

# **Synthetic Nicotine: Science, Global Regulatory Landscape and Regulatory Considerations**

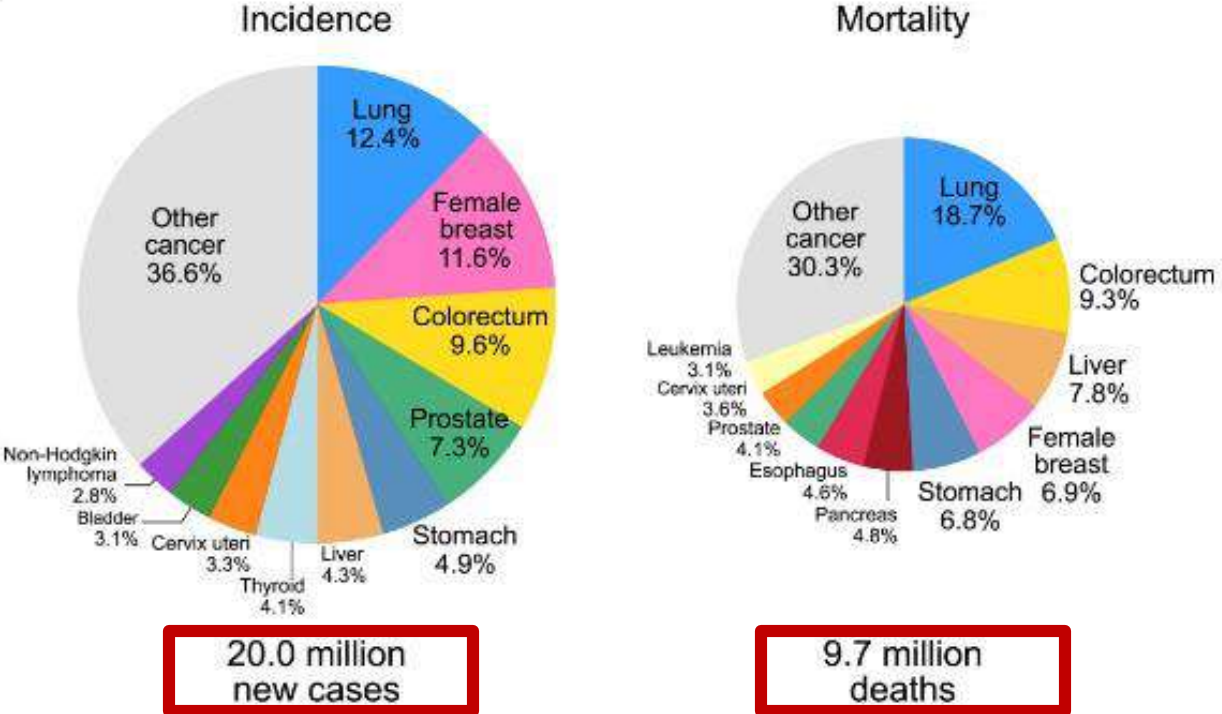
**Taking Decisive Action in Tobacco Control  
Barcelona, Spain  
December 9, 2024**

**Ghazi Zaatari, MD  
Professor & Chair  
Department of Pathology & Laboratory Medicine  
American University of Beirut  
Chair, WHO Study Group on Tobacco Product Regulation (TobReg)  
Director, WHO-FCTC Knowledge Hub-Waterpipe Tobacco Smoking**

# Global Cancer Statistics

a)

Both sexes

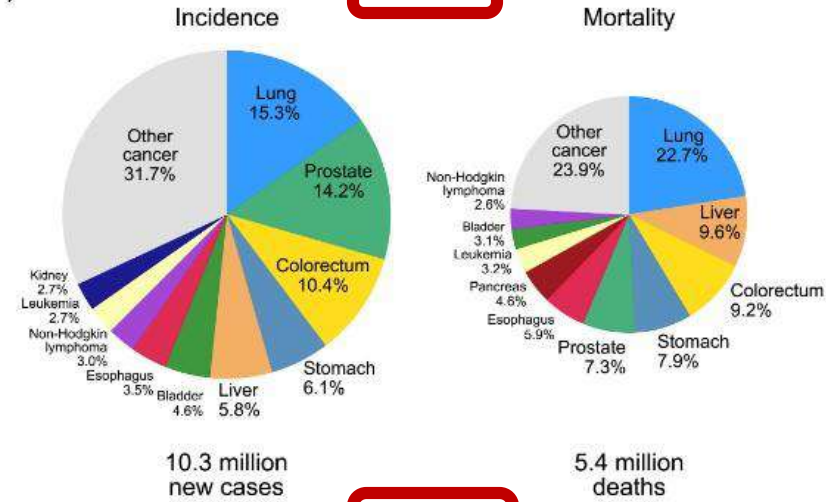


<https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21834>

# Global Cancer Statistics

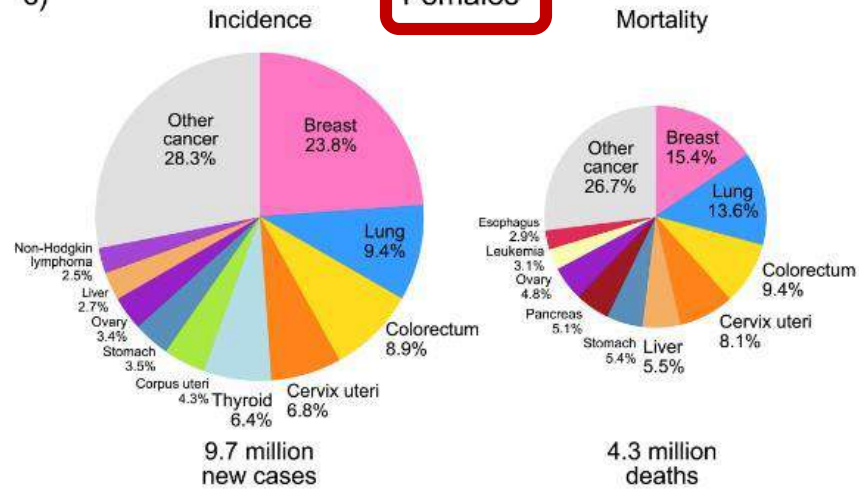
b)

**Males**



c)

**Females**



## New Cases and Deaths for All Cancers in 2022

Cancer site	Incidence			Mortality		
	Rank	New cases	% of all sites	Rank	Deaths	% of all sites
Lung	1	2,480,301	12.4	1	1,817,172	18.7
Female breast	2	2,308,897	11.6	4	665,684	6.9
Colorectum	3	1,926,118	9.6	2	903,859	9.3
Prostate	4	1,466,680	7.3	8	396,792	4.1
Stomach	5	968,350	4.9	5	659,853	6.8
Liver	6	865,269	4.3	3	757,948	7.8
Thyroid	7	821,173	4.1	24	47,485	0.5
Cervix uteri	8	661,021	3.3	9	348,189	3.6
Bladder	9	613,791	3.1	13	220,349	2.3
Non-Hodgkin lymphoma	10	553,010	2.8	11	250,475	2.6
Esophagus	11	510,716	2.6	7	445,129	4.6
Pancreas	12	510,566	2.6	6	467,005	4.8

## New Cases and Deaths for All Cancers in 2022

Larynx	20	188,960	0.9	18	103,216	1.1
Multiple myeloma	21	187,774	0.9	17	121,252	1.2
Gallbladder	22	122,462	0.6	20	89,031	0.9
Nasopharynx	23	120,416	0.6	21	73,476	0.8
Oropharynx	24	106,316	0.5	23	52,268	0.5
Hypopharynx	25	86,276	0.4	25	40,917	0.4

What is a **common etiologic factor** in the 8 highlighted cancers that have high rates of morbidity and mortality?

# Types of Nicotine

- Tobacco derived Nicotine
- Synthetic Nicotine
- Nicotine Salts
- Nicotine Analogues

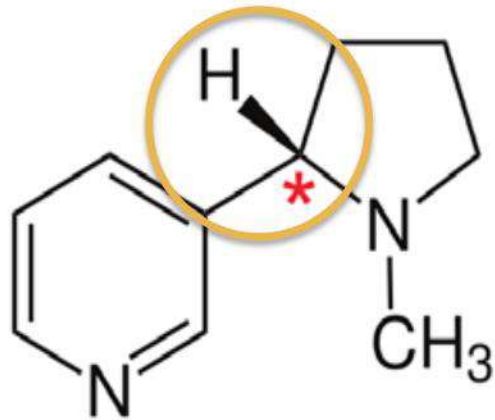


# Nicotine

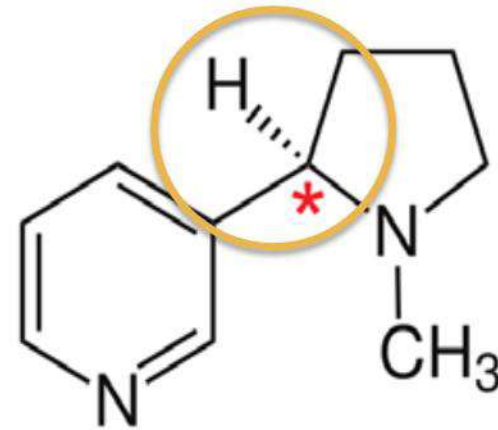
- Nicotine is an **alkaloid** found in the tobacco leaf, *Nicotiana tabacum* & *Nicotiana rustica*.
- It has a role as a phytogenic insecticide, a teratogenic agent, a neurotoxin, an anxiolytic drug, a nicotinic acetylcholine receptor agonist, a biomarker, an immunomodulator, a mitogen, a peripheral nervous system drug, a psychotropic drug, a plant metabolite and a xenobiotic.
- It has **two racemic forms**: **(S)-nicotine** is a 3-(1-methylpyrrolidin-2-yl)pyridine in which the chiral center has S-configuration. The second is **(R)-nicotine**.
- **(S)-form** accounts for about **90-99% of tobacco alkaloid** while (R)-form accounts for 0.1-4.3%. It is 7-16 times **more potent** than its R isomer.
- (R)-form is less biologically active and is potentially toxic.

# Nicotine

- It has **two racemic forms**: **(S)-nicotine** is a 3-(1-methylpyrrolidin-2-yl)pyridine in which the chiral center has S-configuration. The second is **(R)-nicotine**.



S-nicotine



R-nicotine



# S-Nicotine vs. R-Nicotine

- **Toxicity:** Lethal dose (LD50) for S-nicotine was 0.33 mg/kg for S-nicotine and 6.15 mg/kg for R-nicotine, which is > 18 times higher, suggesting that R-nicotine is less acutely toxic than S-nicotine under these experimental conditions.
- **Pharmacologic effect:** Long-term administration of either form of nicotine increases the number of nicotine binding sites in rat brain. However, R-nicotine is about 10 times less potent as an agonist of nicotine receptors than S-nicotine.

In a tobacco industry-sponsored study on acetylcholinesterase, the enzyme that degrades the neurotransmitter acetylcholine in the synaptic cleft to terminate neurotransmission, revealed that R-nicotine is a more potent inhibitor of the enzyme than S-nicotine, binding to a different site on the enzyme protein. The experiments were performed with acetylcholine esterase isolated from electric eels and at nicotine concentrations much higher than those received by smokers.

- **Behavioral effect:** Studying the capability of rats to discriminate injected R- or S-nicotine from saline: S-nicotine was nine times more potent than R-nicotine. S-Nicotine was four to five times more potent than R-nicotine in conditioned taste aversion assays in rats.
- **Metabolism:** Studies in guinea pigs showed that S-nicotine formed only oxidative metabolites, whereas R-nicotine formed both oxidative and N-methylated metabolites.
- **Psychophysical studies:** Odor or irritant sensations: lower thresholds for detection of S- than for R-nicotine and greater burning and stinging intensity, while olfactory perceptions were elicited at similar levels. In electrical recordings of mucosal potential, S-nicotine elicited stronger responses than R-nicotine.

# Knowledge Gaps

- Consumers who use products containing racemic nicotine inhale much higher amounts of R-nicotine than users of tobacco-derived nicotine or pure S-nicotine, which raises questions about the long-term safety of such products.
- In none of the published pharmacological studies were animals exposed for longer than 1–2 weeks, and in none were subsequent pathological effects examined.
- In none were their effects compared after inhalation and after ingestion, the routes through which consumer products dispense nicotine.

# Nicotine

- **Synthetic nicotine** is a chemically synthesized substance rather than derived from tobacco plants.
- First synthesized in **1904**; **racemic mixture 50:50 ratio**.
- Industry considered using it in the 1960s.
- Major manufacturers:
  1. Next Generation Labs (USA) – Tobacco Free Nicotine; PHARMANIC
  2. Contraf-Nicotex-Tobacco (Germany)
  3. Zanoprime Life Sciences Ltd (UK)
  4. Hangsen International Group (China) – Motivo (sale outside USA)
  5. NJOY (USA)

# Terms Used to Market Synthetic Nicotine

- tobacco-free nicotine
- imitation nicotine
- nicotine substitutes
- nicotine analogue
  
- Marketed as being “virtually tasteless and odorless”

**Arecoline**- alkaloid extracted from areca or betel nuts; it can be synthesized

# Major manufacturers of synthetic nicotine and their synthesis strategies

Manufacturer Name	Starting material	Resulting product	Stereoselective step
Next Generation Labs LLC (NGL)	ethyl nicotinate	racemic (50/50) <i>R-/S-nicotine</i>	n/a
Contraf-Nicotex-Tobacco GmbH (CNT)	ethyl nicotinate	<i>S-nicotine</i>	stereoselective recrystallization
Zanoprime Lifesciences Ltd	Myosmine	<i>S-nicotine</i>	enzymatic stereoselective step
Hangsen International Group	Myosmine	<i>S-nicotine</i>	enzymatic stereoselective step
NJOY LLC	racemic (50/50) <i>R-/S-nicotine</i>	<i>S-nicotine</i>	stereoselective recrystallization

Berman M, et al: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10516533/>

**Price of synthetic nicotine remains significantly higher than that of tobacco-derived nicotine**

# Synthetic Nicotine - Hangsen International Group



**MOTiVO**  
SYNTHETIC NICOTINE  
NOT DERIVED FROM TOBACCO

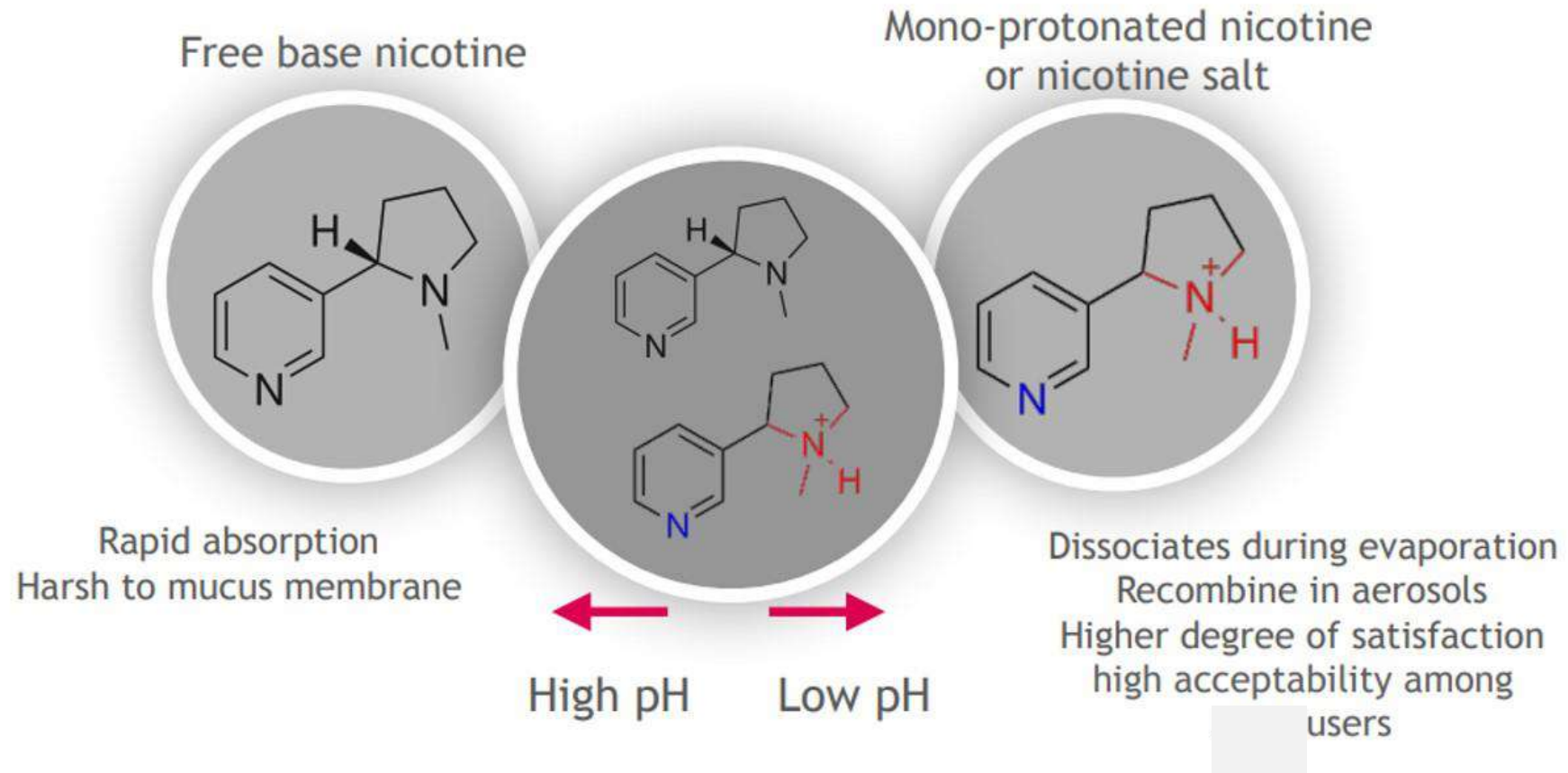
*Synthetic Nicotine*

- Not derived from tobacco
- Fewer restrictions on entering new markets
- Tasteless and odorless
- No residue of harmful impurities
- Same satisfaction for smokers as other nicotine
- Manufactured to exceed ISO 9001, GMP standard

# Manufactured Synthetic Nicotine Unflavored & Flavored

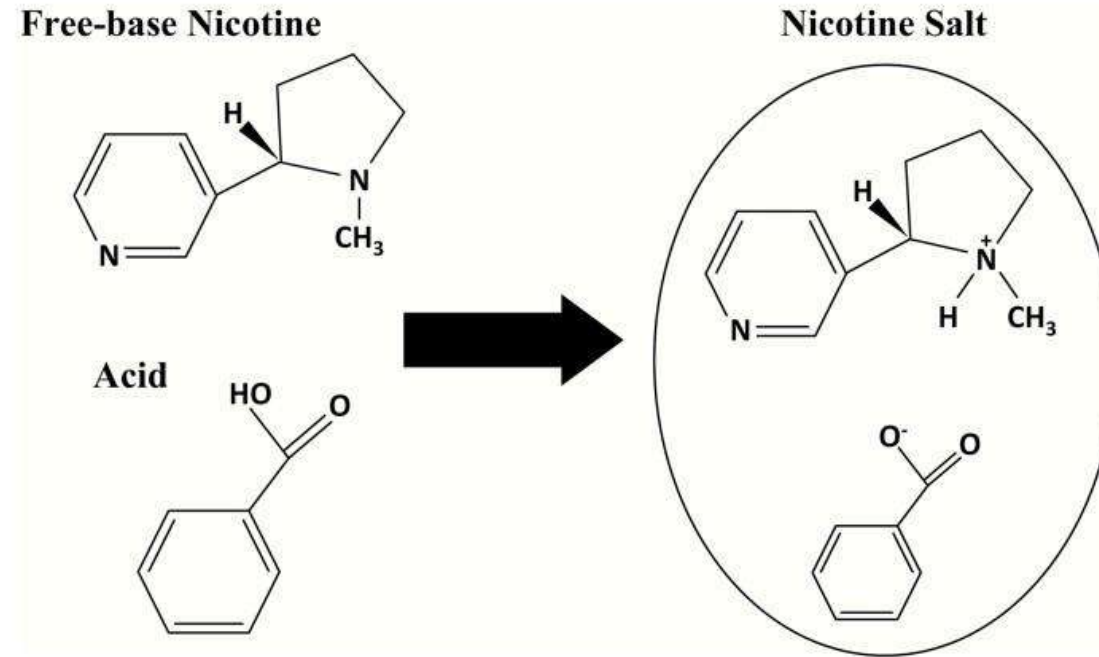


# Chemical States of Nicotine



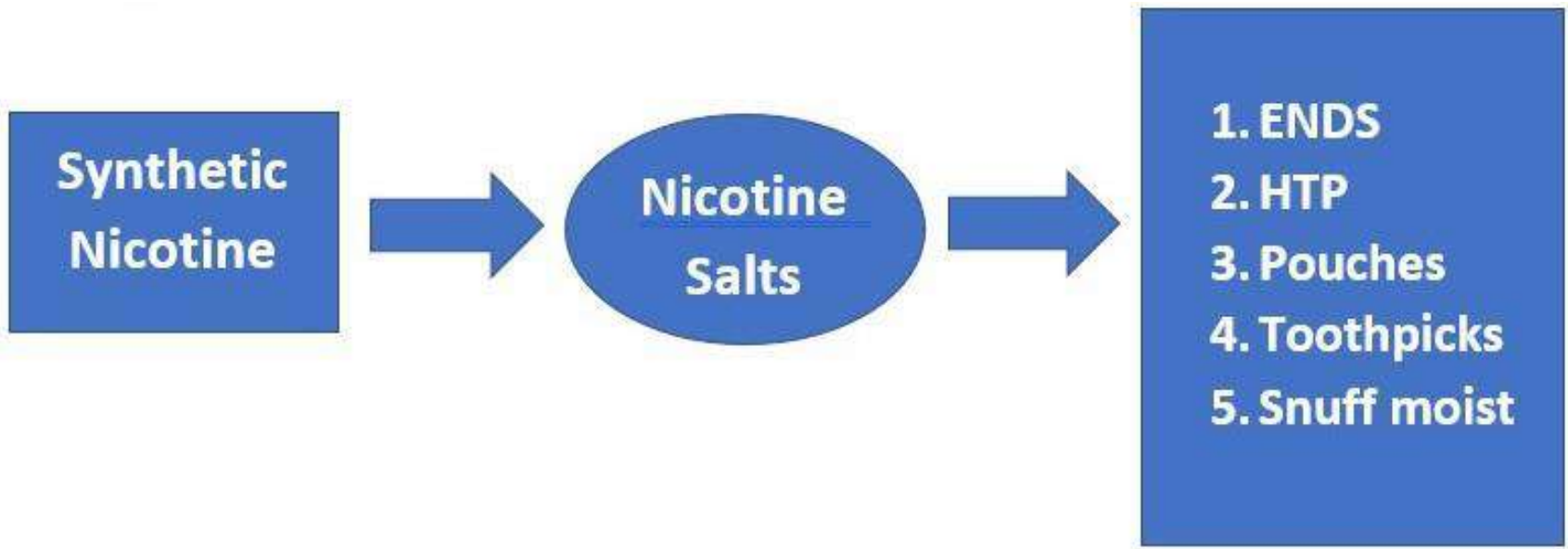


# Formation of Nicotine Salt



Nicotine Tob Res, Volume 22, Issue 7, July 2020, Pages 1239–1243, <https://doi.org/10.1093/ntr/ntz232>

The three most common acids used in the formation of nicotine salts were **lactic acid, benzoic acid and levulinic acid**. Benzoic acid is the most used acid to create a nicotine salt.



# ENDS Products Using Synthetic Nicotine



In a study of 16 disposable Puff devices, nicotine concentrations ranged from 40.6 to 52.4 (average 44.8 mg/mL). Chemical Research in Toxicology 35(8), 2022. DOI: 10.1021/acs.chemrestox.1c00423

# Nicotine Pouches Using Synthetic Nicotine



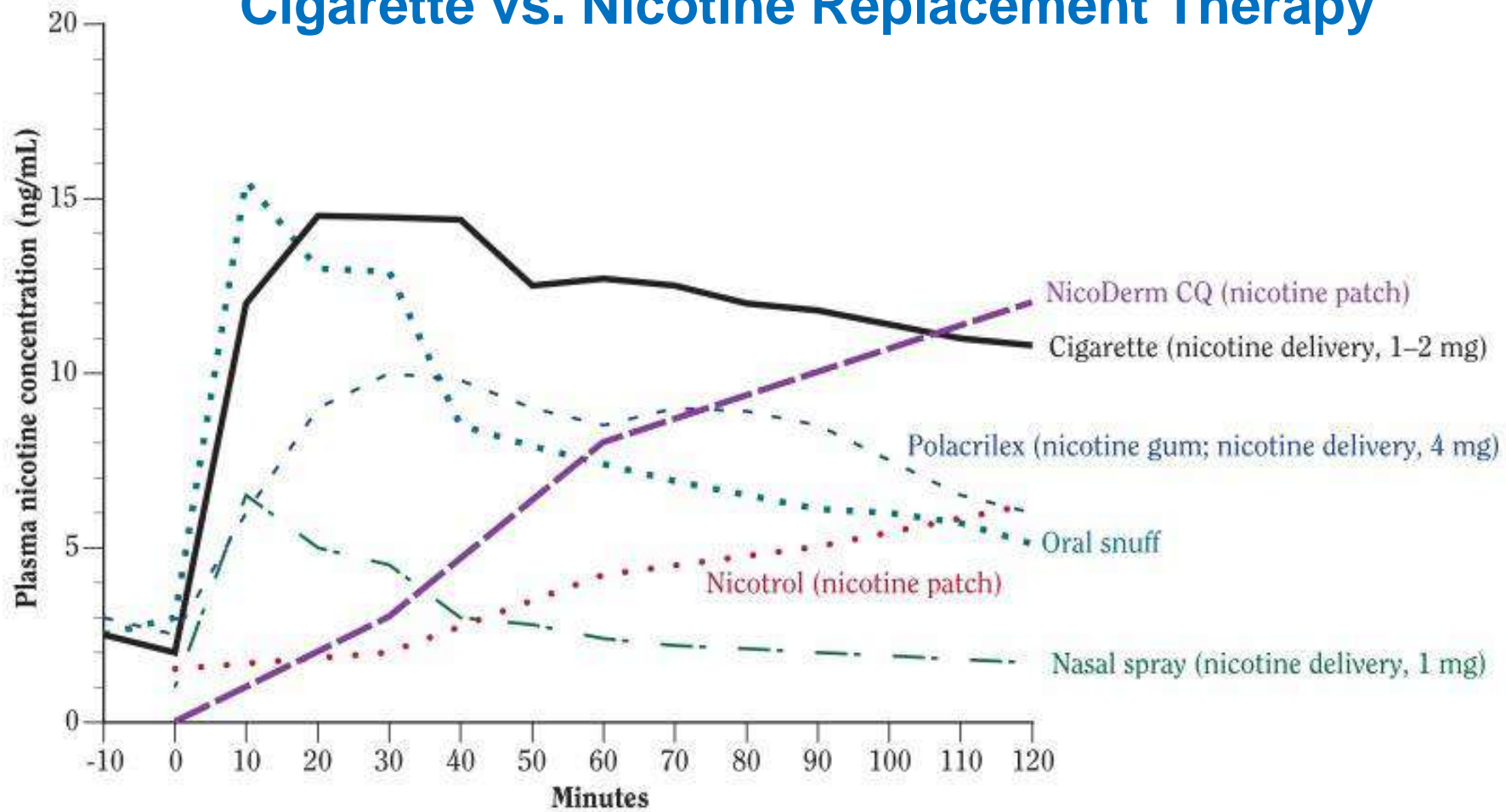
Some of these products contain nicotine up to a concentration of 30 mg per pouch.

Misleading promotion as healthier tobacco free products and effective aids for smoking cessation

# Nicotine Salts

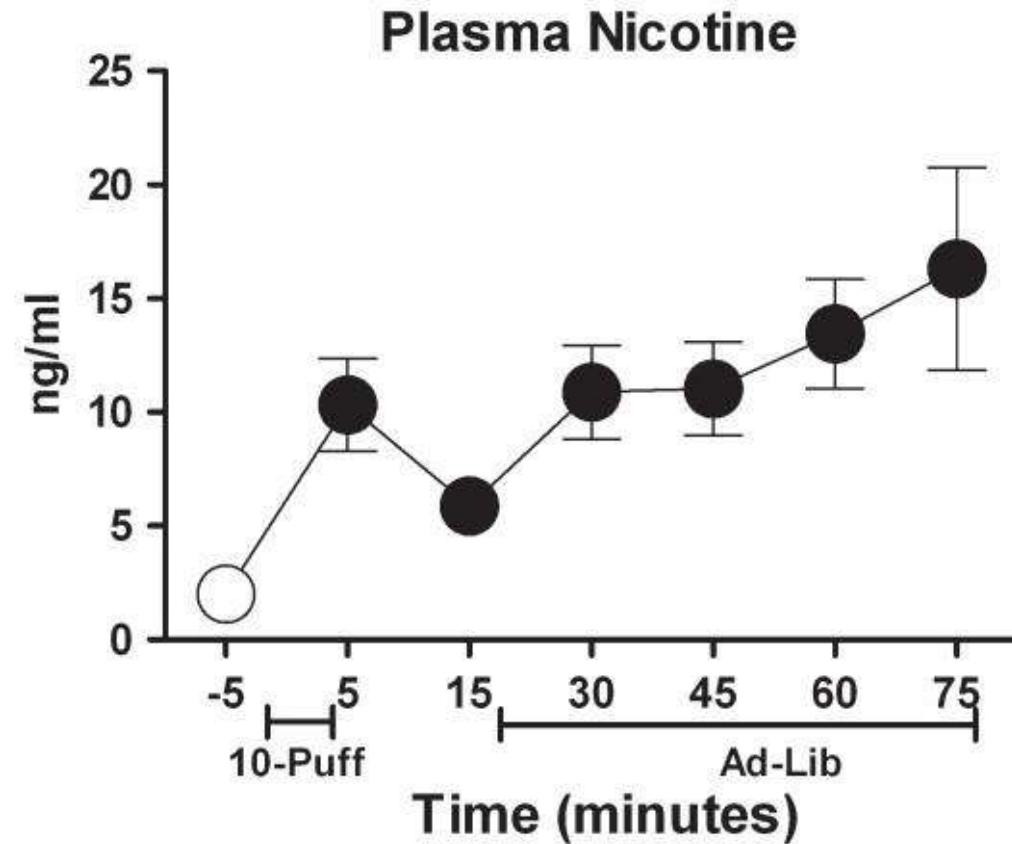
Pax Labs' patent has shown nicotine salts, which give **mostly protonated nicotine**, give **higher plasma nicotine concentrations** (C<sub>max</sub>) than free base nicotine of the same concentration at a given puff profile. As per the clinical study carried out by PAX labs, **2% nicotine benzoate results in three times higher C<sub>max</sub>** than the 2% free base nicotine. Similarly, a study carried out by O'Connell et al. showed that **nicotine lactate** gives **higher plasma nicotine concentration** (C<sub>max</sub>) than the free base nicotine of the same concentration using the same device and puff profile conditions such as puff duration, puff interval, and number of puffs. These recent clinical studies provide strong evidence that **protonated nicotine is responsible for higher and faster nicotine absorption than free base nicotine**.

## Plasma Nicotine Concentration: Cigarette vs. Nicotine Replacement Therapy



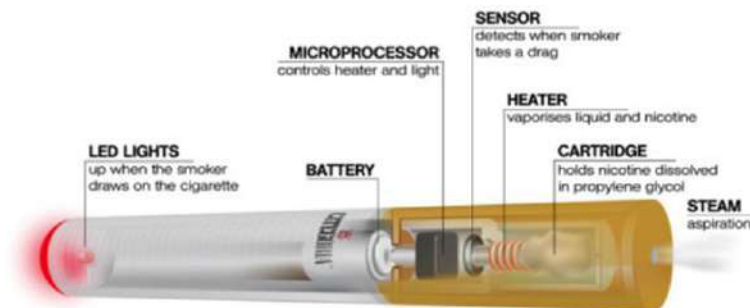
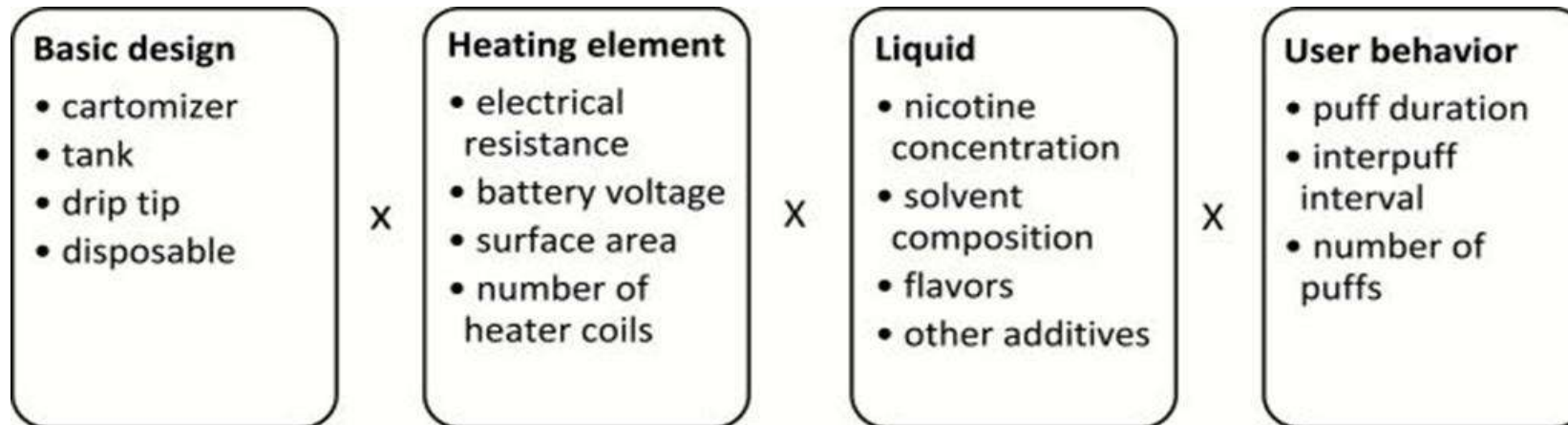
The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.  
National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health.  
Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.

# Plasma Nicotine After ENDS Use



# Nicotine Delivery in ENDS

The extent to which ENDS deliver nicotine depends upon a variety of device characteristics, heating elements, liquid constituents, and user behavior. Some emissions exceed those of conventional cigarettes

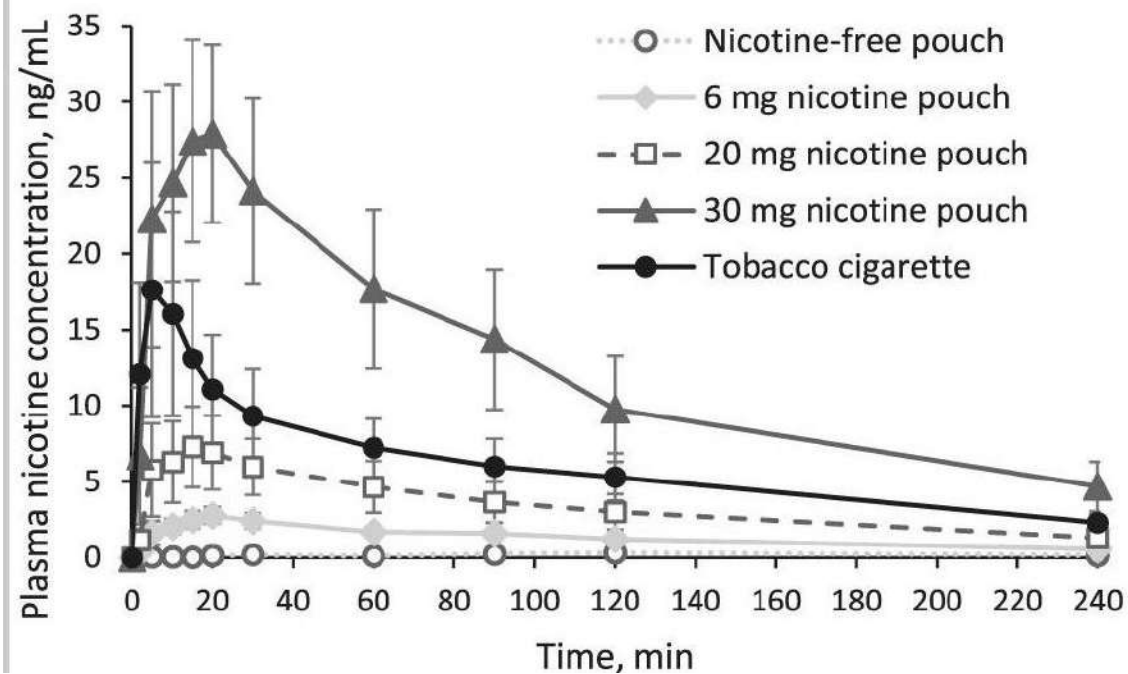


**Nicotine salts** allow the e-liquid mixture to be vaped at lower temperatures with higher concentrations of nicotine; can reach nicotine levels as high as 50mg

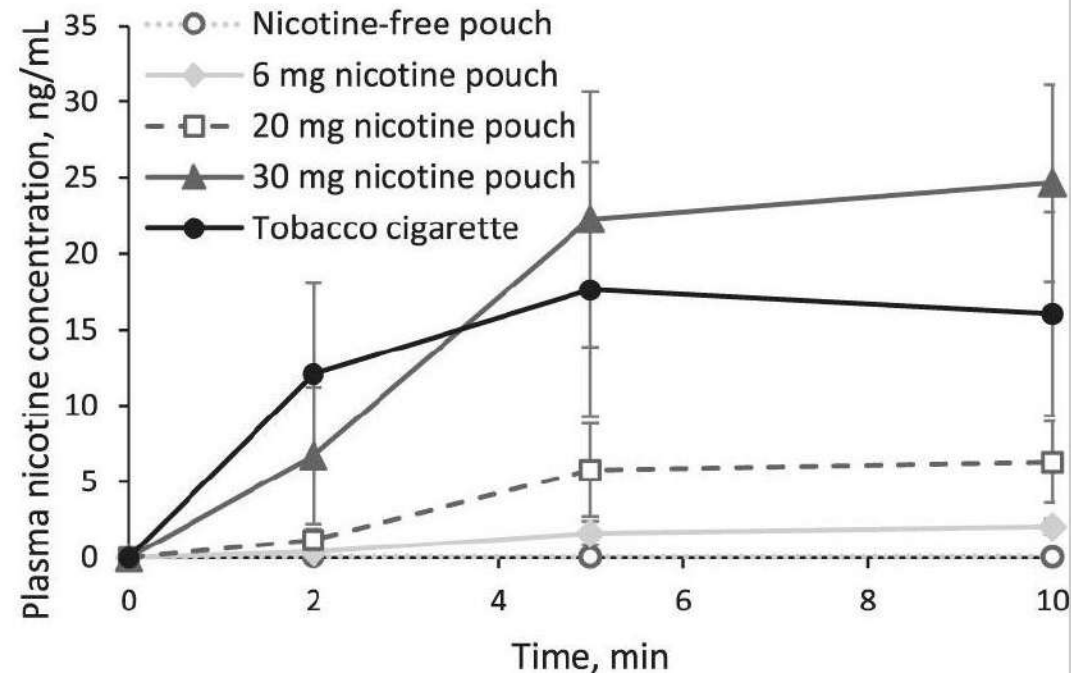


# Mean Plasma Concentrations (ng/mL) vs Time (min)

**A** Plasma nicotine curves



**B** Acute phase of nicotine delivery



# Legal Landscape of Synthetic Nicotine

- Laws that do not cover synthetic nicotine products
- Laws that clearly cover only certain synthetic nicotine products
- Laws that cover synthetic nicotine products more broadly
- Laws that are unclear regarding synthetic nicotine product coverage

# Findings

Our review covered tobacco control regulations pertaining to market entry requirements, sales restrictions, packaging and labeling requirements, and advertising regulations.

We excluded other kinds of tobacco-related laws, such as tax laws, smoke-free laws, and the regulation of flavours.

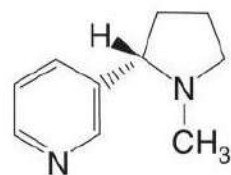
Category	Number of Jurisdictions
Laws That Do Not Cover SN Products	92
Laws that Clearly Cover Only Certain SN Products	52
Laws that Cover SN Products More Broadly	29
Laws for which coverage of SN Products was unclear	17
Laws that Were Unavailable	21
<b>Total in Sample</b>	<b>211</b>

# FCTC Definition of Tobacco Products

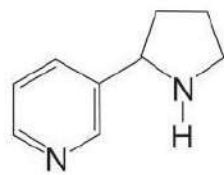
“Products entirely or partly made of the leaf tobacco as raw material which are manufactured to be used for smoking, sucking, chewing or snuffing”

- “Synthetic nicotine refers to nicotine that is chemically synthesized through laboratory processes rather than extracted from the tobacco plant. This definition includes all forms of nicotine, regardless of isomeric composition or production method, when synthesized artificially.”
- “For regulatory purposes, any product containing synthetic nicotine shall be classified and regulated as a tobacco product. This includes e-cigarettes, nicotine pouches, gums, lozenges, and any other nicotine delivery systems containing synthetic nicotine.”
- “Manufacturers must disclose detailed information on contents, toxicological data, and assessments of the product’s potential for addiction and abuse.”
- “Advertising, promotion, and sponsorship of synthetic nicotine products shall be restricted or prohibited. Misleading claims, including ‘tobacco-free,’ ‘safe,’ ‘non-tobacco nicotine,’ ‘non-addictive,’ or ‘cessation tool’ are prohibited unless substantiated by scientific evidence.”
- The **USFDA** definition: “Any product made or derived from tobacco or containing nicotine from any source that is intended for human consumption, including any component, part, or accessory of a tobacco product”.

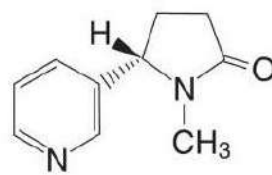
# Structures of Tobacco Alkaloids



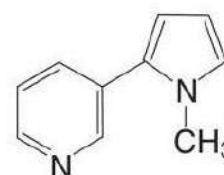
(S)-Nicotine



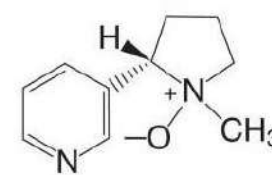
Nomicotine



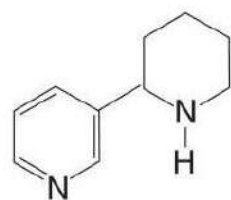
(S)-Cotinine



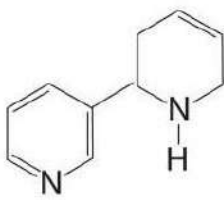
$\beta$ -Nicotyrine



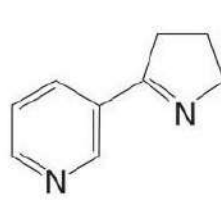
(S)-Nicotine-N'-Oxide



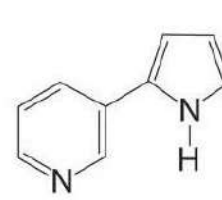
Anabasine



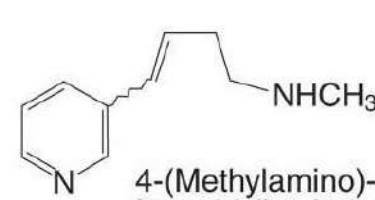
Anatabine



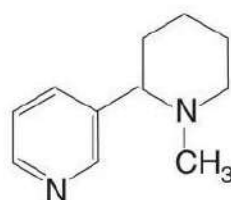
Myosmine



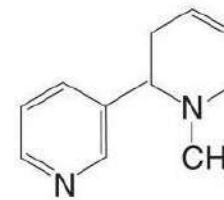
$\beta$ -Nomicotyrine



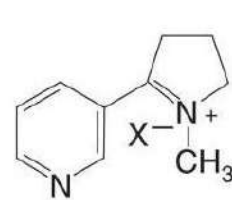
4-(Methylamino)-1-(3-pyridyl)-1-butene  
(Metanicotine)  
cis or trans



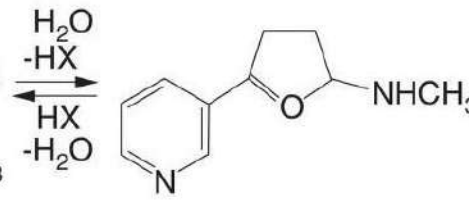
N'-Methylanabasine



N'-Methylanatabine



N'-Methylmyosmine



4-(Methylamino)-1-(3-pyridyl)-1-butanone  
(Pseudooxynicotine)



2,3'-Bipyridyl

# Nicotine Analogues

- Anabasine
- Nornicotine
- Anatabine
- Cotinine
- Myosmine



From the makers of Charlie's Chalk  
Dust & PACHAMAMA comes

# SPREE BAR

**DISPOSABLE**

6000 flavor-packed puffs,  
**Zero nicotine!**

# Policy Recommendations

1. Countries in which there is a **regulatory gap** for synthetic nicotine products (as compared to products containing nicotine derived from tobacco) should consider **amending** their tobacco control laws to ensure that they include synthetic nicotine products.
2. Countries that **choose to amend** their tobacco control laws to cover synthetic nicotine products should consider legal adjustments that **extend the coverage of the laws to the full range of synthetic nicotine products** that are currently marketed **as well as products that may emerge**. These may include products that contain synthetic **nicotine analogues**, other chemicals with similar properties or chemical systems that generate nicotine or analogues in situ.



# Policy Recommendations

3. Countries are advised to enforce standards for the purity of synthetic nicotine in products, preferably those of the European and US pharmacopoeias. Regulators should consider implementation of product standards to ban the mixing of tobacco-derived nicotine with synthetic nicotine in marketed products.
4. Policy-makers are advised to enforce uniform labelling rules for products containing nicotine, either natural or synthetic, and to declare the content of S-nicotine and, separately, the content of R-nicotine and any other nicotine analogue or any other chemical with similar properties.

# Policy Recommendations

5. Countries should consider **banning** synthetic nicotine products that contain **R-nicotine, or any nicotine analogue apart from S-nicotine, at levels that exceed those in tobacco-based products**, until the safety of consumption of these chemicals in such products is established.
6. Regulators should consider **restricting marketing practices** for promotion of synthetic nicotine as generally “tasteless and odourless”, “purer” or “healthier” than purified tobacco-derived nicotine, unless scientific evidence to support such claims is provided.

# Conclusions

- Companies are marketing an increasingly wide range of synthetic nicotine products, which, if not regulated, may undermine work to reduce use of tobacco and nicotine addiction and the work of WHO Member States to regulate tobacco and nicotine products comprehensively.
- Knowledge about the effects on human health of synthetically derived nicotine in different types of consumer products is still incomplete.

# WHO study group on tobacco product regulation

Report on the scientific basis of tobacco product regulation:  
ninth report of a WHO study group

