




# 6-Methylnicotine: a new nicotine alternative identified in e-cigarette liquids sold in Australia

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In Australia, electronic cigarette (e-cigarette) use has nearly tripled since 2019, despite legal restrictions.<sup>1</sup> These vaping products generally contain the carrier fluids propylene glycol and glycerine, flavouring chemicals, cooling agents, and nicotine.<sup>2</sup> Most users purchase their products outside intended sources,<sup>3,4</sup> in what the federal government describes as a “black market”.<sup>5</sup> At the time of the study reported in this article, a prescription was required for purchasing nicotine-containing e-cigarette products in Australia.<sup>6</sup> To enable over-the-counter sales and prevent seizure during customs controls, some suppliers have modified the products and their packaging.<sup>2</sup>

We investigated new e-cigarette products advertised in Australia as containing a nicotine alternative (Box 1) that manufacturers claim passes routine nicotine testing (ie, no nicotine detected), facilitating their legal sale to Australian adults without prescription. We purchased e-cigarette products from three manufacturers in November 2023: four concentrated solutions for dilution before use and five ready-to-use products. All samples were analysed using gas chromatography–mass spectrometry methods described in our earlier publication<sup>2</sup> (Supporting Information). The nicotine alternative was purified and fully characterised by nuclear magnetic resonance spectroscopy and high resolution mass spectrometry. We did not seek formal ethics approval for our analysis.

All nine products contained an ingredient that would not be identified by standard analytical testing for nicotine; complementary chemical characterisation techniques (Supporting Information) identified it as 6-methylnicotine (Box 2, Box 3).

Only one other study has identified 6-methylnicotine in an e-cigarette product (one United States brand), but without complete chemical characterisation to confirm its structure.<sup>7</sup>

The *in vitro* affinity of 6-methylnicotine for nicotinic cholinergic receptors is higher than that of nicotine, and its psychotropic potency three times greater.<sup>8</sup> The cytotoxicity of 6-methylnicotine exceeds that of nicotine at similar concentrations, and a lower dosage has been recommended for e-cigarette products.<sup>9</sup>

The difference in toxicity between nicotine and 6-methylnicotine is particularly concerning given the concentration of 6-methylnicotine in the products we assessed. Samples ALT-01 and ALT-02, each labelled “100 mg/mL [nicotine] equivalent”, respectively contained about one-third and one-fifth of the equivalent listed nicotine concentration, whereas ALT-03 and ALT-04, labelled as “10%” solutions, contained as much as 100 mg/mL 6-methylnicotine (Box 2). While instructions on the retailers’ websites recommended using lower concentrations of the nicotine alternative than of nicotine, this was not indicated on the product or its packaging. The differences in labelling and actual concentrations in these products could confuse users, increasing the risk of accidental exposure to high concentrations of a compound with unknown health effects. Ready-to-use products (ALT-05 to ALT-09) contained 6-methylnicotine concentrations about an order of magnitude lower than the equivalent nicotine content of currently available nicotine-containing e-cigarette products<sup>2</sup> (Box 2). Benzoic acid, included to reduce throat irritation by high nicotine concentrations by converting it to nicotine benzoate,<sup>10</sup> was detected in seven of the nine samples. Whether conversion of 6-methylnicotine to its benzoate salt has the same effect is unknown.

One limitation of our study was the small number of samples we analysed. We undertook a thorough internet search to identify, purchase, and analyse all products including nicotine alternatives, but compounds other than 6-methylnicotine may also be used as nicotine alternatives.

## 1 Text transcription of labels from e-cigarette products containing a nicotine alternative: a concentrated product (ALT-02, left) and a pod-based (ready-to-use) product (ALT-05, right)\*

<p><b>NICOTINE ALTERNATIVE</b></p> <p><b>SALTS STYM E-LIQUID BOOSTER</b></p> <p><b>100ml</b></p> <p><b>PG</b></p> <p><b>EQUIVALENT TO 100MG/ML</b></p> <p><b>This Product contains a nicotine derivative which is a highly addictive substance</b></p>	<p>Made and bottled in New Zealand by [redacted]</p> <p>Ingredients: 10% Nicotine Derivative and 90% Propylene Glycol</p>	<p>[redacted] is pre-filled with flavoured e-liquid containing Metatine in lieu of nicotine. Metatine is a synthetically derived molecule that is structurally similar to, but chemically different from, other vaping alkaloids.</p> <p>Metatine is not made or derived from tobacco or nicotine and Metatine does not consist of or contain nicotine from any source. Metatine may be addictive. [redacted] is NOT for sale to anyone under the age of 21.</p>
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\* Brand names redacted. ♦

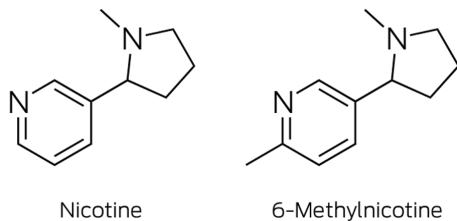
We found that nine “nicotine alternative”-containing e-cigarette products sold in Australia contained 6-methylnicotine. The concentration range determined and the limited information on the toxicity and potential health effects of 6-methylnicotine are both concerning. The toxicology of 6-methylnicotine and the consequences for health of inhaling it should be investigated, particularly as a long term alternative to nicotine in e-cigarette products. Clinicians should be aware of the availability of these products in Australia, including without prescription. Recent changes to Australian regulation have banned the

## 2 E-cigarette products tested for 6-methylnicotine concentration

Sample designation	Nicotine-related labelling	Labelled concentration (mg/mL equivalent)	Methylnicotine concentration (mg/mL, mean (SD))*	Benzoic acid detected†	Manufacturer
Concentrated solution (for dilution)					
ALT-01	"nicotine derivative"	"100 mg/mL nicotine equivalent" (100 mg/mL)	31.4 (0.8)	No	1
ALT-02	"nicotine derivative"	"100 mg/mL nicotine equivalent" (100 mg/mL)	20 (1)	Yes	1
ALT-03	"nicotine alternative agent"	10% (100 mg/mL)	100 (10)	No	2
ALT-04	"nicotine alternative agent"	10% (100 mg/mL)	57 (4)	Yes	2
Ready-to-use (disposable devices or pod cartridges)					
ALT-05	"nicotine-like experience, without the nicotine"	5% (50 mg/mL)	3.4 (0.4)	Yes	3
ALT-06	"nicotine-like experience, without the nicotine"	5% (50 mg/mL)	5.4 (0.6)	Yes	3
ALT-07	"nicotine-like experience, without the nicotine"	5% (50 mg/mL)	5.2 (0.6)	Yes	3
ALT-08	"no-nicotine nicotine solution"	None listed	3.0 (0.2)	Yes	2
ALT-09	"no-nicotine nicotine solution"	None listed	2.9 (0.3)	Yes	2

SD = standard deviation. \* For three replicate measurements. † Presence of benzoic acid indicates that the nicotine alternative is present as a benzoate salt; its absence suggests that the nicotine alternative is present as the base.

## 3 Chemical structures of nicotine and the nicotine alternative used in e-cigarette products, 6-methylnicotine



sale of any e-cigarette products without prescription, closing the loophole manufacturers were using to legally distribute these products.<sup>4,5</sup> However, further novel e-cigarette products could be developed to circumvent the new regulations.

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**Data sharing:** The data underlying this study are available on request by contacting the corresponding author. ■

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## Supporting Information

Additional Supporting Information is included with the online version of this article.