



August 31, 2021



# The Synthetic Nicotine Loophole:

## Regulatory Issues and Technical Challenges

Panelists:

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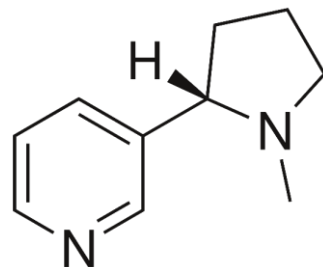
# Overview of Topics

- What is synthetic nicotine?
- What is known about the pharmacology/toxicology of synthetic nicotine?
- How is nicotine synthesized?
- Who regulates synthetic nicotine?
- How has the tobacco industry been affected by synthetic nicotine?
- What are the potential regulatory paths and product standards?
  - CTP v CDER
- Can we distinguish synthetic nicotine from tobacco derived nicotine?

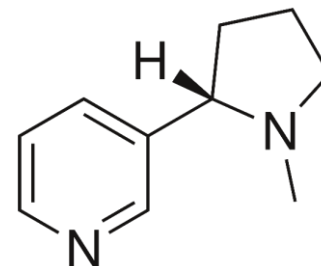
# Synthetic Nicotine Confusion

- TDN (tobacco derived nicotine)
- Synthetic nicotine
- TFN (tobacco-free nicotine)
- Terminology is nonstandard and confusing
- Some companies are extracting nicotine from tobacco
- Some companies are synthesizing nicotine

# What is the difference between nicotine from different sources?



Can you spot the difference?



- Tobacco Derived Nicotine (TDN)

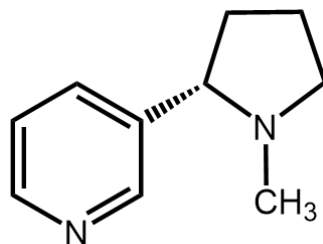
- Nicotine is extracted from tobacco leaf
- Chemical purification to get >99% nicotine is often required

- Synthetic Nicotine

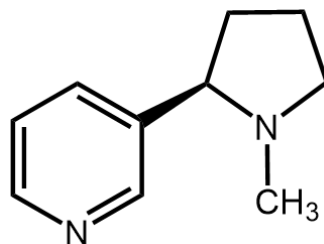
- Chemical or enzymatic processes to 'build' the nicotine molecule
- Chemical **AND** Enantiomeric purification is often required

# Synthetic Nicotine

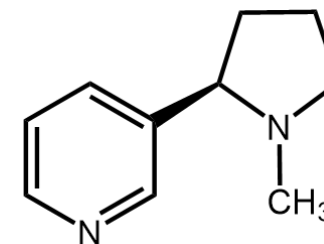
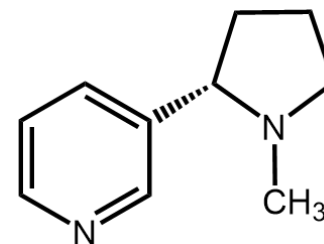
- Nicotine from tobacco is predominantly (S)-nicotine (99.3%)



(S)-Nicotine  
CAS #: 54-11-5



(R)-Nicotine  
CAS #: 25162-00-9



(S)-Nicotine + (R)-Nicotine  
Racemate CAS #: 22083-74-5

- Synthetic Nicotine can be a racemic mix (50/50) of (S)- and (R)-nicotine or >99% (S)-nicotine (identical to tobacco derived)

# Cost Vs Quality

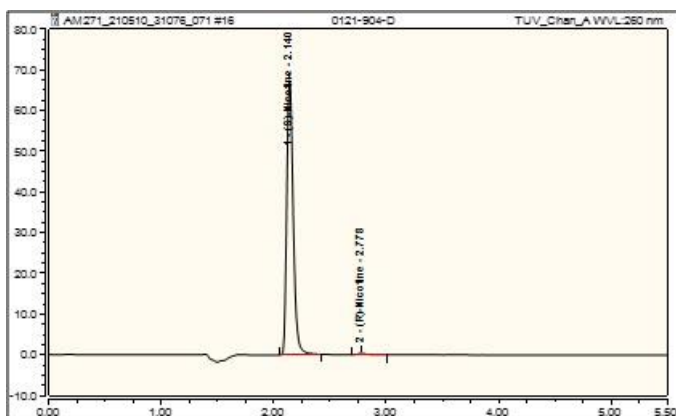
## *Meeting the Pharmaceutical (USP) Standard?*

- Cost was originally 65-200x of TDN
  - Increase in demand has brought cost to 3x-20x of TDN
  - Quality varies greatly
- USP Requirements:
    - Description of color
    - IR-Spectrum
    - Clarity/color of solution
    - Specific rotation
    - Water- NMT 0.5%
    - Related substances (nicotine degradants)- NMT 0.8% sum of impurities
    - NLT 99% S-Nicotine
    - CAS# 54-11-5
  - Only CAS 54-11-5 from either tobacco derived or synthetic nicotine can meet the USP criteria

# Quantitation of Nicotine Enantiomers by Chiral Chromatography

## Tobacco Derived Nicotine

99% S-Nicotine

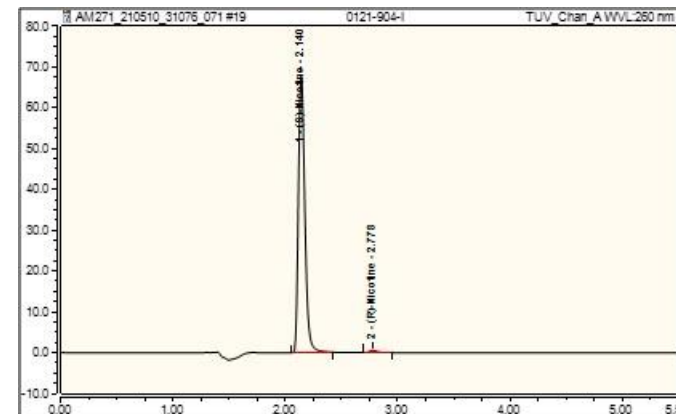


Can you spot  
the difference?

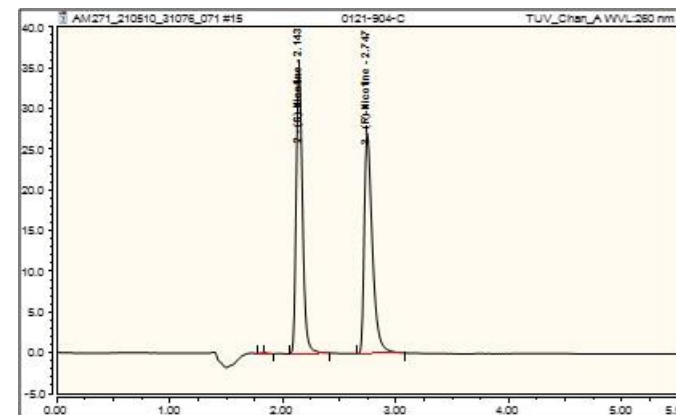
- If the chiral chromatogram is <99% (S)-nicotine then it is possibly a synthetic nicotine sample

## Synthetic Nicotine

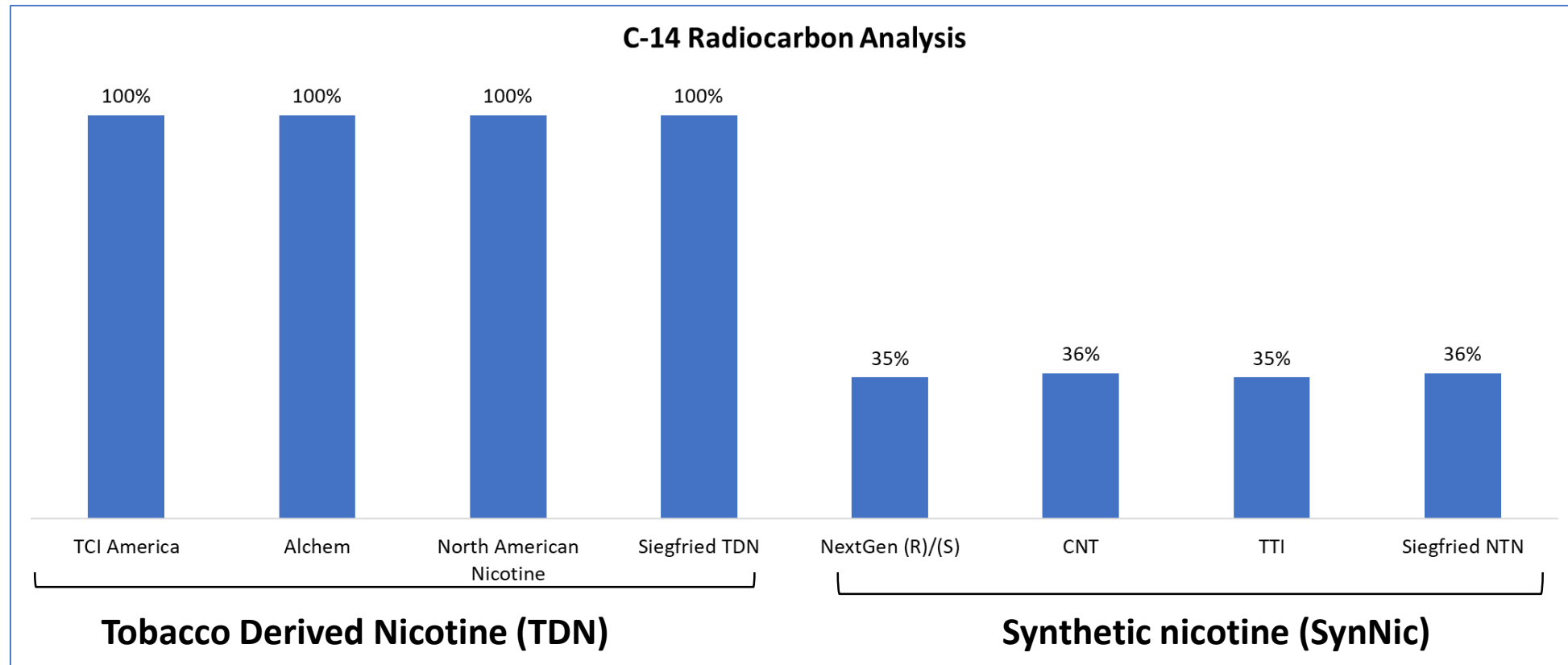
99% S-Nicotine



Racemic (50:50)

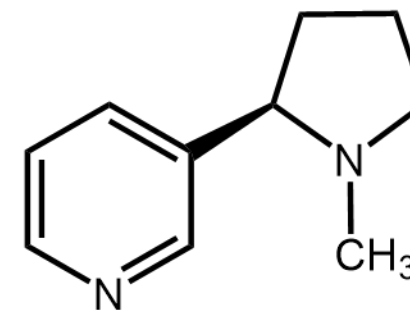
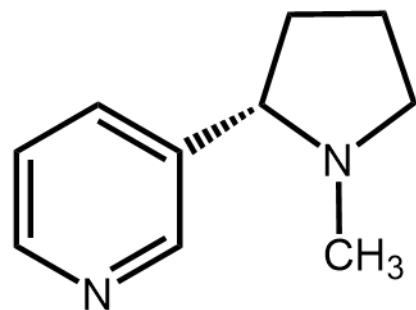


# Radiocarbon Analysis May Distinguish TDN vs. Synthetic Nicotine in Pure Form



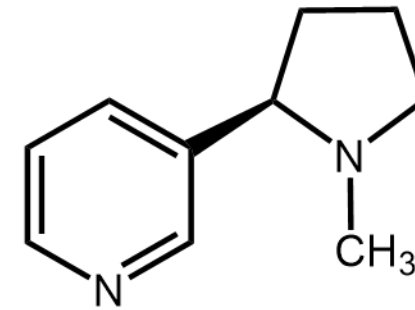
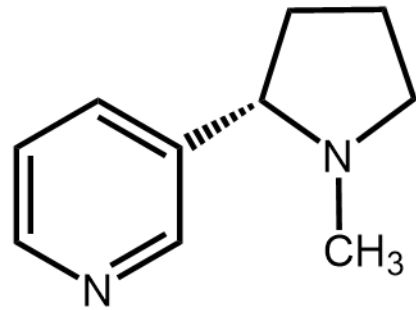


# Pharmacology of (S) and (R) nicotine is very different



(S)-Nicotine	(R)-Nicotine
•Classical nicotine pharmacology (millions of person-years worth of data)	•Pharmacology not well characterized in humans
•Strong Agonist at Nicotinic Acetylcholine Receptors (nAChRs)	•7-20x less potent than (S) at nAChRs
•No direct action on acetylcholinesterase (AChE)	•Binds and inhibits acetylcholinesterase (AChE)
•99% of TDN is S enantiomer	•50:50 of R:S enantiomers in racemic nicotine
•CAS 54-11-5	• CAS 25162-00-9

# Toxicology of (S) and (R) nicotine is very different



- Little to no toxicity data in humans for (R)-nicotine and its metabolites
  - (R) nicotine produces many metabolites that (S) does not (e.g. the carcinogen N-methylcotininium)<sup>1</sup>
  - (S) and (R) forms of the major metabolites (e.g. nor nicotine, cotinine) also have different activity and toxicity
- Sensory/Olfactory contribution of nicotine is not well understood
- Consumer Perception (misperceptions that synthetic nicotine is “safer”)



1. Gorrod 1989

# The Synthetic Loophole: Impacts on the Tobacco Industry

## Question from 2021 SRNT to Mitch Zeller

- **Q.** Does CTP regulate synthetic nicotine? If not, who does? How do you handle companies that claim the use of synthetic nicotine?
- **A.** It comes down to our assessment on a case-by-case basis on how to apply the statutory definition of a tobacco product.
- Currently there is regulatory ambiguity regarding synthetic
  - Federal laws do not prohibit SynNic while state laws may (e.g. AL HB273) .

# Closing the Loophole: Potential Regulatory Paths and Product Standards

- Place TDN and synthetic nicotine on a level playing field
- CTP the logical regulatory body
- Set a nicotine standard for both TDN and synthetic nicotine
- Change the statutory definition of nicotine
- Implementation of regulation

# Panel Q&A Session

*Email your questions*



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