Reducing the Adverse Health Impact of Cigarettes on Smokers Who Will Not or Cannot Abstain Through Modification of Leaf Nicotine Content

Abstract:

Past research has demonstrated the potential benefits of a cigarette that delivers a satisfactory level of nicotine while reducing the delivery of whole smoke.

22nd Century Limited owns technology for and is currently developing commercially viable flue-cured tobacco lines that will enable the production of low tar to nicotine ratio (TNR) cigarettes.

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Outline

1. Background: 22nd Century Limited, LLC.
2. Dose-response relationships of smoking-related diseases and whole smoke
3. Compensation and history of tar and nicotine yields and per smoker consumption
4. Human-smoking-behavioral studies on increasing nicotine
5. Brand ABC's low tar to nicotine ratios (TNRs)
6. Research design considerations for future human trials of Brand ABC

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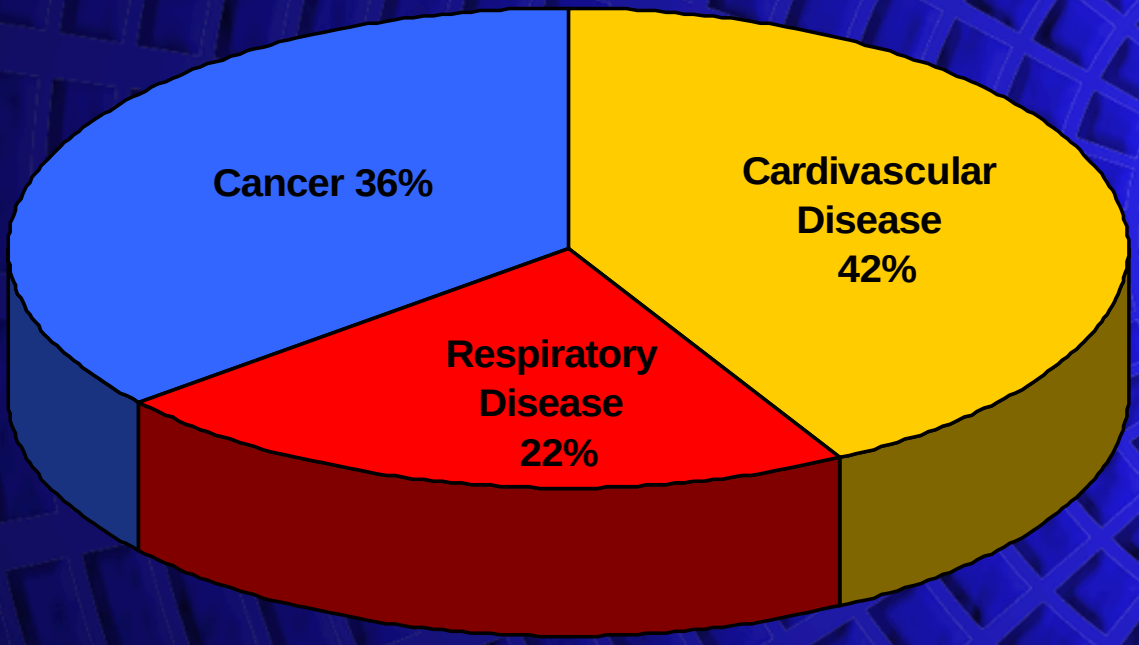
Causes of Smoking-Related Deaths from 1990-1994 in U.S.



Source: U.S. DHHS, 2000

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“There is strong evidence that in the range of exposures involved in smoking, there is a quantitative relationship between the magnitude of exposure and the incidence of cancer, coronary vascular disease, pulmonary disease, and several other tobacco-related illnesses.”

p. viii, Preface, IOM Report

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Dose-Response Relationship:

- The relationship between disease-risk regression and exposure regression
  - The higher the dose of whole tobacco smoke, the greater the incidence of disease.

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Cardiovascular Disease

"Highly informative information on the existence of a dose-response relationship between cigarette exposure and cardiovascular risk comes from many studies such as the CPS-2 (Thun et al., 1997) and Harvard Nurses' Health Studies (Kawachi et al., 1997b).

In both instances, there is a relationship between the number of cigarettes smoked and the incidence of cardiovascular events."

p. 486, IOM Report

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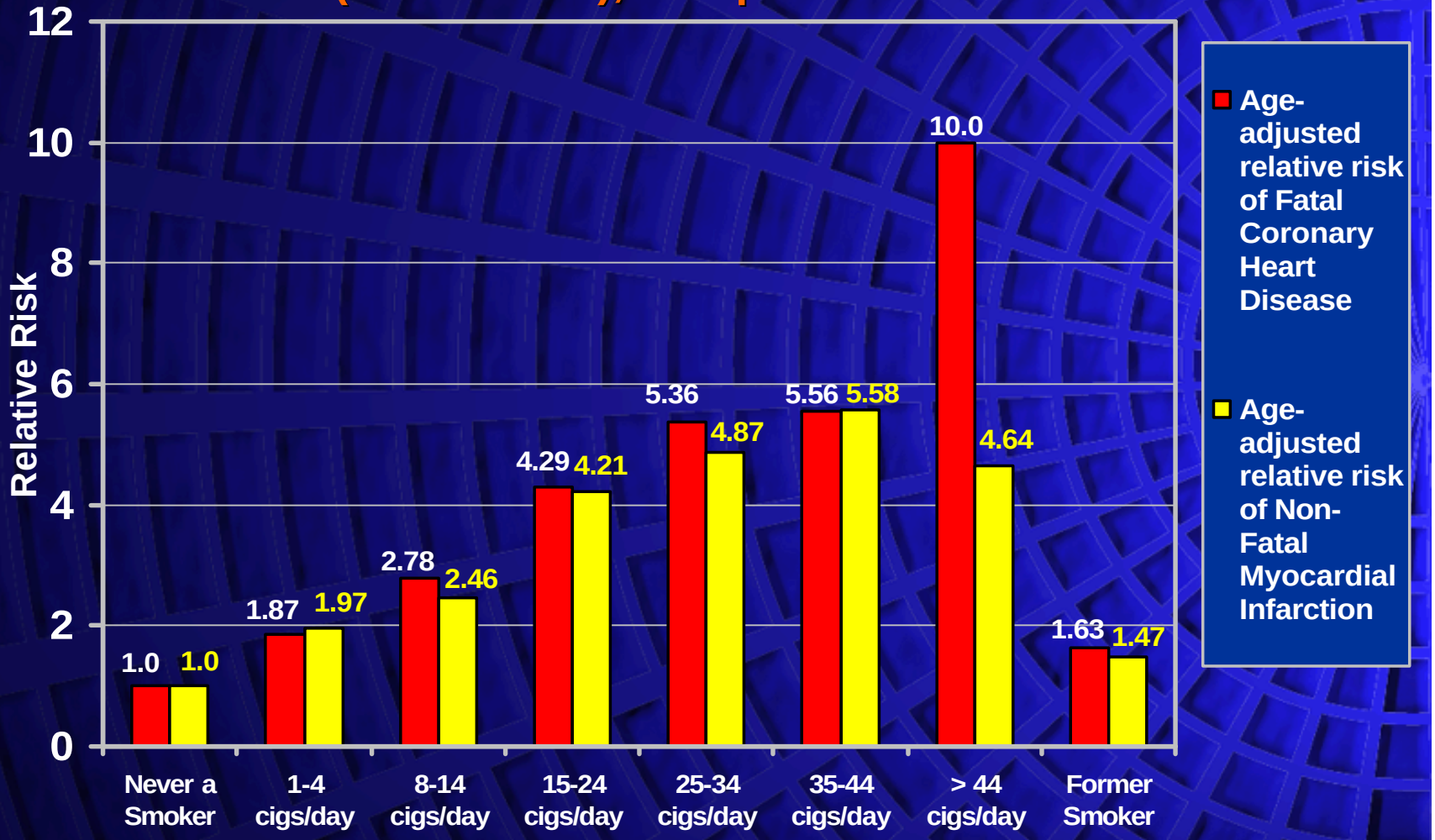
Number of Cigarettes Smoked Daily and Age-Adjusted Relative Risks of Fatal Coronary Heart Disease and Non-Fatal Myocardial Infarction (heart attack), Compared with Never Smokers



Data for figure from Kawachi et.al. 1994

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“Both case-control and cohort studies published since the 1990 Surgeon General’s report have confirmed the epidemiologic association of cigarette smoking with the main subtypes of stroke. (i.e., ischemic stroke and subarachnoid hemorrhage).”

A Report of the Surgeon General, 2004, p. 394

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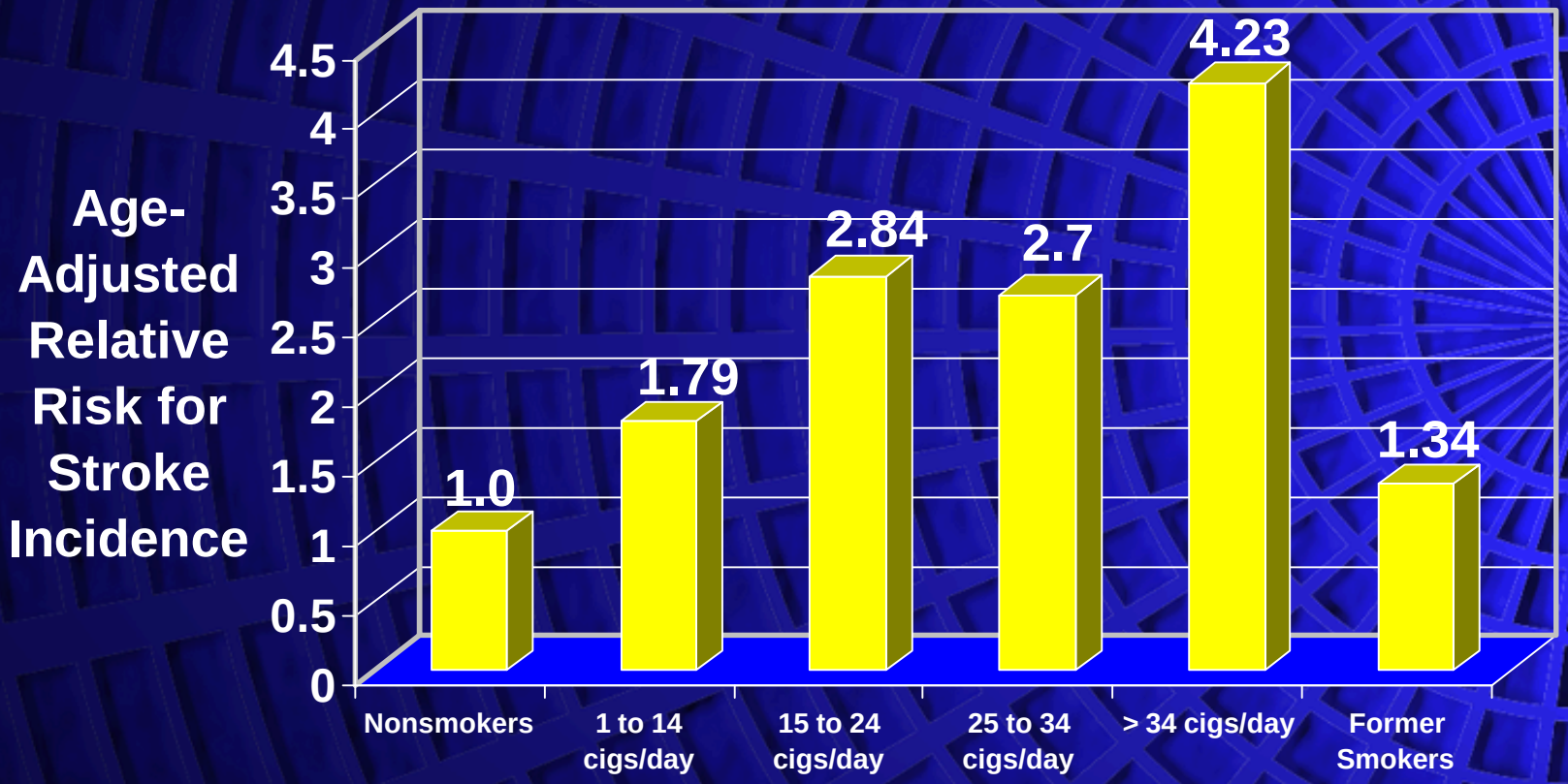
Age-Adjusted Relative Risk of Stroke (Fatal and Non-Fatal Combined) by Daily Number of Cigarettes Consumed Among Current Smokers



Data for figure from Kawachi et.al. 1993

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Cancer

"A dose-response relationship between cigarette smoking and lung cancer has been established in cohort studies of both men and women.

(Chyou et al., 1992; Doll and Peto, 1976; Engeland, 1996; Friedman et al,. 1979; Nordlund et al., 1997; Shaten et al., 1997; Thun et al., 1995; Tverdal et al., 1993; Winter et al., 1985)

These studies show remarkable consistency."

p. 395, IOM Report

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“In smokers, the risk of lung cancer depends largely on the duration of smoking and the number of cigarettes smoked”

Samet, 1996

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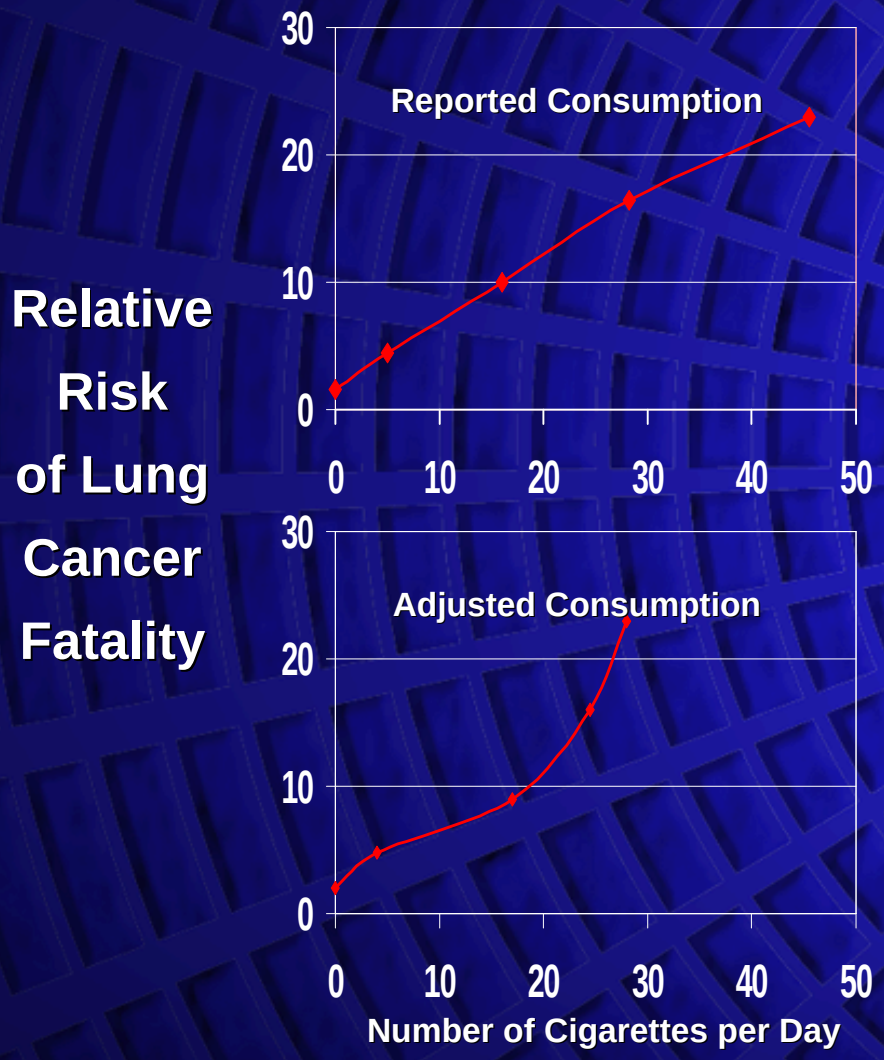
Reported and Adjusted Consumption of Cigarettes Smoked per Day and Relative Risk of Fatal Lung Cancer



Source: Law et al. 1997

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Respiratory Disease

"Jansen and colleagues (1999) found a dose-response relationship between the number of cigarettes smoked and any occurrence of chronic respiratory symptoms."

A report of the Surgeon General; p. 488, 2004

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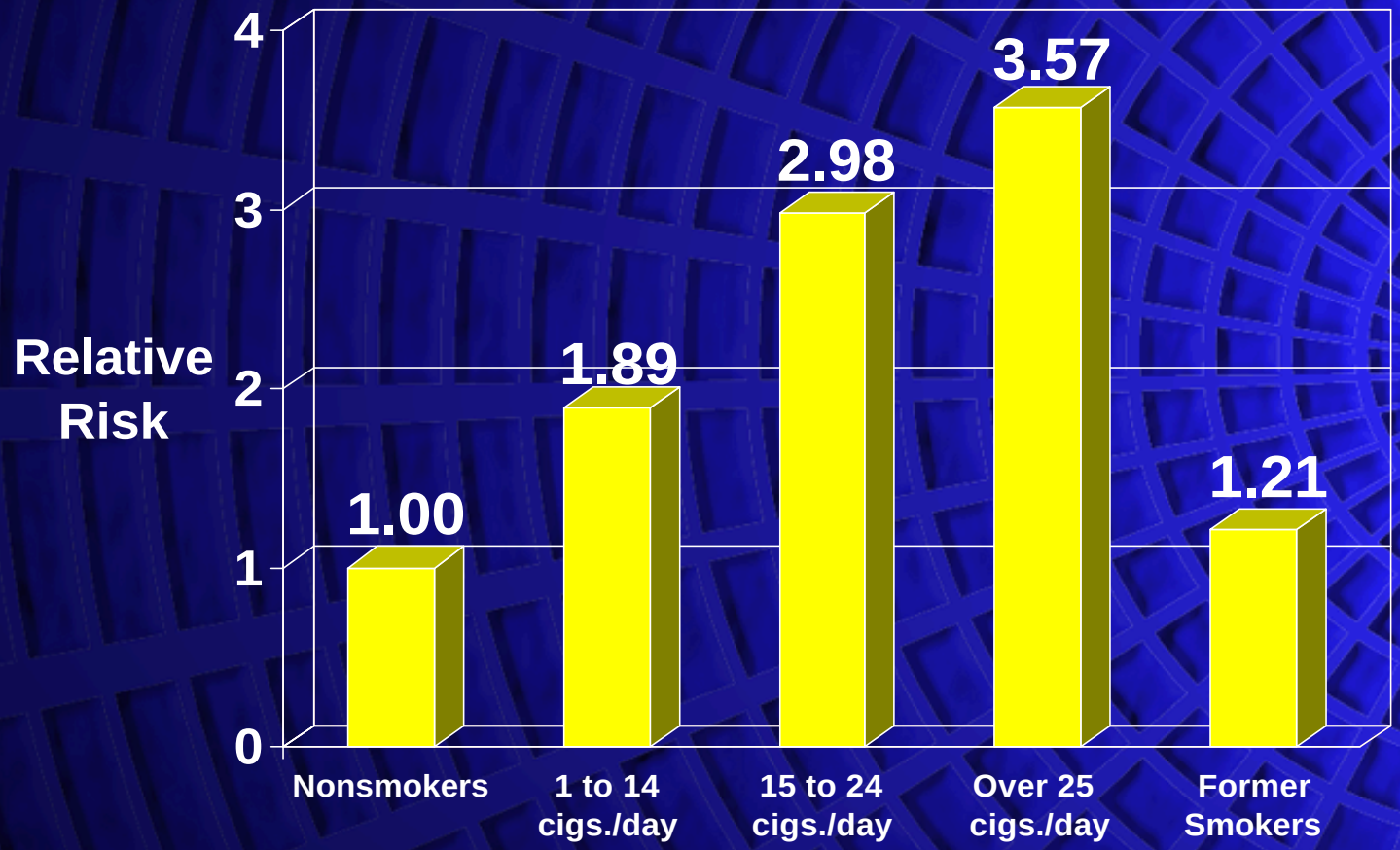
A Dose-Response Relationship Between the Number of Cigarettes Smoked and Any Occurrence of Chronic Respiratory Symptoms



Source: Jansen, D.F. et al., 1999

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Conclusion:

The only PREP capable of reducing risk from the three major groups of smoking-related diseases

- **Cardiovascular Disease**
- **Cancer**
- **Respiratory Disease**

is one that reduces the smoker's dose of whole tobacco smoke.

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Compensation

- Increase puff volume and/or number of puffs
- Inhale deeper and/or hold in for a longer period
- Block ventilation holes
- Smoke more cigarettes per day

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“For nicotine alone it became apparent--with some exception for extremely low yield cigarettes– that smokers in general manage to utilize an average of about 1 mg of nicotine from cigarettes of any brand, regardless of the smoking machine yields on the standard FTC smoking machine.”

Gori, Virtually Safe Cigarettes, 2000

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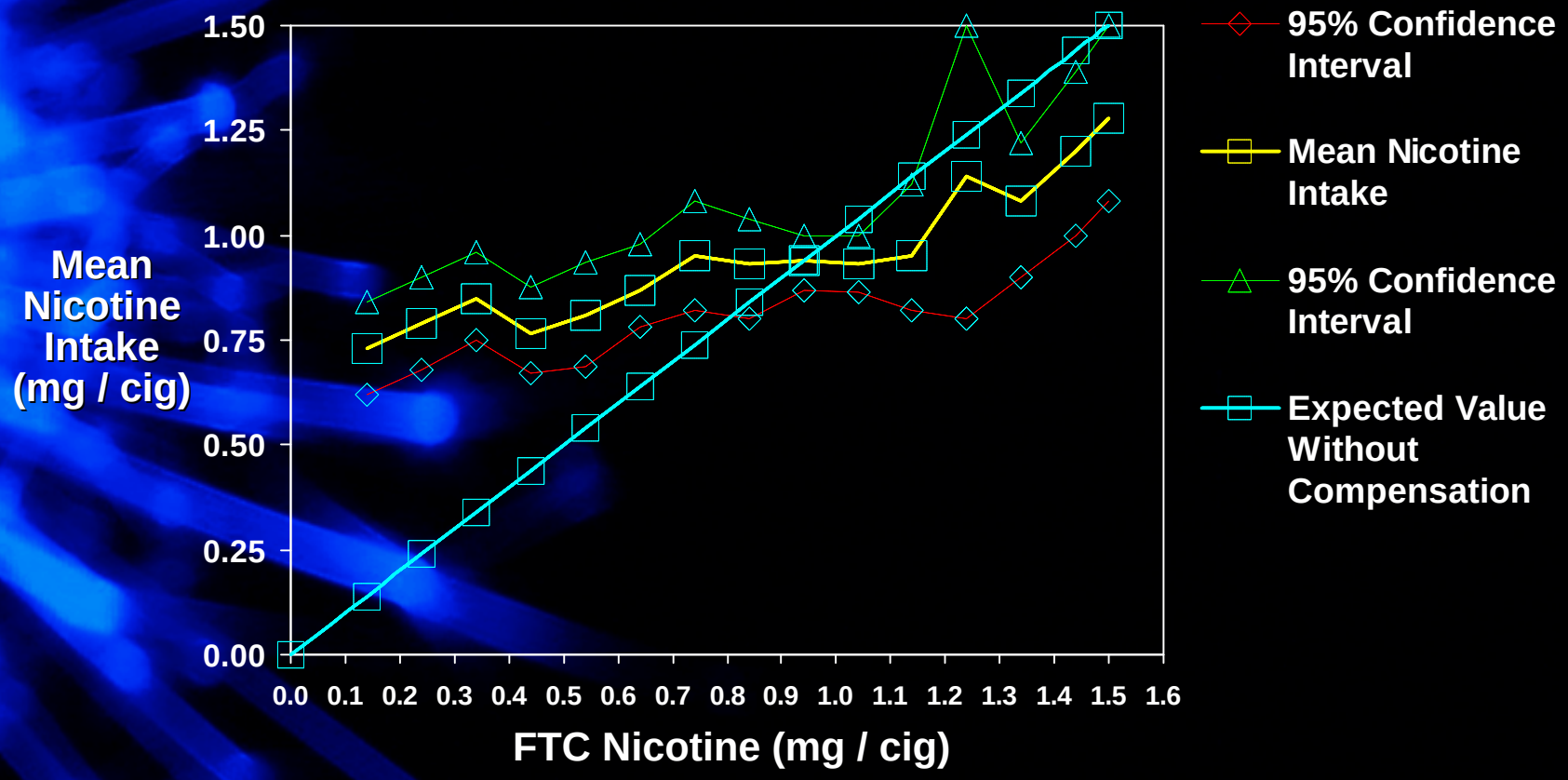
Mean Trends of Nicotine Intake per Cigarette vs. FTC Nicotine Yields



Data for figure gathered from Gori and Lynch, 1985

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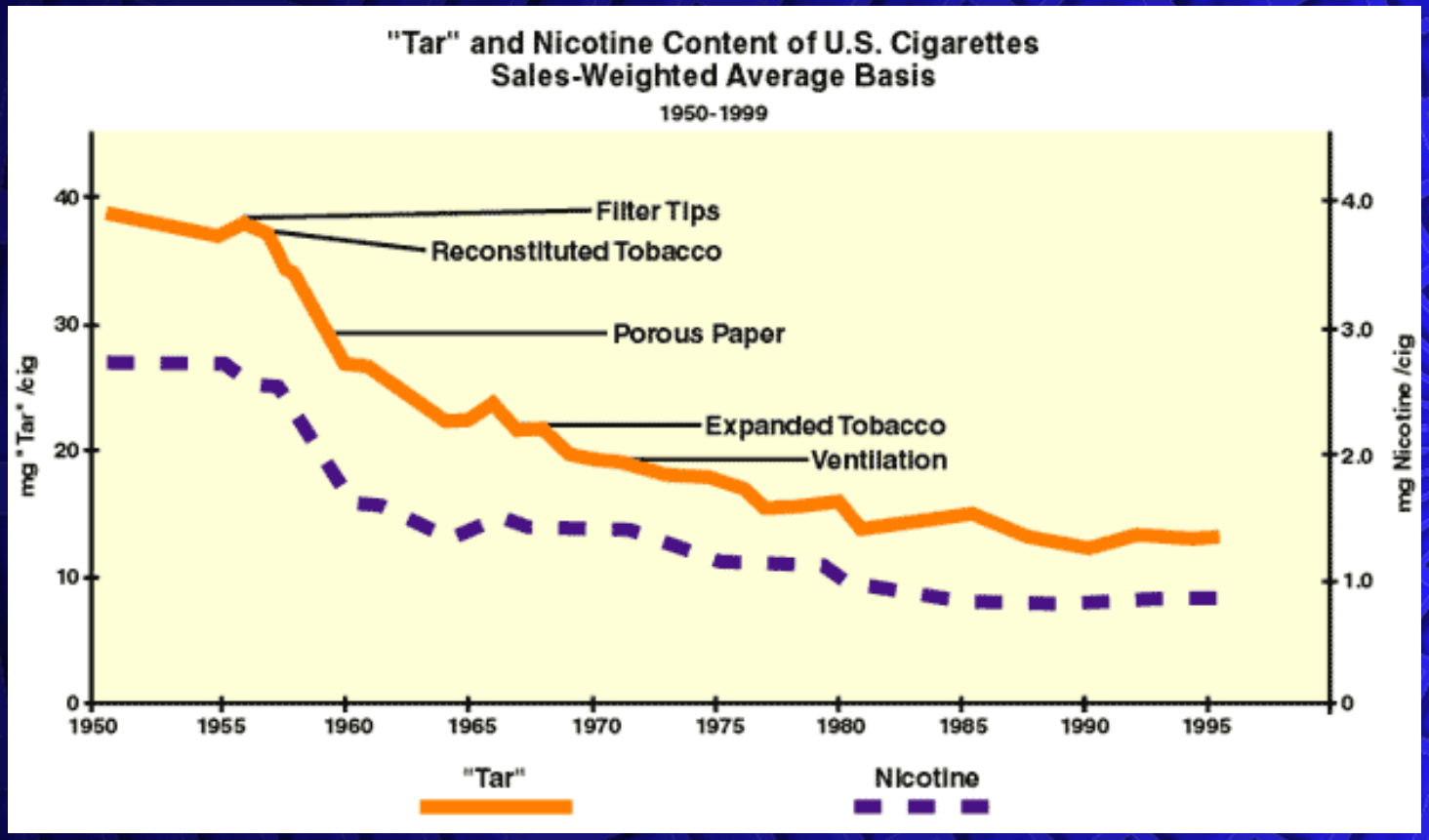
Comparison of Tar to Nicotine Yield Ratios (TNRs) of Popular Brands*

	Tar	Nic.	TNR	
Marlboro Kings Filter Soft Pack	15	1.1	13.64	
Marlboro Medium Kings Filter Soft Pack	11	0.8	13.75	
Marlboro Lights Kings Filter Soft Pack	11	0.8	13.75	
Marlboro Ultra Lights Kings Filter Box	6	0.5	13.75	
Marlboro 100's Filter Box Red	15	1.1	13.75	
Basic Full Flavor Kings Filter Box	16	1	16.00	
Basic Lights Kings Filter Box	10	0.7	14.29	
Basic Ultra Lights Kings Filter Soft Pack	6	0.5	12.00	
Basic Full Flavor 100's Filter Soft Pack	16	1	16.00	
Virginia Slims Full Flavor 100's Filter Box	15	1.1	13.64	
Virginia Slims Lights 120's Filter Menthol Box	14	1.1	12.73	
GPC Full Flavor King	**15**	**0.8**	**18.75**	**(Highest)**
GPC Lights King Box	9	0.6	15.00	
GPC Ultra Lights King	5	0.4	12.50	
GPC Menthol Full Flavor 100	13	0.8	16.25	
Lucky Strike Non-Filter	23	1.5	15.33	
Lucky Strike Filter King Box	15	1.1	13.64	
Lucky Strike Lights King Box	**9**	**0.8**	**11.25**	**(Lowest)**

* 2003 yields; these brands represent about 50 % of U.S. market.

Simple Average TNR: 14.22

History of “Tar” & Nicotine Yields



- 1950 : Sales Weighted Average TNR (39/2.7) = 14.44
- 2004 : Simple Average (from SLIDE 19): TNR = 14.22

Source: www.FTC.gov

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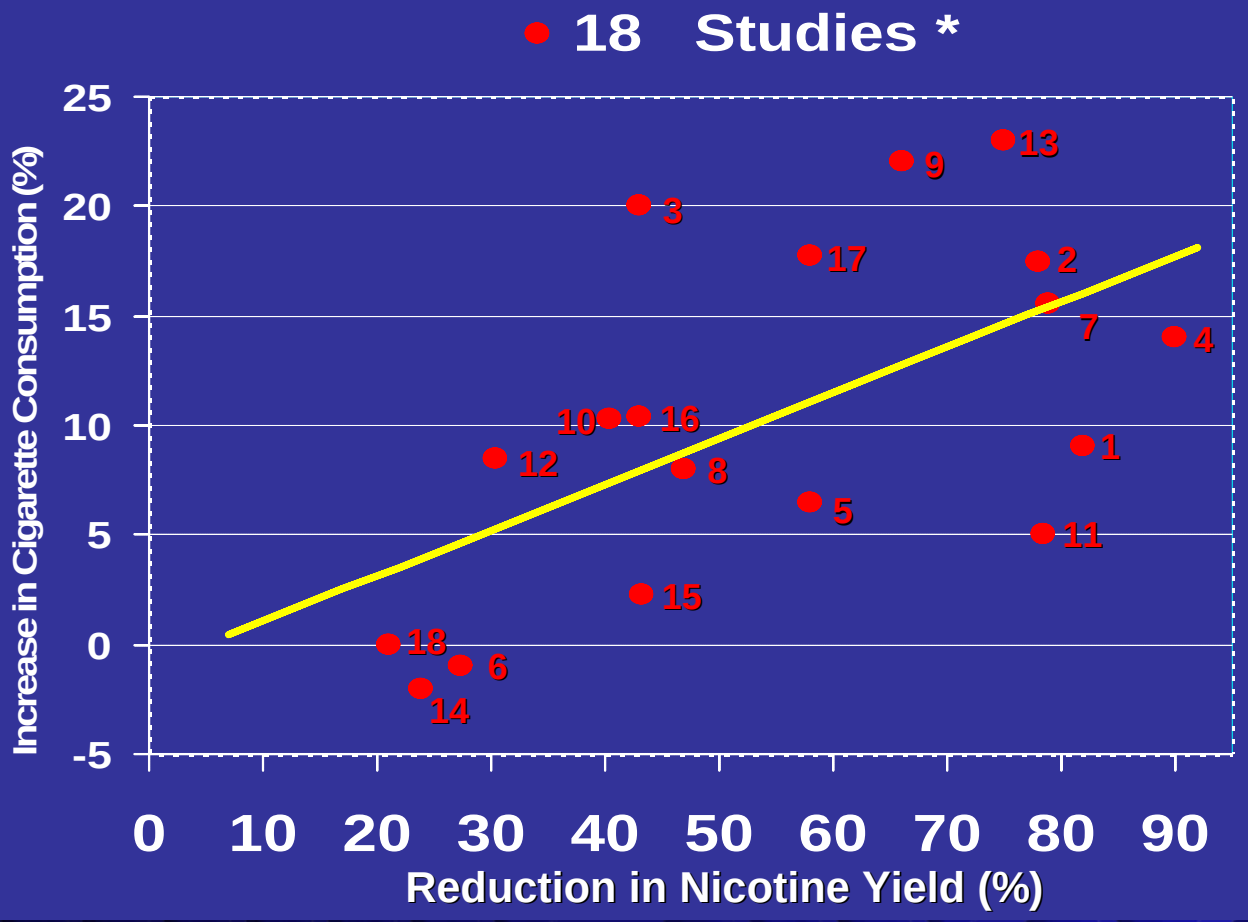
Increase in Cigarette Consumption Related to Change in Nicotine Yields: Data from Experiments



1. Finnegan, Larson, and Haag (1945)
2. Russell et al. (1973)
3. Turner, Sillett and Ball (1974)
4. Turner, Sillett and Ball (1974)
5. Guillerm et al. (1974)
6. Freedman and Fletcher (1976)

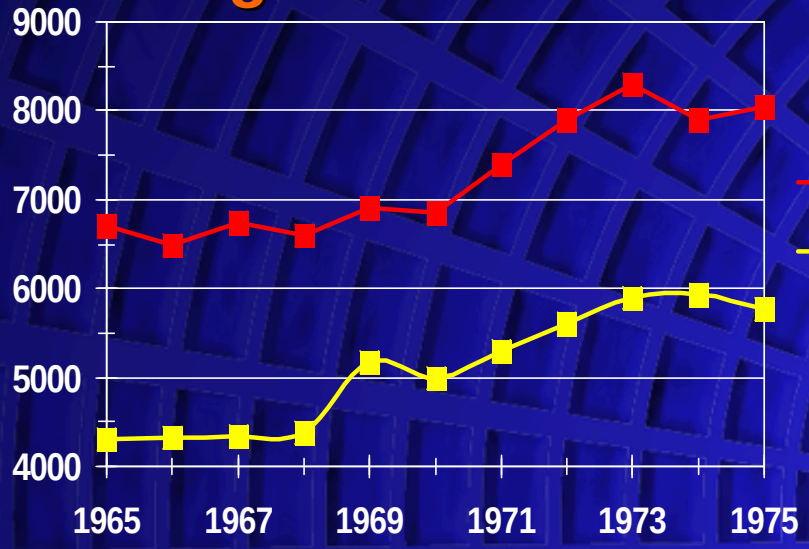
7 to 11. Goldfarb et al. (1976)

12. Forbes et al. (1976)
13. Schachter (1977)
14. Mangan and Golding (1978)
15. Creighton and Lewis (1978b)
16. Adams (1978)
17. Ashton, Stepney and Thompson (1978c)
18. Guillerm and Radziszewski (1978)

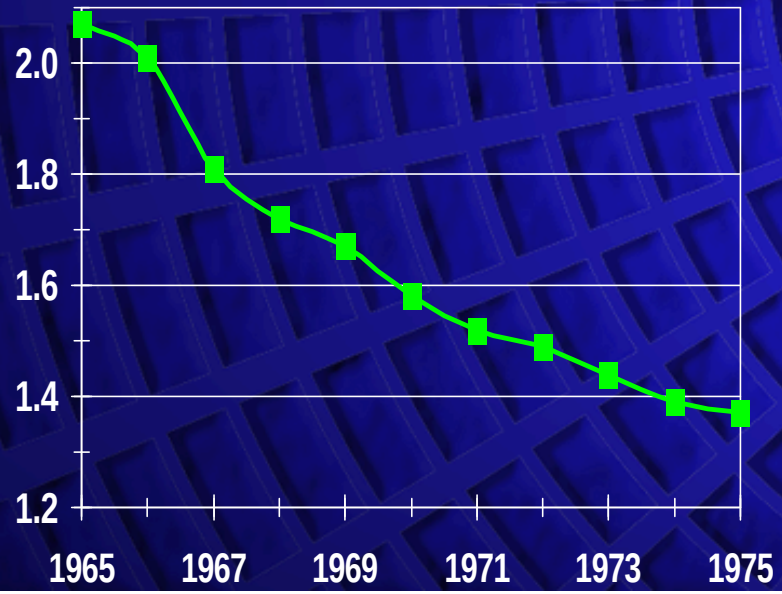
Source: Minnesota Tobacco Litigation, Bates Nos.: 403626692- 403626803 (also No. 536000447), British American Tobacco Company

Sales Weighted Nicotine Delivery and Annual Consumption of Cigarettes in the UK (1965 to 1975)

Annual consumption of cigarettes per smoker



Nicotine delivery mg/cig



Source: Minnesota Tobacco Litigation, Bates Nos.: 403626692- 403626803, (also, 536000448) British American Tobacco Company

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Increased Consumption is Related to Reduced Nicotine

But on this basis:

10% reduction in nicotine = 1% rise in consumption.

50% reduction in nicotine = 10% rise in consumption

Therefore, MOST COMPENSATION MUST OCCUR AT THE INDIVIDUAL CIGARETTE LEVEL.

Source: Minnesota Tobacco Litigation, Bates Nos.: 403626692- 403626803, (also, 536000449) British American Tobacco Company

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Studies demonstrate that **DECREASING** a cigarette's tar to nicotine yield ratio by **INCREASING** the tobacco leaf's nicotine content reduces the intake of tar and carbon monoxide into the respiratory tract.

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PUBLIC HEALTH AND LEVELS OF NICOTINE: SHOULD NICOTINE LEVELS IN CIGARETTES BE MINIMIZED OR MAXIMIZED?

Michael A. H. Russell, FRCP, FRC Psych
Chapter 15, *Nicotine and Public Health;* 2000;
American Public Health Organization

Low-Tar, Medium-Nicotine (LTMN) approach vs. Benowitz / Henningfield approach:

LTMN APPROACH (Low tar to nicotine ratio cigarettes):

- **People smoke for nicotine but die from tar and harmful gases**
- **TMN approach is a cleaning strategy for the modern cigarette as a nicotine delivery system**
- **Based on the "nicotine regulation" model of smoking**
- **Assists in *COMPENSATION* of light and ultra-light cigarettes**

BENOWITZ / HENNINGFIELD APPROACH:

- **Similar to QUEST® 1-2-3 approach.**

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Michael A.H. Russell Summarizes Three Studies Pertaining to the Low-Tar, Medium-Nicotine Approach for PREPs:

1. Armitage et al., 1988
2. Fagerstrom, 1982
3. Stepney, 1981

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Evaluation of a Low to Middle Tar/Medium Nicotine Cigarette Designed to Maintain Nicotine Delivery to the Smoker

A.K. Armitage et al., Psychopharmacology (1988); 96:447-453

Tar, nicotine and CO yields of three cigarette products

Cigarette:	Tar Yield (mg/cig)	Nicotine Yield (mg/cig)	CO Yield (mg/cig)	T/N Ratio
Maintained Nicotine (MN)	11.2	1.4	9.9	8.0
Middle Tar (MT)	16.9	1.7	15.1	9.9
Low Tar (LT)	9.1	0.8	8.5	11.4

Results related to maintained-nicotine cigarette:

- Intake of tar into respiratory tract was about 25 percent less than MT.
- CO delivery was about 30% less than MT and 15% less than LT

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Effects of a Nicotine-Enriched Cigarette on Nicotine Titration, Daily Cigarette Consumption and Levels of Carbon Monoxide, Cotinine and Nicotine

Karl-Olav Fagerstrom, Pharmacology (1982); 77:164-167

Tar, nicotine and CO yields of three cigarette products

Cigarette:	Tar Yield (mg/cig)	Nicotine Yield (mg/cig)	CO Yield (mg/cig)	T/N Ratio
Nicotine Enriched	5.8	1.1	4.1	5.3
Commercial Brand	4.8	0.5	4.0	9.6
Smokers' own brands averaged:	14.0	1.1	12.0	12.7

Results:

- Levels of smokers' expired-air CO was 36% lower from the Nicotine-Enriched brand than the smokers' own brands (which averaged 14 mg/tar/cig) and 31% less than the control commercial brand (4.8mg/tar/cig).
- No differences were found in smokers' blood nicotine and cotinine levels or in heart rate increases. It also shows that smokers compensated the 4.8 mg-tar brand.

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Evaluation of a Low to Middle Tar/Medium Nicotine Cigarette Designed to Maintain Nicotine Delivery to the Smoker

R. Stepney, Br. Med. Journal (1981); 283: 1292-1296)

Tar, nicotine and CO yields of three cigarette products

Cigarette:	Tar Yield (mg/cig)	Nicotine Yield (mg/cig)	CO Yield (mg/cig)	T/N Ratio
Medium-nicotine, Low-Tar	10.0	1.1	6.0	9.0
Own medium-tar brands (mean)	19.0	1.55	18.0	12.0
Control low-tar	11.0	0.7	13.0	16.0

Results:

- Intake of CO (Ecolyzer monitor) with the Medium-nicotine, Low-tar cigarette was 51% less than the smokers' usual brand and 23% less than the control low-tar brand.
- Russell believes the author erred in concluding that tar exposure of medium-nicotine cig. was equal to the control brand since mouth-level exposure (from tar retained by the filter) was measured. Russell concluded that it actually had about a 14% advantage over the control low-tar brand (based on nicotine) and a 25% advantage over the smokers' usual brands.
- The medium-nicotine, low-tar cigarette was more acceptable than the control brand.

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Russell's conclusion regarding the Low-Tar, Medium-Nicotine approach from the Fagerstrom, Armitage and Stepney studies:

"The results of these few studies are far from definitive but do provide some evidence that lowering tar/nicotine yield ratios appears to reduce compensatory smoking from low-tar cigarettes, thereby reducing tar intake."

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The Separate Effects of Tar and Nicotine on the Cigarette Smoking Manoeuvre

G. Woodman et al., Eur. Jour. Respir. Dis (1987); 70, 316-321

Tar, nicotine and CO yields of three cigarette products

Cigarette:	Tar Yield (mg/cig)	Nicotine Yield (mg/cig)	CO Yield (mg/cig)	T/N Ratio
Brand A	10.0	1.4	9.0	7.1
Brand B	10.0	1.0	10.0	10.0
Brand C	17.0	1.4	16.0	12.1

Results of Brand A:

- Inhaled smoke volume (using a Kr radiotracer technique) was 21% less for Brand A vs. Brand B and 23% less for Brand A vs. Brand C

Woodman's Conclusions:

- "For a given tar yield, and subject to there being sufficient nicotine to satisfy the smoker, we conclude that a cigarette with a low tar to nicotine ratio, rather than simply a low-tar, low-nicotine cigarette, will result in the smoker inhaling less tar."
- "Tar and nicotine (yields) appear to exercise independent control over the volume of smoke inhaled."

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Fourth Report on the Independent Scientific Committee on Smoking & Health

Sir Peter Frogatt, MD, PhD, British Library, 1988

"While the overall aim should be towards reductions in the tar/nicotine ratio this should not be through the enhancement nor solely through the maintenance of present-day middle range nicotine levels (around 1.3 mg/cigarette). In general the sales weighted average nicotine yields should fall, and on the lines of the suggestion made in our Third Report (para 20) there should continue to be some brands available to the public with nicotine yields below 1 mg and with tar yields reduced to a proportionately greater extent (below 8 mg)."

(para 34)

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The Influence of Changing Nicotine to Tar Ratios on Human Puffing Behaviour and Perceived Sensory Response

M. Dixon (B.A.T.) et al., Psychopharmacology (2003); 170, 434-442

Tar, nicotine and CO yields of five cigarette products

Cigarette:	Tar Yield (mg/cig)	Nicotine Yield (mg/cig)	CO Yield (mg/cig)	T/N Ratio
RS33	9.5	0.77	7.9	12.3
RS32	8.8	0.48	7.3	18.3
RS30 (Reference Sample)	8.7	0.81	7.3	10.7
RS31	8.1	0.10	6.7	81.0
RS34	7.7	0.22	6.6	35.0

Results:

- "The differences of the nicotine to tar ratios of the samples did not significantly influence the puffing behaviour patterns, i.e. puff number and interval, total and average puff volume, integrated pressure and puff duration. Additionally, the pre-to-post-exhaled CO boosts were not significantly influenced by the experimental samples used in the study."

Dixon et al. Conclusions: "These observations imply that these puffing variables are not controlled by the nicotine yield of the cigarette."

Major study flaw:

- It is impossible for the author to make these generalizations by only decreasing nicotine yields from conventional yields and not increasing nicotine yields over conventional cigarettes.

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The Industry and Low TNR Cigarettes

- **Project Greendot: 1990; BAT**
  - Bates # 562400102-562400107
  - 4 mg. Greendot Product (0.6 mg. nicotine: TNR=6.7)
  - "Product tested in Germany with consumers (2,600 people)…. Scored comparable to Marlboro Lights (6 mg)."
- **Low Tar Cigarette Modification (LTCM): 1992; PM**
  - Bates # 2060529433-2060529435;
  - 2.5 mg. Tar, 0.45 mg. nicotine (TNR=5.55)

  "The strategy pursued in this program was promising. Cigarettes produced exhibited response much higher that any cigarettes of similar tar levels. Members of the Technology Program have recommended that the program be revitalized. The program should be resumed."
- **Project XB: Early 1990s; RJR**
- **1990: RJR**
  - Bates # 51252 5050
  - "RJR has developed the technology to produce cigarettes with substantial nicotine yields (˜ 1mg, FTC) with T:N ratios far below 10 and which have virtually no harshness."
- **Many Others**

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Two Current PREPS:

- Do not sufficiently address cardiovascular-related illnesses
- Unlikely to be scientifically proven to be safer in the near future

Eclipse® doesn't reduce, and in fact may increase cardiovascular-related illnesses further due to higher carbon monoxide levels.

- "… Some evidence suggests that smokers who already have cardiovascular disease and who switch to Eclipse may further increase their health risk."

Source: www.eclipse.rjrt.com, 2004

Advance® reduces carbon monoxide by 19 percent and also reduces select carcinogens (9 in total) by various percentages.

- "Again, we don't have any real way of determining if a product is safer. Basically, it will take 20 years or more of looking at public health statistics to determine whether, say, a product with less toxins were to impact public health."

Source: www.bw.com, 2004

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IOM Report Findings Relevant to Low TNR Cigarettes:

- "Retaining nicotine at pleasurable or addictive levels while reducing the more toxic components of tobacco is another general strategy for harm reduction" (p.29).
- ". . .nicotine is one of the factors crucial to the success of a tobacco product." (p.29).
- "Since we do not know which of many toxins may be the cause of specific harmful effects, we can only infer but we cannot know the health effects of the elimination of any one or several tobacco components" [p viii (8 of 656)].
- "No one knows the dose-response relations, the specific toxins, the pathogenic mechanisms, or the interrelationship between the many components of tobacco smoke with enough precision to make scientifically reliable quantitative judgments about the risk or actual harm reduction associated with use of any tobacco product" [p viii (8 of 656)].
- "Currently available data allow estimation, albeit imprecise, of a dose response relationship between exposure to whole tobacco smoke and major diseases that can be monitored for evaluation of harm reduction potential" (p. 9).

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An efficient method to decrease tar to nicotine ratios and therefore whole tobacco smoke delivery to smokers is to develop new leaf varieties that contain enhanced nicotine levels.

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22nd Century is Currently Enhancing Nicotine Genetically in Tobacco.

Flue-Cured varieties:

Total Alkaloid Target:
6.0 to 6.25 percent (FW)

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Enhanced-Nicotine Leaf Permits:

Low Tar to Nicotine Ratio PREP (Cigarettes)

Brand: ABC

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Objective of a Low Tar to Nicotine Ratio Cigarette:

To produce a reduced-risk cigarette by efficiently delivering nicotine while reducing tar and gas phase deliveries and also maintaining acceptable taste.

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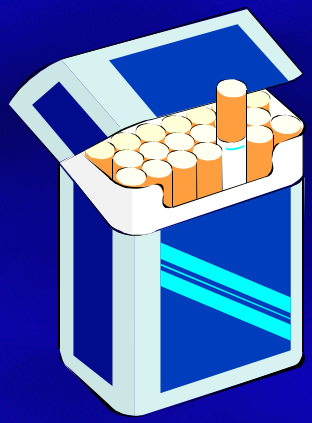
GM Hi-Nic Tobacco

Low-Yield Cigarette Design



ABC Brand Styles:

		Tar	Nicotine	TNR
ABC	928	10	1.3	7.7
ABC	817	8	1.1	7.3
ABC	617	6	0.9	6.7
ABC	476	4	0.66	6.0
ABC	123	1	0.30	3.3

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Compensation Should Not Occur with *Brand ABC*

"Because nicotine limits its own inhalation, it also limits the inhalation of smoke. Hence, the higher the smoke concentration of nicotine, the sooner inhalation is inhibited, the lower the dose of whole smoke to the lungs, and the lower the risk to be expected."

Gori, TabExpo Congress, Barcelona, November 28, 2003

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Why *ABC Brand* Should be Superior to PREPs that Reduce Certain Smoke Constituents

- **Whole Smoke Deliveries to smokers will likely be reduced with ABC Brand.**
  - The dose-response relationship can be quantified for **ABC**.
    - This cannot easily be done for PREPS that reduce smoke constituents.
  - The scientific community, especially the FDA, can more quickly verify **ABC** as a reduced-exposure cigarette.
    - PREPs that reduce smoke constituents will likely require years to verify as reduced-exposure
    - All tobacco-related diseases should be reduced.
- **Technologies that reduce smoke constituents (e.g., such as in the Advance® brand) can be "stacked" with ABC BRAND for a reduced risk "multiplier effect."**

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Important Research Design Considerations For Future Human Trials of Brand ABC

- Recruit enough smokers to create a statistically significant sample size
- Utilize smokers of popular commercialized brands
- Incorporate state of the art biomarkers of exposure for studies

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Advisory Committee

- John E. Bunch, Ph.D.
- Michael R. Moynihan, Ph.D.
- James L. Myracle

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