

# Nicotine addiction: from biology to regulatory policy

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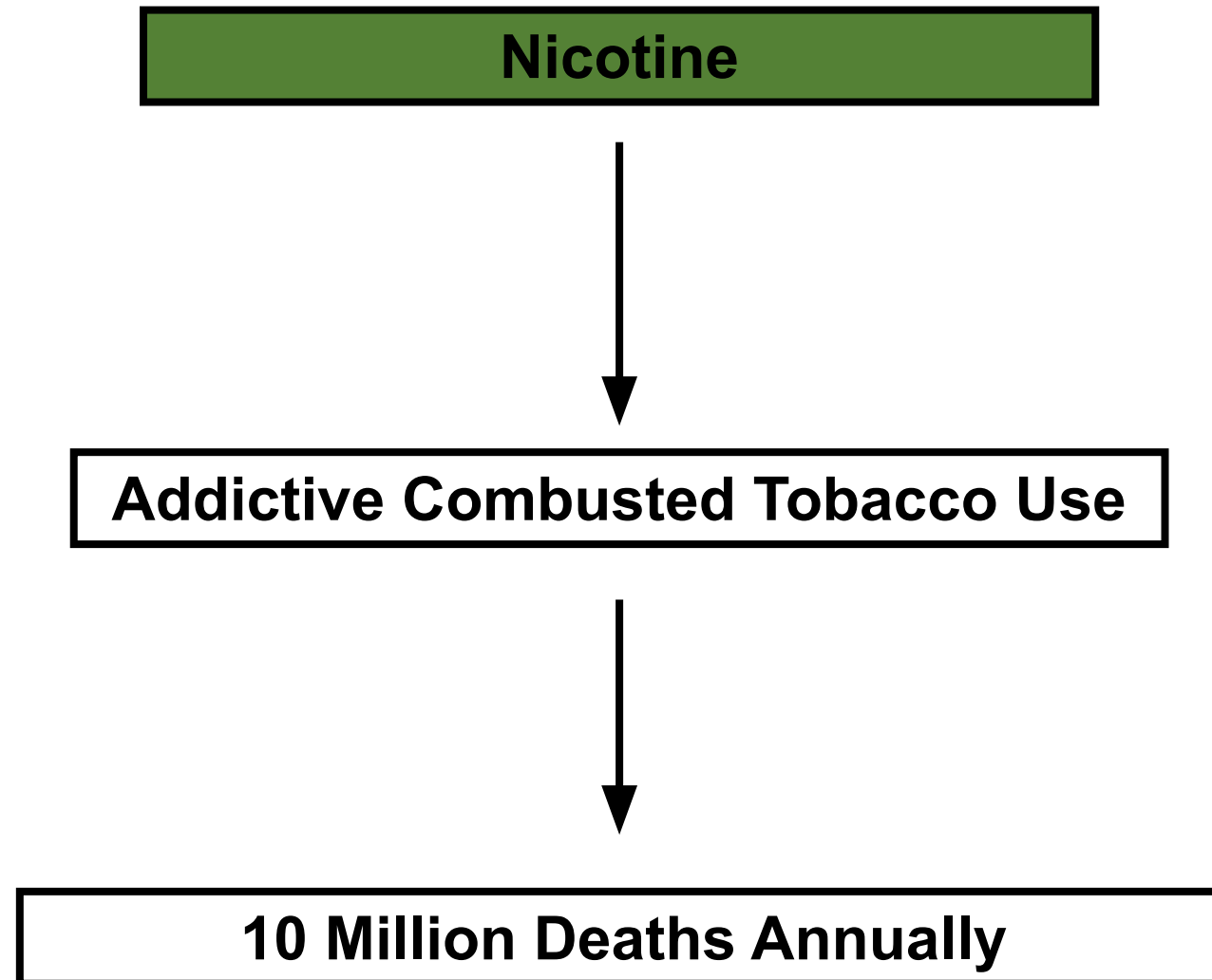
**May 18, 2023**



# **Conflict of Interest Statement**

- **I am a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications.**
- **I serve as an expert witness in litigation against tobacco companies**

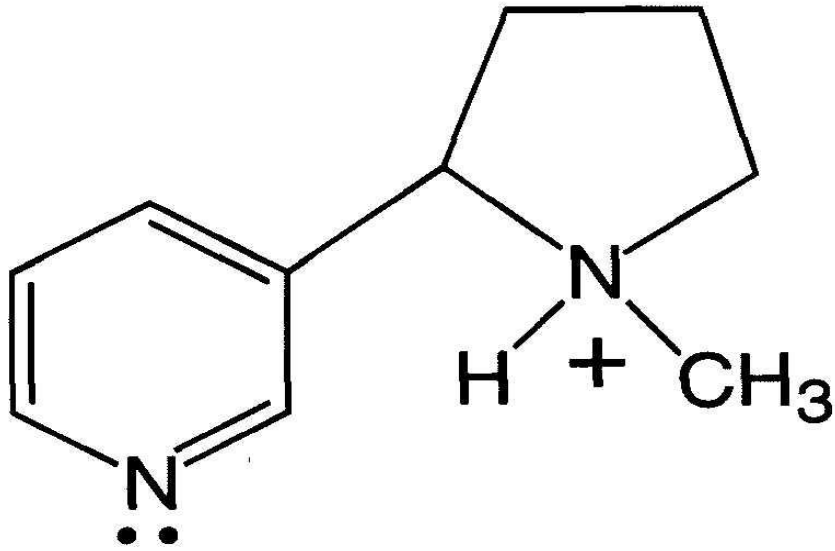
# **Tobacco Combustion Products Responsible for Most Tobacco-related Disease, but People Smoke for Nicotine**



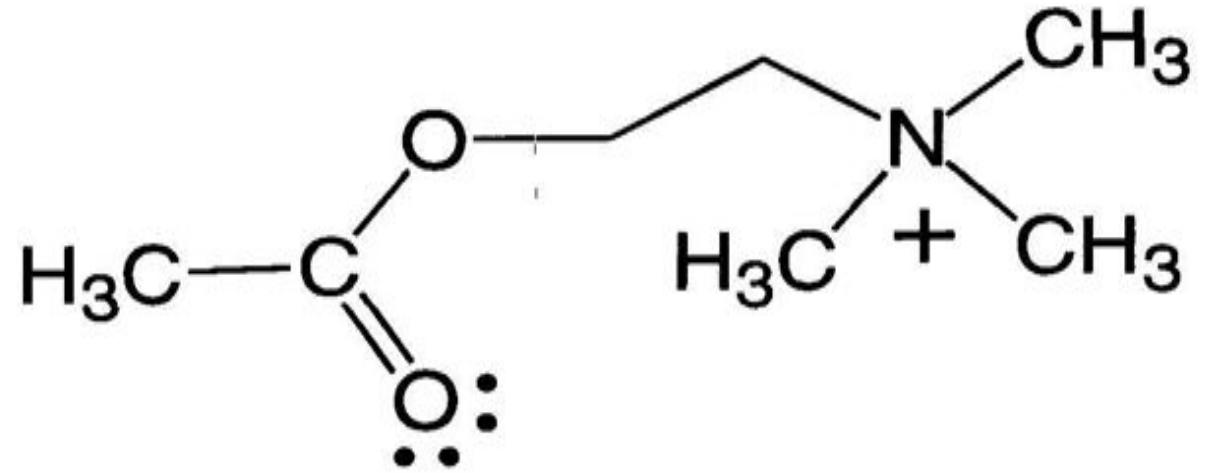
# Why cigarettes are so harmful

**Cigarettes (and other combusted tobacco products) are particularly harmful because they are highly addictive. Addiction means loss of control of drug use. 70% of cigarette smokers are daily smokers and rarely go through a day without smoking**

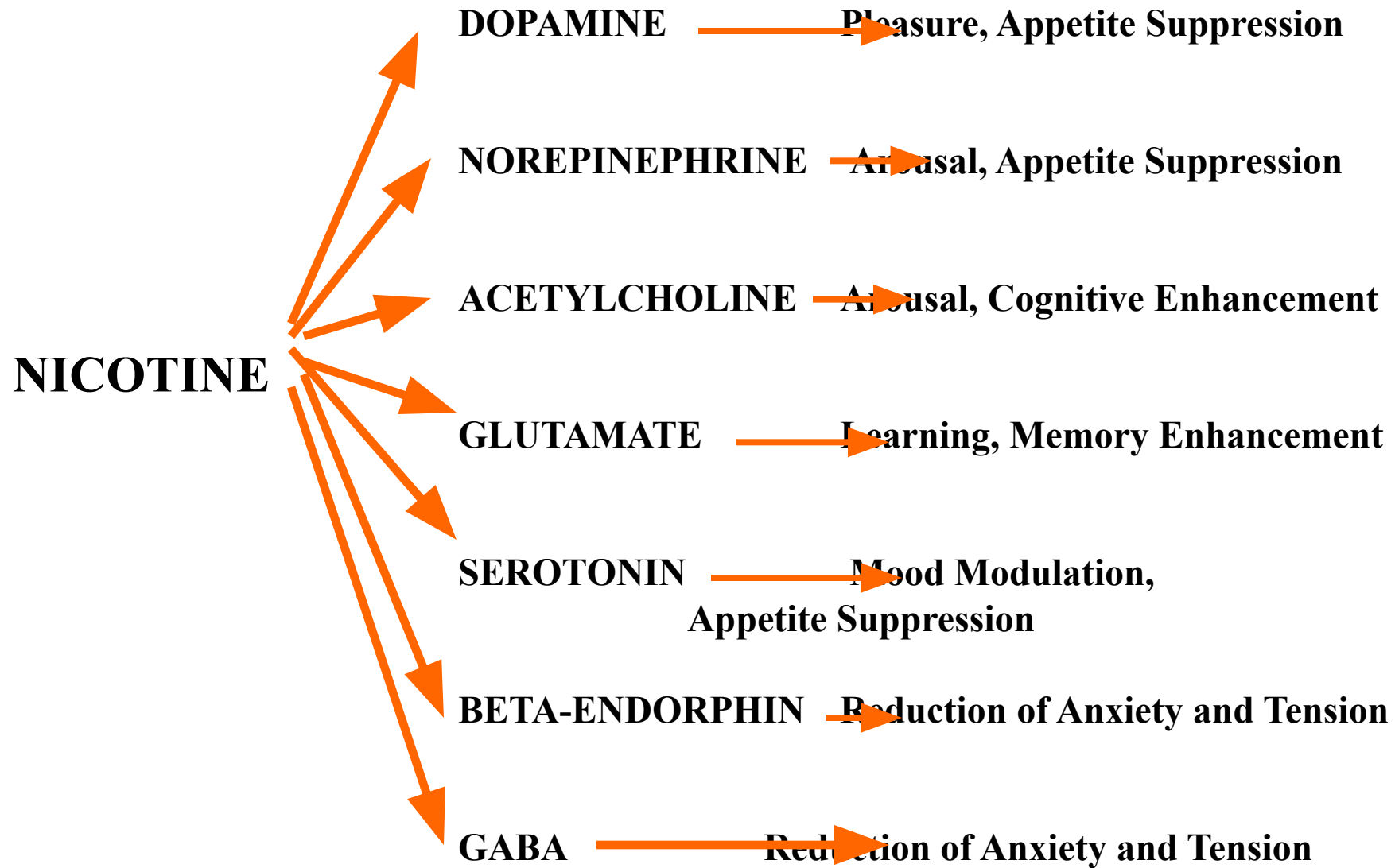
# Nicotine Mimics the Neurotransmitter Acetylcholine: Both Bind to “Nicotinic Cholinergic Receptors”



NICOTINE



ACETYLCHOLINE



# Tolerance to effects of nicotine

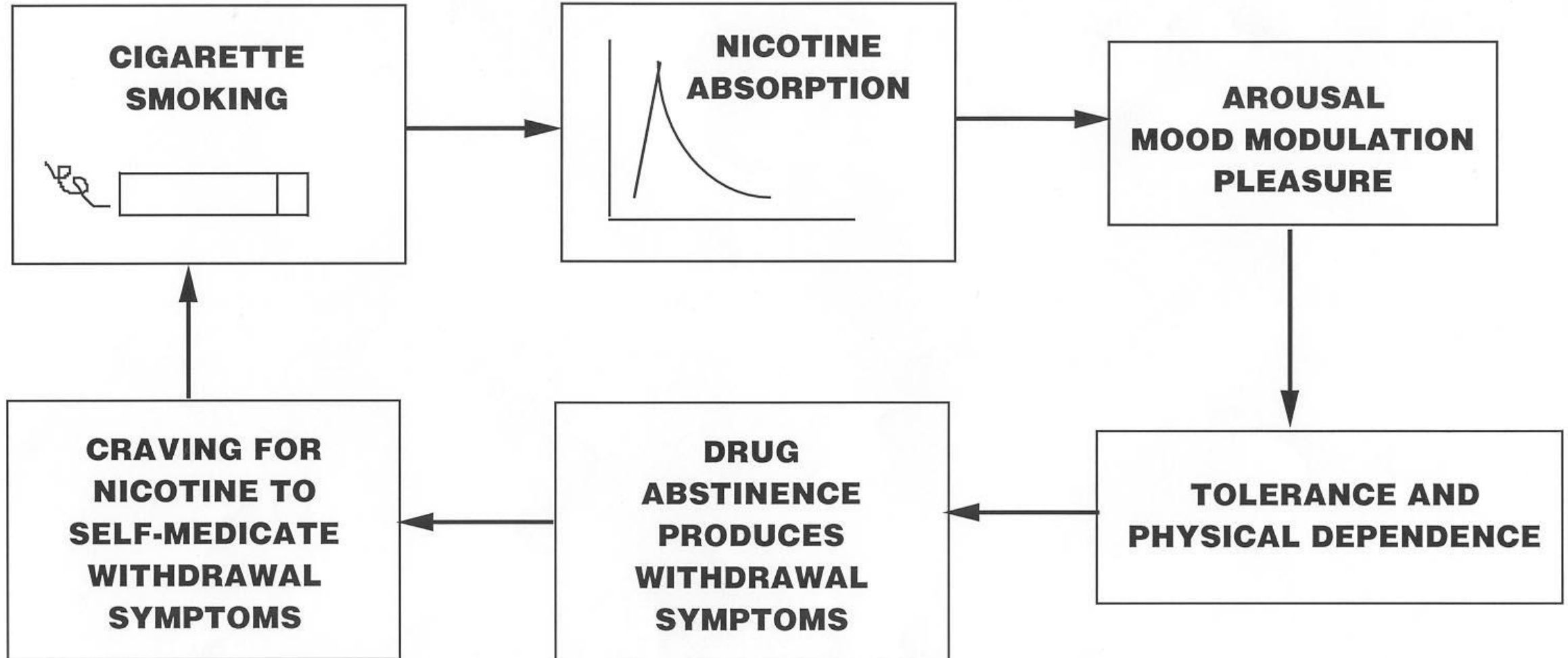


# **Tobacco Abstinence Symptom Clusters**

- **PSYCHOLOGICAL DISTRESS:**  
Irritability, Anger, Impatience, Anxiety
- **DIFFICULTY CONCENTRATING:**  
Cognitive and Performance Impairment
- **HUNGER AND EATING:**  
Weight Gain
- **HEDONIC DYSREGULATION**
- **TOBACCO CRAVING**



# NICOTINE ADDICTION CYCLE



**“To lower nicotine too much might end up destroying the nicotine habit in a large number of consumers and prevent it from every being acquired by new smokers”**

British American Tobacco Company internal document, June 1959

***THE CIGARETTE SHOULD BE  
CONCEIVED NOT AS A PRODUCT BUT  
AS A PACKAGE. THE PRODUCT IS  
NICOTINE ... THINK OF THE  
CIGARETTE PACK AS A STORAGE  
CONTAINER FOR A DAY'S SUPPLY OF  
NICOTINE... THINK OF A PUFF OF  
SMOKE AS THE VEHICLE OF NICOTINE  
AND THE CIGARETTE THE MOST  
OPTIMIZED DISPENSER OF SMOKE.***

**WILLIAM DUNN, RESEARCHER,  
PHILIP MORRIS TOBACCO**

**PM conference 1975**

## **DEFINITION OF A DRUG ...**

**... articles other than food  
intended to affect the structure or  
any function of the body of man  
or other animals.**

*Federal Food, Drug and Cosmetic Act of  
1938*

# A Workplace Smoking Ban Is Proposed

*Continued From Page 1*

Commissioner of Food and Drugs, testified that one tobacco company, which he would not identify, had suppressed its own research that indicated that nicotine was addictive in animal studies.

Banning nicotine, Mr. Waxman said, is "starting to look like it might well be a reasonable way to deal with this problem."

Eliminating nicotine and thereby removing the addictive property, he added, would allow those who wanted to quit to do so and would provide more of a choice to those who wanted to continue to smoke, rather than forcing them to continue by virtue of their addiction.

However, removing nicotine would not necessarily reduce the health risks associated with smoking.

## **Another Era of Prohibition?**

The tobacco industry strenuously objected to today's anti-smoking pronouncements, the latest in a persistent



# Establishing a Nicotine Threshold for Addiction

- **Goal:**
  - To prevent nicotine addiction in youth.
- **Threshold for Addiction:**
  - Dose to establish and maintain addiction  
~ 5 mg/day.
- **Proposal:**
  - A gradual reduction of nicotine content of cigarettes over 10-15 years.



The NEW ENGLAND  
JOURNAL of MEDICINE

Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. (1994) *N Engl J Med*, 331(2), 123-125.



**Nicotine in cigarettes and smokeless tobacco is a drug and these products are nicotine delivery devices under the Federal Food, Drug, and Cosmetic Act.**

*U.S. Food and Drug Administration*

**Fed. Reg. Vol. 60, No. 155**

**Aug. 11, 1995**

# **Rationale for reducing nicotine in cigarette tobacco**

**The initial rationale was to prevent children who experiment with smoking from becoming addicted later in life. To provide freedom of choice.**

**Another benefit would be that addicted smokers, most of whom would like to quit, will move toward cessation.**



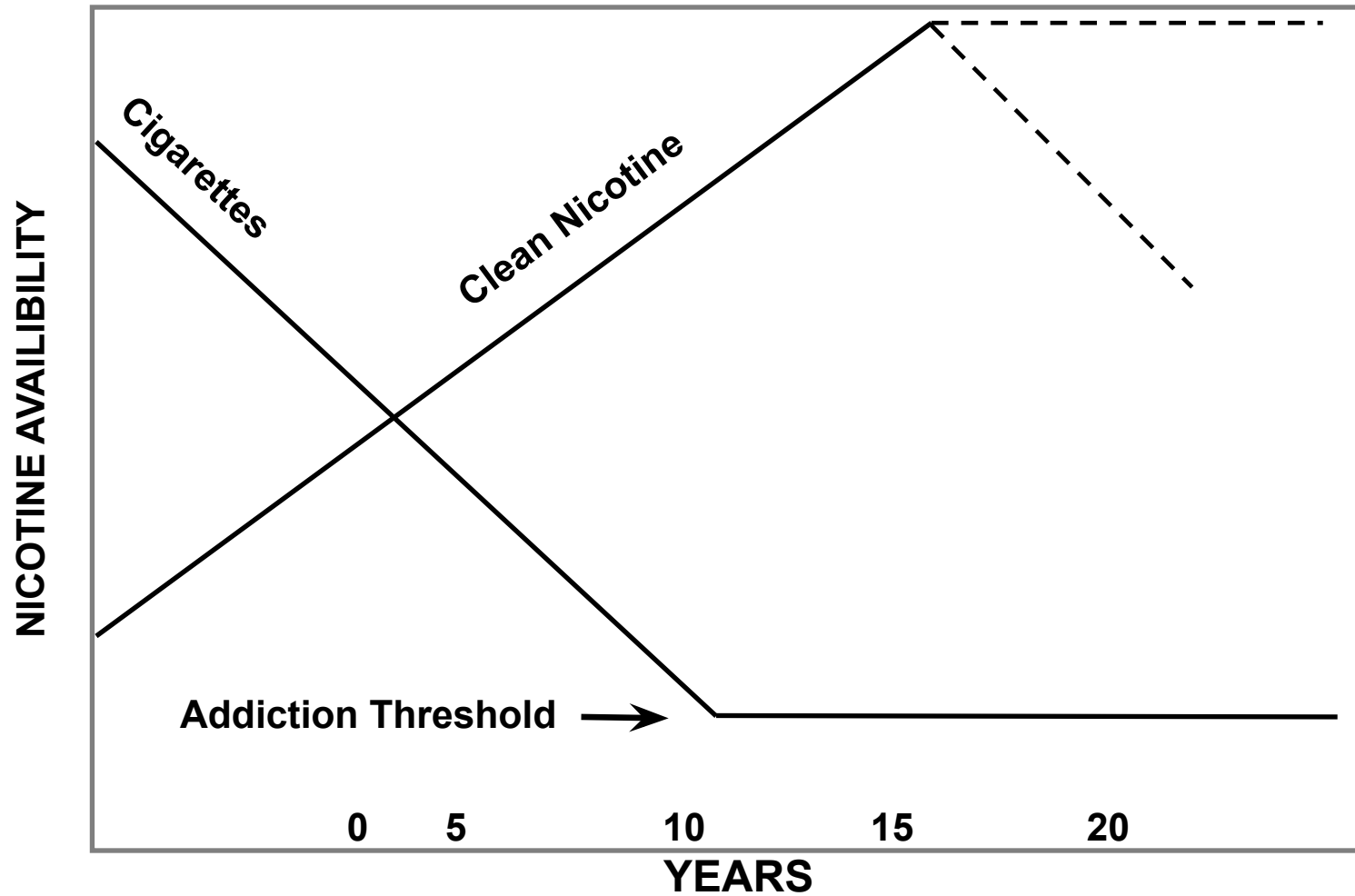
# ASSUMPTIONS IMPLICIT IN A NICOTINE REDUCTION STRATEGY

- **There is a threshold nicotine exposure level that is necessary to sustain nicotine addiction**
- **It is technically feasible to manufacture cigarettes with low enough nicotine content to fall below the threshold for most people**
- **Smokers would not fully compensate for reduced nicotine cigarettes by smoking more cigarettes or smoking each cigarette more intensely**

# Estimating the nicotine threshold for addiction

- **Threshold to establish and maintain addiction**  
~ 5 mg/day – based on studies of non-addicted smokers
- **Maximum bioavailability 40% based on nicotine content.**
- **Assuming up to 30 cigarettes per day - absolute limit of 0.4-0.5 mg nicotine content per cigarette.**

# Reducing Addictiveness of Cigarettes: A Nicotine Reduction Strategy



# Cancer Epidemiology, Biomarkers & Prevention

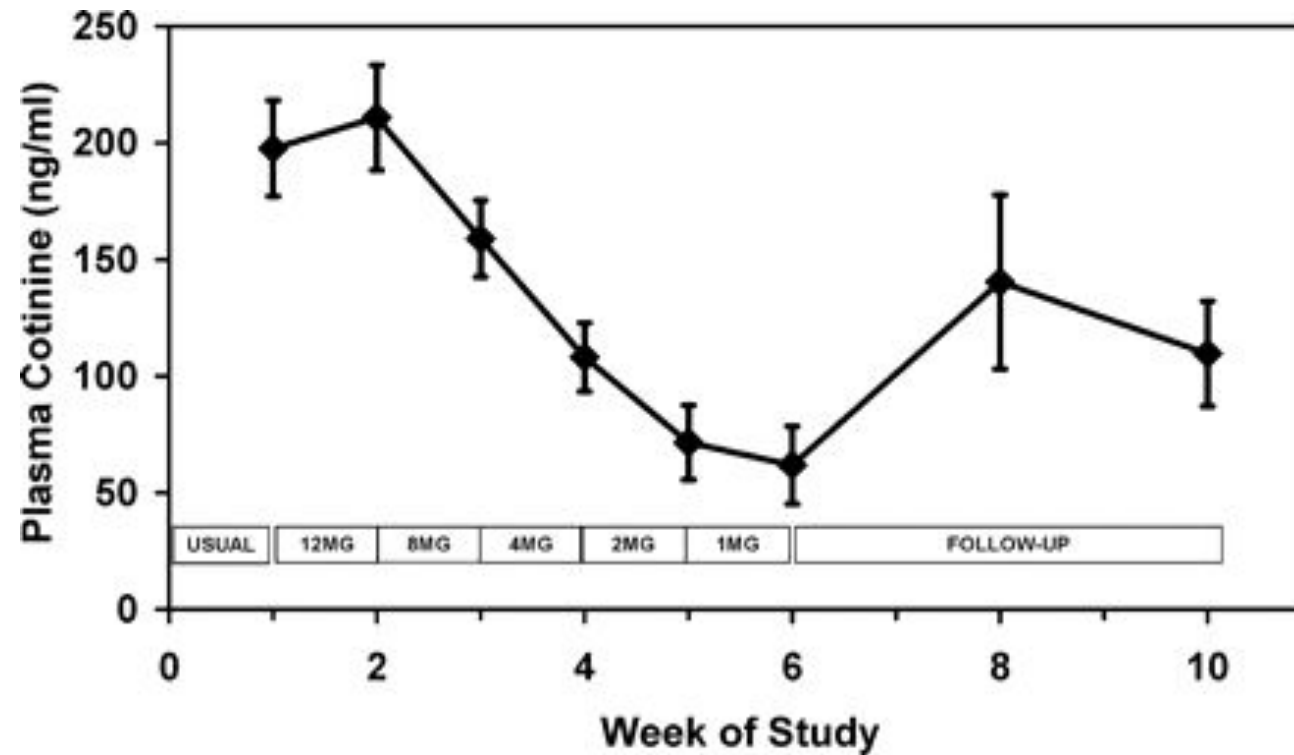
Global Perspectives

## Nicotine and Carcinogen Exposure with Smoking of Progressively Reduced Nicotine Content Cigarette

Neal L. Benowitz, Sharon M. Hall, Susan Stewart, Margaret Wilson,  
Delia Dempsey, and Peyton Jacob III

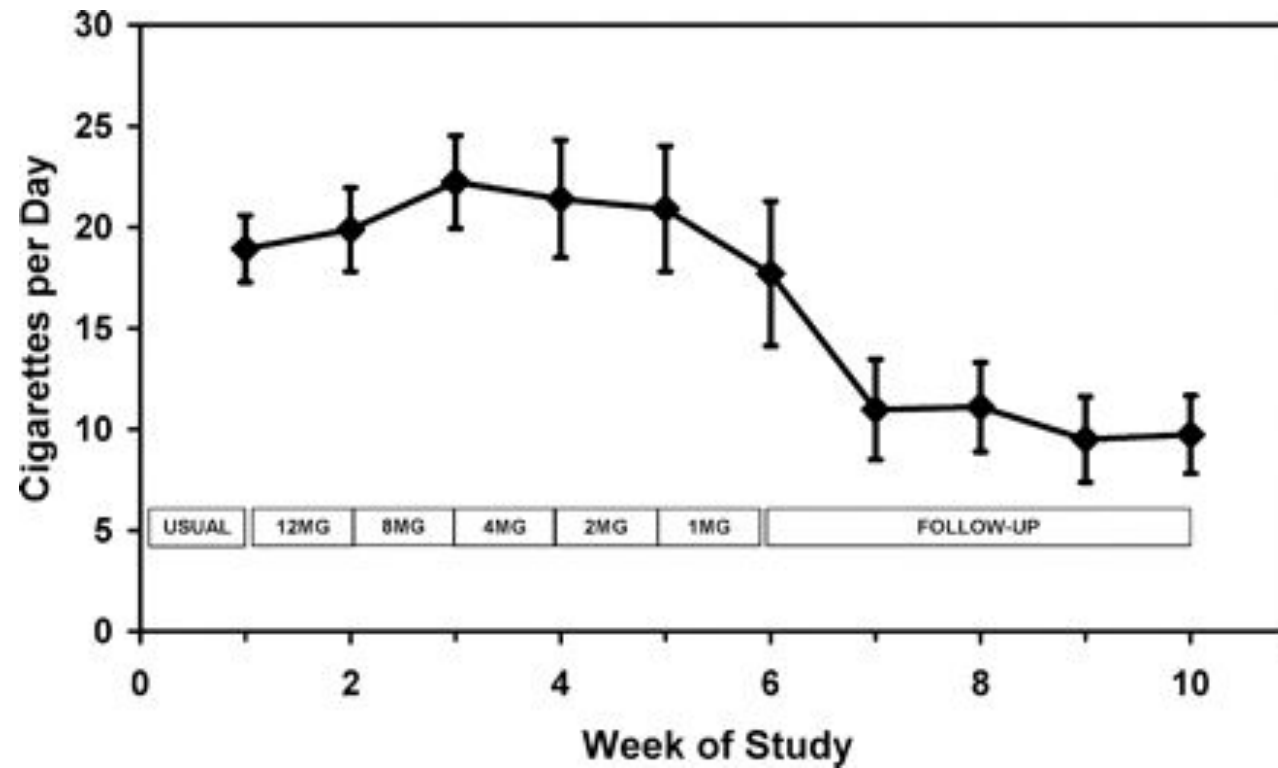
Division of Clinical Pharmacology and Experimental Therapeutics, Medical Service, San Francisco General Hospital  
Medical Center, Departments of Medicine, Psychiatry, and Biopharmaceutical Sciences,  
University of California, San Francisco, California

# 6-week Nicotine Content Taper: 75% reduction in nicotine intake



*Benowitz et al, CEBP 2007; 16:2479*

# Evidence of reduced nicotine dependence



*Benowitz et al, CEBP 2007; 16:2479*

# Quotes from Reduced Nicotine Content Cigarette Smokers

- “I no longer feel the need to have coffee and cigarettes first thing in the morning.”
- “experiencing less craving”
- “smoking these cigarettes are like quitting and therefore, might as well quit.”
- “smoking is losing its pleasure”.

# Conclusions

- **Addiction to nicotine sustains cigarette smoking. The cigarette delivery system causes most of the harm.**
- **Reducing the nicotine content of cigarette reduces the addictiveness of cigarettes.**
- **The result of a national nicotine reduction policy would be preventing children from becoming addicted smokers and giving established smokers greater freedom to stop smoking when they decide to quit.**