LSRO Reduced Risk Project

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Swedish Match North America

Smokeless Tobacco and Risk Reduction

- **Key issues**
  - Reduced Risk does not imply zero risk
  - The inhalation of *smoke* is the principle cause of the harm associated with cigarettes
  - The Swedish Experience demonstrates that public health benefits can be achieved in societies with substantial tobacco use if
    - Smoke inhalation decreases
    - Smokeless tobacco is the predominant source of tobacco based nicotine
  - There is evidence in the scientific literature to support the reduced risk of smokeless tobacco
  - American smokeless tobacco and snus are similar products
  - Smokeless tobacco products can supply the nicotine needs of moderate to heavy smokers
  - Smokeless tobacco does not appear to be a gateway to daily cigarette smoking
  - US and Swedish smokeless tobacco do not appear to be associated with increased oral cancer risk
  - Perceived risk needs to be addressed through education

What is Reduced Risk?

- **Currently, approximately 45 million Americans consume cigarettes regularly**
- **The standard for reduced risk is relative to this consumer base NOT the non-smoking public**
- **Most of these individuals are dependent upon nicotine**
  - Efforts to reduce nicotine levels in tobacco products are counterproductive
    - Smokers self-dose with their chosen product to achieve the desired nicotine level
  - The key to risk and harm reduction is in the delivery vehicle for nicotine
- **Substantial reduction in risk can be achieved through smokeless tobacco**
  - 2002 Royal College of Physicians assessment that Smokeless Tobacco (ST) is 10 – 1000 less hazardous than cigarettes
  - Levy et al (2004) consensus that low TSNA ST was at least 90% less hazardous than cigarettes

Smokeless Tobacco Harm Debate

- **Why is there a debate in the literature regarding Smokeless Tobacco and disease risk?**
  - Many of the reports group Asian smokeless tobacco products with US and Swedish products, e.g. IARC report
    - Many of these products contain Areca nut, lime, and occasionally a little tobacco
    - These Asian products are not typical of the modern ST products
    - When the data are combined they skew the resulting risk assessments
  - Some of these studies, e.g. Henley et al. (2005), do not assess changes in tobacco use patterns over the course of the assessment
  - Much of the oral cancer risk is based on the work of Winn et al (1981) which suffered from major methodological limitations
  - Some of the studies lack the rigor to establish a reliable association between the disease(s) cited and ST
  - Some studies have very few cases and limited controls, e.g. Blot et al (1998) found a 6 fold increase in risk among females based on 6 cases and 4 controls
  - Some studies were based on ST users who were smokers or former smokers

Snus Disease Summary

- **Snus does not increase the risk of**
  - Oral Cancer
  - Esophageal Cancer
  - Stomach Cancer
  - Pancreatic Cancer
  - Respiratory Diseases
    - Lung Cancer
    - Chronic Obstructive Pulmonary Disorder (COPD)
    - Emphysema
  - Cardiovascular Diseases
    - Myocardial Infarction (Heart Attack)
    - Atherosclerosis (hardening of the arteries)
    - Stroke
    - Peripheral Artery Disease

Cardiovascular Diseases

- There is no evidence of an increased risk of myocardial infarction in snus users
- There is no association between the use of snus and atherosclerosis or risk factors for atherosclerosis
- There is a relationship between the use of snus and the acute effects on the cardiovascular system such as acute increase in blood pressure and heart rate and impaired response of the blood vessels to increases in blood flow. [This is a nicotine effect and even NRT causes the same response]
- It remains unclear whether the use of snus is a risk factor for hypertension
- There is no association between snus use and stroke.

Insulin Resistance and Type 2 Diabetes

- **One cross-sectional study of the relationship of snus use to risk factors for heart disease suggests that snus use is linked to an increase in insulin levels. Three other studies do not support this finding.**
- **One cross-sectional study suggests that snus use is linked to an increased prevalence of type 2 diabetes. Risk estimate was based on only 4 cases of diabetes among snus users.**
- **One cross-sectional and prospective follow-up study in northern Sweden found no significant risk of type 2 diabetes among snus users. Smoking was however associated with an elevated risk.**

GOTHIATEK® Limits for Undesired Components (based on 50% water content in the finished product)

Component	Limit
Nitrite	< 3.5 mg/kg
TSNA	< 5 mg/kg
NDMA	< 5 µg/kg
BaP	< 10 µg/kg
Pesticides	According to the Swedish Match Pesticide Policy

Component	Limit
Cadmium	< 0.5 mg/kg
Lead	< 1.0 mg/kg
Arsenic	< 0.25 mg/kg
Nickel	< 2.25 mg/kg
Chromium	< 1.5 mg/kg

American Smokeless Tobacco

- **Head and Neck Cancer**
  - Rodu and Cole (2002) found no significant risks of any head and neck cancer associated with the use of moist snuff even though the risks were not for exclusive ST users
  - The literature does not show a reliable association between ST use and oral cancer
    - Brown et al (1977), Link et al (1992), Marshall et al (1992), Martinez (1969), Muscat and Wynder (1998), Muscat et al. (1996), Smith (1975), Wynder and Stellman (1977), Wynder et al. (1983), and Young et al (1986) failed to find an association between ST and oral cancer
    - Six (6) other studies suggested an association between ST and oral cancer but did not quantify the magnitude of risk
    - It is noteworthy that the ten studies that found no association are more recent than the 6 that did
    - Bouquot and Meckstroth (1998) found no increase in oral cancer in West Virginia males it was actually lower than the national average

American Smokeless Tobacco

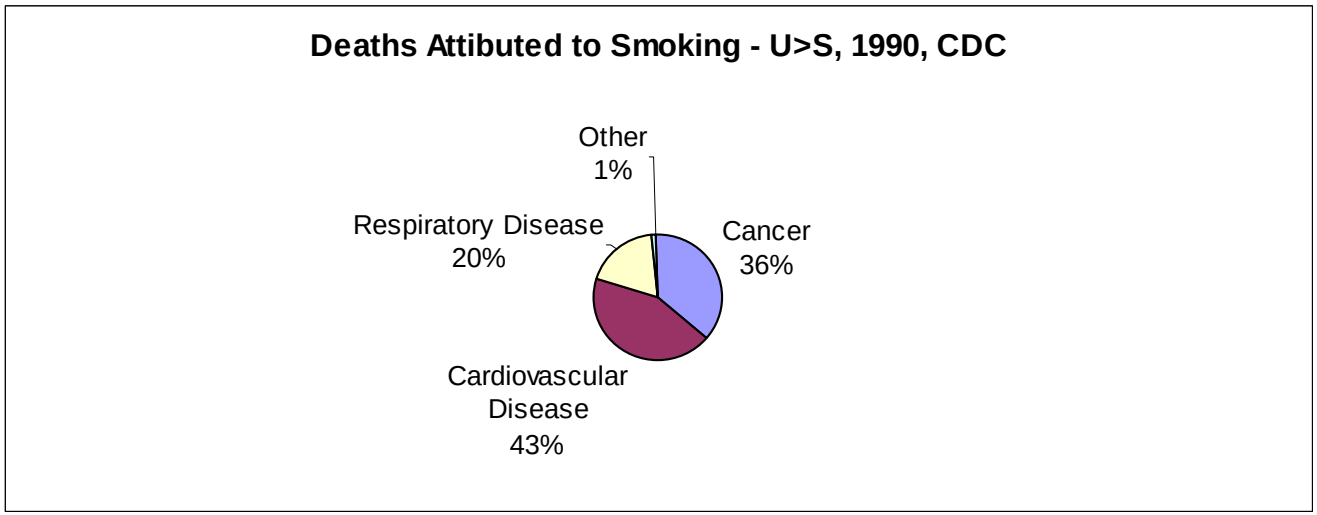
- **Head and Neck Cancer (continued)**
  - The literature does not show a reliable association between laryngeal, esophageal, or nasal cancer and ST use.
- **Gastrointestinal Cancer**
  - No reliable association between smokeless tobacco use and the risk of gastrointestinal cancers
  - Limited number of studies
  - Not designed to examine the risks associated with ST use
  - Four analytic studies assessing the role of ST in the development of stomach cancer and none found increased risk with ST use
- **Lung Cancer**
  - No evidence of an association between ST and increased risk of lung cancer is found in the literature.

American Smokeless Tobacco

- **Pancreatic Cancer**
  - Farrow and Davis (1990), Muscat et al (1997) found no increase in risk of pancreatic cancer from chewing tobacco
  - Zheng et al (1993) reported no increase in death from pancreatic cancer associated with ST use after controlling for age, alcohol consumption, and smoking
- **Acute Cardiovascular Effects**
  - Nicotine effect on transient blood pressure and heart rate are observed

Smoking Attributable Deaths

1990 CDC Data



Causes of Smoking Related Deaths

- **There are 2 principal causes of smoking related deaths**
  - Cardiovascular disease
  - Pulmonary disease (including lung cancer)
- **Smokeless tobacco does not display an increase in risk of these diseases in excess of that for non-tobacco users**

Bronchus and Lung Cancer Incidence Rates (ICD 162; Males)

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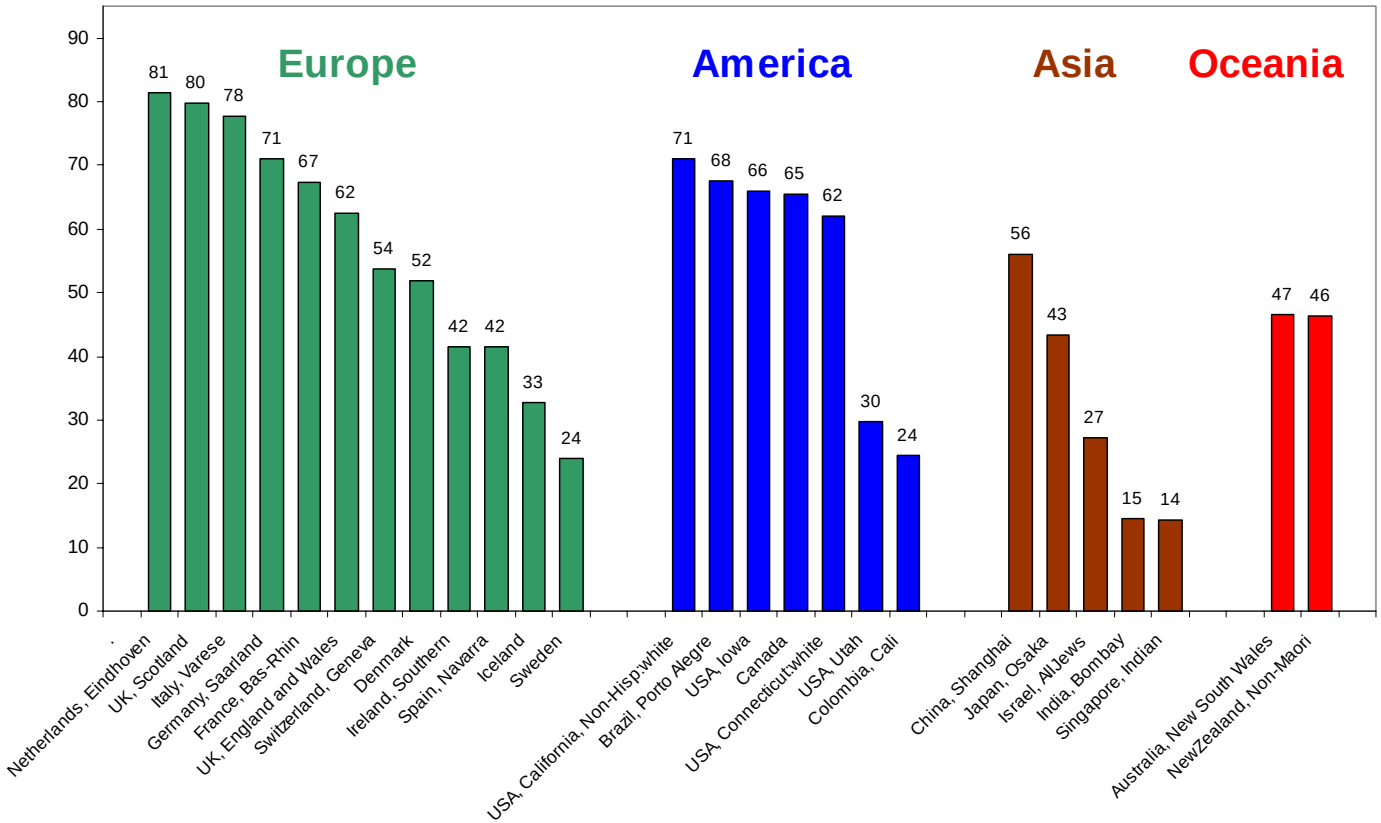

Age-Standardized (World) Incidence Rates in Males of Bronchus and Lung Cancer (ICD 162) per 100,000. Extract from Cancer Incidence in Five Continents, Volume VII, IARC Sci. Publ. 143, Lyon, France, 1997.

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Oral Cancer Incidence Rates (ICD 141;143-145; Males)

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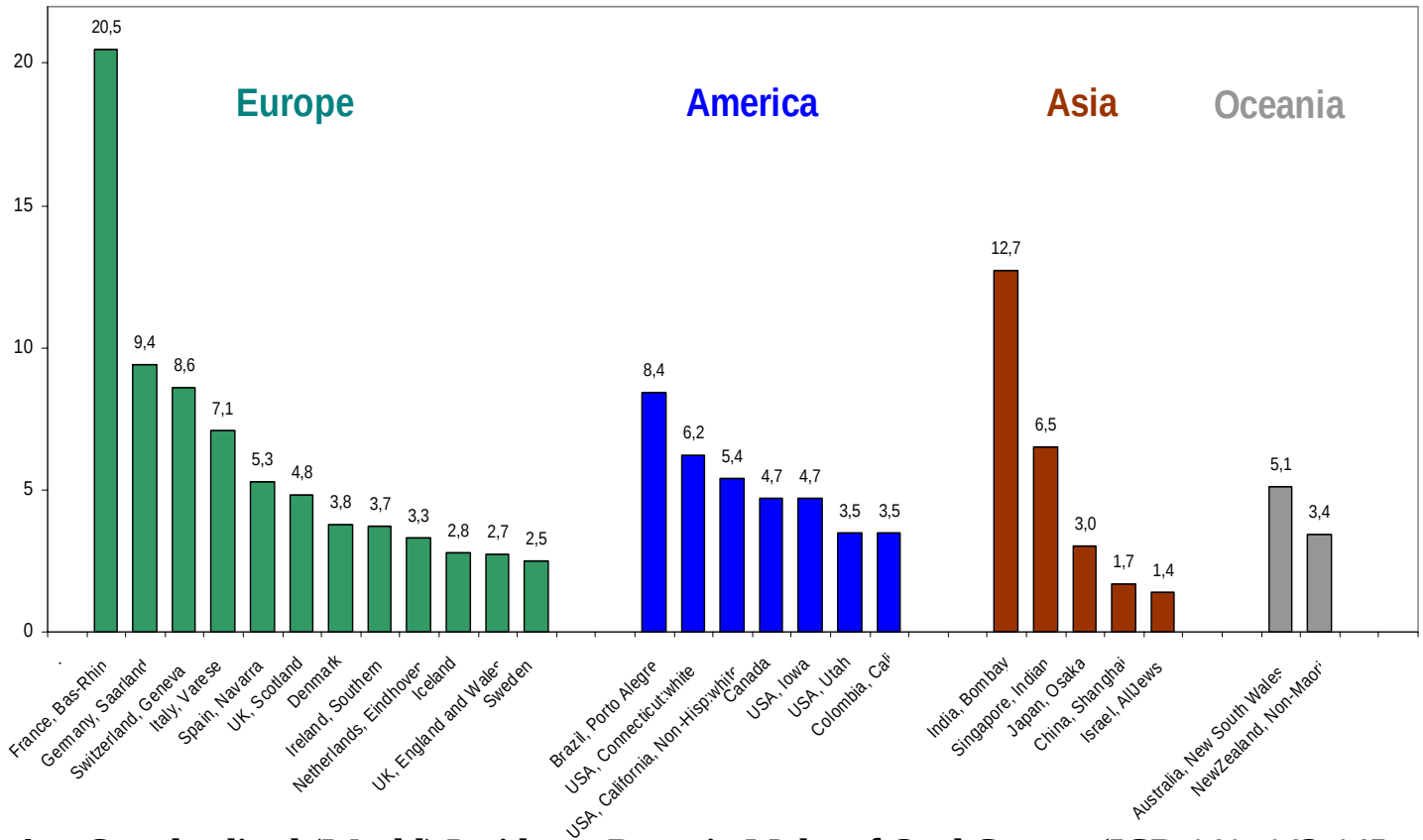

Age-Standardized (World) Incidence Rates in Males of Oral Cancer (ICD 141; 143-145 per 100,000. Extract from Cancer Incidence in Five Continents, Volume VII, IARC Sci. Publ. 143, Lyon, France, 1997.

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Nicotine Uptake Summary

- **Inhaled nicotine is absorbed through the pulmonary venous system and thus reaches the brain in 10-20 seconds (Le Houezec (2003); Benowitz (1995); Benowitz et al (1988); Guthrie et al (1999).)**
- **Inhaled nicotine enters the blood almost as rapidly as I.V. injection (9-16 seconds NIDA (1990)) and the peak level may be higher and the time to brain entry may be shorter.**
- **Oral absorption rates are slower than the absorption from smoke in the lungs (Institute of Medicine Report 2001.)**
- **Nicorette (2mg) produces a peak concentration of 5ng/ml at ~25 minutes compared to a peak of 16 – 35ng/ml within 5 minutes from a cigarette (Nicorette literature.) Repeat dosing required to achieve 25ng/ml concentration.**

Nicotine Uptake Summary

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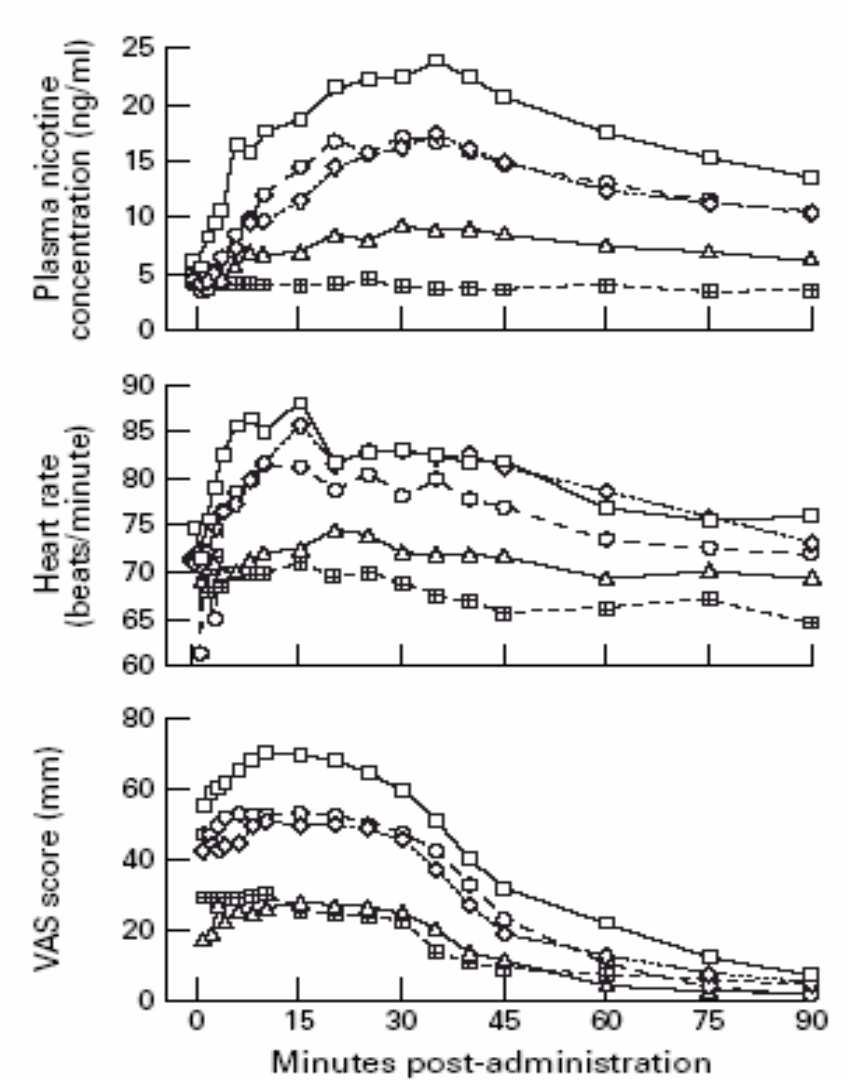

Mean plasma nicotine concentration, heart rate, and visual analogue scale (VAS) score (product "strength") after administration of each of four smokeless tobacco products, or mint snuff.

Source: Fant et.al. (1998)

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Nicotine Uptake Summary

TABLE 2. *Nicotine effects after inhalation: Temporal considerations*

Action	Seconds
Puff time	2.0
Pulmonary circulation time	7.5
Left ventricle to cerebral circulation time	-1.0
Brain transit time	8.5
Total circulation time	19.0

NOTE: Estimates derived from Mapleson (1973).

Source: NIDA (1990)

Nicotine Pharmacokinetics

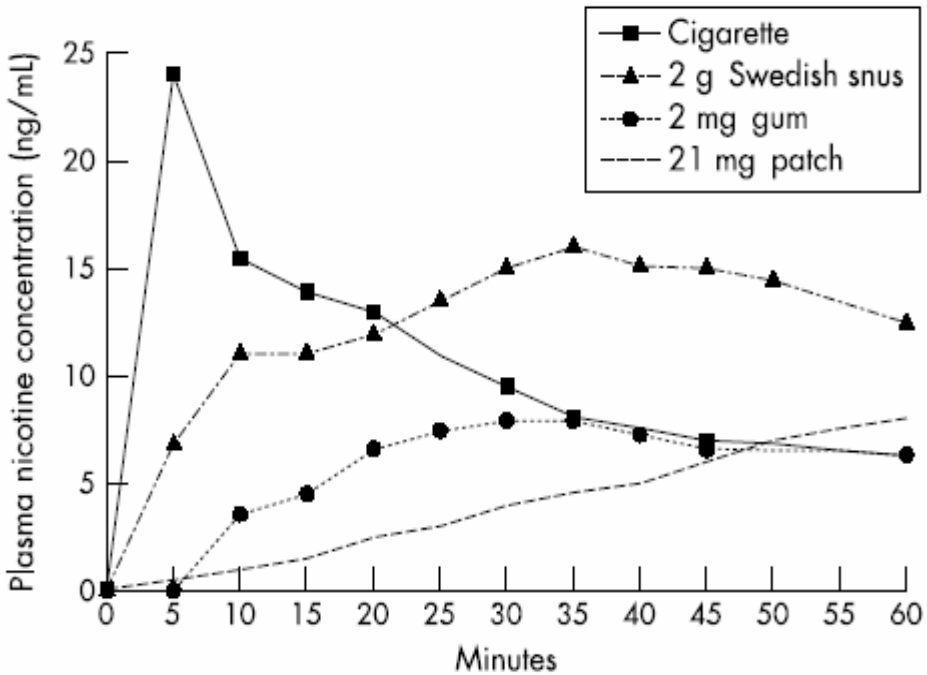

Figure 1 Venous blood concentrations in nanograms of nicotine per millilitre (ng/ml) of plasma as a function of time for various nicotine delivery systems; all plasma nicotine concentrations have been reconfigured such that the pre-absorption level starts at 0 ng/ml (that is, to take out the baseline differences). Cigarette, and 2 mg nicotine gum, adapted from Russell *et al*,[24] and 21 mg patch adapted from Stratton *et al*,[3] page 100. Swedish snus plasma nicotine concentrations in 10 Swedish snus users from a single 2 g pinch of loose snus adapted from Holm *et al*.[21]

Nicotine Uptake Summary

- **Nicotine levels in smokers is complex and is affected by many factors.**
  - Number of cigarettes per day
  - Smoking behavior
  - Brand consumed.
  - Individual clearance rates
  - Etc.
- **Smokers titrate their intake to achieve a personal level based on their needs**
- **Oral tobacco products can achieve the same steady state levels as smoking**
- **Rate of nicotine delivery of an oral product is a function of nicotine content of the tobacco, amount of tobacco, pH of the tobacco and format related effects**
- **Oral products take longer to achieve peak levels and decrease at a slower rate probably associated with continued absorption**
- **Oral tobacco products can deliver more nicotine than NRT and deliver it more rapidly**
- **Moist Snuff and Snus allows for relatively rapid nicotine absorption but not as fast as cigarettes**
- **Speed of behavioral reinforcement is an important aspect of nicotine delivery**

Relevance of Nicotine Pharmacokinetic Data

- **The pharmacokinetics of nicotine affect**
  - The addictive potential of nicotine
    - Time from dosing to reward
    - Dose level
  - The dosing interval
- **The dosing form affects the pharmacokinetics**
  - Uptake rate
  - Maximum nicotine level per dose
  - Steady state nicotine level
  - Dosing frequency
  - Exposure to other harmful chemicals

Nicotine Uptake

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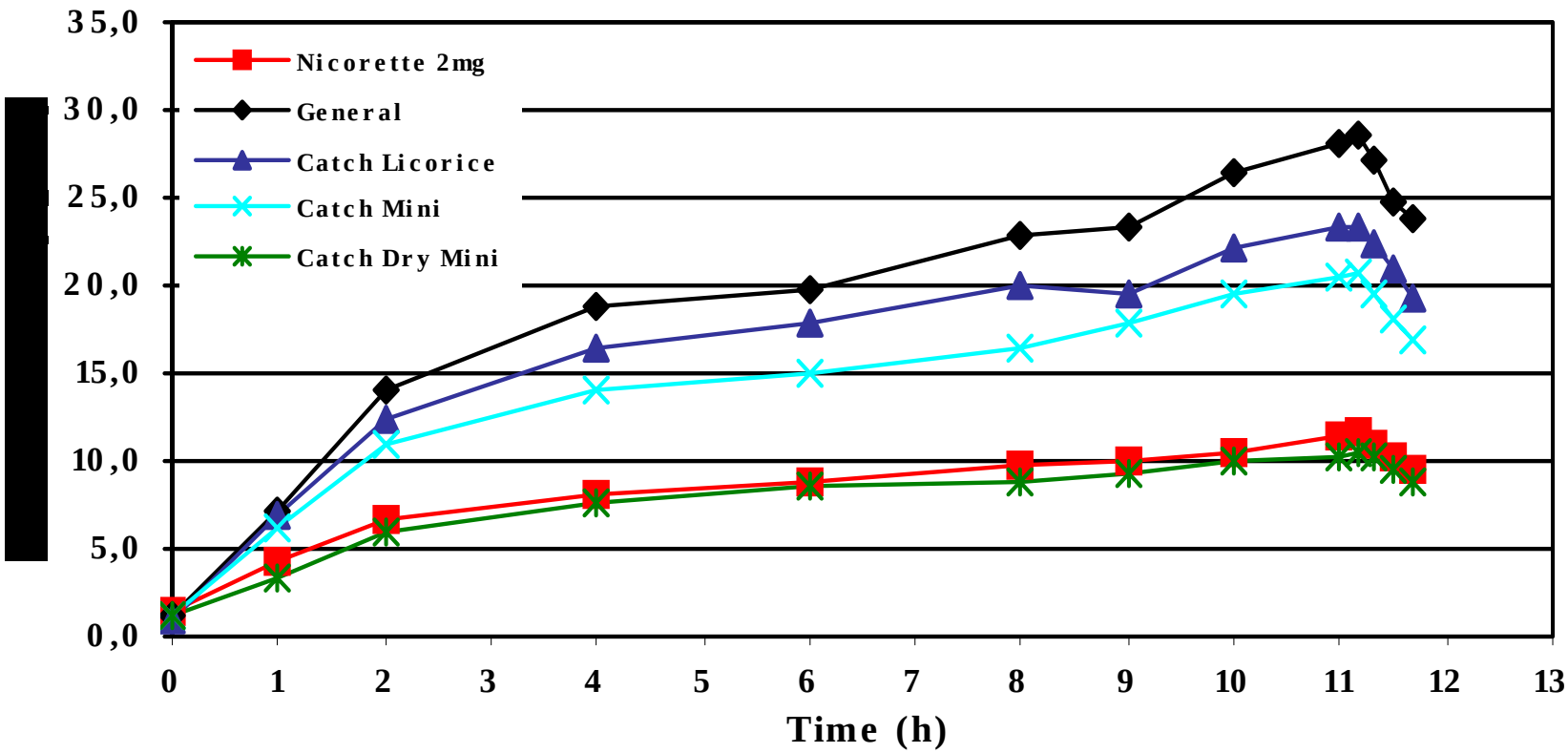
Plasma concentration-time curve



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Nicotine

- **Two studies have shown that the steady-state level of nicotine and cotinine in plasma is similar in Swedish snus users and cigarette smokers - nicotine ca. 37 ng/ml and cotinine ca. 300 ng /ml. Holm, H. et al 1992. Nicotine intake and dependence in Swedish snuff users. Psychopharmacology 108: 507-511. Larsson, I. et al 1987. Disposition of nicotine and cotinine in plasma, saliva and urine of snuff-users. Proc. Third Eur. Congr. Biopharm. Pharmacokin. pp. 318-324.**

Nicotine

- **The initial uptake of nicotine from Swedish snus is initially quite fast, the nicotine concentration in plasma increasing by ca 10 ng/ml during the first 10 minutes. After that the uptake rate was somewhat slower and the plasma concentration reached a maximum level of ca 15 ng/ml at 35 min. after the pinch had been taken out. Holm, H. et al. 1992. Nicotine intake and dependence in Swedish snuff users. Psychopharmacology 108: 507-511.**

Nicotine

- **Decrease of the nicotine content of snus by 50% results in a decrease of the nicotine intake by about 50%, i.e. Snus users do not compensate when switching to a low-nicotine product. Andersson, G. et al. 1995. Reduction in nicotine intake and oral mucosal changes among users of Swedish oral moist snuff after switching to a low-nicotine product. J. Oral. Pathol. Med. 24: 244-250.**

Increases in Cancer Death Rates

- **Since 1940 only four types of cancer have seen a significant increase in the age adjusted death rates to 2001**
  - Lung and Bronchus Cancer - highly associated with cigarette smoking (the most significant)
  - Prostate Cancer in men associated with more men living to be older
  - Leukemia
  - Breast Cancer in females

Age-Adjusted Cancer Death Rates, for Males by Site, US, 1930–1997

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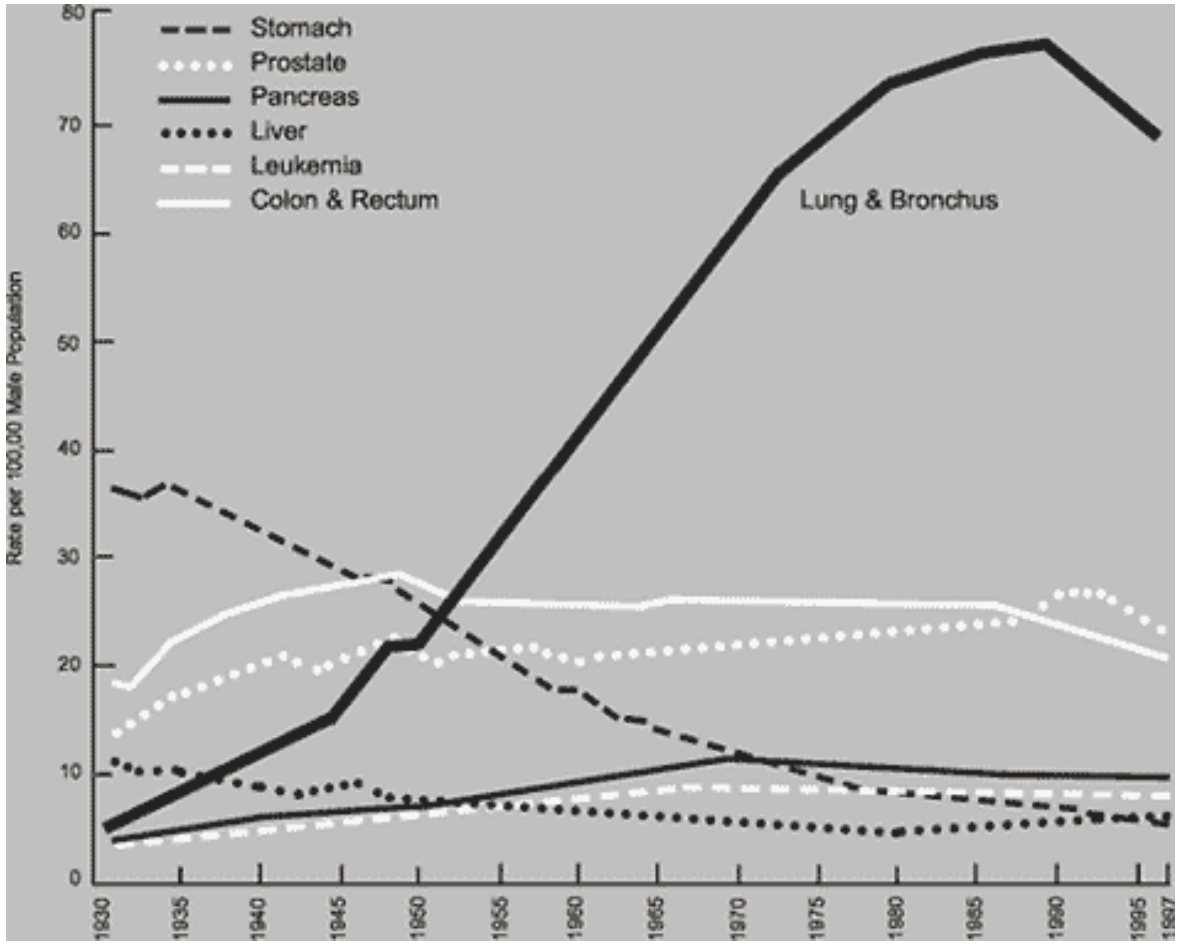

Source: Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin 2001; 51:28.

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Age-Adjusted Cancer Death Rates, for Females by Site, US, 1930–1997

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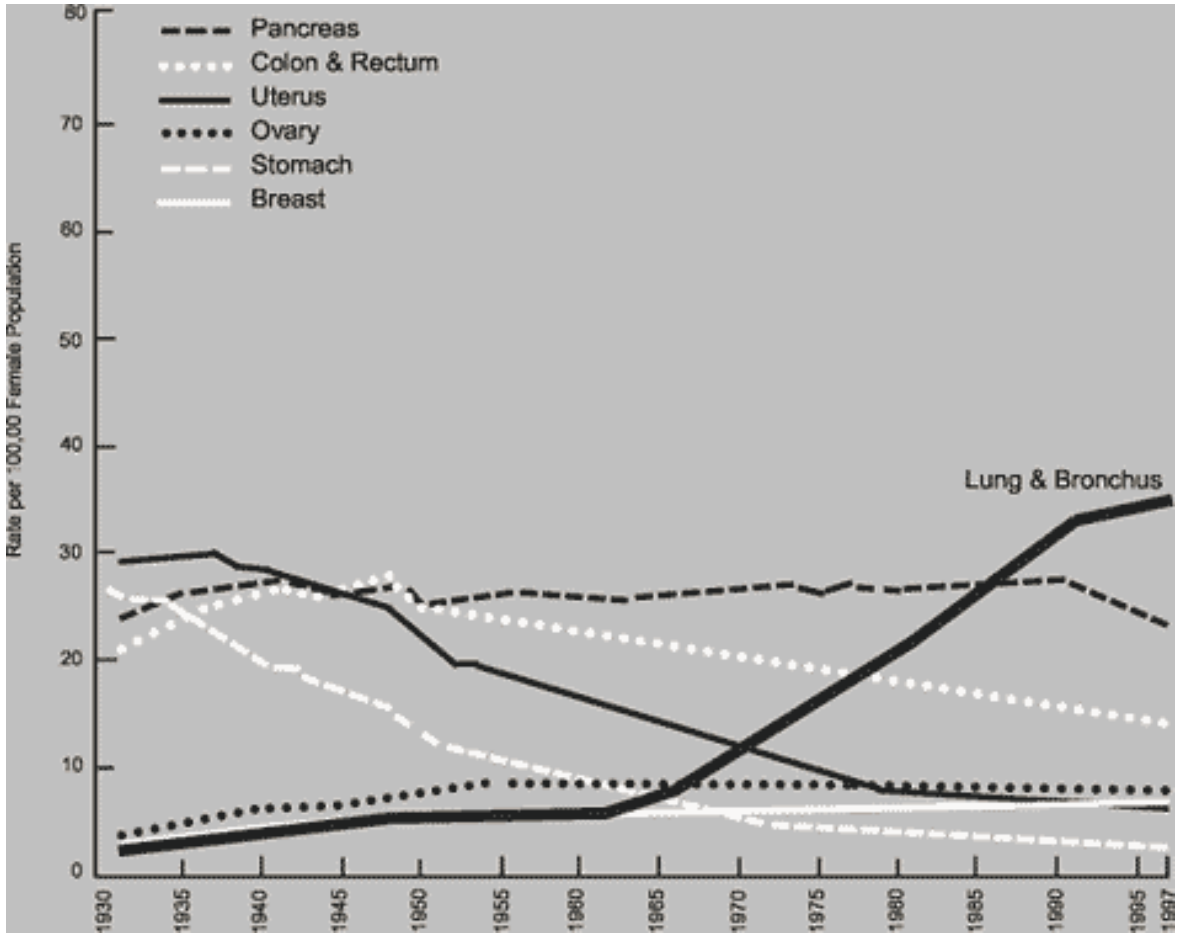

Source: Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin 2001; 51:27.

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Sales of Snus and Cigarettes in Sweden 1916 - 2002

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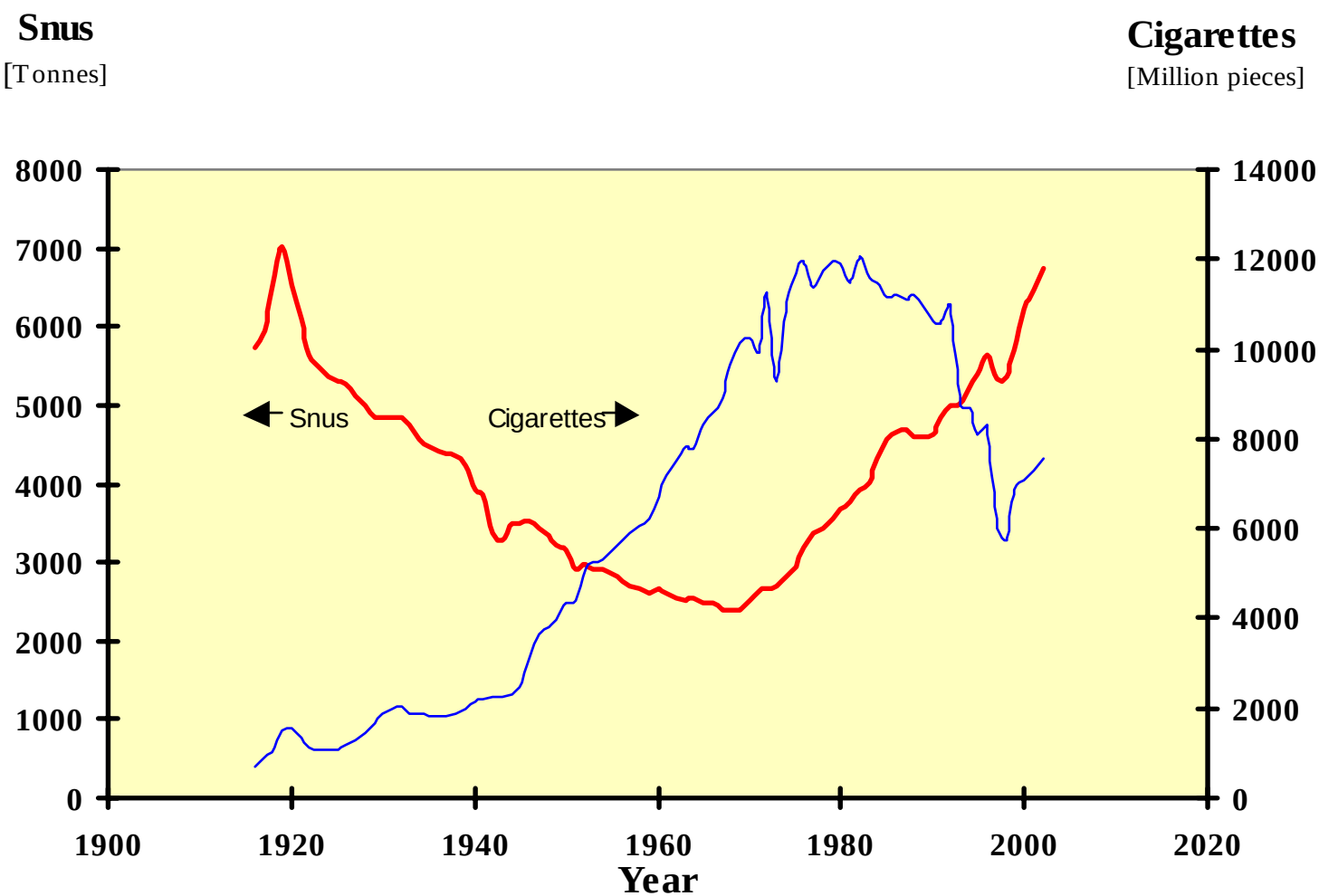

(Source: Swedish Match 2003)

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Sales of Cigarettes in Sweden

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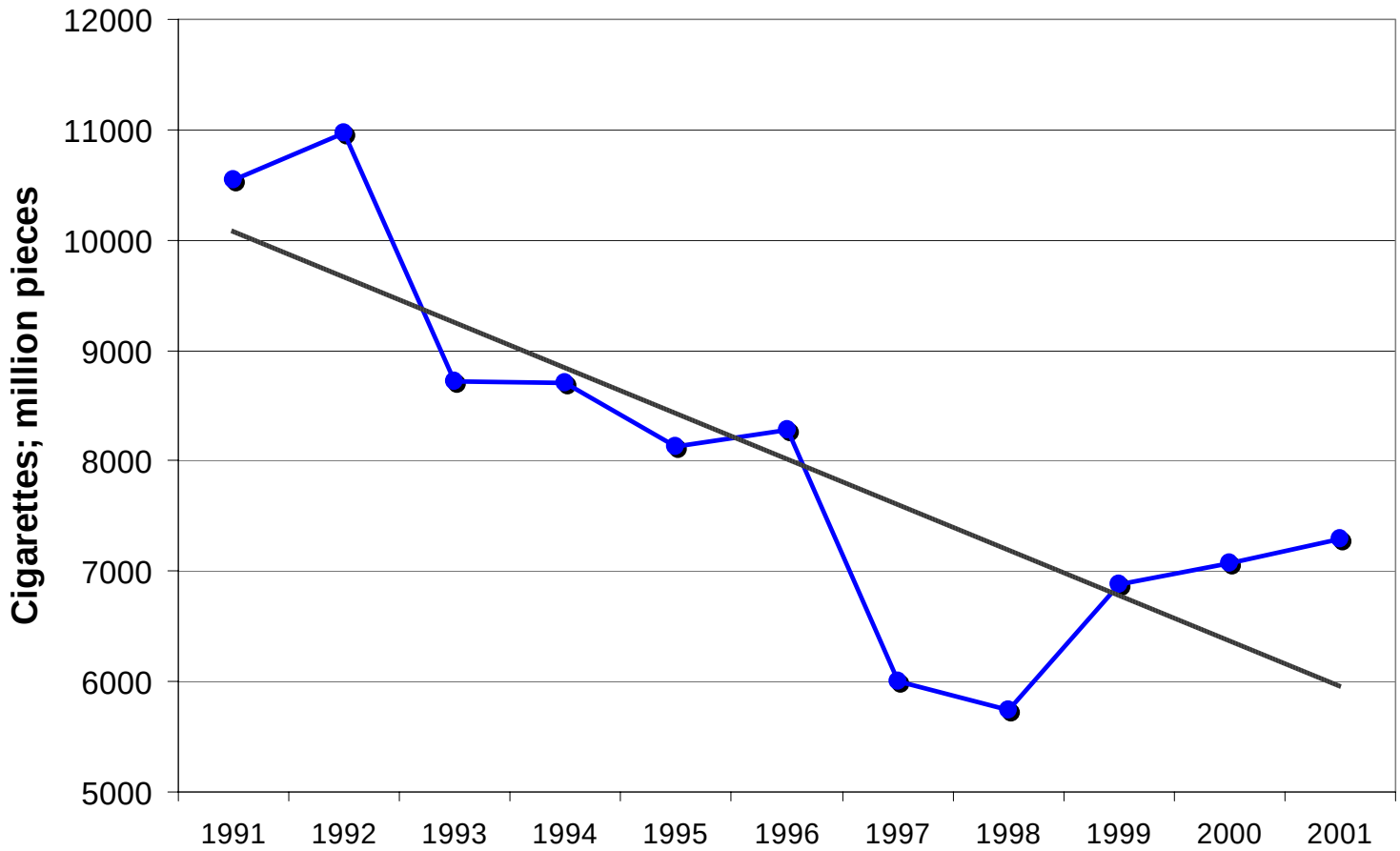

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Sales of Snus in Sweden

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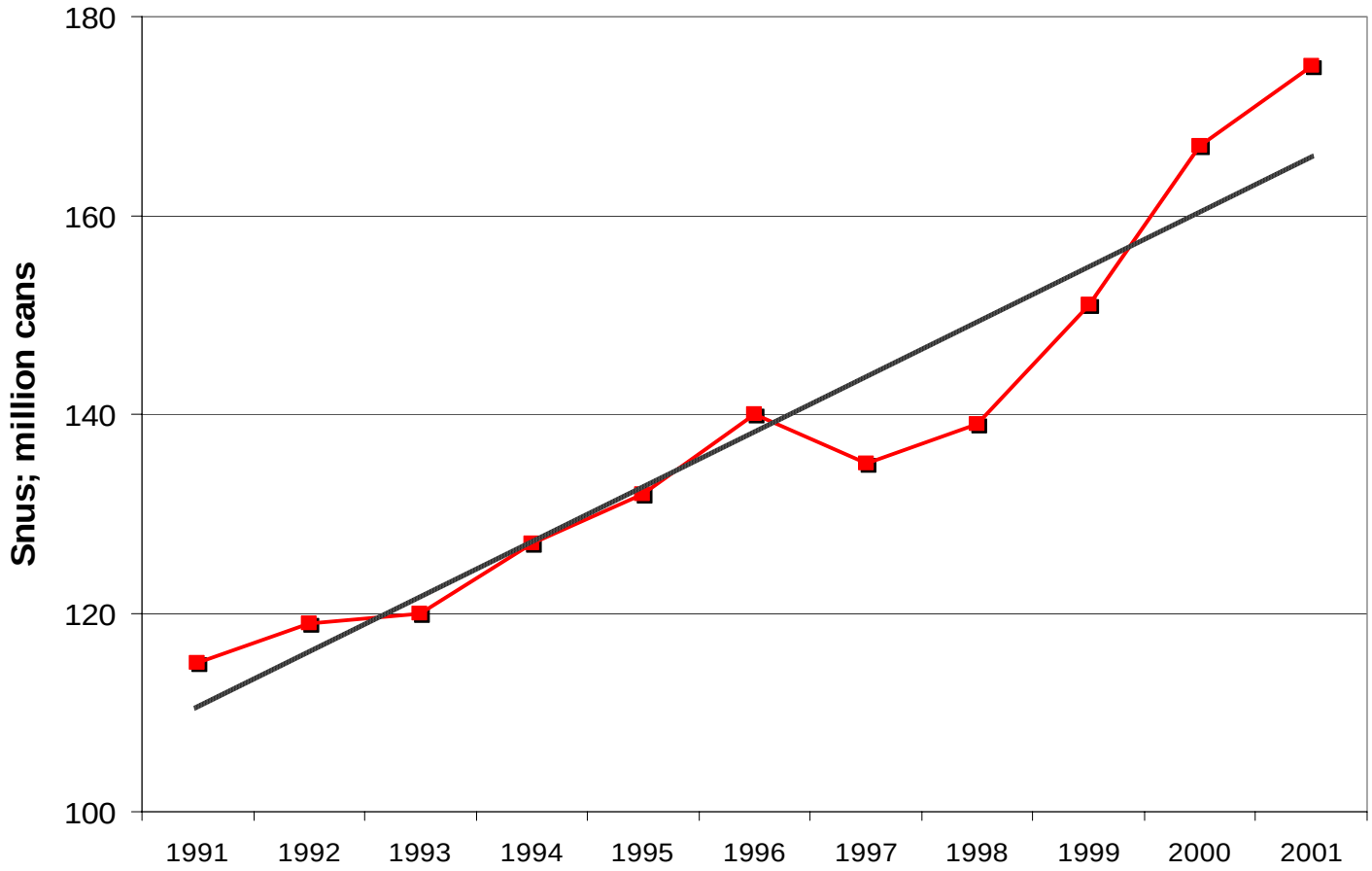

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Percentage Daily Smokers in Europe

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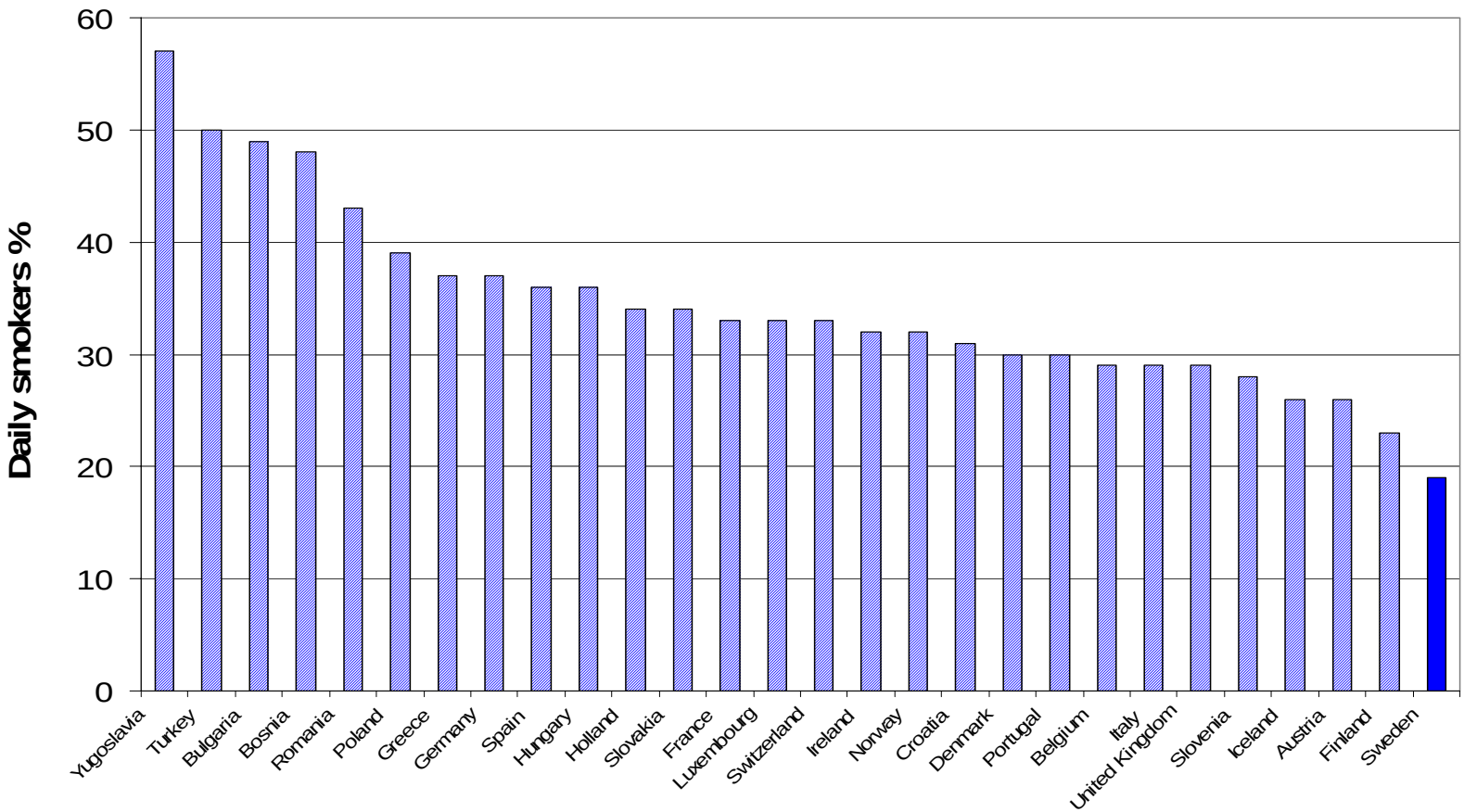

Source. Nordisk tobaksstatistik

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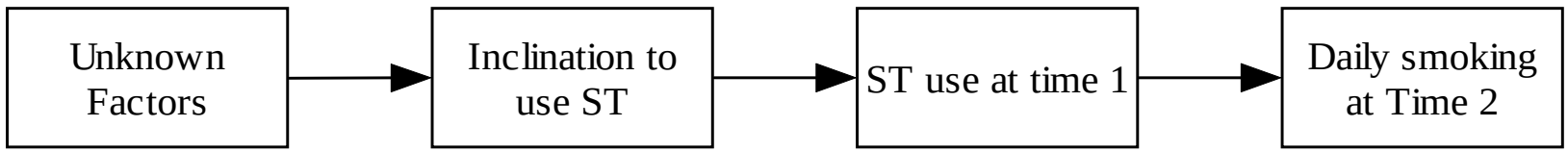
The Gateway Issue

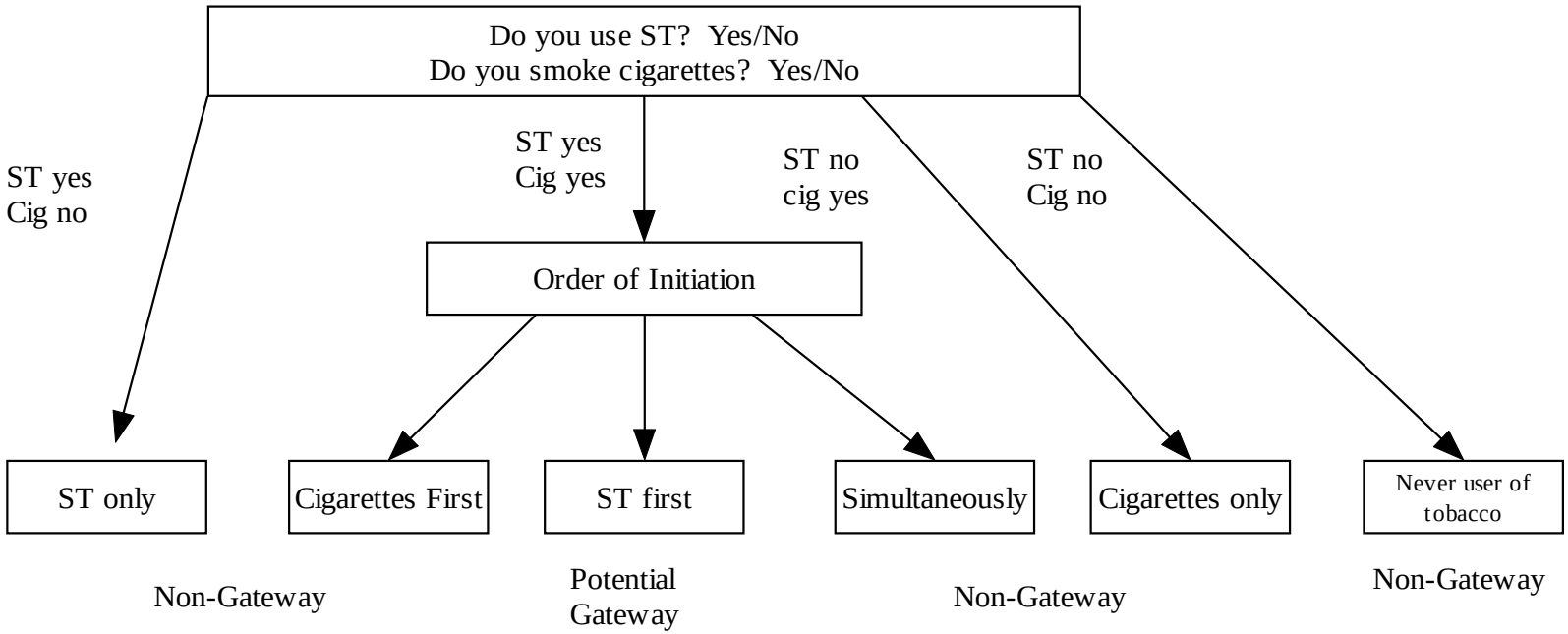


Gateway model adapted from Phillips 2004

The Gateway Issue

- **For ST to be a causal gateway to smoking it is critical that the pattern of use be investigated**
  - ST use must precede smoking for ST to be a causal gateway
  - Each pattern of uptake provides information on the gateway effect
    - Longitudinal data on product use at two time points
  - Kozlowski et al. (2003) determined that there are two categories of ST use
    - Non-gateway: ST use with no subsequent cigarette smoking or cigarette use first, i.e. potentially an exit from smoking
    - Gateway: ST use first followed by smoking later
    - The order of initiation is critical to understanding whether or not ST is a gateway to cigarettes
    - The order of initiation is *not sufficient* to draw causal conclusions about ST as a gateway to cigarettes

The Gateway Issue



Categories of Tobacco Use including Gateway and Non-Gateway use of Snus/Smokeless Tobacco
Adapted from Kozlowski et al. (2003)

The Gateway Issue

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- **Six Studies contribute relevant data on the order of initiation**
  - Four from Sweden (Ramstrom, 1991), TEMO (2002), Galanti et al. (2001), Rodu et al. (2003)
  - Two from the US (Kozlowski et al. (2003), Tomar (2003)

		NON-GATEWAY			POTENTIAL GATEWAY	
Study	Age	Snuff Only (% of Snuff Users)	Cigarettes First (% of Snuff Users)	Total Non-Gateway	Snuff First (% of Snuff Users)	Total
Swedish Snus						
Ramstrom 1991	18-34	45.0%	37.5%	82.5%	17.5%	100%
TEMO 2002	18-34	56.8%	32.8%	89.6%	10.4%	100%
	23-34	56.3%	34.1%	90.4%	9.6%	100%
Galanti et al. 2001	11-12	100%	0%	100%	0%	100%
Rodu et al. 2003	25-64	89.7%	8.3%	98.2%	1.8%	100%
U.S. Smokeless						
Kozlowski et al. 2003	18-34	44.1%	33.0%	77.1%	22.9%	100%
	23-34	34.1%	43.2%	77.3%	22.7%	100%
Tomar 2003	15-23	86.1%	1.4%	87.5%	12.5%	100%

Note that this table includes ONLY those men in each population who use or have used snus/smokeless. It does not include never-users of tobacco; men who have smoked cigarettes but never used snus/smokeless; and men who began use of both products simultaneously (such use was uncommon in these surveys).

The Gateway Issue

- **The data in the previous table must be interpreted cautiously**
  - The studies differ in many important ways
    - They differ with respect to hypothesis, study design, data collection methodology, and definitions of product use
    - Some of the data are taken from the studies (Kozlowski et al (2003)) while others were derived from post-hoc analyses conducted as part of this review (e.g. Tomar (2003), TEMO (2002)
  - In spite of the limitations these studies are very similar in result and lead to the same conclusion: THE VAST MAJORITY OF ST USE IS NOT COMPATIBLE WITH THE GATEWAY THEORY
  - Greater than 75% of all ST users in the US and Sweden are non-gateway users
  - Even among the minority of potential gateway users it cannot be concluded that the progression from ST to cigarettes is causal
  - In 2002, Ramstrom reported that the onset of daily smoking in a sample of 2756 Swedish men was 40% while only 20% of primary daily snus users progressed to daily smoking
  - Rodu et al (2003) examined a cohort of men in northern Sweden (153 men) and none progressed to cigarettes in the 5-13 year follow-up.
  - Thus, ST may prevent cigarette smoking in some people

Perceived Risk of Smokeless

- **Waterbor et al. (2004) reviewed 4 dozen health education brochures on the dangers of ST printed between 1981 and 2001 and found claims of**
  - Oral leukoplakia
  - Other oral conditions
  - Oral cavity cancer
  - Laryngeal cancer
  - Esophageal cancer
  - Stomach cancer
  - Pancreatic cancer
  - Lung cancer
  - Breast cancer
  - Prostate cancer
  - Bladder cancer
  - Kidney cancer

Perceived Risk of Smokeless

- **Waterbor et al. (2004) reviewed the scientific literature to determine which claims were substantiated and found**
  - Oral leukoplakia
  - Other oral conditions
  - They stated that the evidence for oral cancer was suggestive
  - The evidence for other cancers was absent or contradictory
- **The communication of the risk should be accurate and based on sound scientific methodology**

Summary

- Smokeless tobacco (American moist snuff and Swedish snus) are considerably less harmful than cigarettes
- Snus and American smokeless are similar in health effect though the products differ
- The major diseases caused by cigarettes can be reduced by a change in the nicotine delivery vehicle to a smokeless system
- Smokeless tobacco can provide the nicotine needs of moderate to heavy smokers
- The Swedish Experience demonstrates the benefits of smoking reduction even with unchanged tobacco use
- There is little if any gateway effect
- The public needs access to accurate and rigorous scientific data to make informed decisions
- Public Health officials must place public health above other agendas in the tobacco debate

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