Biomarkers of exposure related to premium cigar use

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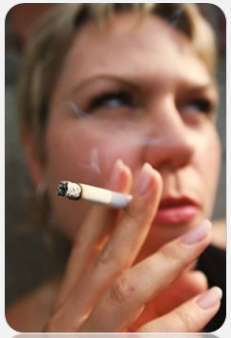
The Tobacco – Health Effect Continuum

Tobacco Product Lab

Cigarettes
Smokeless
ENDS
Cigars

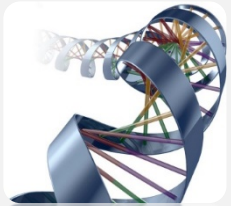
Mainstream
Smoke
Sidestream
Smoke



Topography

Biomonitoring Labs

Serum
Blood
Urine
Saliva

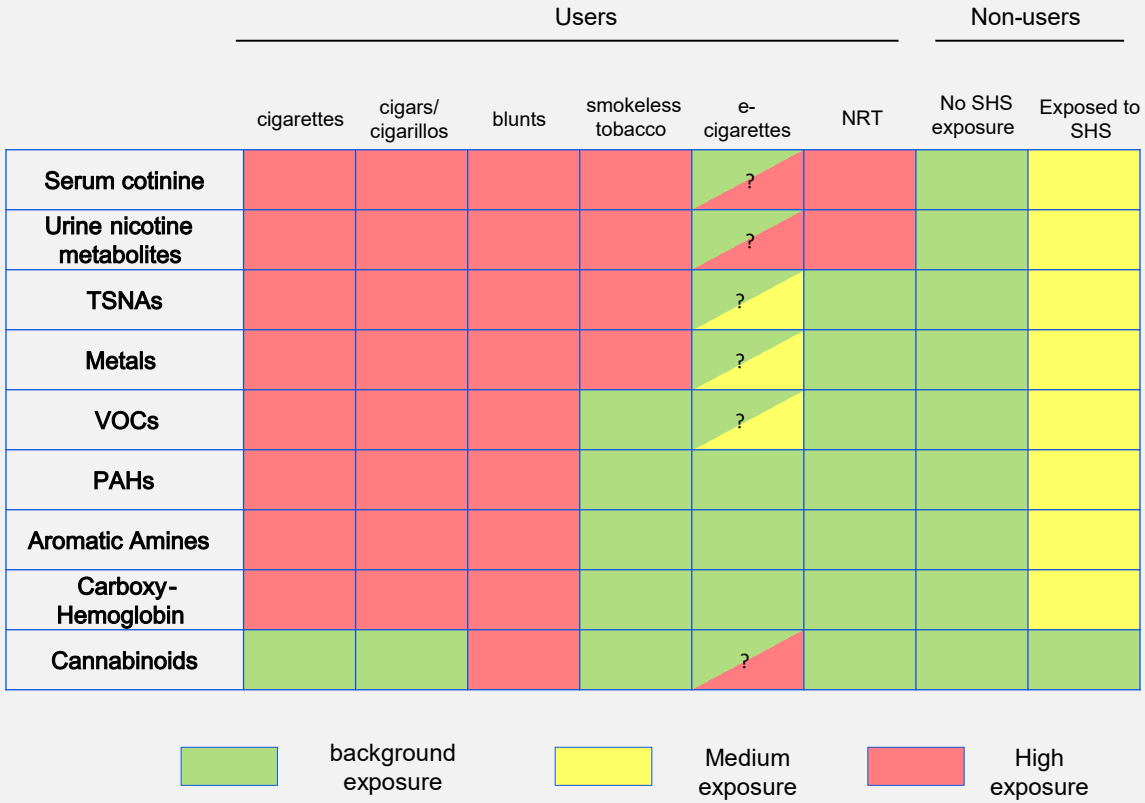


Markers of
Potential
Harm

Biomarkers of Exposure to Tobacco and Smoke

- Documented uptake of nicotine and toxicants from cigar smoke
- Insights about product use intensity and co- or dual-use of tobacco and cannabis
- Internal dose measures connect the dots from exposure to harm and disease
- Quantitative measure against which intervention efficacy can be evaluated

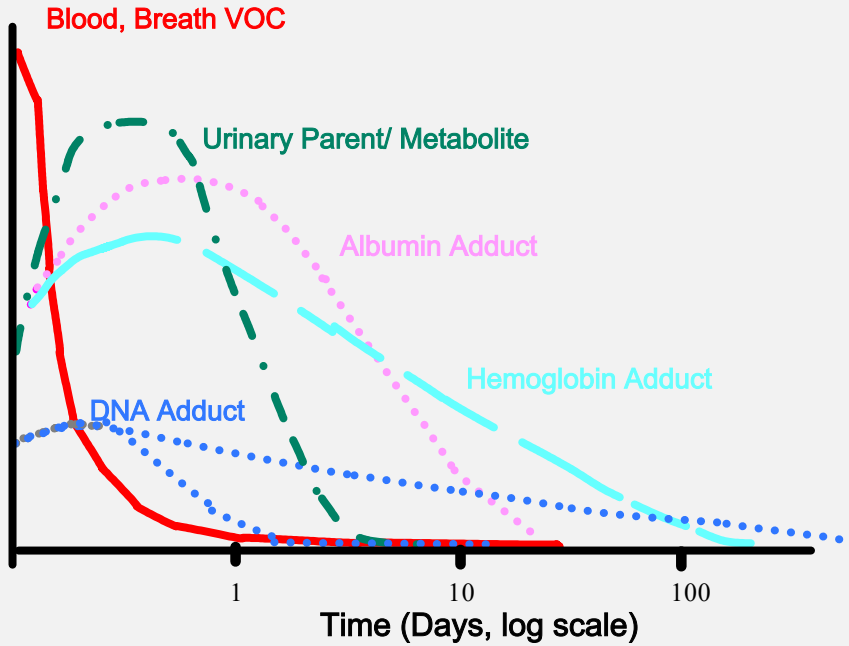
Biomarker patterns to differentiate tobacco product use



Adapted from Schick et al (2016): Am J Physiol Lung Cell Mol Physiol 313: L425–L452, 2017. doi:10.1152/ajplung.00343.2016

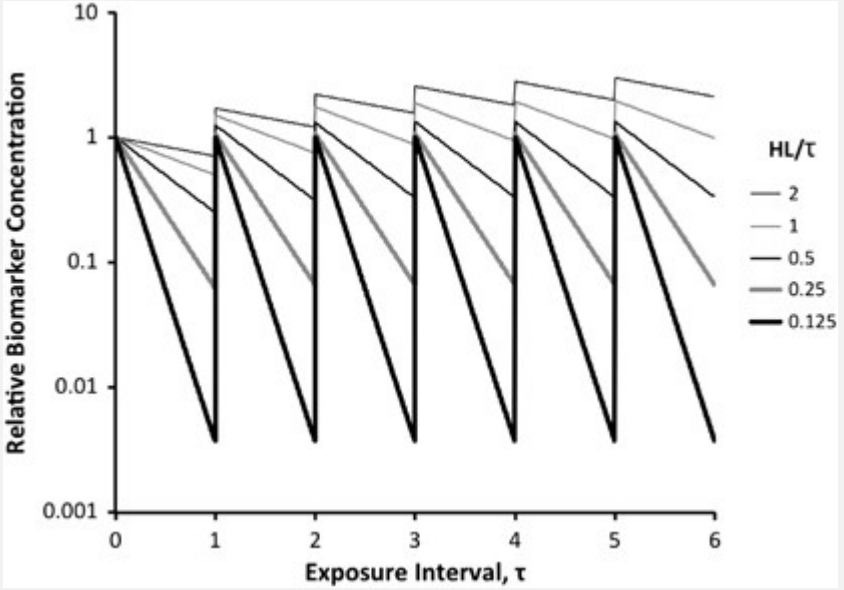
Kinetics of biomarker/matrix selection

- Parent chemicals in serum, urine, breath
- Metabolites in serum, urine, saliva
- Protein adducts (albumin or hemoglobin) in serum or whole blood



Biomarker levels impacted by exposure interval and biomarker half life

- Simulated biomarker concentration *vs* time curves for a repeated constant dose at a consistent interval assuming different values for half-life of elimination (HL) as a fraction of the exposure interval, τ.
- Timing of urine collection relative to last product use can be important for interpreting biomarker levels, especially for short half life biomarkers and longer exposure intervals
- Timing especially important for infrequent/non-daily smokers



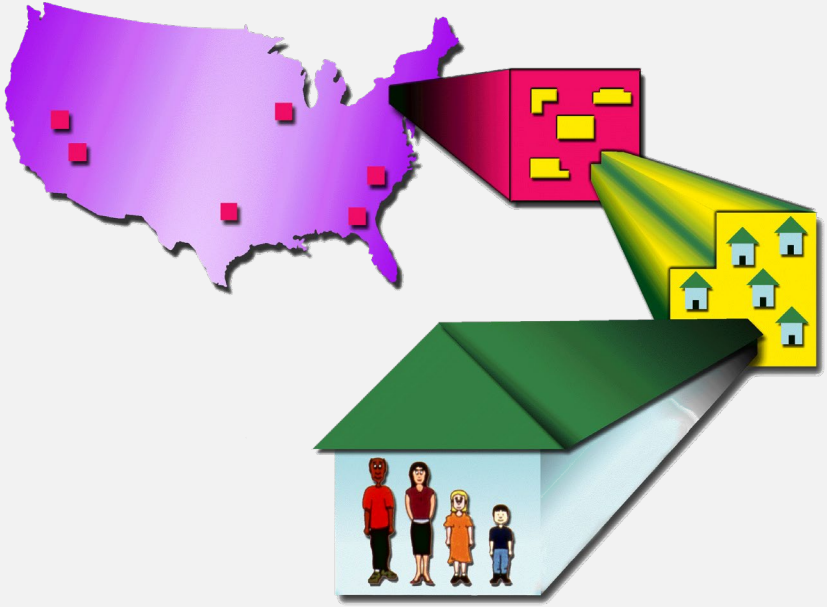
Aylward et al (2012): Interpreting variability in population biomonitoring data: role of elimination kinetics. doi: 10.1038/jes.2012.35

U.S. population-based studies of biomarkers of exposure in cigar smokers

- Chen J, Kettermann A, Rostron BL, Day HR. Biomarkers of exposure among U.S. cigar smokers: an analysis of 1999-2012 National Health and Nutrition Examination Survey (NHANES) data. *Cancer Epidemiol Biomarkers Prev* 2014;23:2906–15
- Chang C, Rostron B, Chang J, et al. Biomarkers of exposure among U.S. adult cigar smokers: Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013-2014). *Cancer Epidemiol Biomarkers Prev* 2019 May;28(5):943-953.

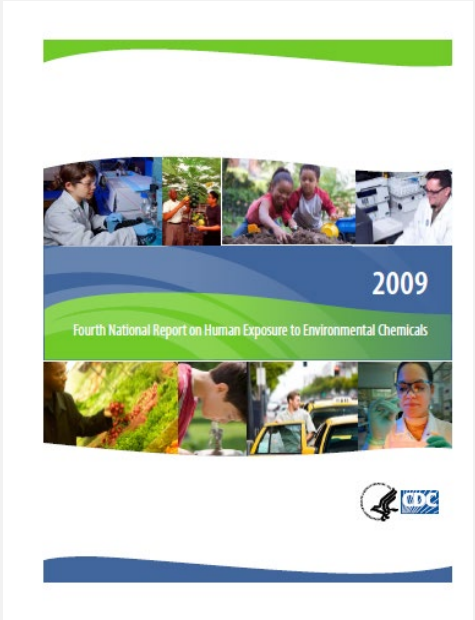
National Health and Nutrition Examination Survey (NHANES)

- Ongoing CDC survey designed to collect data on the health and nutritional status of the U.S. population
- Conducted by National Center for Health Statistics
- Complex, multistage, area probability design: samples the U.S. population based on age, sex, race/ethnicity, income.
- NHANES surveys: I (71-75), II (76-80), III (88-94); and every 2 years since 1999



- Thorough interview and physical exam, including blood and urine collection
- Biomarkers of exposure to environmental chemicals quantified in blood and/or urine

CDC National Exposure Report
includes smoking categorization



Urinary N-Acetyl-S-(2-cyanoethyl)-L-cysteine

Metabolite of Acrylonitrile

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. adult population from the National Health and Nutrition Examination Survey by smoking status.

	Survey years	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval) 50th	75th	90th	95th	Sample size
Cigarette Smokers							
Total	11-12	**122** (106-141)	**140** (119-166)	**277** (240-310)	**504** (439-580)	**717** (513-827)	889
Age group							
20-49 years	11-12	**114** (90.4-143)	**132** (105-172)	**265** (214-306)	**515** (372-717)	**717** (467-888)	532
50 years and older	11-12	**137** (118-159)	**146** (125-184)	**306** (232-344)	**481** (384-699)	**705** (439-846)	357
Gender							
Males	11-12	**123** (98.8-153)	**156** (131-183)	**306** (261-355)	**552** (463-745)	**780** (608-858)	536
Females	11-12	**121** (104-140)	**128** (116-146)	**240** (201-277)	**403** (289-652)	**652** (344-786)	353
Nonsmokers							
Total	11-12	**1.50** (1.35-1.67)	**1.33** (1.22-1.45)	**2.35** (2.16-2.52)	**4.81** (3.79-5.80)	**12.1** (7.05-18.2)	1308
Age group							
20-49 years	11-12	**1.67** (1.38-2.02)	**1.45** (1.25-1.65)	**2.49** (2.23-3.00)	**5.84** (4.64-10.3)	**13.4** (7.05-79.9)	655
50 years and older	11-12	**1.34** (1.18-1.53)	**1.23** (1.07-1.36)	**2.19** (1.83-2.44)	**3.65** (3.03-4.36)	**6.84** (3.89-10.6)	653
Gender							
Males	11-12	**1.90** (1.65-2.20)	**1.64** (1.44-1.85)	**2.96** (2.53-3.24)	**7.05** (4.06-12.4)	**14.7** (8.19-58.5)	625
Females	11-12	**1.24** (1.06-1.45)	**1.19** (1.02-1.26)	**1.90** (1.74-2.09)	**3.55** (2.95-4.36)	**6.84** (3.97-10.8)	683

Tobacco product users who did not smoke cigarettes were excluded. See Adult Cigarette Smokers and Nonsmokers: Analysis of Select Chemicals in a Special Sample.
Limit of detection (LOD, see Data Analysis section) for Survey year 11-12 is 0.5.

http://www.x.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf

Tobacco-Related Biomarkers in NHANES

- serum cotinine
- urine nicotine metabolites
- urine anatabine, anabasine
- urine aromatic amines
- urine NNAL/TSNAs
- urine heterocyclic amines
- urine volatile nitrosamines
- urine thiocyanate
- blood VOCs
- urine VOC metabolites
- urine hydroxyPAHs
- urine metals
- urine arsenic
- albumin aldehyde adducts
- hemoglobin adducts
- serum hsCRP

Tobacco-Related Biomarkers in NHANES: Challenges

- Cross-sectional study design: different people sampled in different locations each two-year cycle
- Not all analytes measured in all NHANES cycles: assays cycled in/out (primarily because of funding restraints)
- Some analytes measured in all study participants, while others are measured only in a 1/3 subsample of population or in a reduced age range
- Special sample of adult smokers (NHANES 2011 – 2016)
- Small N for tobacco use categories other than cigarettes

Chen et al: Biomarkers of exposure among U.S. cigar smokers (NHANES 1999-2012, cotinine and NNAL)

- Non-daily cigar smokers < daily cigar smokers
- Non-smokers << daily cigar-only smokers < daily cigarette smokers and dual users
- Biomarkers increase with increasing number of cigars smoked per day
- Daily users: Primary cigar smokers (N=26) < Secondary cigar smokers (N=24)
- Non-daily users: Primary cigar smokers (N=76) < Secondary cigar smokers (N=54)

Biomarkers of exposure among U.S. cigar smokers (NHANES 1999-2012): Caveats

- No distinction between premium cigars, cigarillos, and little filtered cigars
- Cadmium findings explainable by past accumulation from historical smoking
- Arsenic findings explainable by dietary sources of organic arsenic
- Data pooled over a 14-year period, but still relatively small N (especially for NNAL)

Population Assessment of Tobacco and Health (PATH) Study

Chang C, et al. Biomarkers of exposure among U.S. adult cigar smokers: Population Assessment of Tobacco and Health (PATH) Study Wave 1 (2013-2014)

- The most definitive and current study of US cigar smokers
- Exclusive cigar smokers Wave 1: Sept 2013 – Dec 2014
- Data analyzed by all cigars combined and also stratified by cigar type
- Single spot urine collected at study participant residence along with tobacco use questionnaire information
- Analyzed biomarkers of exposure to nicotine, TSNAs, metals, PAHs, and VOCs

PATH
Population Assessment of Tobacco and Health
A collaboration between the NIH and FDA

Tobacco-related biomarkers in PATH cigar smokers

- Never users << some day cigar-only smokers < every day cigar-only smokers
- Every day cigar-only smokers (n = 61) had lower TNE-2 (cotinine+trans-3'-hydroxycotinine) compared to every day cigarette-only (n = 2217; P < 0.0001; GMR = 1.9) and dual cigar/cigarette smokers (n = 601; P < 0.0001).
  - Similar results from Multi-Ethnic Study of Atherosclerosis (MESA) cohort (Rodriguez et al., 2010)
- Other biomarkers tended to be lower in every day premium cigar smokers vs every day cigarette smokers, but the difference did not reach statistical significance in many cases because of small N (N=12 premium cigar smokers).
- GMs for NNAL and most smoke biomarkers for every day cigarette smokers were approximately double that of every day premium cigar smokers

Tobacco-related biomarkers in PATH cigar smokers

- Daily dual users had biomarker levels more like cigarette smokers than cigar smokers
- “Close, but no cigar”: every day filtered cigar-only (*n* = 7) smokers had higher biomarker concentrations compared with every day traditional cigar-only smokers (*n* = 12) and cigarillo-only smokers (*n* = 24)
- biomarkers tend to be lowest in cigarillo smokers (24) < premium cigar (12) < filtered cigar (7) ≈ cigarette smokers (2218)
- Increasing exposure to nicotine, NNK, acrylonitrile, and acrolein with increasing numbers of cigars smoked per day

Summary

- The levels of exposure biomarkers are consistently higher in daily vs. non-daily premium cigar smokers, and biomarker levels increase with increasing numbers of cigars smoked per day
- Nicotine, TSNAs, and smoke biomarker levels are consistently much higher in all every day smokers compared with never users.
- Biomarker levels among daily cigar smokers: cigarillo < premium/traditional < filtered cigar ≈ cigarette, although these differences rarely reached statistical significance (small N)
- Additional data would be useful to better characterize cigar-related exposures in the US population

Thank you

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