
Smoke chemistry: Is there a correlation with lung cancer epidemiology?

John H. Lauterbach, PhD, DABT
Lauterbach & Associates, LLC
Fan Chen, MD, DrPH
Mercer University

Outline

- Background
- Objective
- Tobacco chemistry and cigarette design
- Epidemiological data
- Cigarette mainstream smoke (MSS) chemical data
- Use of the Rozman scale to select analytes that may be associated with the epidemiology
- Conclusions

Background

- All cigarettes are dangerous
- Are some more dangerous than others?
- This is an important question because
 - If some products are more dangerous than others, can they be distinguished from less dangerous products by current test methods used to evaluate cigarettes?
 - If methods are incapable of distinguishing more dangerous from less dangerous, then should they be used to evaluate additives or PREPS?

Objectives

- Use epidemiological data on lung cancer to see if some types of cigarettes are more dangerous than other types of cigarettes
 - Numerous epidemiological studies have been carried out on smokers of different types of cigarettes in various regions of the world
 - Epidemiological data most likely represents effects of many pack-years of smoking, including smoking behavior
- Determine if differences in epidemiological results can be correlated with differences in MSS chemistry and/or bioassays

Tobacco chemistry & cigarette design - 1

- Three main types of blends used in commercial cigarettes around the world
 1. All Virginia or Virginia with Oriental tobacco
 - Tobaccos are heat-cured; high sugars/low nitrogen
 - Generally do not use tobacco additives, but may contain reconstituted and/or expanded tobaccos
 - Major markets - U.K., Australia, Canada, China, India
 2. All black (*a/k/a* dark air-cured) tobacco
 - Tobaccos are air-cured then fermented; very low sugars, but high in nitrogen including nitrate nitrogen
 - Generally do not use tobacco additives
 - Major markets - France and southern Europe, some countries in central and south America

Tobacco chemistry & cigarette design - 2

- Three types of blends (continued)
 3. US blended (and other blended types)
 - Blend is mixture of burley (air-cured, but not fermented), Virginia and Oriental tobaccos
 - Blends often include reconstituted tobacco, expanded tobacco, processed tobacco stem
 - Depending on blending and additives strategy, there can be a wide range in sugar, nitrogen, and nitrate levels
 - Generally extensive use of additives although some additive-free products available
 - Major markets - USA, Japan, Brazil, Germany

Tobacco chemistry & cigarette design - 3

■ Three major cigarette designs

1. Non-filter

- 70-85 mm long, ~8 mm diameter
- Only tobacco, cigarette paper, sideseam adhesive
- Volume declining, hard to meet tar ceilings

2. Cellulose-acetate filtered

- Most popular type of cigarette worldwide
- Typically 84 mm long with 20-27 mm filter, ~8 mm diameter (king size), but other configurations sold
- Filter ventilation ranging from 0% to 80+%

3. Cellulose acetate plus selective filtration

- Typically KS cigarette with ventilated filter containing 30-60 mg activated charcoal and/or other media
- Major market is Japan

Epidemiological studies – lung cancer

Study	Dates	Location	Principal adjustment factors	RR (Black/Blond) & 95% CI
Matos, '98	'94-'96	Argentina	Age, cigs/day	M 1.31 (0.85 to 2.02)
Pezzotto, '93	'87-'91	Argentina	Age, cigs/day, years smoked	M 1.70 (1.19 to 2.43)
Suzuki, '94	'91-92	Brazil	Age, gender, race, pack-years	M,F 2.80 (1.00 to 7.70)
Joly, 83	'78-'80	Cuba	None	F 1.73 (0.85 to 3.53)
de Stefani, '96a	'88-'94	Uruguay	Age, various socio-economic	M 1.89 (1.41 to 2.52)
de Stefani, '96b	'93-'96	Uruguay	Age, various socio-economic, BMI	M 2.38 (1.62 to 3.52)
Benhamou, '84	'76-'80	France	Age, cigs/day, years smoked	M 1.73 (0.92 to 3.26)
Benhamou, '87	'76-'80	France	Age, cigs/day, years smoked	F 2.04 (0.75 TO 5.57)
Benhamou, '93	'77-'80	Italy	Age, cigs/day, years post quit	M 1.30 (0.98 to 1.73)
Agudo, '94	'89-'92	Spain	None (for tobacco-type comparison)	F 2.63 (0.56 to 12.30)
Armadans-Gil, '99	'86-'90	Spain	Age, cigs/day, years smoked, Fil/NFil	M 4.68 (1.90 to 11.80)

Adapted from Peter N. Lee, *Inhalation Toxicology* 2001, 13:951-976 2001

Other epidemiological evidence

- Some studies have shown that smokers of black tobacco cigarettes have a higher incidence of bladder cancer than do smokers of blond tobacco cigarettes
 - Attributed to higher levels of aromatic amines in MSS of black tobacco cigarettes than in MSS of blond cigarettes
 - Urines from smokers of black tobacco cigarettes reportedly more mutagenic in Ames assay than those from smokers of blond cigarettes

Epidemiological studies – questions

- Misclassification bias on cigarette type?
 - Did blond mean a Virginia or modified Virginia blend or did it mean a US style blend?
 - Without running chemical analyses, no easy way to tell “one blond from another”
 - US-style blends contain burley tobaccos, generally higher in NO_3^- , TSNAs, and proteins, potentially similar to the black tobaccos
- Confounding factor: filter versus nonfilter?
 - Whether filter is in place may be a considerable confounding factor when comparing the effect of black versus blond tobacco; however, Armadans-Gil *et al.* appear to have controlled this potential confounder.

MSS components & lung cancer

- Hecht, 1999, weight-of-evidence approach
 - TSNA's \approx specific PAHs \gg metals, free radicals/oxidative damage, miscellaneous organics
- Laugesen and Fowles, 2005; Fowles and Dybing, 2003; Hausmann *et al.*, 2001, risk-assessment approaches
 - 1,3-butadiene, acetaldehyde, acrylonitrile, benzene
- Pryor, 1997, free radicals derived from reaction of NO_x with isoprene and free radicals derived from the quinone-hydroquinone-semiquinone system

Routine parameters – ISO smoking

Style	Filter Ventilation (%)	Dry Tobacco Weight (mg/cig)	ISO TPM (mg/cig.)	ISO Water (mg/cig)	ISO Nicotine (mg/cig)	ISO PMWNF (mg/cig)	ISO CO (mg/cig)	ISO NO (mg/cig)	ISO HCN (mg/cig)	ISO Puffs	ISO CO/ISO Nicotine
UK Regal KS (UK blend)	0	620	13.8	2.36	0.90	12.0	13.9	0.113	0.139	7.7	15
UK Marlboro KS (US blend)	19	770	15.7	2.08	0.91	12.7	12.8	0.157	0.132	8.6	14
UK Gitanes Caporal Filter 70 mm (black blend)	14	680	14.8	2.17	0.64	12.0	12.6	0.296	0.127	7.0	20
KY1R4F KS (US blend)	27	~800	10.7	0.93	0.71	9.0	12.3	0.277	0.125	8.5	17

Source: UK Brand Study for Commercial Products obtained Nov./Dec. 2001 see <http://www.the-tma.org.uk>

Hoffmann analytes – ISO smoking

Style	Acetaldehyde (mg/cig)	Acrylonitrile (mg/cig)	Benzene (mg/cig)	Pyridine (mg/cig)	1,3-Butadiene (mg/cig)	Isoprene (mg/cig)	4-Amino- biphenyl (mg/cig)	HQ (mg/cig)	B[a]P (mg/cig)	NNN (mg/cig)	NNK (mg/cig)
UK Regal KS (UK blend)	0.872	0.012	0.058	0.0095	0.042	0.369	0.00000063	0.063	0.000012	0.000023	0.000030
UK Marlboro KS (US blend)	0.716	0.011	0.049	0.0093	0.036	0.417	0.0000012	0.047	0.000010	0.000105	0.000084
UK Gitanes Caporal Filter 70 mm (black blend)	0.687	0.013	0.056	0.0213	0.037	0.305	0.0000021	0.036	0.000011	0.000500	0.000258
KY1R4F KS (US blend)	0.709	0.0081	0.041	0.0041	0.031	0.343	0.0000013	0.03 4	0.000007	0.000107	0.000093

Source: UK Brand Study for Commercial Products obtained Nov./Dec. 2001 see <http://www.the-tma.org.uk>

Hoffmann analytes – ISO smoking

Style	Acetaldehyde ($\mu\text{g}/\text{cig}$)	Acrylonitrile ($\mu\text{g}/\text{cig}$)	Benzene ($\mu\text{g}/\text{cig}$)	Pyridine ($\mu\text{g}/\text{cig}$)	1,3-Butadiene ($\mu\text{g}/\text{cig}$)	Isoprene ($\mu\text{g}/\text{cig}$)	4-Amino- biphenyl (ng/cig)	HQ ($\mu\text{g}/\text{cig}$)	B[a]P (ng/cig)	NNN (ng/cig)	NNK (ng/cig)
UK Regal KS (UK blend)	872	11.7	57.5	9.54	42.2	369	0.63	62.7	15.6	22.8	30.2
UK Marlboro KS (US blend)	716	10.9	49.0	9.31	35.6	417	1.21	47.2	9.88	105	84.3
UK Gitanes Caporal Filter 70 mm (black blend)	687	13.2	55.8	21.3	37.4	305	2.06	35.8	10.9	500	258
KY1R4F KS (US blend)	709	8.07	40.6	4.14	31.0	343	1.30	34.2	7.07	107	93.0

Source: UK Brand Study for Commercial Products obtained Nov./Dec. 2001 see <http://www.the-tma.org.uk>

Dose and dosage

- Calculating daily dose (DD) per analyte
 - $DD = \text{cigs/day} \times \text{analyte/cig} \times SF$
 - Assume 60 cigs per day
 - SF = smoking factor to adjust analyte levels to estimated values for other smoking regimens
 - Analyte values used here for cigarettes with low levels of filter ventilation – minimal effect on vent-blocking
 - St. Charles *et al.* (2004) have shown that most smokers of the “higher” lights and full flavor cigarettes obtain “tar” and nicotine yields close to the FTC and ISO methods and that more intense protocols overestimate yields.
- Dosage calculations done assuming 70 kg body weight

Rozman-scale introduction & examples

- Rozman scale uses chemical potentials to estimate thresholds for carcinogenicity
 - Used to estimate rodent thresholds from chronic rodent carcinogenicity studies (e.g., NTP studies)
 - Plot percent-tumor data versus dosage expressed as molecules of toxicant/kg body weight/day and use linear regression to estimate dosage where regression line crosses x-axis
 - Estimated human dosage of toxicant expressed on same basis and compared with rodent threshold
 - Recent examples of use of Rozman scale given by W. J. Waddell (*Tox. Sci.* 2002, 68:275-279)

Rozman scale and pyridine

- Based on NTP data, Waddell estimated threshold values for pyridine
 - Values were around 10^{20} molecules/kg/day for several tumor types in rats and mice
 - Human intake from foods estimated to be about 10^{15} molecules/kg/day
- Based on MSS pyridine data and 60 cigs/day,
 - Smokers of cigarettes have estimated intake of about $10^{16.8}$ to $10^{17.1}$ molecules/kg/day
 - Estimated level $\sim 100X$ food level, but over $100X$ less than estimated threshold for carcinogenicity

Rozman scale and NNK – 1

- In 1988, Rivenson *et al.* reported results for a 2-year carcinogenicity study of NNK in drinking water in male F344 rats (*Cancer Res.* 1988, 48: 6912-6917)

	Group I NNK, 0.5 ppm	Group II NNK, 1.0 ppm	Group III NNK, 5.0 ppm	Group VII Water only
Number of rats	80	80	30	80
Total dose (millimol/kg)	0.073	0.17	0.68	N/A
Dosage (molecules/kg/day)	$10^{16.7}$	$10^{17.1}$	$10^{17.8}$	N/A
Total number of rats with lung tumors	9	20	27	6

Rozman scale and NNK – 2

- Based on the data of Rivenson *et al.*, threshold for NNK carcinogenicity about $10^{16.7}$ molecules/kg/day
- Based on concentrations of NNK in MSS, intake is about 10^{14} molecules/kg/day for smokers of blond tobacco cigarettes and about 10^{15} molecules/kg/day for smokers of black tobacco cigarettes
- Do these results explain the epidemiology?

Conclusions

- Several epidemiological studies have found that smokers of black tobacco cigarettes have a higher incidence of lung cancer than do smokers of blond cigarettes
- MSS from black tobacco cigarettes has higher levels of some nitrogen-containing compounds believed related to lung cancer than does MSS from blond tobacco cigarettes
- In cases where there are sufficient data, the Rozman scale may be useful for comparing estimated human exposures with rodent carcinogenicity thresholds