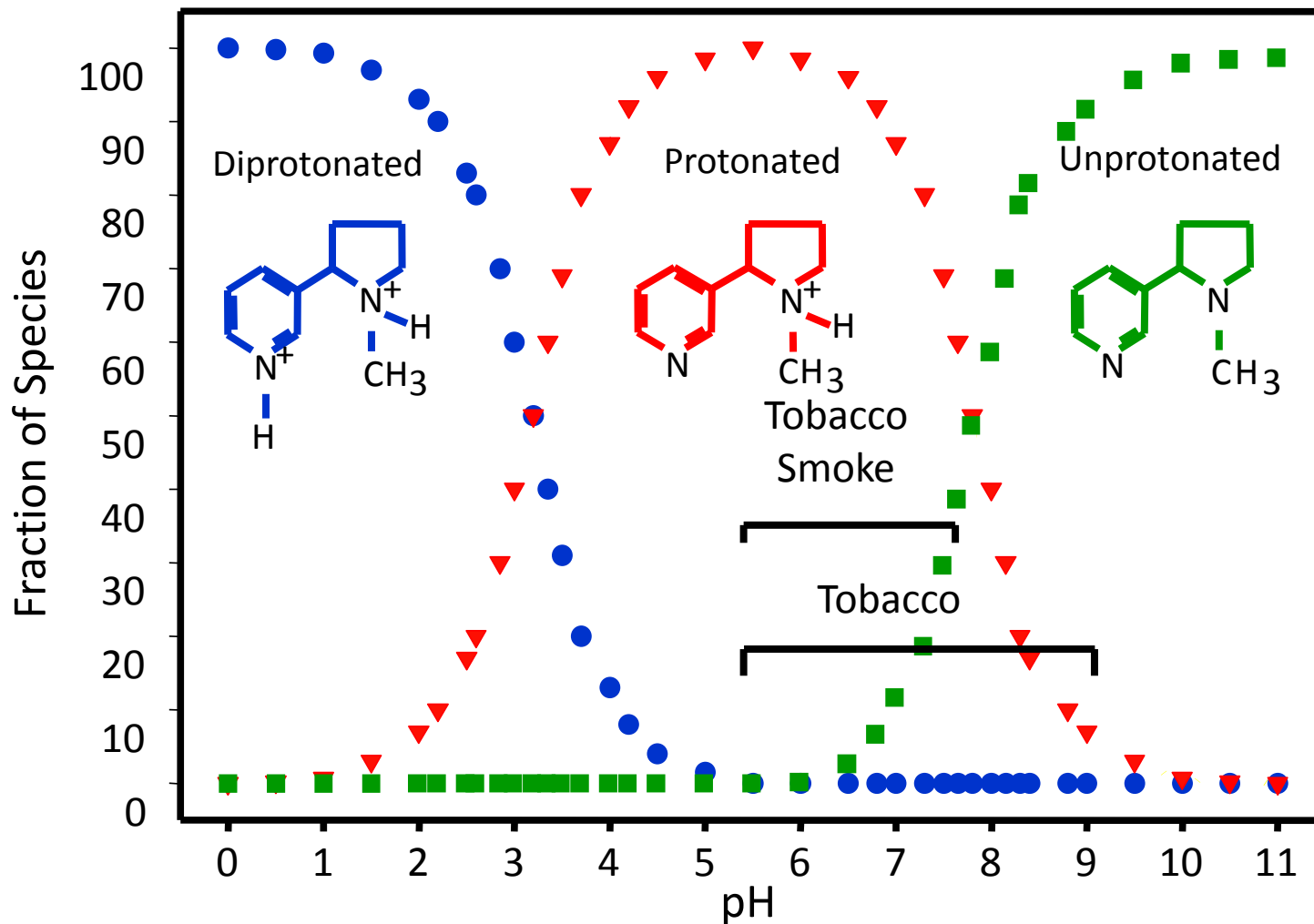
Hausmann H-J. Use of hazard indices for a theoretical evaluation of cigarette smoke composition. Chem Res Toxicol, 2012;25:794-810.

VOLATILE ORGANIC COMPOUNDS CAN BE REDUCED BY USING CHARCOAL IN THE FILTER



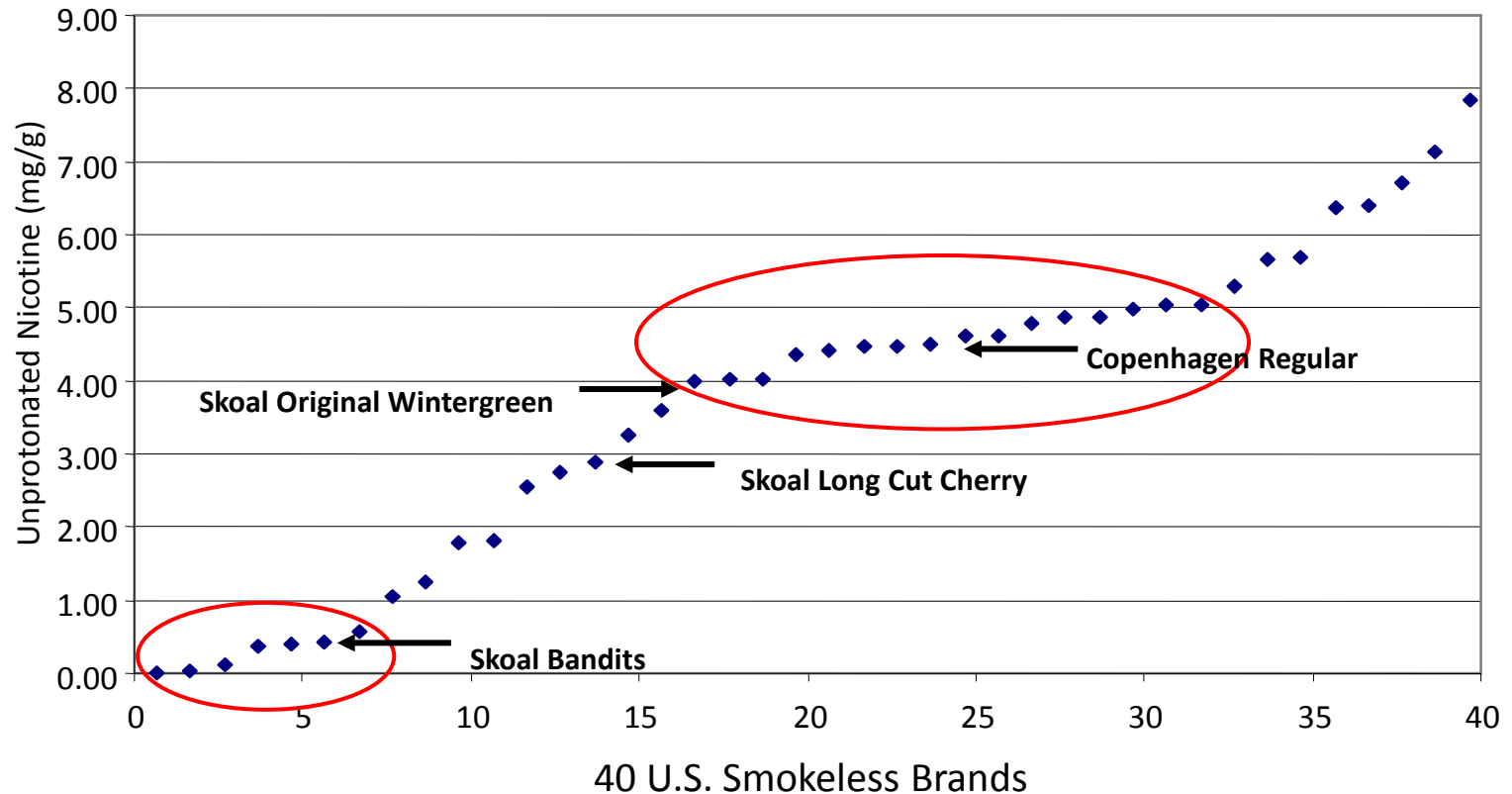
Polzin GM, Zhang L, et al. Effect of charcoal-containing cigarette filters on gas-phase volatile organic compounds in mainstream cigarette smoke. *Tobacco Control* 2008;17:i10-67.

TOBACCO pH ALTERS THE RELATIVE LEVELS OF THE FORMS OF NICOTINE



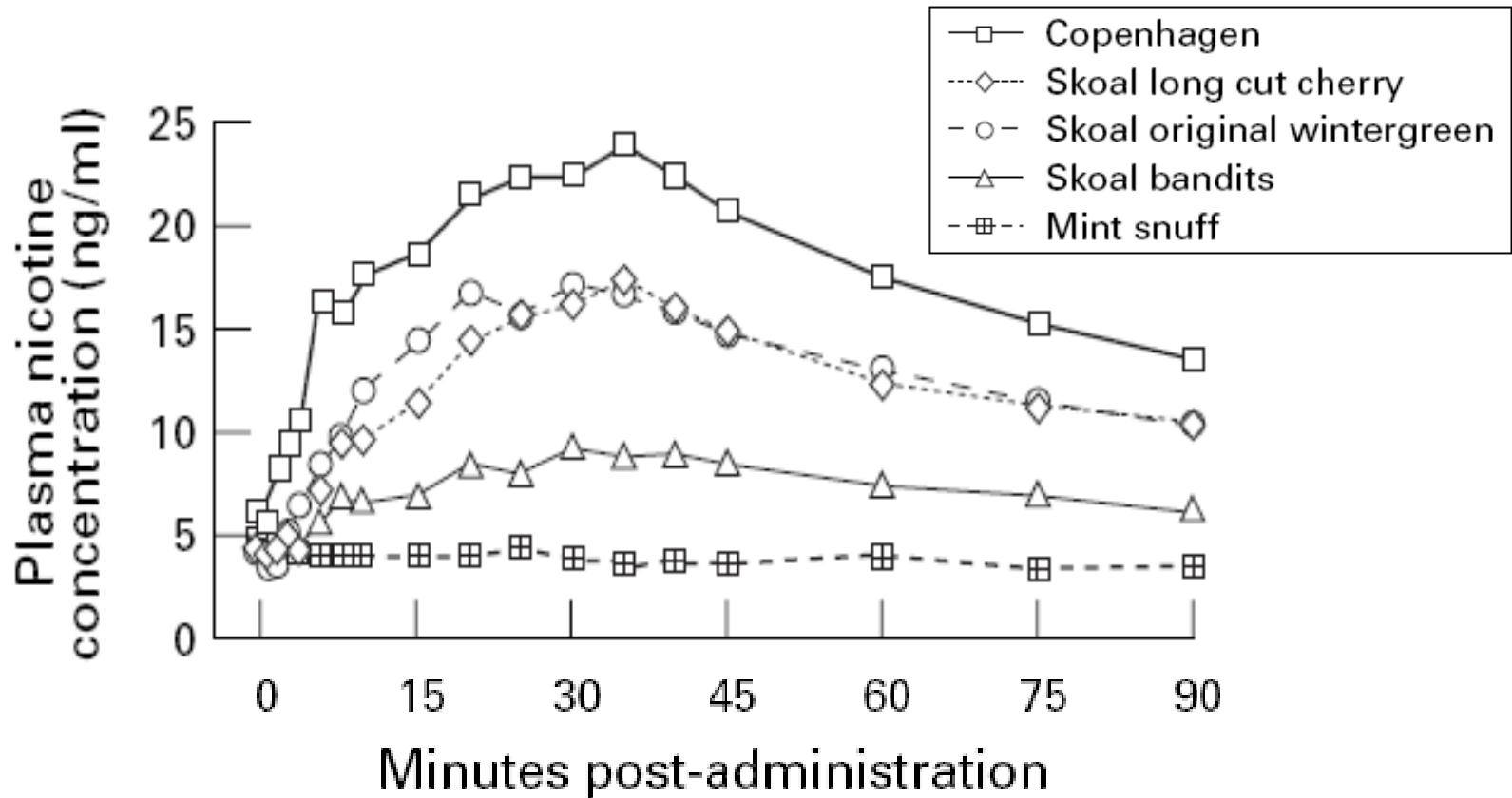
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SMOKELESS UNPROTONATED (FREE) NICOTINE DELIVERY IS CONTROLLED THROUGH pH OF THE PRODUCT



Richter P, et al. Surveillance of moist snuff: total nicotine, moisture, pH un-ionized nicotine, and tobacco-specific nitrosamines. *Nicotine and Tobacco Research* 2008;10(11):1645-52.

UNPROTONATED (FREE) NICOTINE CONTROLS DELIVERY KINETICS TO USERS OF SMOKELESS TOBACCO



Fant RV, Henningfield JE et al. Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tob Control* 1999; 8:387-92.

RESEARCHING SCIENTIFIC PRIORITIES

- Diversity of Tobacco Products
- Reducing Addiction
- Reducing Toxicity and Carcinogenicity
- Adverse Health Consequences
- Communications
- Marketing of Tobacco Products
- Economics and Policies



THANK YOU



FDA

CENTER FOR
TOBACCO
PRODUCTS