**Report: Carbon and Water Footprints of Tobacco-Based vs. Synthetic Nicotine**

# EXECUTIVE SUMMARY


What is the carbon footprint of nicotine? It depends on the source, and the difference is large.

An independent study finds that **nicotine derived from tobacco plants emits up to 12 times the amount of greenhouse gases, and uses vastly more water, compared to synthetic nicotine**.


How does method of nicotine production affect climate change (greenhouse gases) and water security? Commissioned by Zanoprima, the attached independent study compares the environmental impact of producing S-nicotine from tobacco and from chemical synthesis. Eric Johnson, Managing Director of Atlantic Consulting of Zurich, authored the report. Johnson is a sustainability expert with decades of experience and extensive peer-reviewed publications.

The study measures carbon intensity and water intensity: the amount of greenhouse-gases emitted and water consumed per unit of S-nicotine produced. The scope of the analysis is “cradle-to-gate”: from raw materials, to the gate of the plant supplying pharma-grade nicotine.

## NICOTINE’S CARBON AND WATER FOOTPRINTS: KEY FINDINGS[1]

***Carbon footprint.*** Fuel-curing and cultivation account for nearly all of plant-derived nicotine’s carbon footprint (carbon intensity). Compared to synthetic nicotine, for each unit of nicotine produced…

- The carbon intensity of nicotine from fuel-cured tobacco is 12 times higher.
- The carbon intensity of nicotine derived from air-cured tobacco is 2 - 4 times higher.

***Water footprint.*** Due to irrigation, the water intensity of plant-derived nicotine is enormously larger compared to synthetic nicotine.

- At a 1.1% nicotine concentration in tobacco, it takes nearly 440 thousand kilograms of water to produce 1 kilogram of tobacco based nicotine. That’s roughly equal to 3,900 bathtubs full of water (typical U.S. size), said Johnson.
- Synthetic nicotine production has a *negative* water intensity. Some of the chemical processes in its production chain generate water.

***Significance of findings.*** The difference between two products’ carbon or water footprints should be at least 15%. “Less than that can be random error,” Johnson said. “Twelve times higher is a long chalk from fifteen percent.”

An example illustrates the environmental benefit of a switch from fuel-cured tobacco-based nicotine to synthetic nicotine. “The carbon savings – per kilogram of nicotine – would be roughly equal to driving a typical European car for 10,000 kilometers,” said Johnson. “That’s about the average per-year per-person travel by car in Europe.”

We often assume “natural” sources are better. When it comes to protecting the environment, this study finds high-quality synthetic nicotine to be significantly superior to tobacco-based nicotine.

[1] *Comparing synthetic nicotine (from Zanoprima’s ZSN process) to tobacco based nicotine.*


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## Synthetic nicotine: New frontier for sustainability

Until recently, assessment of the environmental impact of tobacco products focused on cigarette butts and packaging waste[4]. Advances in nicotine synthesis open a new ESG frontier. We can now compare the environmental footprints of tobacco-based and synthetic nicotine.

Synthetic nicotine is not a regulatory workaround or gimmick. It's used today in both medicinal and recreational products. Historically, many pharmaceutical ingredients began as plant medicines; think dried willow bark and aspirin. As technology advances and costs come down, synthetic alternatives can provide consistent purity and traceability, and save trees.

New reduced-risk tobacco products, such as e-cigarettes and tobacco-free pouches, are agnostic regarding nicotine source. Reduced harm to health and to the environment can go hand in hand.

With synthetic nicotine now a feasible option, and more life-cycle data available on nicotine production, it makes sense to assess the environmental footprint of synthetic nicotine vs. tobacco-derived nicotine.

## Studying nicotine's carbon and water footprints

To this end, Zanoprima Lifesciences commissioned an independent study of how nicotine production affects climate change (greenhouse gases) and water security. The attached independent report gives the results of that study, comparing the environmental impact of producing S-nicotine from tobacco and from chemical synthesis.

The report was authored by Eric Johnson, Managing Director of Atlantic Consulting of Zurich. Johnson is an independent expert with decades of experience and extensive peer-reviewed publications. Using life-cycle assessment, Johnson routinely measures the environmental impact of products and services.

The study measures two well-known environmental impacts: carbon intensity and water intensity. Put another way, it's the amount of greenhouse-gases emitted and water consumed per unit of S-nicotine produced. The scope of the analysis is "cradle-to-gate": from raw materials, to the gate of the plant supplying pharma-grade nicotine.

## Key study findings

*Comparing synthetic nicotine (from Zanoprima's ZSN process) to tobacco based nicotine.*

**Difference in carbon footprint.** Fuel-curing and cultivation account for nearly all of plant-derived nicotine's **carbon footprint** (a.k.a. carbon intensity).

**Compared to synthetic nicotine**, for each unit of nicotine produced…

[4] https://doi.org/10.1111/add.16046

- The **carbon intensity** of nicotine from **fuel-cured tobacco** is **12 times higher**
- The **carbon intensity** of **nicotine derived from air-cured tobacco** is **two to four times higher.**

**DIFFERENCE IN WATER FOOTPRINT.** Tobacco plants are thirsty. Due to irrigation, the water intensity **of plant-derived nicotine is enormously larger** compared to synthetic nicotine.

- At a 1.1% nicotine concentration in tobacco, it takes nearly **440 thousand kilograms of water** to produce **1 kilogram of tobacco based nicotine**. That's roughly equal to 3,900 bathtubs full of water (typical U.S. size), said Johnson.
- **Synthetic nicotine production** actually has a ***negative*** **water intensity**. Some of the chemical processes in its production chain generate water, ending with a net water gain.

**Is this a meaningful difference?** Johnson says yes. To be significant, the difference between two products' carbon or water footprints should be at least 15%. "Less than that can be random error," he said. "Twelve times higher is a long chalk from fifteen percent."

Here's another way to visualize the environmental benefit of a switch from fuel-cured tobacco-based nicotine to synthetic nicotine. "The carbon savings – per kilogram of nicotine – would be roughly equal to driving a typical European car for 10,000 kilometers," said Johnson. "That's about the average per-year per-person travel by car in Europe."

**What difference could it make** if all nicotine used were switched to synthetic? Here's one example, employing that car analogy.

Researchers estimated[5] that in 2020, 68 million people worldwide were using e-cigarettes. Based on median amounts of nicotine concentrated in vapes, and used per person, Johnson calculated that vapers consumed about 2.5 million kilograms of nicotine that year. Suppose that in 2020 the entire vaping world had used tobacco-based nicotine. "If they'd all switched to synthetic," said Johnson, "it would be like eliminating the annual emissions of 2.5 million average European cars."

The shift from smoking to reduced-risk products is accelerating[6]. In 2021, an estimated 82 million people were vaping globally[7]. Other reduced-harm nicotine alternatives attract millions more (from pouches to NRTs to shisha).

Over a billion humans still obtain nicotine from deadly combustible tobacco. Synthetic nicotine shows huge potential to bring about positive change—benefiting forests, farms, and lungs.

[5] Data for estimates from https://doi.org/10.1186/s12954-021-00556-7 and https://doi.org/10.18332/tid/128319
[6] https://doi.org/10.1186/s12954-022-00722-5
[7] https://doi.org/10.1108/DHS-07-2022-0028

# Benefits of SyNic: ultra-pure synthetic nicotine made using Zanoprima Lifesciences' patent-protected process

1. **Trackable and traceable**. All chemicals used in the SyNic process —in each production batch, in each part of the process — are accompanied by a certificate of analysis, in the same way that pharmaceutical products are produced. Each batch is made in an FDA/EMA/MHRA approved facility under GMP conditions. In the case of natural nicotine, track and trace requires tracking the ingredients all the way back to the farm.

2. **Environmentally responsible**. SyNic production creates a lower carbon footprint than tobacco-derived nicotine or synthetic nicotine produced using a racemic process, and uses significantly less water. In fact, the SyNic process produces a water surplus.

3. **A more efficient process**. The SyNic process produces almost 100% S-isomer: the naturally occurring nicotine isomer found in tobacco and other nicotine-producing plants. By contrast, racemic processes used to produce synthetic nicotine give a mixture of S-isomers and R-isomers, at a ratio of 50:50. To produce a high purity saleable nicotine product, the racemic process requires extra steps: remove the R-isomer, release the S-isomer from the salt, and then distil the resulting liquid to obtain the S-isomer. These extra steps make the racemic process both expensive and low yielding. The racemic process typically obtains a 25% yield from its final step; the SyNic process produces a 90% yield from its entire process. Thus, the racemic process also produces significantly more $CO_2$.

4. **Unmatched purity**. SyNic is typically 99.9% pure nicotine. It is devoid of heavy metals and nitrosamines, which do not exist in the chemicals used in the SyNic process. To achieve a similar level of purity from tobacco-derived nicotine, these closely-related materials must be removed from the nicotine mix, sometimes by distilling twice—adding to cost.

5. **Consistent (no) taste and odour**. SyNic has no taste or odour. This also means it has consistency of taste and odour in every batch produced.

6. **No colour**. SyNic is colourless when distilled and stored appropriately.

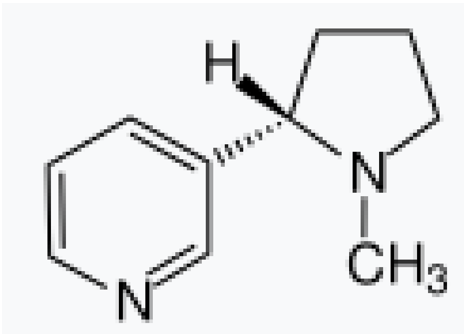
7. **Greater stability**. Because of the high purity of SyNic, it has greater stability than lower-purity nicotine products.

8. **Verified supply chain**. Zanoprima can verify all the sources of the components in the supply chain to assure continuity of production.

9. **Valid and enforceable patents**. The SyNic process is patented in over 35 territories across the globe. On 28 July 2023, the Patent Trial and Appeal Board of the US Patent and Trademark Office denied a petition to invalidate Zanoprima's US SyNic patent. On 22 September 2023, a final judgment was issued by the US District Court for the Western District of Texas, Waco Division, ordering, adjudging, and decreeing, amongst other things, that the SyNic US patent is valid and enforceable in all respects.

10. **Competitive cost**. Zanoprima's SyNic is price competitive with pharmaceutical grade tobacco-derived nicotine, and is cheaper than comparative forms of synthetic nicotine.

# Nicotine
# Carbon Intensity and Water Intensity Comparison




*Atlantic Consulting*

February 2024

# Nicotine CI & WI comparison



**FIGURES**

## 1 Introduction

Smoking of tobacco – a practice dating back centuries – has been recognised as a risk to human health since the 1960s. Anti-smoking campaigns since then have encouraged many to quit or not to start. The fraction of the population that smokes has declined from around one-half in the late 1950s to under one-fifth today (roughly one billion people)[1]. Tobacco companies have also attempted – by introducing filters and low-tar cigarettes – to lower the health risk.

As a recent review in the journal *Nature* states, "Nicotine is the addictive compound in tobacco and is responsible for continued use of tobacco despite harms and a desire to quit– but nicotine is not directly responsible for the harmful effects of using tobacco products." (Le Foll, 2022).

Nicotine is increasingly being viewed separately from tobacco. Nicotine is also used in reduced-harm consumer products, in nicotine replacement therapies, and in pharmaceuticals being studied to treat conditions such as Parkinson's disease and Alzheimer's disease (Alhowail, 2021).

Tobacco companies are expanding their offerings of 'smoke-free' nicotine. While volume sales of cigarettes are steadily declining, smoke-free volumes are growing at double- and even triple-digit percentages (Foundation for a Smoke-Free World, 2021). Smoke-free nicotine comes in two main types: in tobacco, or tobacco-free. The former comprises heated-tobacco (not burned) and chewing tobacco; the latter comprises vapes, oral nicotine and smoking cessation aids.

***Creation of synthetic nicotine***

Nicotine for tobacco-free, smoke-free products traditionally comes from natural nicotine that is extracted from tobacco. Chemical synthesis of nicotine was first reported in 1904[2]. In the 1960s-70s, the cigarette industry examined the feasibility of introducing it at commercial scale. Development was abandoned, because at the time synthetic nicotine was 1) too costly to be economic and 2) was an stereo-isomeric mix of S-nicotine and R-nicotine, whereas natural nicotine is 99+% S-nicotine (Jordt, 2021) (Berman et al., 2023).

Progress in chemistry has since reduced the cost of making synthetic nicotine. Introduced in the USA in 2015, it has since been marketed by numerous companies in Canada and South Korea as well. The initial products were isomeric mixtures of S- and R-nicotine. Including the R- isomer in nicotine raises "concerns about inaccurate labelling and the poorly understood health effects of R-nicotine" (Jordt, 2021, p. e113), and thus has been challenged by regulators such as the US Food and Drug Administration. Three companies – Alchem, Contraf-Nicotex-Tobacco (CNT) and Zanoprima Life Sciences – have developed and operate processes to make synthetic nicotine of 99+% S- isomer, the same as nicotine from tobacco.

[1] https://www.who.int/publications/i/item/9789240039322
[2] https://www.britannica.com/science/nicotine

CNT and Alchem use a resolution method; Zanoprima uses an enzymatic process (Jordt, 2023) (Berman et al., 2023)[3] (Perfetti et al., 2023).

***Goals of this report***

The study presented in this report is a comparison of the environmental impact of producing S-nicotine from tobacco and from chemical synthesis. Two well-known environmental impacts are measured:

1) *carbon intensity* (commonly called carbon footprint): the amount of greenhouse-gases emitted per unit of S-nicotine produced, and

2) *water intensity*: the amount of water consumed per unit of S-nicotine produced.

This report presents the findings of the study, an appendix on Zanoprima's process for synthesising S-nicotine, references, and a note about the author.

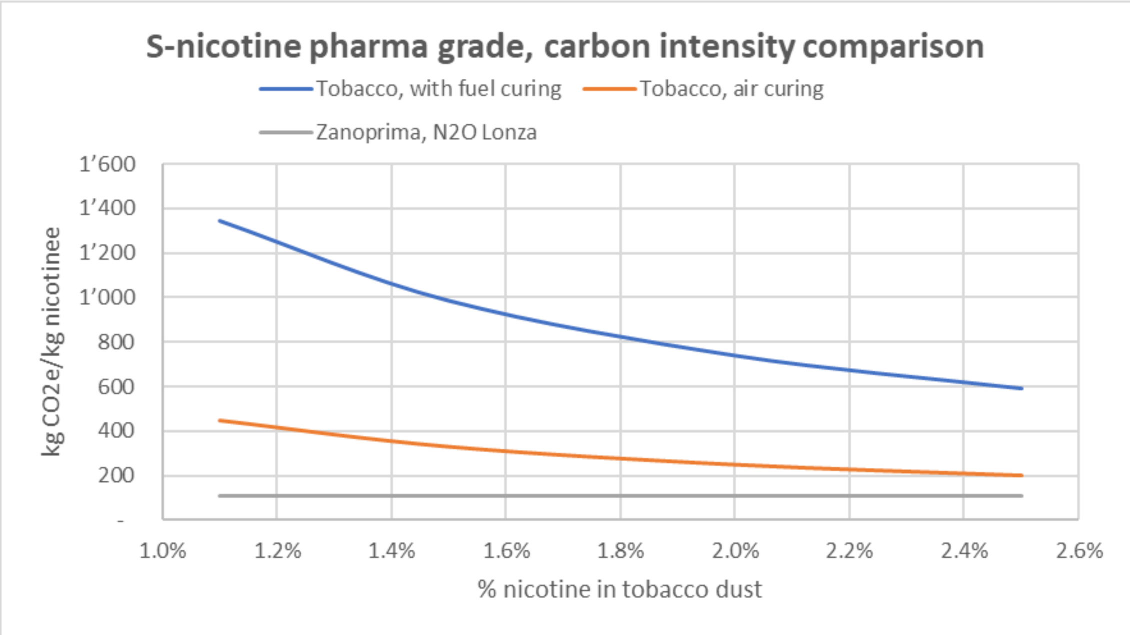
[3] Both of these references imply that a company called NJOY produces synthetic nicotine. NJOY has a patent, but is not known to produce commercial product.

# 2 Study summary

Zanoprima makes synthetic nicotine (ZSN) that competes with tobacco-based nicotine (TBN). Atlantic Consulting, a specialist in life-cycle assessment and carbon footprinting, was engaged to estimate and compare the carbon intensities (CIs) and the water intensities (WIs) of the two.

The **first main finding** is that the carbon intensity of TBN is 2-12 times higher than that of ZSN (Figure 1). The base case is 12 times higher, that is when the TBN comes from cigarette tobacco, which is fuel-cured and has an average 1.1% nicotine concentration. However, this concentration can vary in commercial practice between 0.6-2.8%[4]. If the TBN comes from air-cured tobacco, its carbon intensity is 2-4 times higher, depending on the nicotine concentration (ranging between 1.1-2.5%).

**Figure 1: Carbon intensities of nicotine**




Two-thirds of TBN's CI – the base case is 1,344 kg $CO_2e$[5]/kg TBN – is created by **fuel-curing** of tobacco. **Cultivation** of tobacco accounts for almost all of the remaining one-third. Together with tobacco **processing**, these three steps account for 99+% of the TBN CI. Of ZSN's CI, 106 kg $CO_2e$/kg ZSN[6], 60% comes from nitrous oxide[7] emitted in the production of nitric acid and nicotinic acid, both precursors to the production of ZSN. Nitric acid and nicotinic acid each account for about 30% of the total. The remaining 40% of its CI is distributed across ZSN's chain of synthesis.

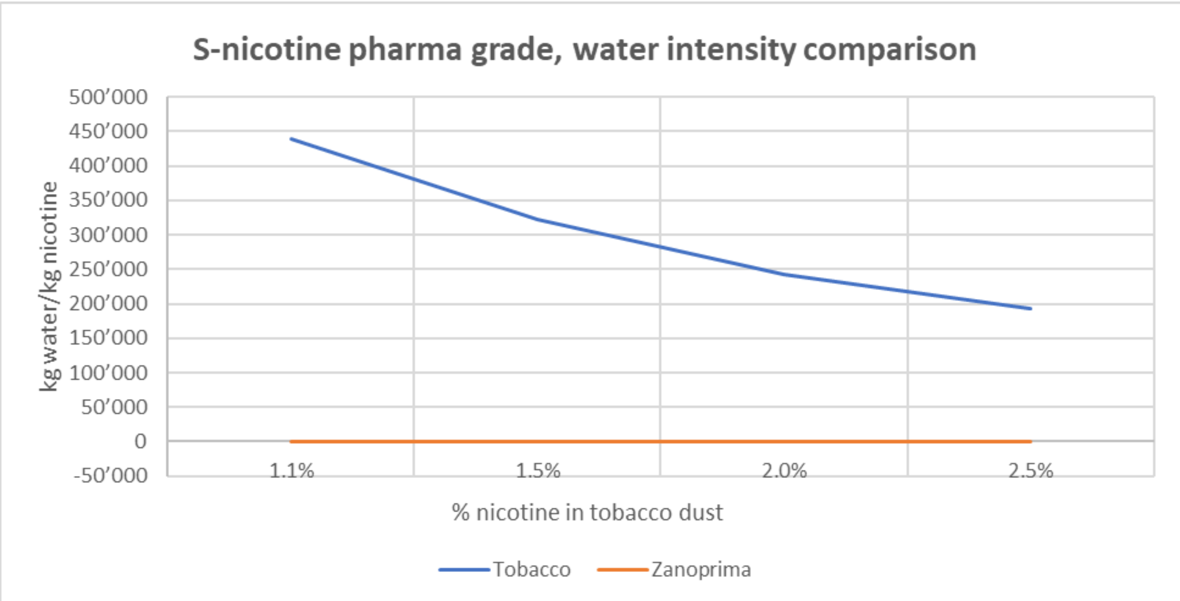
It is possible that the nitrous oxide portion of ZSN's footprint could be reduced, if nitrous-oxide-capture-and-destruction were introduced by manufacturers of nitric acid and nicotinic

[4] https://www.healthline.com/health/how-much-nicotine-is-in-a-cigarette#nicotine-in-cigarettes
[5] Carbon dioxide equivalent, the common unit of carbon intensity.
[6] Unlike TBN, ZSN has only one case, because there is no variation of concentration and there is no curing.
[7] According to the Intergovernmental Panel on Climate Change's most recent Assessment Report (AR6) of 2021, the global warming potential of nitrous oxide is 273 times that of carbon dioxide. I.e. one kg of $N_2O$ creates 273 times more 'radiative forcing' (heat) than a kg of $CO_2$.

acid. The technology is proven, albeit potentially costly. The major producer of nicotinic acid, Lonza, is reportedly considering installation of such equipment at its plant in Visp, Switzerland, but actual installation and operation could not be confirmed, so this report presumes that such emissions have not been abated.

The **second main finding** is that the water intensity of TBN is enormously larger than that of ZSN (Figure 2). TBN's WI ranges from 439,687 kg $H_2O$/kg TBN at a 1.1% nicotine concentration in tobacco to 193,462 kg $H_2O$/kg TBN at a 2.5% nicotine concentration. Over 99% of TBN's WI comes from the cultivation (**irrigation**) of tobacco. ZSN's WI is actually *negative* at -783 kg $H_2O$/kg ZSN. A negative WI might surprise some readers, but generation of water is common to many chemical processes (as oxygen reacts with hydrogen), and it is significant in the production-chain of both NVP[8] and methyl nicotinate, the main feedstocks for Zanoprima's ZSN process.

**Figure 2: Water intensities of nicotine**




The rest of this report presents a review of: the method of the CI and WI analyses; sources of data; description of the nicotine production chain, and a discussion of key sensitivities.

# 3 Method of the carbon intensity (CI) and water intensity (WI) analyses

**Life cycle assessment** (LCA) is an accounting method to measure environmental impact of products (and services). A 'full' LCA measures consumption of resources and emission of pollutants over a product's lifetime (life cycle) - from production of raw materials to disposal of the product. Most LCAs are 'partial', i.e., they measure not all resources and pollutants, and cover not cradle-to-grave but rather a subset thereof.

[8] n-vinyl pyrrolidone

This study is partial. First, it covers only the **resource of water** and only the pollutants comprising **greenhouse gases**. These measurements are known as water intensity (WI) and carbon intensity (CI), often called **water footprint** and **carbon footprint**. Second, coverage is of the product only from "**cradle-to-gate**," i.e., from raw materials to the gate of the plant supplying pharma-grade nicotine.

LCA was created in the 1970s; by the 1990s it began to see widespread use by regulators and policy-makers (Guinée et al., 2011). CIs rose to prominence from the 2000s, starting with assessment of renewable fuels. Today 'carbon labels' are common for fuels, transport, construction, food and other products. WIs are less prominent than CIs, yet clearly are of known interest to the public and to policy-makers. Plentiful guidance now exists for LCA and its subsets, from (ISO, 2006a) (ISO, 2006b) (BSI et al., 2011) and many others. The guidance is not uniform in its detail, but in broad terms there is general agreement on method.

Atlantic Consulting has conducted approximately 50-60 LCAs/CIs. About 20-25 of these have been published in the peer-reviewed literature, such as a recent study of the carbon footprints of grills by type and fuel (e.g., gas, wood-pellet, charcoal, electricity) (Johnson, 2022).

The author of this study, Eric Johnson, is the Editor for Oil & Gas, Chemicals and Plastics for the world's largest LCA database, ecoinvent. Recently he was ranked by Stanford University as one of the top 2% most-cited authors in the field of energy[9]. He has published extensively in respected journals such as *Environmental Impact Assessment Review* and *Chemistry & Industry*[10].

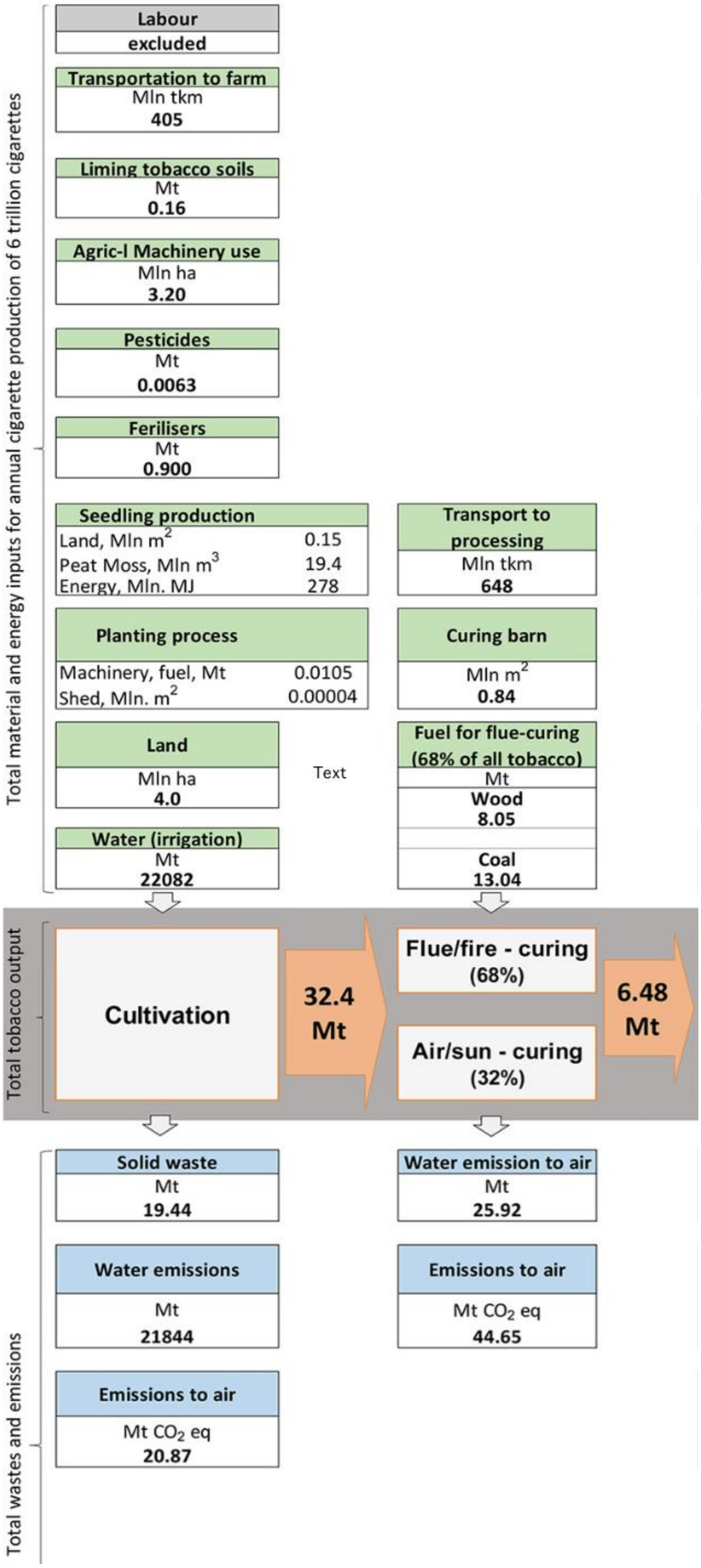
## 4 Sources of data

The bulk of 'life cycle data' are of energy/material-inputs/outputs to a process. For instance, the process of tobacco cultivation has **energy inputs** of fuel and electricity plus **material inputs** of seeds, fertiliser, water, and such. Its **outputs** include various pollutants and a 'reference product' of harvested tobacco. Next there is the process of tobacco curing, which has an input of harvested tobacco and an output of dry tobacco – and so on.

This study drew on multiple sources of life cycle data. For tobacco production, the primary source of data was the supplementary material in (Zafeiridou et al., 2018b), authored by a research team at Imperial College London. This research, clearly the most detailed, authoritative study in the field (
Figure **3: Analysis of global cultivation and curing of tobacco (Zafeiridou et al., 2018b)**
was adopted and published by the World Health Organisation as part of its *Framework Convention on Tobacco Control* 'Global Study Series' (Zafeiridou et al., 2018a). Additional data for tobacco processing were found in (Vetrivel, 2021), (Kheawfu et al., 2021), (Barbooti et al., 2002) and at Healthline[11].

[9] https://elsevier.digitalcommonsdata.com/datasets/btchxktzyw/6
[10] See https://scholar.google.com/citations?user=J4rsUqMAAAAJ&hl=en
[11] https://www.healthline.com/health/how-much-nicotine-is-in-a-cigarette#nicotine-in-cigarettes

**Figure 3: Analysis of global cultivation and curing of tobacco (Zafeiridou et al., 2018b)**



Data on production of ZSN were supplied by Zanoprima from its own operating records. Zanoprima also supplied data on conversion of nicotine to nicotinic sulphate and back to nicotine, which are applicable to the final steps of producing TBN. For the precursors to Zanoprima's process, the main source of data was ecoinvent[12]. Some of the precursors were already available in ecoinvent's published database; seven precursors were modelled – using ecoinvent's proprietary chemical model – explicitly for this project[13]. Data for some of the precursors were also found in a database published by Carbon Minds[14]. In addition, three sources – (Blum, 2015), (Lisicki et al., 2022) and (SRI Consulting, 2009) – were useful in establishing and defining ZSN's production chain as well as some of its inputs/outputs.

## 5 The nicotine production chain

From the data described above, both the TBN and ZSN production chains were modelled.

The **TBN production chain** is first that of cigarette production: tobacco is cultivated, cured and processed into flakes/dust. In manufacturing of cigarettes, some of this flake/dust misses its cigarette target. This is collected, and in some cases it is recycled back into cigarettes. In other cases, it is used as a feedstock for extraction of TBN – which, of course, is the case modelled in this study. Nicotine is extracted from the collected flake/dust and stems as a sulphate, which is re-basified and distilled to pharma-grade nicotine.

**ZSN production** can be described as three production chains. The final part of the chain is the Zanoprima process (Figure 4), which reacts NVP with methyl nicotinate to yield myosmine, which is reduced to nor-nicotine that is methylated to nicotine.

**Figure 4: Zanoprima process**

NVP + Methyl nicotinate
=
Myosmine
*reduced with imine reductase*
Nat gas
Methanol
Nor-Nicotine + Formaldehyde
=
Nicotine

This is preceded by the NVP chain (Figure 5) and the methyl nicotinate chain (Figure 6). Both of these chains are well-known within the chemical industry. NVP is mainly used in making high-performance plastics and coatings. Nicotinic acid – commonly known as niacin – is widely used as a pharmaceutical and as a dietary supplement for humans and farm animals.

[12] https://ecoinvent.org
[13] Our thanks to the colleagues at ecoinvent!
[14] https://www.carbon-minds.com/

**Figure 5: NVP chain**

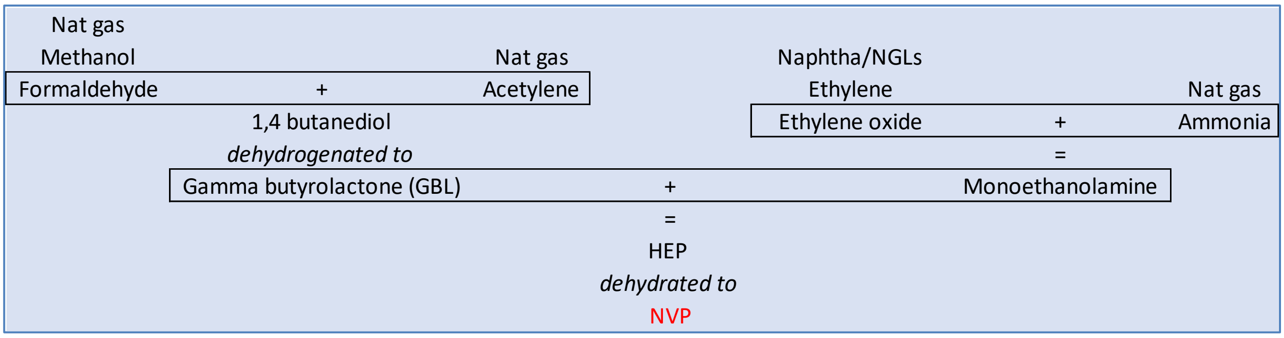
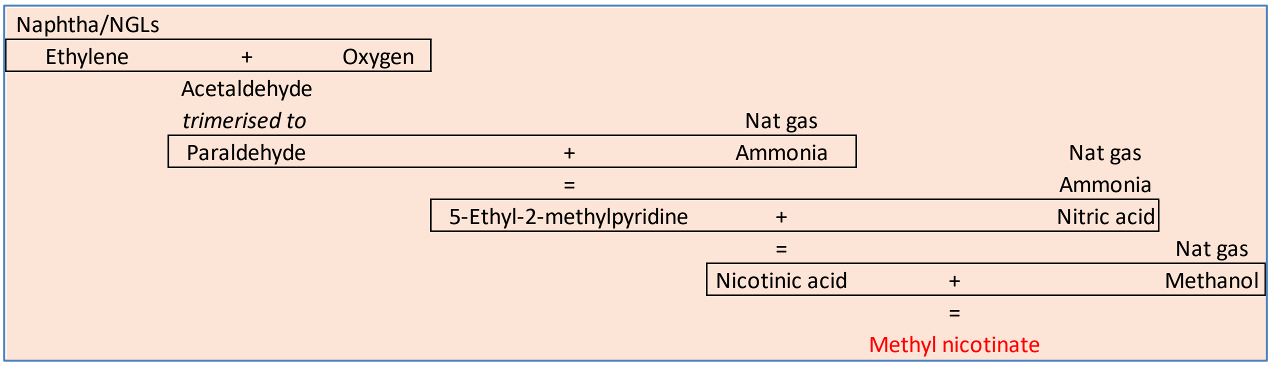



**Figure 6: Methyl nicotinate chain**




# 6 Key sensitivities

Based on general experience and this specific analysis, three potential sensitivities (i.e., issues which could cause variability in results) have been identified.

## *6.1 Is tobacco dust a waste?*

No. It is a product of value that is sold for a positive price. Wastes are materials that are disposed of at a cost (negative price). If tobacco dust were a waste, then according to LCA accounting conventions, nearly all of its footprint would be assigned to the main product, cigarettes.

## *6.2 What about the use phase?*

Nicotine's use – e.g., vaping – is not covered in this analysis. In vaping, presumably the nicotine is metabolised by its consumer to carbon dioxide and nitrogenous compounds. Some might argue that $CO_2$ from metabolised TBN– a 'bio' product – is carbon neutral, whilst $CO_2$ from metabolised ZSN is not. Whether or not this is true, it is insignificant. A combusted kg of nicotine emits 2.7 kg of carbon dioxide. This is immaterial with respect to the cradle-to-gate CIs reported above.

## *6.3 Accuracy of data*

For TBN, the data used are global averages from (Zafeiridou et al., 2018b). The possible variation of nicotine concentration in tobacco is reflected in this study's results. Although surely there is some variation in tobacco footprints by region caused by varying approaches to cultivation, it is hard to imagine that such variation is enough to nullify the general results.

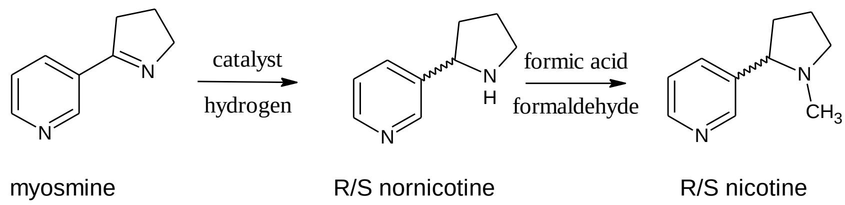
For ZSN, the data from Zanoprima are actual figures from production. The data for its precursors are from the best sources available for well-known production chains. Generally such data are considered to be within 10-15% of the 'true' figures – which, of course, are subject to natural variation.

# 7 Appendix: Synthesising S-nicotine

Nicotine, long available from tobacco, was first synthesised in a laboratory at the turn of the last century. The problem with this synthetic nicotine was that unlike natural nicotine, which is 99+% of its S-isomer, it was a 50:50 mix of S-stereoisomers and R-stereoisomers. Health impacts of R-nicotine are poorly understood, so its use is discouraged by drug regulators, at least until better data are available.

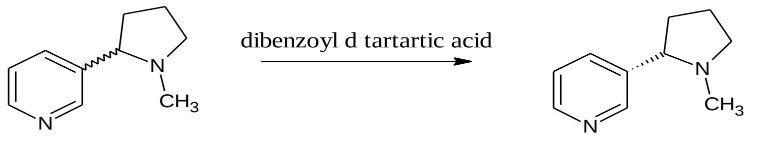
Starting in 2015-16, this synthetic R/S mixture (called TFN, for 'tobacco free nicotine' – the term is now used generically) was marketed in the US by several companies. In 2020, the US Food and Drug Administration (FDA) ordered companies selling certain youth-oriented flavoured vaping products to take them off the market[15]. The companies reformulated their products using synthetic nicotine to evade regulation. In 2022, the FDA gained specific authority to regulate tobacco products containing nicotine from any source, including synthetic nicotine[16]. Discussions between manufacturers and regulators on this issue continue.

This **R/S mixture of TFN** is prepared routinely by hydrogenation of myosmine using a metal catalyst and hydrogen under moderate pressure, followed by methylation.




The product, **racemic nicotine**, can be separated into its 2 constituents, R- and S-nicotine, by use of an optically active acid and crystallisation of the desired isomer. In this case either dibenzoyl or dioluoyl tartrate can be used. This salt is then converted to free nicotine which is distilled to purify.

[15] https://www.fda.gov/news-events/press-announcements/fda-notifies-companies-including-puff-bar-remove-flavored-disposable-e-cigarettes-and-youth
[16] https://www.fda.gov/tobacco-products/ctp-newsroom/new-law-clarifies-fda-authority-regulate-synthetic-nicotine



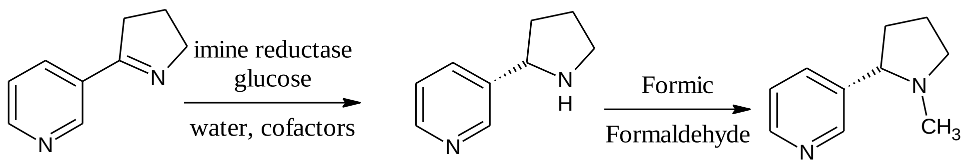

dibenzoyl-d-tartrate salt

There are several disadvantages to this process:

- Maximum theoretical yield is only 50%.
- The molecular weight of the resolving agent is twice that of nicotine, so 2 kg is used per 1 kg of racemic nicotine.
- To obtain good purity of S-isomer, solvents must be used in a mixture (methanol/isopropanol), which hinders recycling.

Actual yields are around 25%. In practice, 8 kg of the dibenzoyl-d-tartaric acid ~~is~~ used per 1 kg S-nicotine obtained. Although both the residual R-isomer enhanced nicotine and recovered dibenzoyl-d-tartaric acid can be recycled, this adds significantly to both cost and environmental impact.

**Zanoprima's process** approaches the synthesis with the aims of higher yield and less environmental impact via methods of green chemistry[17]. The starting material is the same as for the production of R/S nicotine, but myosmine is reduced directly to the S-isomer by use of an enzyme and co-factors, with glucose acting as the effective reductant – this, instead of a metal catalyst and hydrogen. Additionally, the process is carried out in water rather than in organic solvents. Isolation of the intermediate S-nornicotine is not required and methylation takes place directly.




myosmine S-nornicotine S-nicotine

[17] https://www.epa.gov/greenchemistry/basics-green-chemistry

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## 9 About the author

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