


## SYNTHETIC NICOTINE

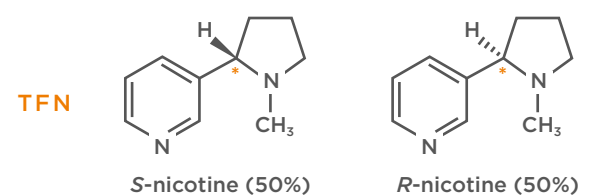



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Synthetic nicotine has been marketed under the trade name TFN (Tobacco Free Nicotine) for pharmaceutical and consumer products since 2015 (Berman et al. 2023). TFN has been used in vapor products in the USA since 2015, but is significantly more expensive than plant-derived nicotine. The starting substances for synthesis include niacin or ethyl nicotinate, which can be obtained from fossil raw materials. Nicotine is a so-called chiral molecule:




 Standard chemical synthesis produces two variants that are basically identical, but analogous to right and left hands, are not congruent. This mixture is also known as a racemate and contains both forms (enantiomers), i.e. S-nicotine and R-nicotine in roughly equal proportions. In the tobacco plant, on the other hand, a stereoselective synthesis takes place in which almost exclusively S-nicotine is formed by enzymatic processes. Although enantiomers have the same physicochemical properties, they can differ in their biological effects (e.g. S-valine tastes bitter, whereas

R-valine tastes sweet). Little is known about the effects and health risks of R-nicotine.



 Synthetic nicotine lost its status as a niche product after 2021, when Puff Bar, a leading manufacturer of disposable e-cigarettes in the USA, announced that it was switching its product range. According to analysts (Jordt, 2021; Berman et al., 2023; section 3.5), an important motive was a regulatory gap in the USA, which meant that synthetic nicotine did not count as a tobacco product and was not under the jurisdiction of the Food and Drug Agency (FDA). This meant that the complex Premarket Tobacco Product Application (PTMA) process, as well as the tobacco tax, sales restrictions on the Internet and restric-

tions on flavors and additives were no longer necessary. This loophole was already closed in the USA in March 2022 (FDA, 2022). In the EU, synthetic and natural nicotine are equally subject to the Tobacco Products Directive as nicotine alkaloids. However, a study published in 2023 shows that synthetic nicotine is not covered by tobacco law in about half of the FCTC contracting states (Berman et al., 2023).

-  The first commercial products used racemic nicotine, although little data is available on the effects and possible risks of the R-form. R-nicotine is significantly less potent, meaning that racemate is only half as effective as herbal nicotine (Ramamurthi et al., 2022). However, there is also speculation that the addition of R-nicotine offers advantages and could, for example, lead to a lower addiction potential.
-  Within a very short space of time, several suppliers have succeeded in developing processes for stereoselective nicotine synthesis that produce almost exclusively the S-form. In the Zanoprima Lifescience process, an important intermediate product (S-nornicotine) is produced by means of a stereoselective enzymatic reaction.
-  Other manufacturers start from the racemate and separate the enantiomers by stereoselective purification steps or recrystallization. The nicotine produced using these processes corresponds to the natural plant substance. Typical impurities, such as traces of carcinogenic nitrosamines, can also be avoided in synthetic products. Currently, natural and synthetic S-nicotine can be distinguished using the radiocarbon method. As the synthetic product is obtained from fossil raw materials, the proportion of the carbon isotope 14 is significantly lower here than in the case of an origin from agricultural cultivation.

## ECONOMIC CONSIDERATIONS

A liter of tobacco derived nicotine costs around 230-430\$, with racemic nicotine being significantly more expensive at \$1,800 per liter. According to study data, however, a liter of Zanoprima SyNic synthetic S-nicotine cost only 1,000\$, which was about 2-4 times more expensive than herbal nicotine (Berman et al., 2023, data from section 3.4.2.2.). With the corresponding amount of nicotine, however, 50 liters of liquid could be produced with the maximum permissible value of 20 mg/ml. The associated costs of 2 cents per ml of liquid are probably of little consequence to the consumer. For a 20 ml refill container, the nicotine costs would be 20 cents instead of 5 to 8 cents, as is the case when using plant-based nicotine.

## ADVANTAGES OF SYNTHETIC

In principle, synthetic nicotine is not affected by the criticism of the socio-ecological impact of tobacco cultivation and could become an important factor in improving sustainability for the nicotine industry.

## SPECIAL RISKS

However, progress in nicotine synthesis also favors research into the use of new nicotine analogues, where 6-methyl nicotine is the first commercially interesting option to emerge.



[www.bvte.de/nikotin](http://www.bvte.de/nikotin)

### References:

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