# Toxic and carcinogenic constituents in Camel Snus and other U.S. smokeless tobacco products

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**FDA Tobacco Products Scientific Advisory Committee Meeting**

**September 13-14, 2018, Silver Spring, MD**

Masonic Cancer Center

University of Minnesota

Comprehensive Cancer Center designated by the National Cancer Institute

# Disclosure

Some of the research included in this presentation was supported by grants form NCI and through the NIH Tobacco Regulatory Science Program (R01-CA180880). The content is solely the responsibility of the author and does not represent the official views of the NIH or FDA.

# Outline

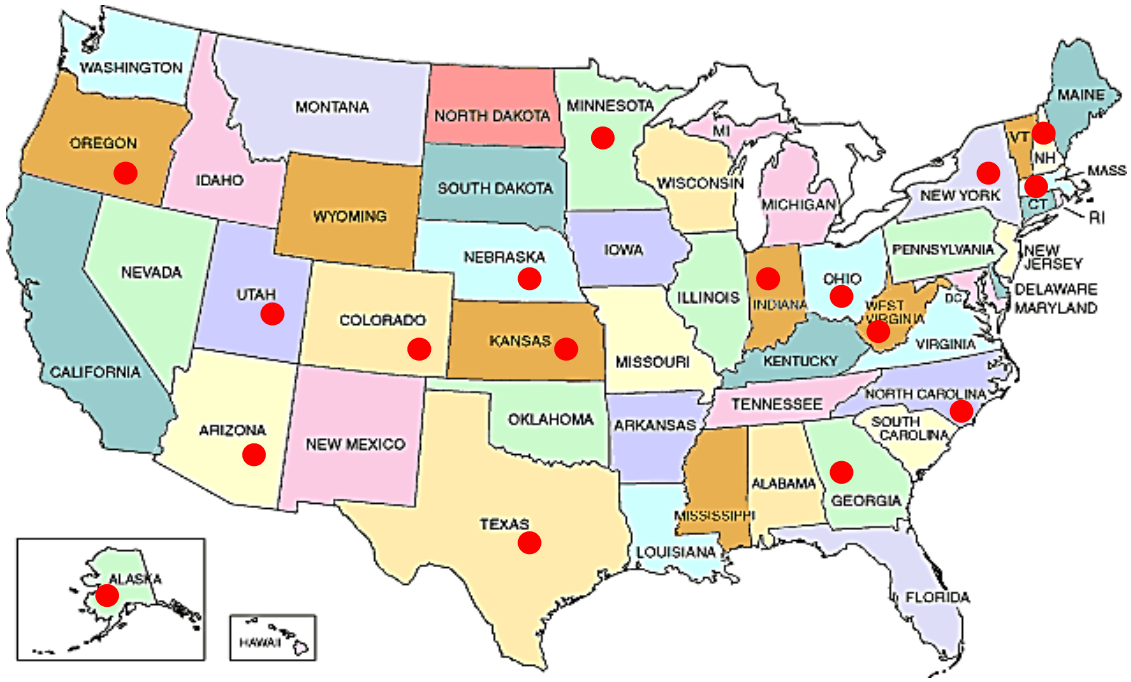
- New Product Watch Project
- Recent data on moist snuff
- Products marketed as snus

# New Product Watch

**Web-based national monitoring network**

**Monitors - State tobacco program staff and their community partners**

**Six regions; three locations per region**



# New Product Watch








**2006 – 2007** | **NPW Round I 2010** | **NPW Round II 2011** | **NPW Round III 2012 – 2013**

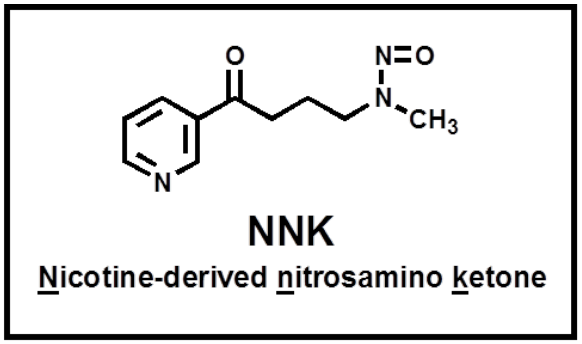
# Carcinogens in smokeless tobacco products

| Group | Constituents |
|---|---|
| Tobacco-specific *N*-nitrosamines | NNN, NNK |
| Volatile *N*-nitrosamines | NDMA,NPYR, NPIP, NMOR, NDELA |
| Nitrosamino acids | NSAR |
| Polycyclic aromatic hydrocarbons | BaP, DBahA, BaA, BbF, BjF, BkF, DBaiP, IcdP, 5MC, NAP |
| Metals and metalloids | As, Be, Cd, Co, Cr VI, Pb, Ni, Po-210 |
| Aldehydes | Formaldehyde, acetaldehyde |
| Inorganic salts | Nitrate, nitrite |
| Fermentation-related compounds | Ethyl carbamate |
| Mycotoxins | Aflatoxin, ochratoxin |
| Other plant material | Areca nut |



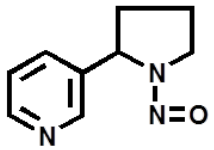
**Stanfill and Stepanov, Ch. 3 in Smokeless Tobacco and Public Health: A Global Perspective (NIH Publication No. 14-7983; 2014)**

# Tobacco-specific *N*-nitrosamines (TSNA)



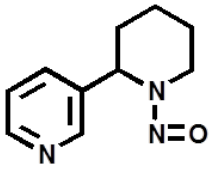

**NNK**

Nicotine-derived nitrosamino ketone

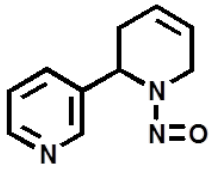



**NNN**

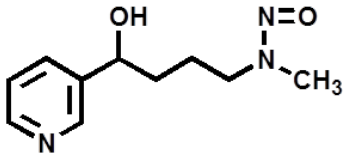
*N*′-Nitrosonornicotine



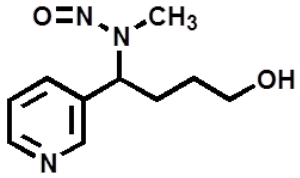

NAB



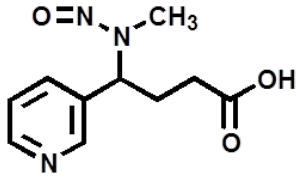

NAT




NNAL




*iso*-NNAL



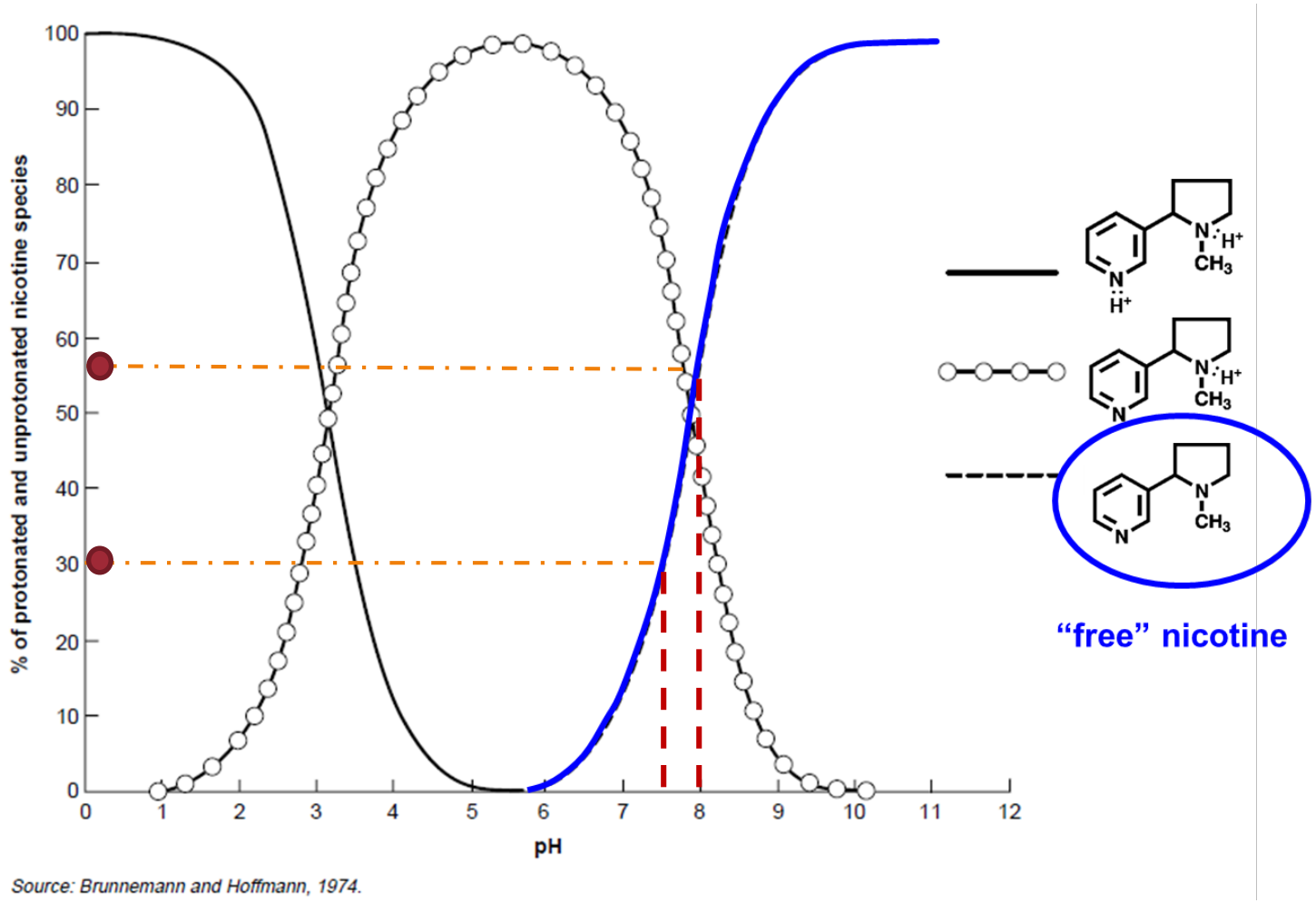

*iso*-NNAC

- **Specific to tobacco exposure (formed from tobacco alkaloids)**
- **Systemic, organ-specific carcinogens**
- **Cancers of target organs are most strongly associated with tobacco use**
- **Classified by IARC as carcinogenic to humans (Group 1)**




Hecht, *Chem. Res. Toxicol.*, 1998;11(6):559-603; IARC vol. 89, 2007
Yuan et al., *Cancer Research*, 2009;69:2990-2995; Yuan et al., *Carcinogenesis*, 2011;32:1366-1371

# Product pH and unprotonated (free) nicotine



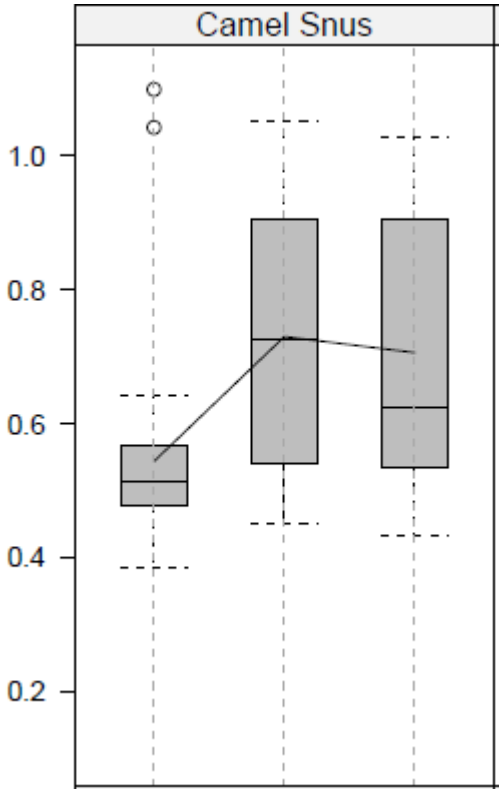

*Source: Brunnemann and Hoffmann, 1974.*

# Constituents and characteristics monitored in the New Product Watch

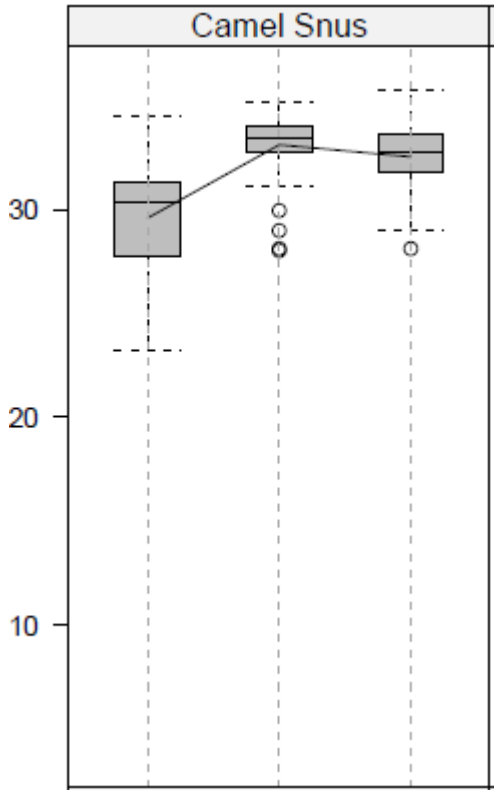
- Pouch size
- Moisture content,
- pH
- Nicotine
- Unprotonated nicotine
- NNN
- NNK

# Selected data: focus on time trends

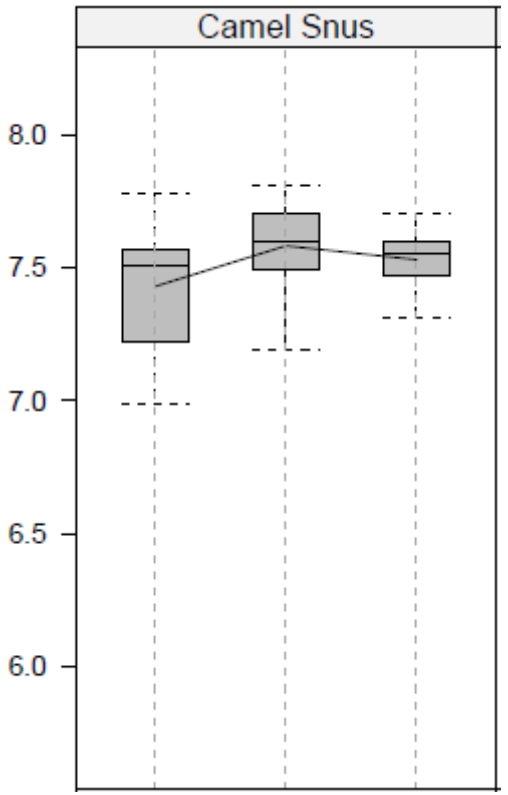
## Pouch weight




## Moisture content

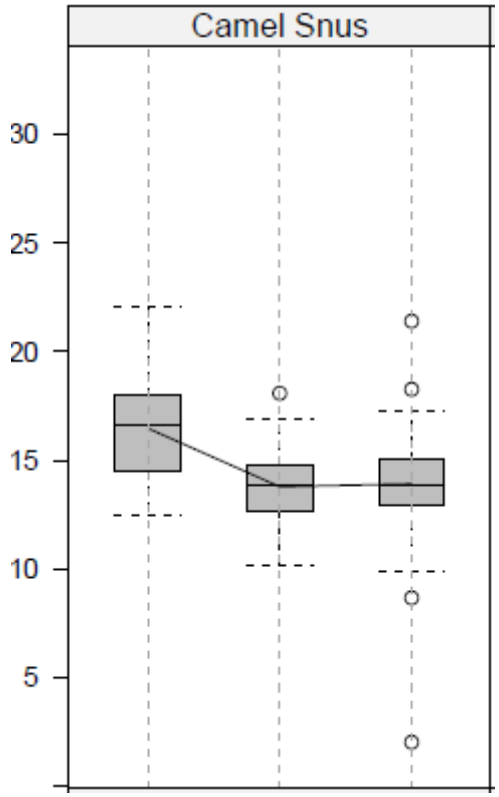



## pH

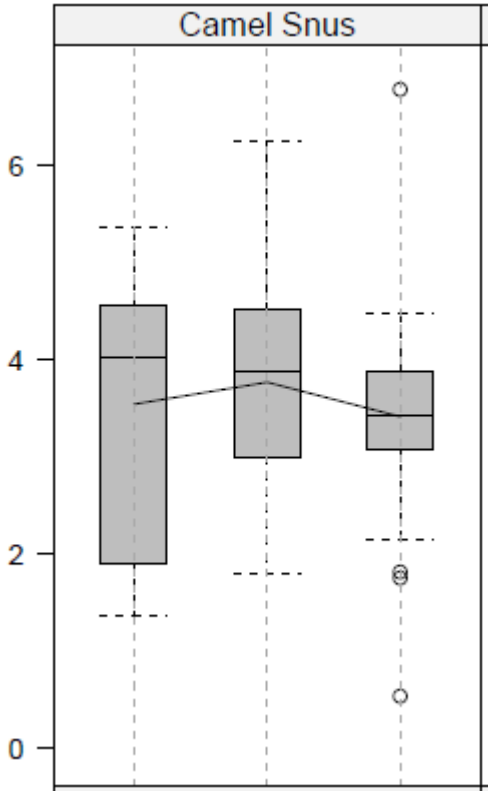


# Selected data: focus on time trends

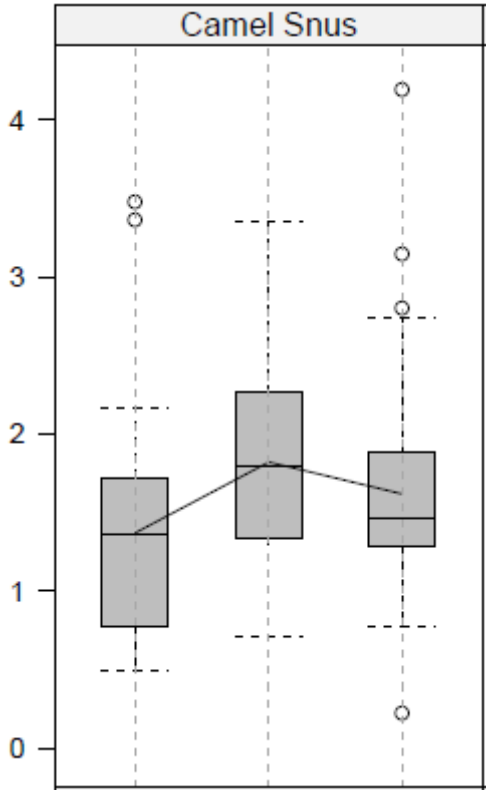
**Total nicotine, mg/dry wt**




**Free nicotine, mg/dry wt**




**Free nicotine, mg/portion**

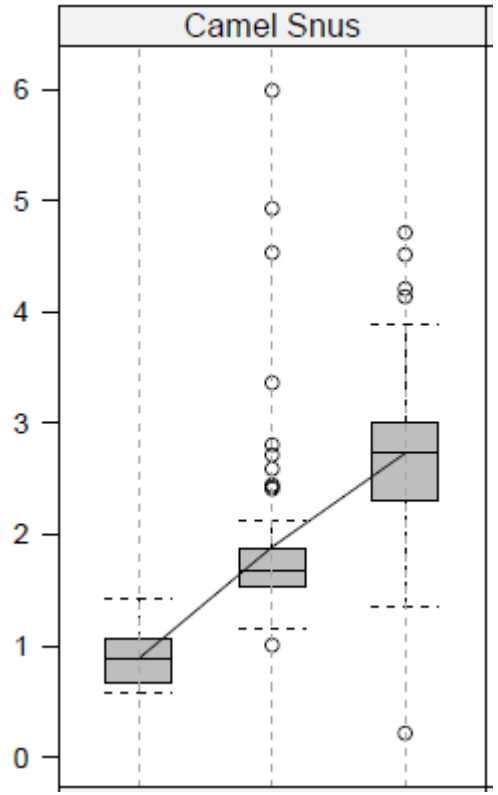




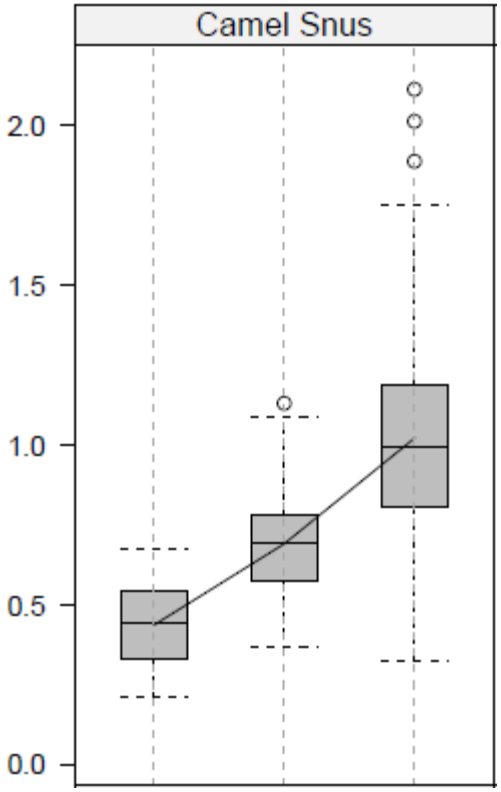

Stepanov Laboratory (manuscript in preparation)

# Selected data: focus on time trends

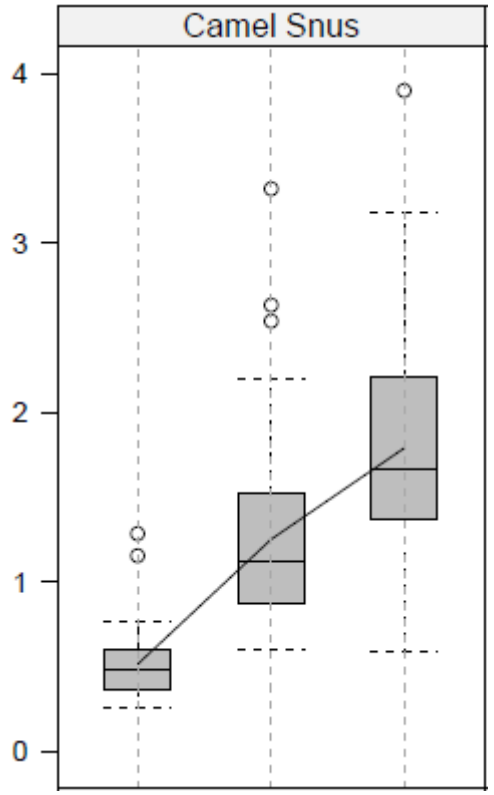
**NNN, µg/dry wt**




**NNK, µg/dry wt**




**NNN+NNK, µg/portion**



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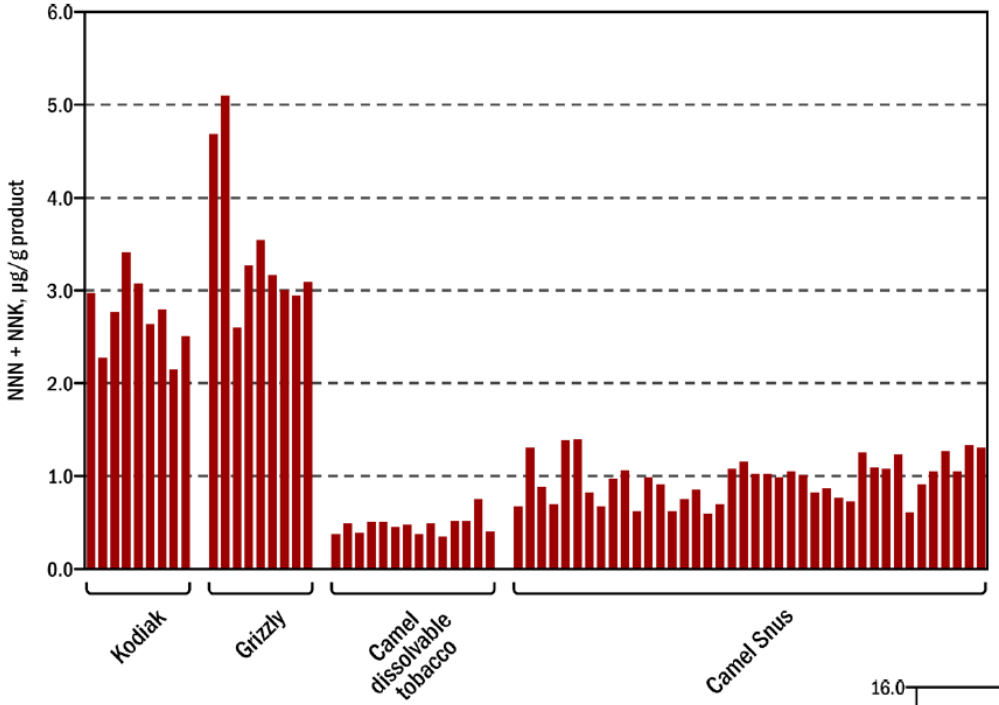
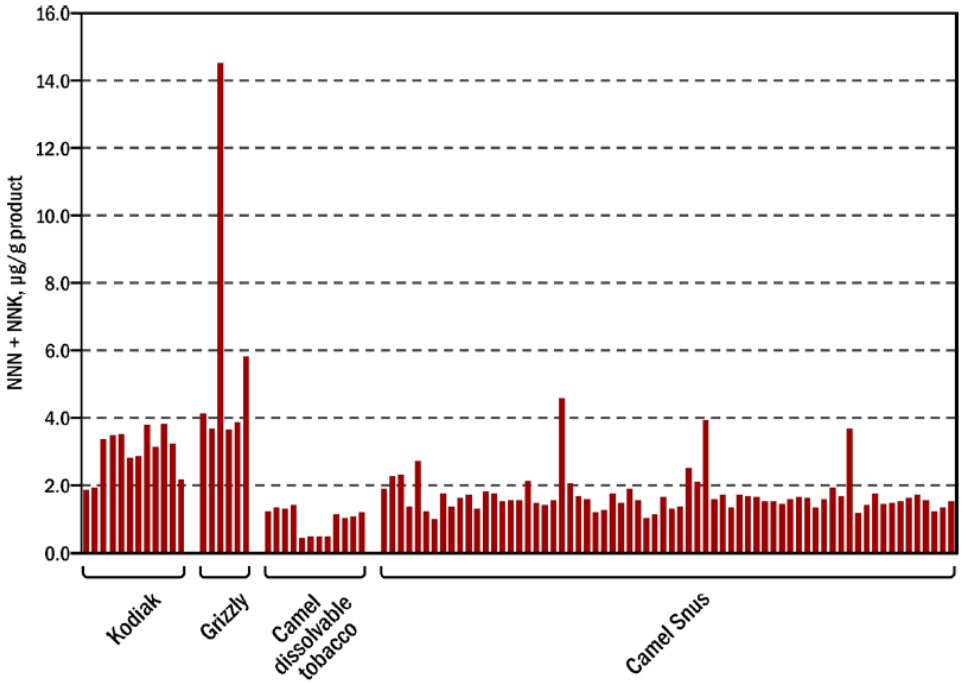
# Comparisons with the U.S. moist snuff data

# Sum of NNN and NNK



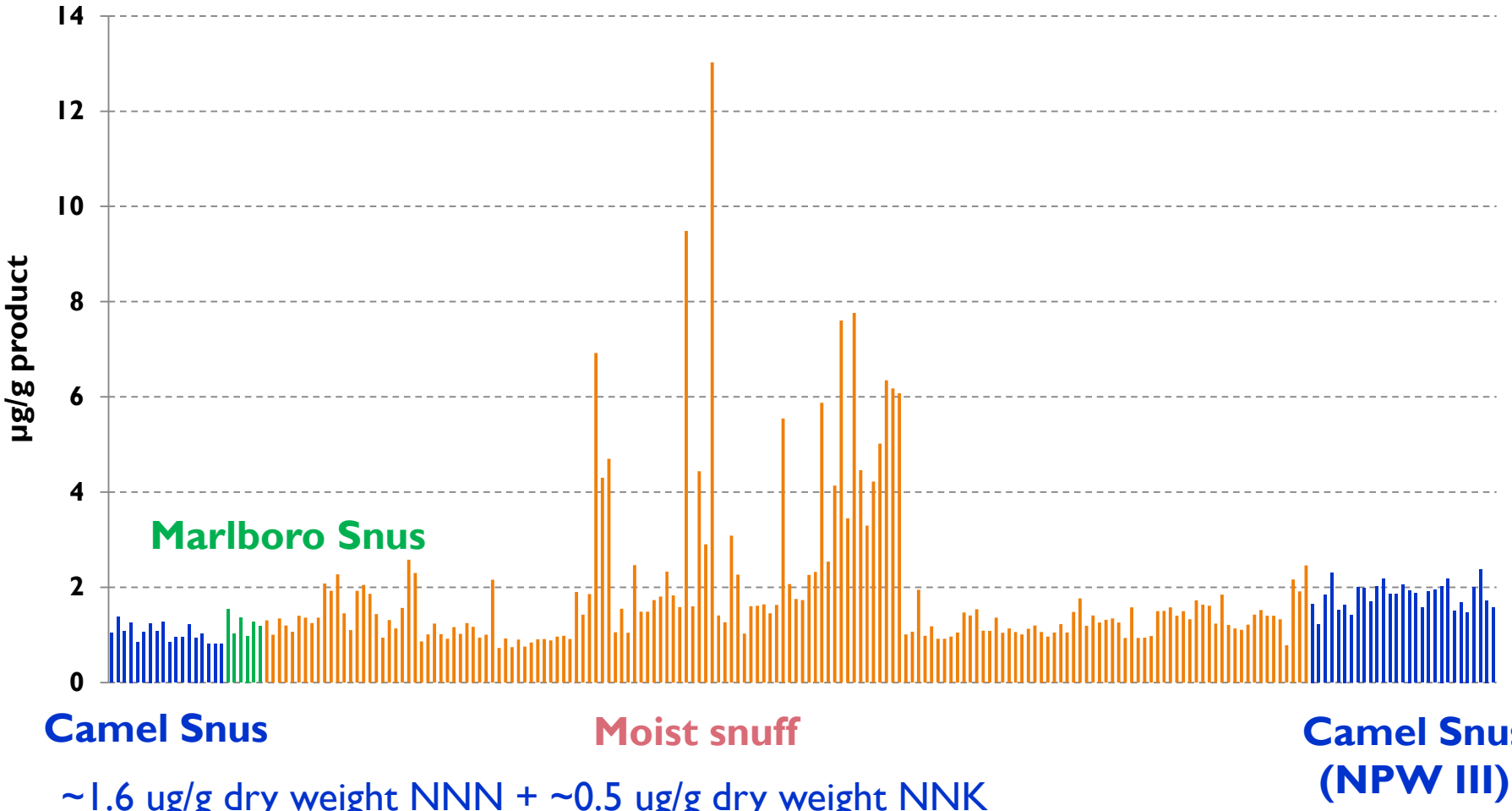

2010

2011




Stepanov and Hatsukami, Tobacco Regulatory Science. 2016;2(1):9-30

# Comparison of NNN data from recent analyses (per gram tobacco)




~1.6 ug/g dry weight NNN + ~0.5 ug/g dry weight NNK



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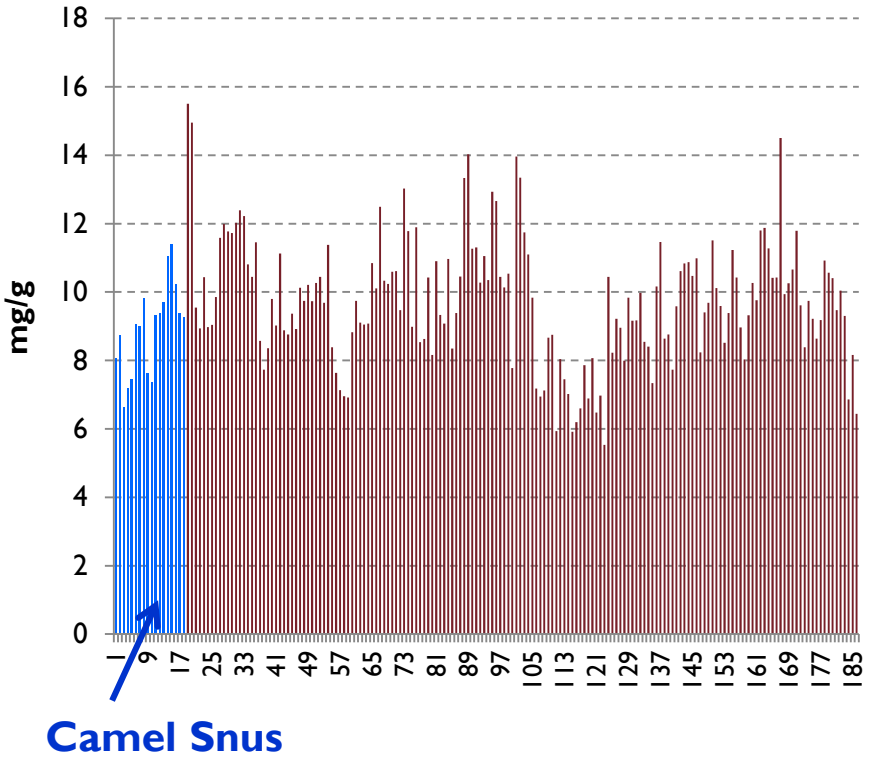
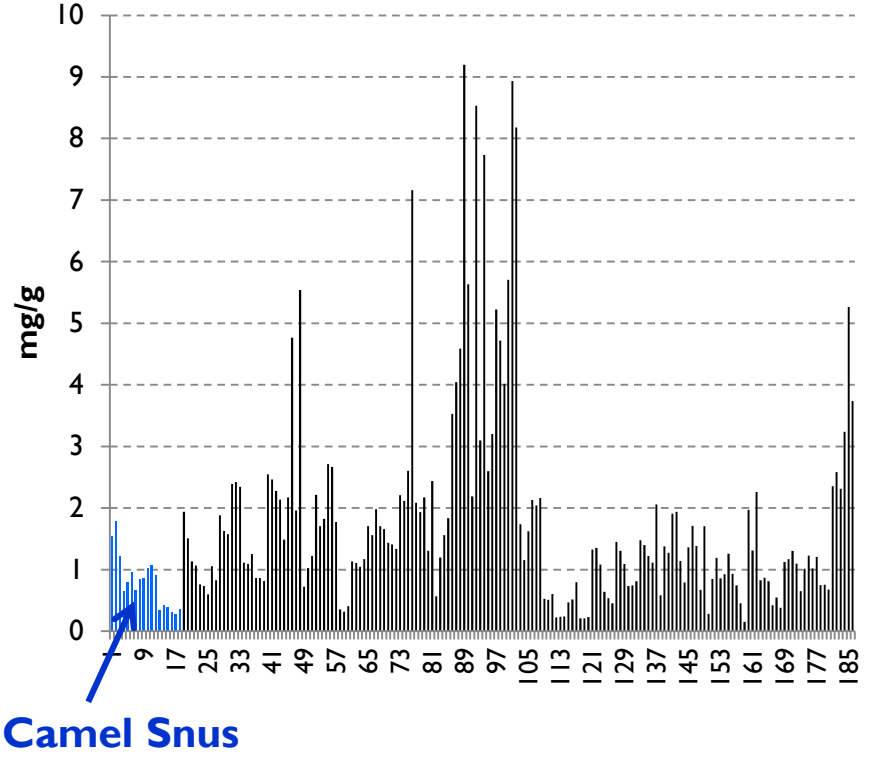
# Other key constituents in recent analyses: Total and free nicotine

## Total nicotine




## Free nicotine



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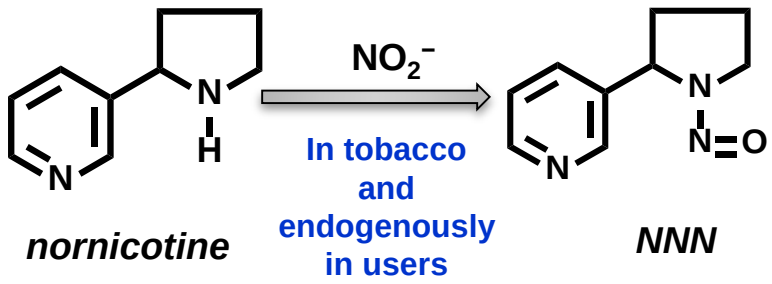
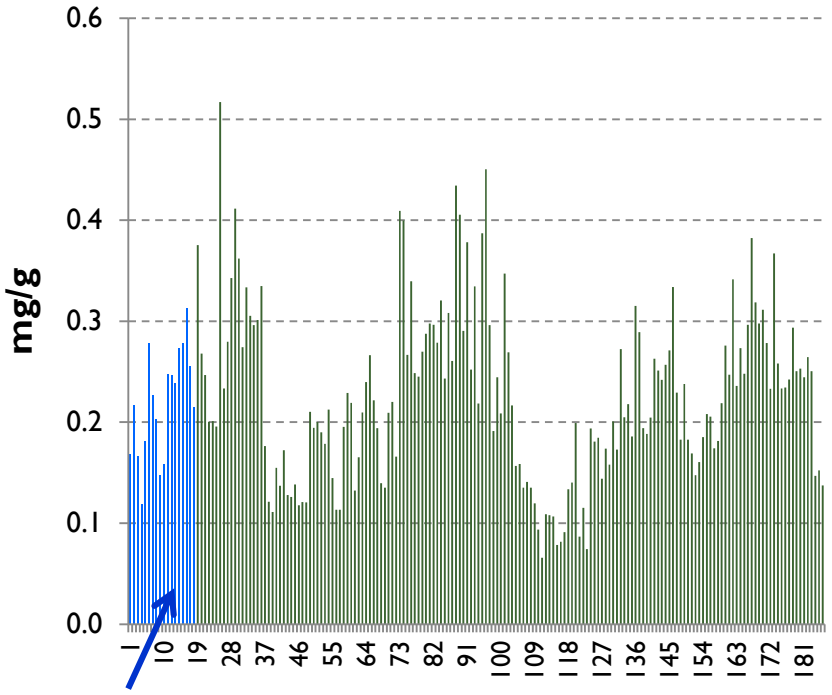
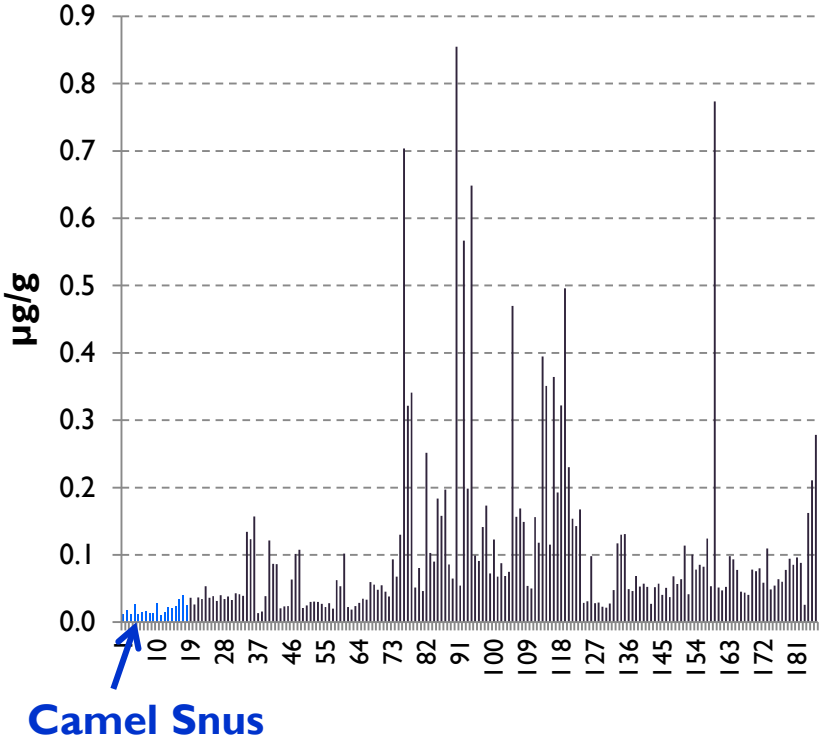
# Other key constituents: Nornicotine and nitrite




## Nornicotine




## Nitrite



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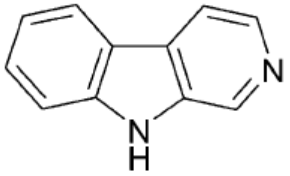
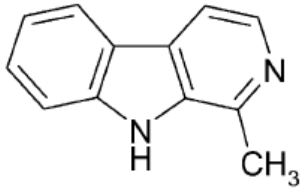
# Minor alkaloids and β-carbolines: potential contribution to addictiveness

- **Minor alkaloids:**
  - **binding to nicotine receptors**
  - **enhancement of nicotine effects**

- **β-Carbolines:**
  - **MAO inhibitors**
  - **Plasma levels increase 10-fold in 5 minutes after smoking a cigarette**
  - **Measured in brain**



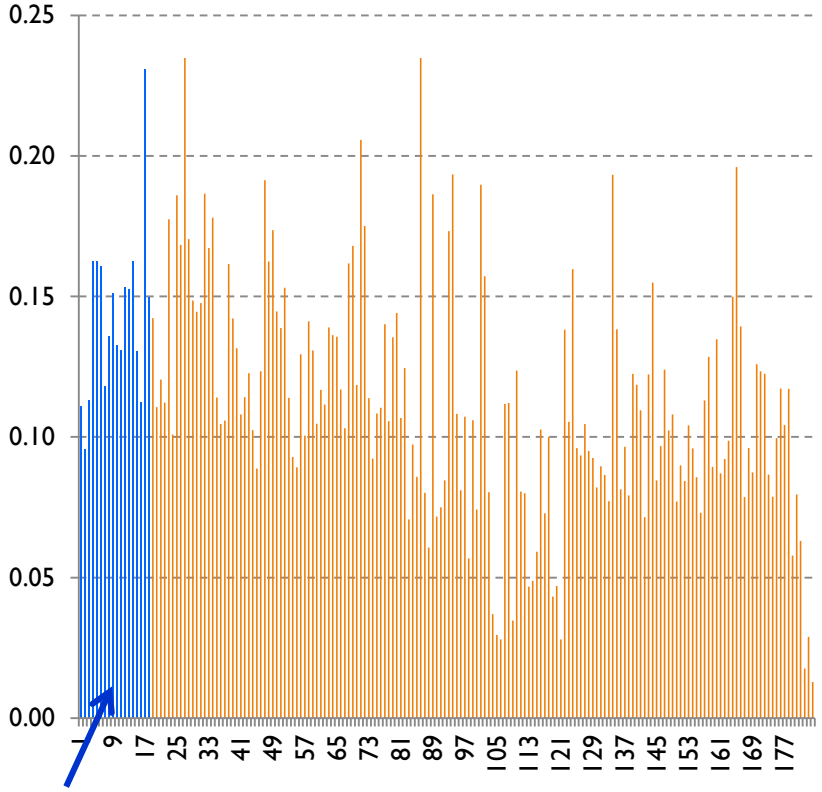
Norharman



Harman

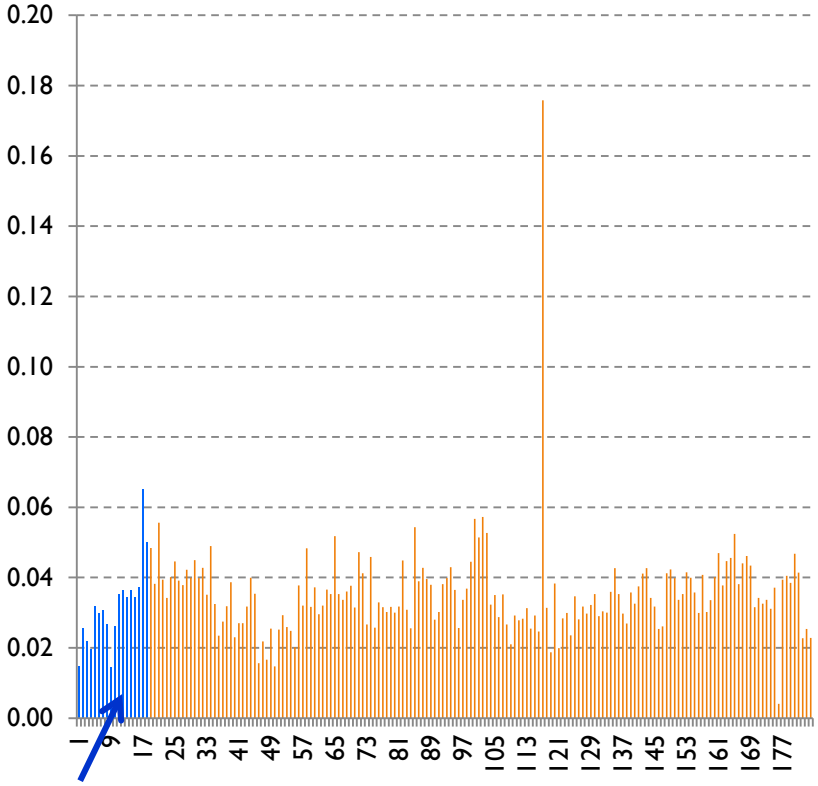
# Anatabine and anabasine data from recent analyses (per gram tobacco)

## Anatabine, mg/g




Camel Snus

## Anabasine, mg/g




Camel Snus



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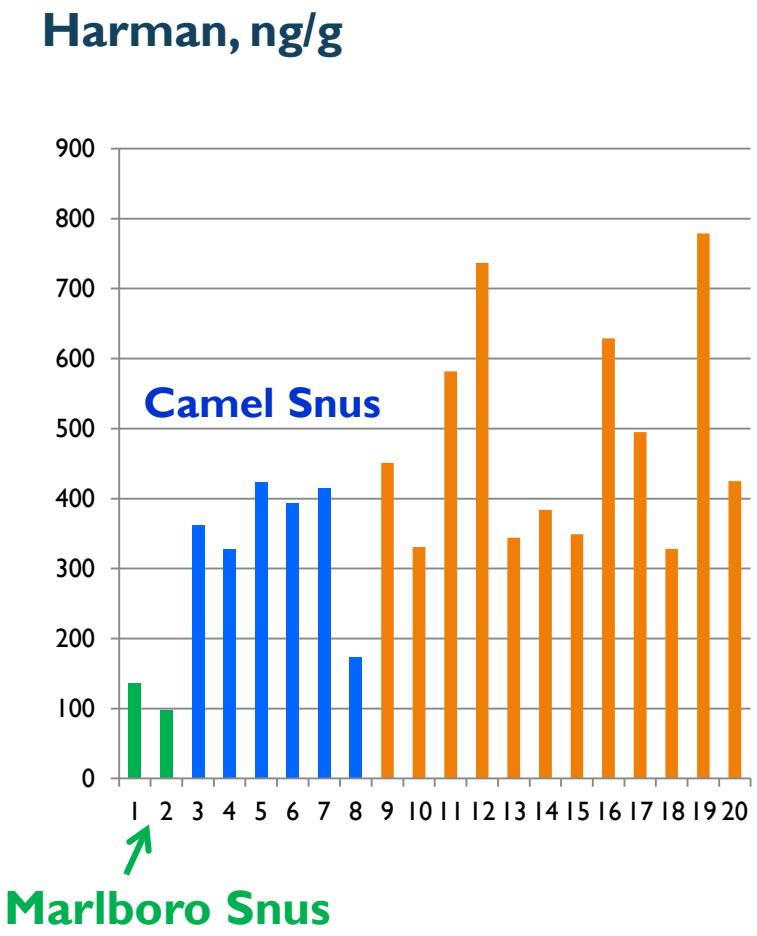
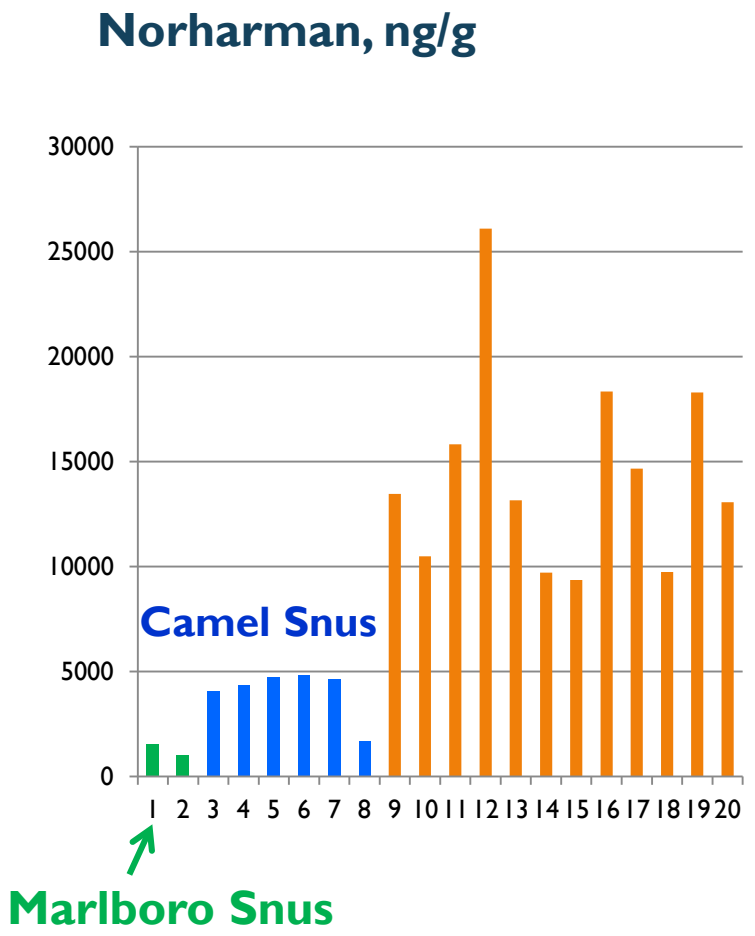
# Harman and norharman data from recent analyses (per gram tobacco)

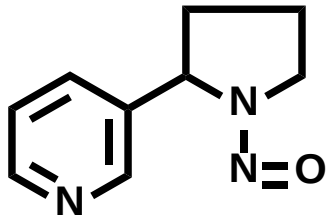


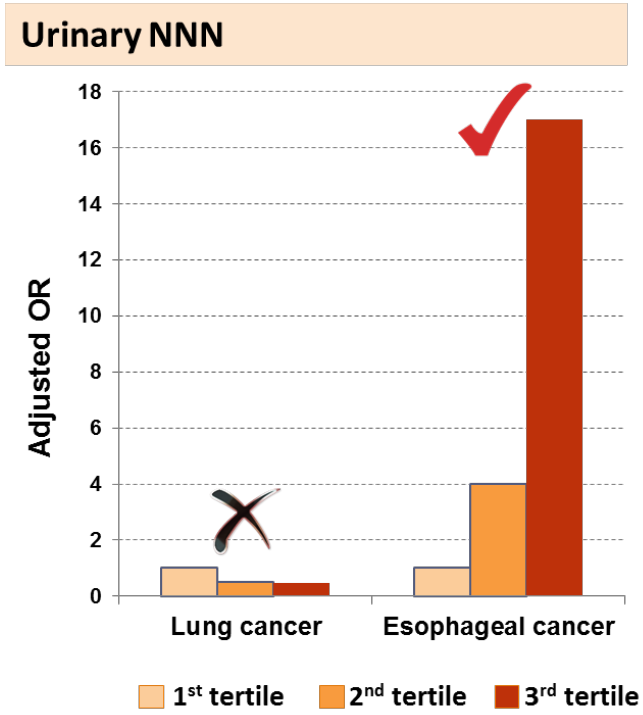



Stepanov Laboratory (manuscript in preparation)

# Particular importance of NNN in smokeless tobacco products




NNN

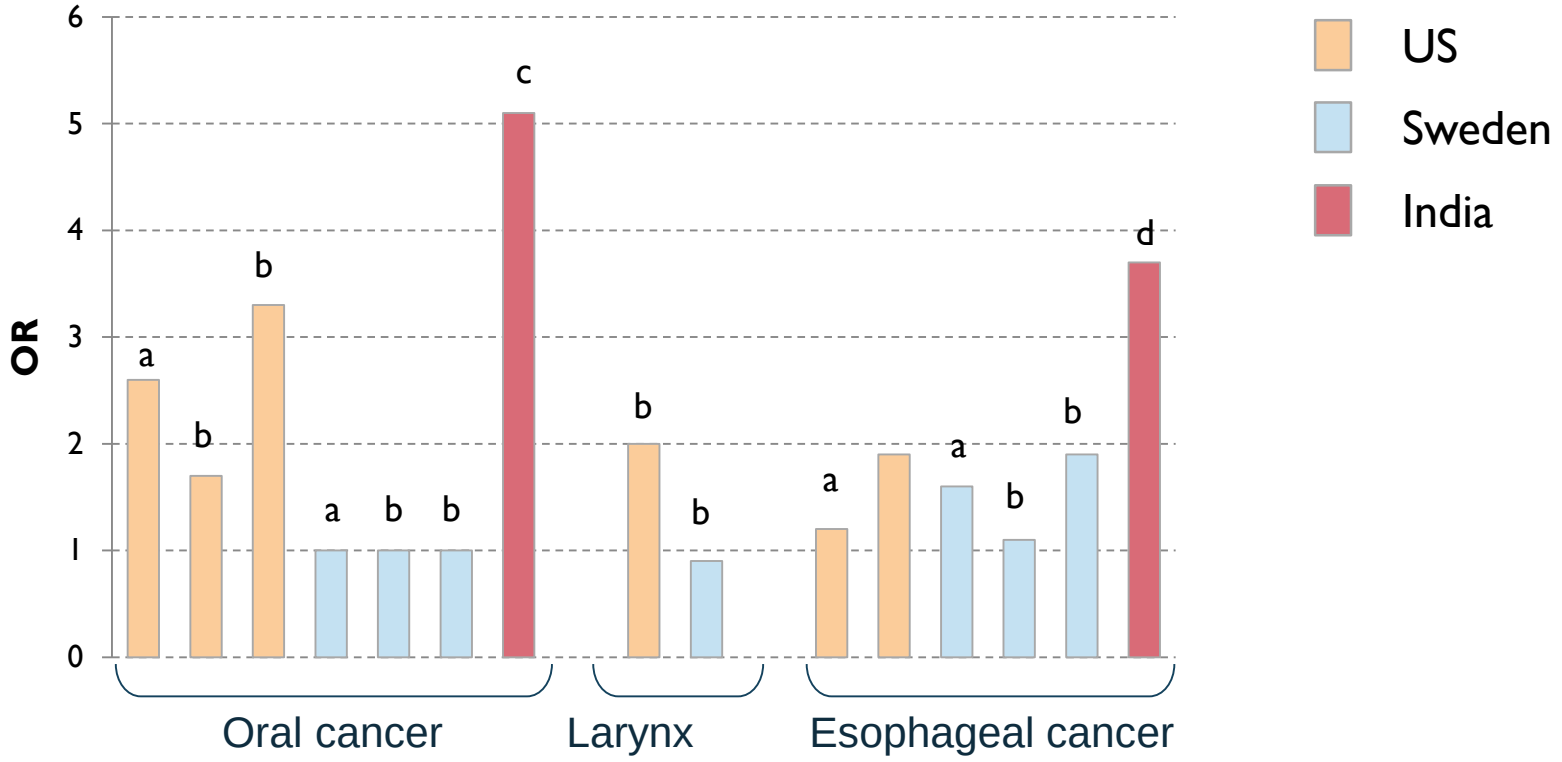



- ✓ Specific to tobacco
- ✓ Potent oral and esophageal carcinogen in laboratory animals
- ✓ Evidence for carcinogenicity in humans



J.-M. Yuan et al, Carcinogenesis 32(9): 1366-1371 (2011);
I. Stepanov et al. Int J Cancer 134:2278-2283 (2014)

# Reported relative risks associated with smokeless tobacco use in various countries




**Average NNN levels in moist snuff (our laboratory):** **~1.7 µg/g product in recent analyses**
**~2.5 µg/g product 10 years ago**



[a]Boffetta, et al. Lancet Oncology, 9: 667-675, 2008; [b]Lee & Hamling, BMC Medicine, 7: 36, 2009; [c]IARC Vol 83, 2004; [d]Pednekar et al. Cancer Causes Control, 22: 859-868, 2011

# There is snus, Snus, and "snus"

| Constituent | Content (2013)* |
|---|---|
| Nitrite (µg/g) | 1.1 (1.0 - 1.1) |
| NNN + NNK (µg/g) | 0.47 (0.46 - 0.48) |
| NDMA (ng/g) | <0.6 |
| B(a)P (ng/g) | <0.6 |
| Cadmium (µg/g) | 0.28 (0.28 - 0.29) |

*http://www.swedishmatch.com/en/Snus-and-health/GOTHIATEK/GOTHIATEK-standard/

**U.S. Snus**

| Product | NNN | NNK |
|---|---|---|
| Marlboro Snus | 0.6 | 0.4 |
| Camel Snus | 1.0 | 0.6 |
| Skoal Snus | 1.6 | 0.2 |

Stepanov Laboratory (2015)

**Swedish snus**

**Indian "snus"**


Stepanov et al. Tobacco Control 2014

# Summary

- **Constituent profile of Camel Snus has been evolving since its first introduction to the market**
- **Current levels of NNN in Camel Snus are comparable to the levels found in many popular moist snuff brands**
- **The increase in NNN levels in Camel Snus occurred while NNN levels in some major moist snuff brands were declining**
- **Available data on other constituents show comparable (minor alkaloids, nitrite, nitrate, harman, metals) or lower (norharman, PAH) levels between Camel Snus and moist snuff**
- **Products marketed as snus vary substantially in their constituent profiles and other characteristics**

# Acknowledgements


**Collaborators**

**University of Minnesota**
Dorothy Hatsukami
Stephen Hecht
Peter Villalta

**Stepanov laboratory members**

Katrina Yershova, Galina Yakovlev, Vipin Jain, Anshu Jain

**Other**
Lois Biener, University of Massachusetts
Amy Nyman, Georgia State University
Yen-Yi Ho, University of South Carolina
Jian-Min Yuan, University of Pittsburgh
Mark Parascandola, National Cancer Institute
Prakash Gupta, Healis-Sekhsaria Institute for Public Health, India

**Funding**
NCI contract HHSN261201200392P
R01 CA180880
R01 CA129534
R01 CA144034
R01 CA-81301
CA-77598 (Mass-Spectrometry)
Global Programs and Strategy (UMN)
Minnesota Masonic Charities


Thank you
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