

Constituent yields and biomarkers of exposure for tobacco product regulation

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Smoke constituents and health outcomes



Addiction

Toxicity

- **Respiratory**
- **Cardiovascular**
- **Reproductive and developmental**

Carcinogenicity

- **19 types of cancer**



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Constituent ranges in cigarette smoke

Constituent	Levels (ng/cigarette)
Acetaldehyde	32,000 – 643,000
4-Aminobiphenyl	0.5 – 3
2-Aminonaphthalene	2 – 17
Benzene	6,000 – 45,000
Benzo[a]pyrene	1 – 14
1,3-Butadiene	6,000 – 54,000
Formaldehyde	2,000 – 52,000
N'-nitrosonornicotine (NNN)	5 – 195
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	13 – 108



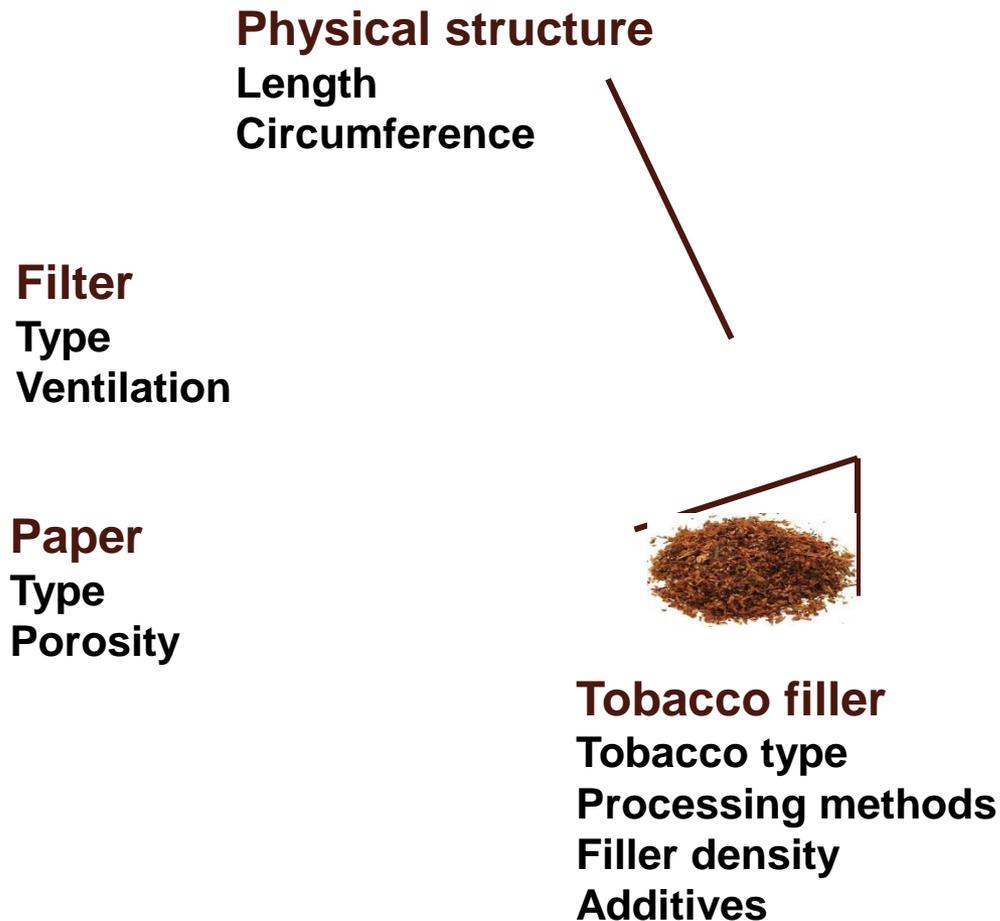
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Counts et al. *Regulatory Toxicology and Pharmacology* 2004;39:111-134

Factors affecting constituent yields



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Family Smoking Prevention and Tobacco Control Act



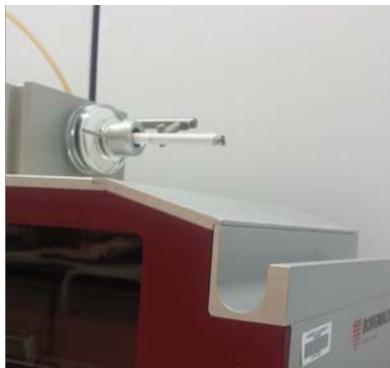
June 22, 2009

Gives the FDA the authority to regulate the manufacture, distribution, and marketing of tobacco products to protect public health.

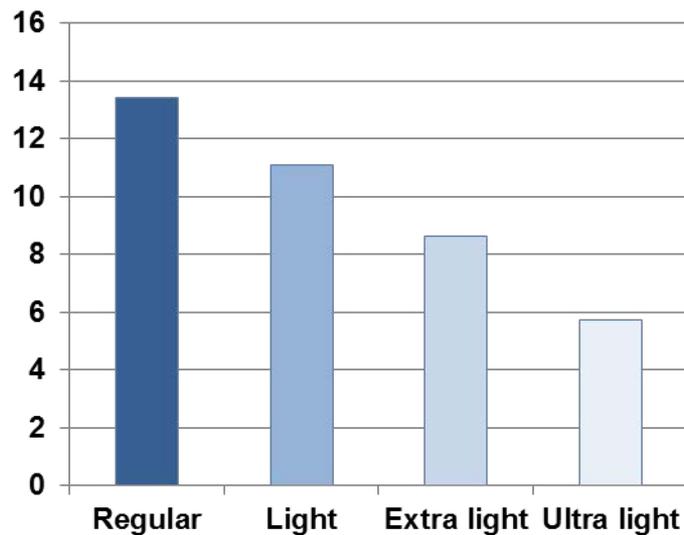


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Constituent yields vs. human exposures



Tar, mg/cigarette



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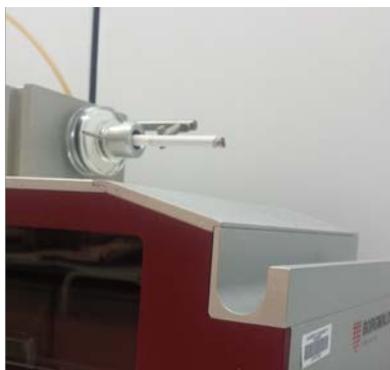
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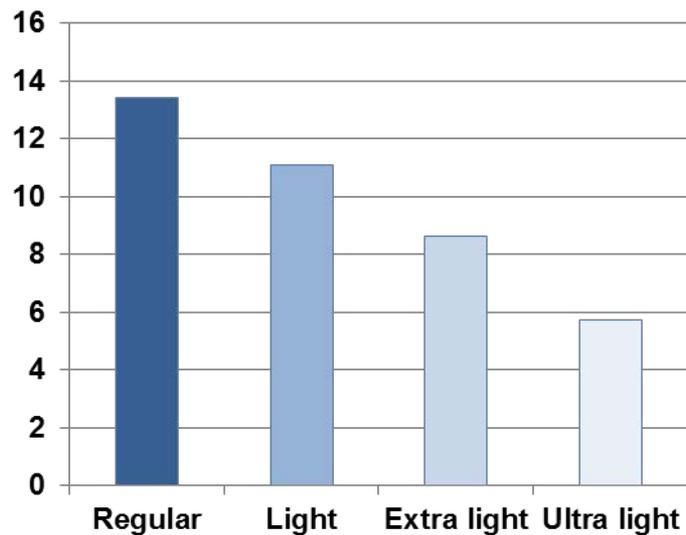
IARC Monograph Vol. 83 (2004)

Hecht et al. *Cancer Epidemiol Biomarkers Prev* 2005;14(3):693-698

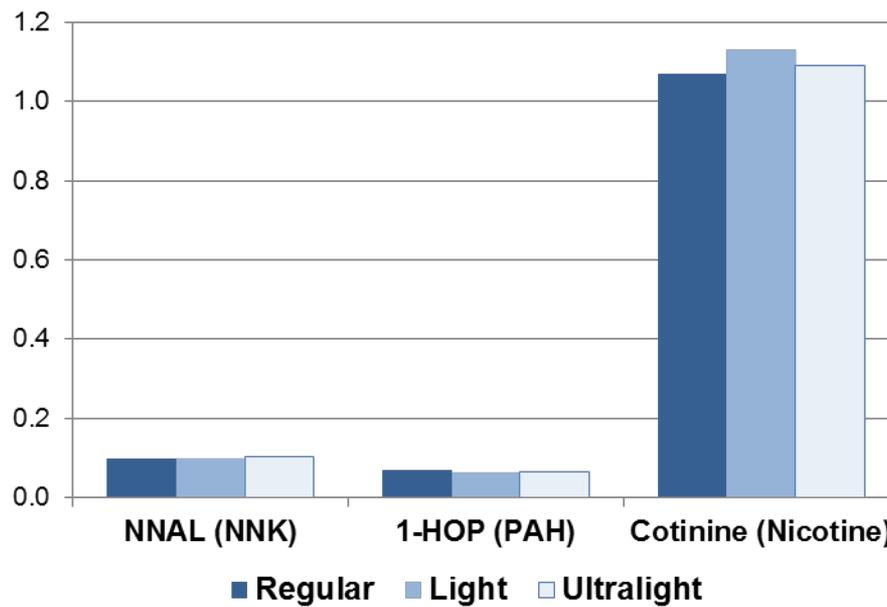
Constituent yields vs. human exposures



Tar, mg/cigarette



Biomarkers, pmol / mg creatinine / CPD



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Constituent yields vs. human exposures

**Machine-measured constituent yields
do not predict human exposures**



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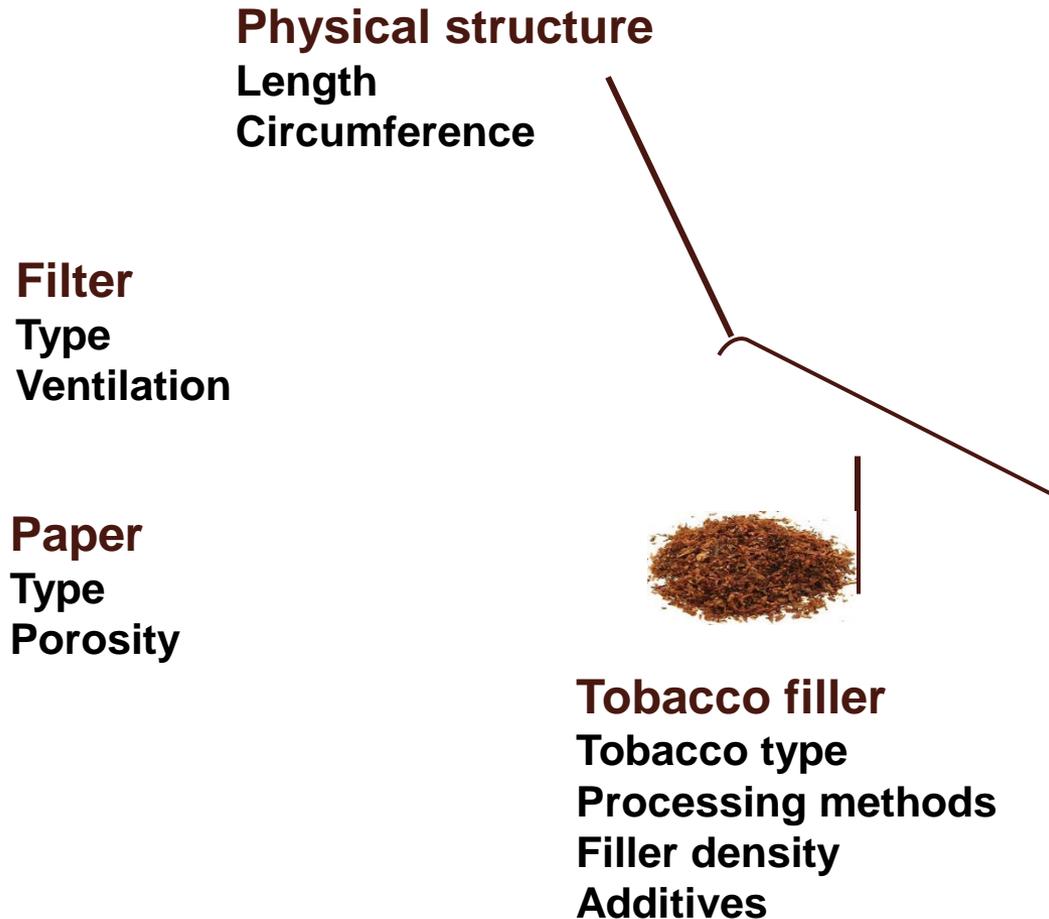
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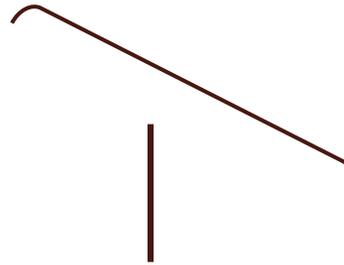
Factors affecting constituent yields



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Factors affecting constituent yields



Puff topography
Volume
Duration
Frequency



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Regulation of constituent yields in smoke



- **Has to rely on machine measurements**



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Regulation of constituent yields in smoke



- Has to rely on machine measurements
- Potential approach:
WHO Study Group on Tobacco Product Regulation recommended that levels of constituents be established **per milligram of nicotine**

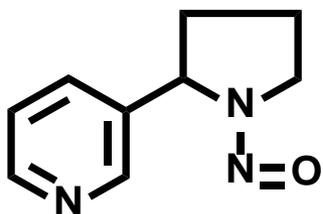


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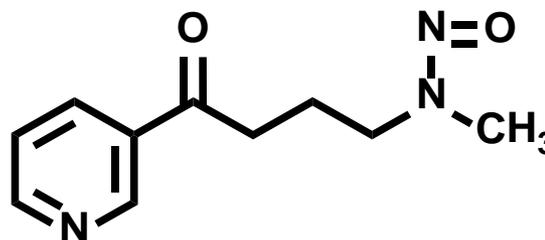
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NNN



NNK

- Tobacco-specific constituents
- Systemic carcinogens, targeting oral cavity, esophagus, lung, pancreas
- Classified by IARC as carcinogenic to humans (Group 1)



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Constituent yields and biomarkers of exposure for tobacco product regulation

Aim 1



Measure 'per nicotine' yields in U.S. cigarettes

Aim 2

Measure corresponding biomarkers in smokers of these cigarettes

Aim 3

Determine factors that affect this relationship



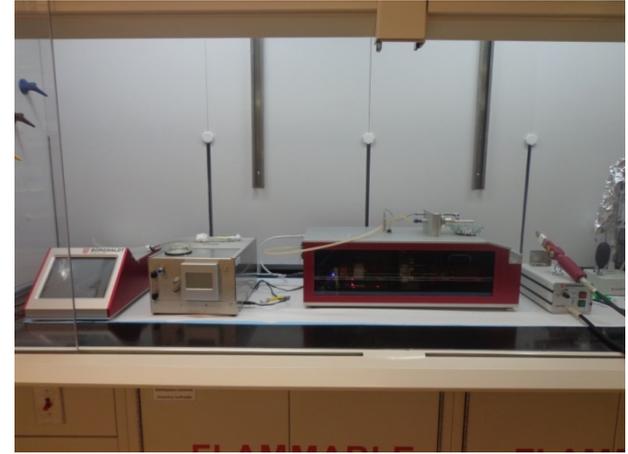
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Progress on Aim 1

LX1 Single-port smoking machine (Borgwaldt)
81 brands (~800 cigarettes)
8 constituents in each sample



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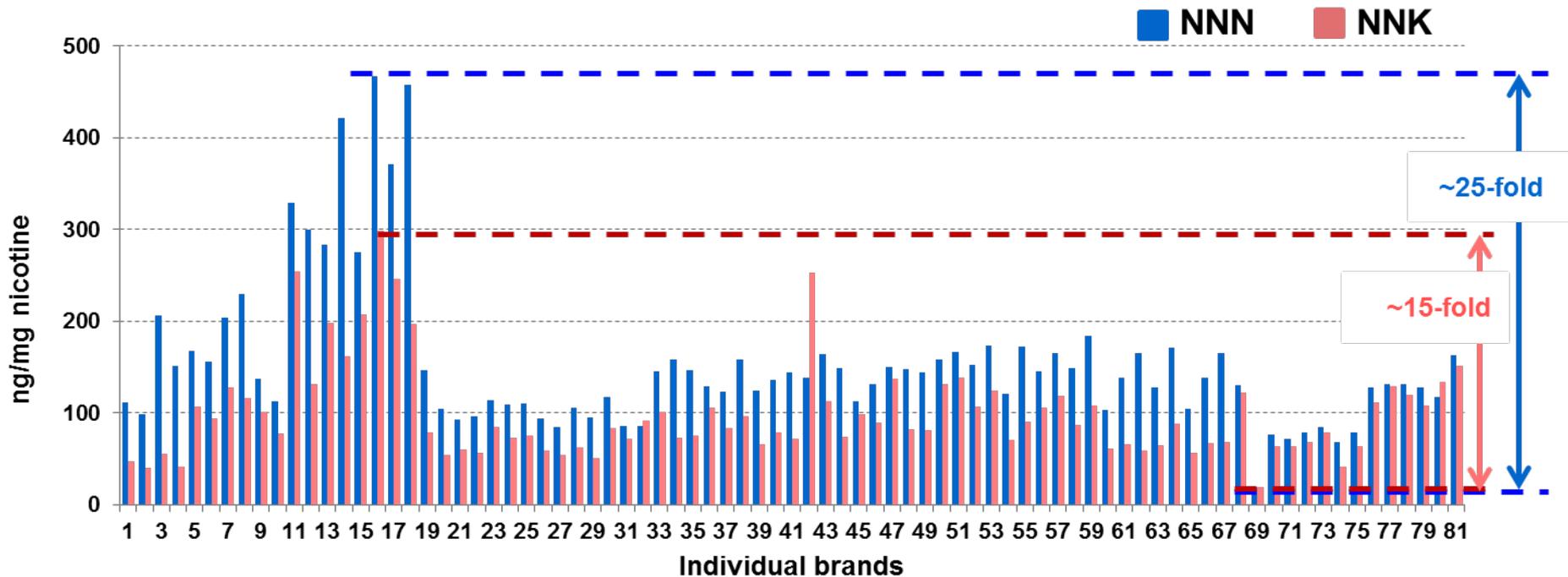
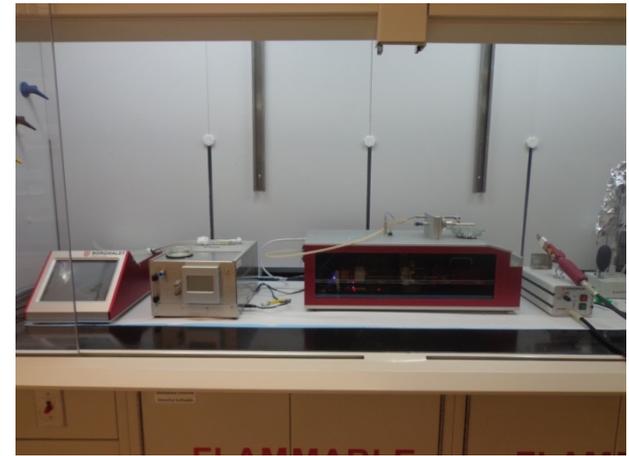
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Unpublished data

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Progress on Aim 1

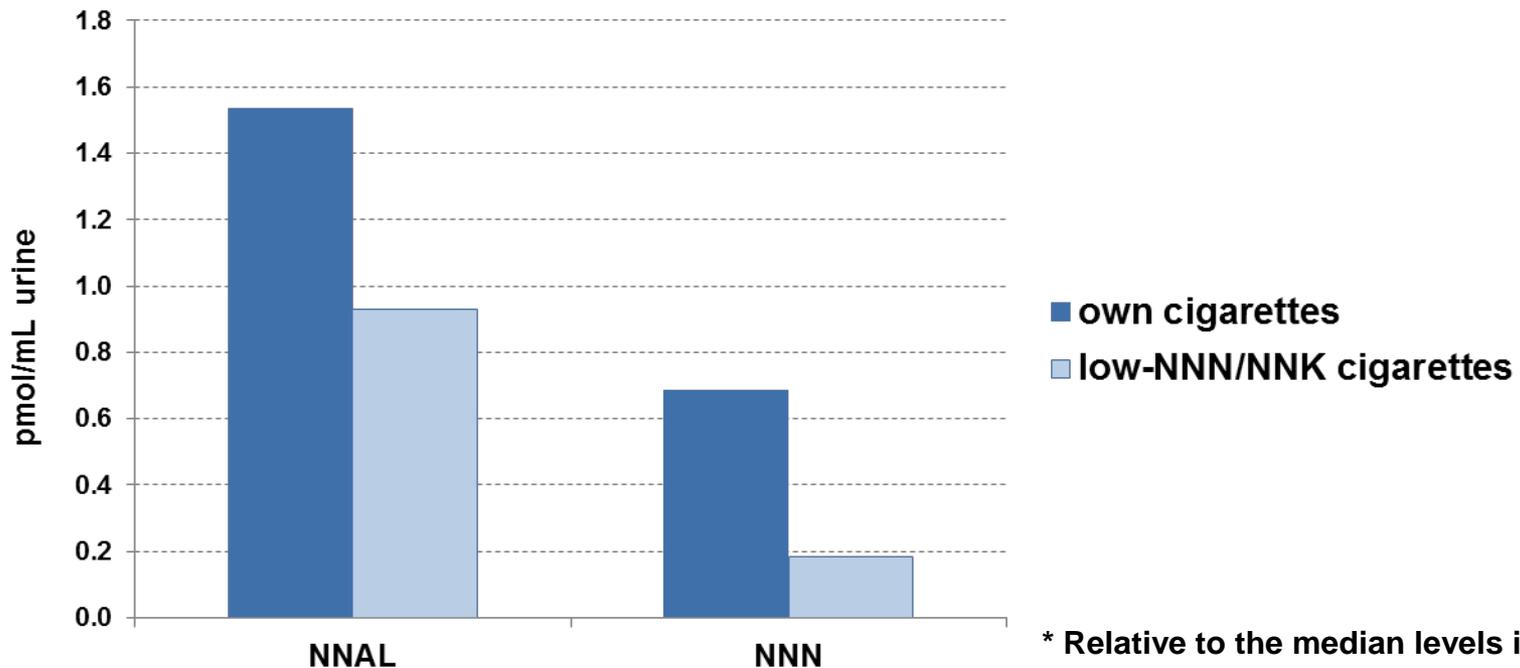
LX1 Single-port smoking machine (Borgwaldt)
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Progress on Aim 2

- Daily smokers of various regular cigarettes (N = 160)
- Switched for 7 days to smoking study cigarettes containing (per mg nicotine)
NNK at 24% of regular level* NNN at 17% of regular level*



* Relative to the median levels in 80 brands

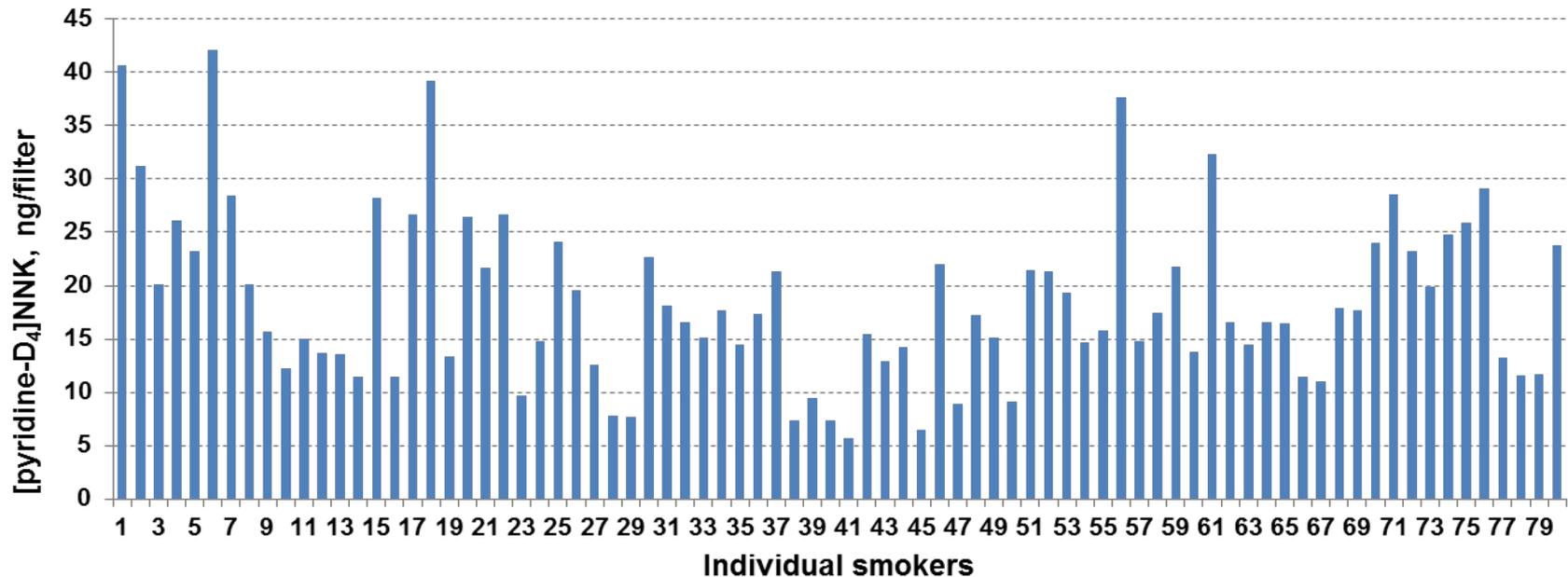
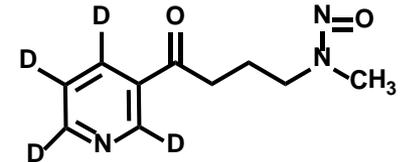


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Progress on Aim 2

Spent cigarette butts as proxy for human exposures

- Smokers switched for 7 days to smoking study cigarettes containing [pyridine-D₄]NNK



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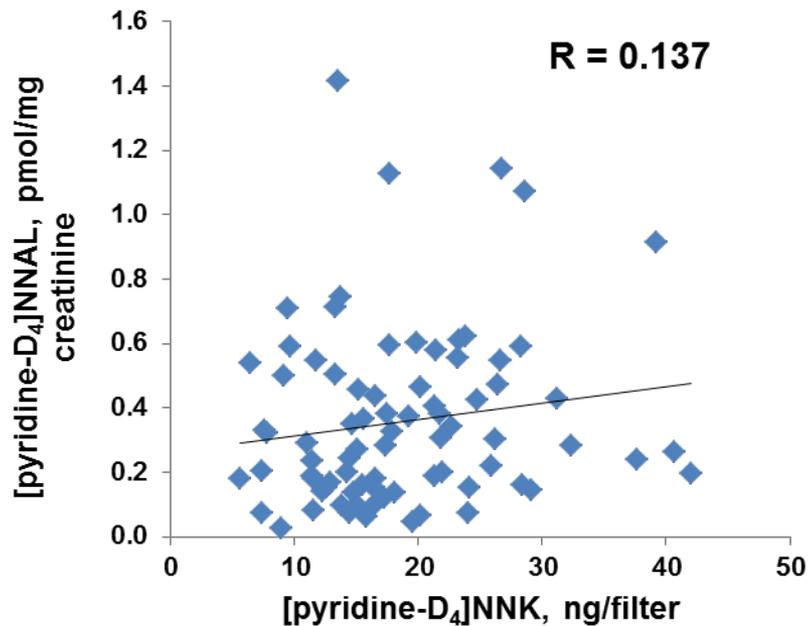
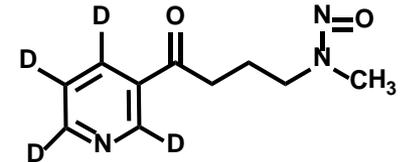
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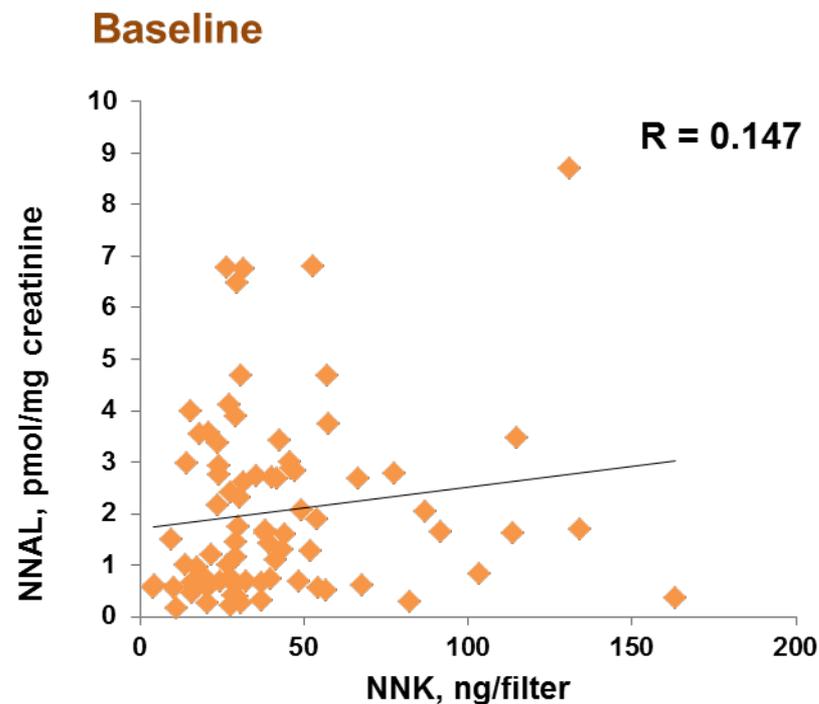
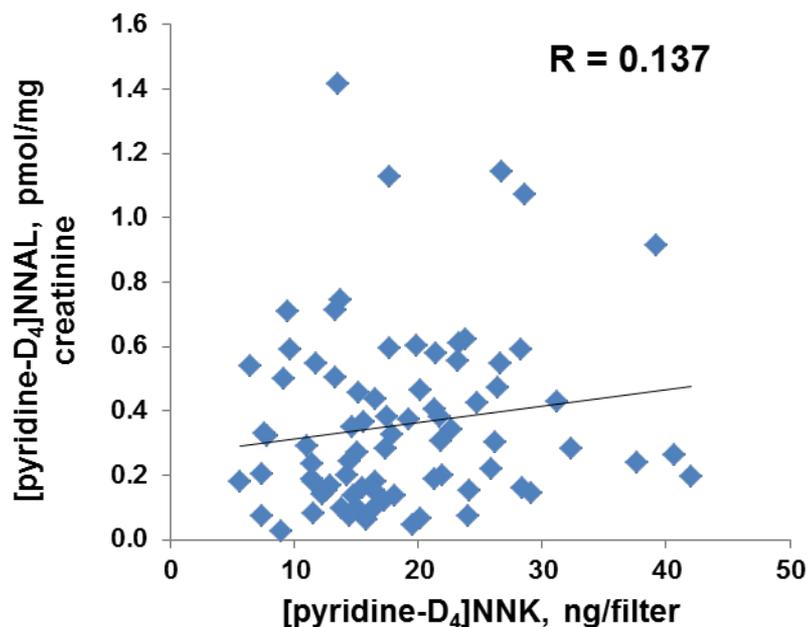
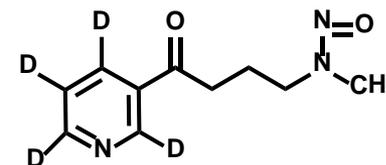
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Looking forward

- **Finalizing product analyses**
- **Finally starting human trial**
- **Writing (many) papers**



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Summary of challenges and solutions

Challenges

- Smoking machine – arrived 9 months after the start of the grant
- Underestimated the time needed to smoke all cigarettes on a single-port machine
- Staff issues (inadequate background, family situations)
- Delayed phase II of the study
- Unspent funds



Summary of challenges and solutions

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Efforts to find solutions

- Developing methodologies for constituents and biomarkers
- Preparation work for the human trial (IRB, recruitment materials, etc.)
- Taking advantage of on-going studies
- Changing project assignments
- Requesting carry-over



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