SUPPORTING SCIENTIFIC DOSSIER

submitted pursuant to Article 2 of the Convention on Psychotropic Substances of 1971 in support of the notification of the Republic of Palau to the Secretary-General of the United Nations requesting a critical review of

NICOTINE (CAS No. 54-11-5)

by the WHO Expert Committee on Drug Dependence

Prepared in accordance with the critical review format of the WHO Expert Committee on Drug Dependence

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This document is a critical review of nicotine, prepared by independent scientific experts in accordance with the format prescribed by the WHO Expert Committee on Drug Dependence (ECDD) for critical reviews under the Convention on Psychotropic Substances of 1971. It is submitted as the supporting scientific dossier accompanying the formal notification of the Republic of Palau to the Secretary-General of the United Nations under Article 2 of the Convention, requesting that nicotine be evaluated for possible scheduling. The document examines nicotine across the domains required by the ECDD critical review framework: substance identification and chemistry (Chapter 01), pharmacology (Chapter 02), toxicology and adverse effects (Chapter 03), dependence and abuse potential (Chapter 04), therapeutic use and medical applications (Chapter 05), and epidemiology of use and public health impact (Chapter 06).

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Executive Summary

This document presents a comprehensive scientific evaluation of nicotine in accordance with the framework of the World Health Organization Expert Committee on Drug Dependence (WHO ECDD), supporting consideration of nicotine for potential international scheduling. It integrates current evidence across chemistry, pharmacology, toxicology, dependence potential, therapeutic use and epidemiology to assess nicotine as a psychoactive substance with significant public health implications.

Nicotine is a naturally occurring alkaloid with well-characterized chemical properties that directly influence its absorption, bioavailability and physiological effects. Modern product innovation, particularly the development of nicotine salts and synthetic nicotine, has enabled higher concentrations, faster delivery and reduced sensory irritation, thereby increasing addiction potential and systemic exposure. Variability in formulation and delivery systems, including cigarettes, e-cigarettes, heated tobacco products and oral nicotine products, results in heterogeneous pharmacokinetic profiles that complicate risk assessment and regulatory oversight.

Pharmacologically, nicotine exerts its effects primarily through activation of nicotinic acetylcholine receptors (nAChRs), leading to widespread neurotransmitter release and stimulation of the mesolimbic dopamine system. These mechanisms underpin its strong reinforcing properties and capacity to induce dependence. Chronic exposure results in neuroadaptations, including receptor desensitization and upregulation, which sustain addiction. Nicotine also activates the sympathetic nervous system, linking its central effects with systemic cardiovascular consequences.

Toxicological evidence demonstrates that nicotine is not biologically inert. It contributes to cardiovascular disease through mechanisms involving oxidative stress, endothelial dysfunction, and sympathetic activation. Acute toxicity can result in poisoning, while chronic exposure affects multiple organ systems, including the respiratory, neurological, and reproductive systems. Nicotine exposure during critical developmental periods, particularly prenatal and adolescent stages, is associated with long-term neurodevelopmental harm. Although not a primary carcinogen, nicotine promotes tumor progression and may interfere with cancer treatment outcomes.

Nicotine is a highly dependence-producing substance. Its addictive potential is driven by rapid brain delivery, high peak plasma concentrations and product design features that enhance user appeal, such as flavouring and formulation chemistry. Emerging nicotine products increasingly replicate or exceed the pharmacokinetic profiles of conventional cigarettes, particularly among youth populations. Dual and poly-use of multiple nicotine products is common, sustaining dependence and increasing cumulative exposure rather than facilitating cessation.

Despite its risks, nicotine has recognized therapeutic use in the form of nicotine replacement therapy (NRT), which is approved for smoking cessation. NRT delivers controlled, lower doses

of nicotine with slower absorption, reducing withdrawal symptoms while minimizing abuse liability. Its favorable risk–benefit profile is based on replacing more harmful exposures, rather than the absence of intrinsic risk. Evidence does not support broader therapeutic applications of nicotine beyond regulated cessation contexts.

Epidemiological data indicate that nicotine use remains widespread globally, with over one billion users of tobacco products and rapidly increasing use of non-combustible nicotine products. A major shift has occurred in initiation patterns, particularly among adolescents, where e-cigarettes and other novel products now serve as primary entry points to nicotine exposure. This transition raises concerns about long-term population health impacts, including increased future burden of cardiovascular, metabolic, and neuropsychiatric disease.

In conclusion, nicotine is a psychoactive substance with well-established dependence potential, significant toxicity and widespread global use. Advances in product design have increased its delivery efficiency and appeal, particularly among youth, amplifying public health risks. While controlled therapeutic use is justified in smoking cessation, the expanding landscape of consumer nicotine products challenges existing regulatory frameworks. The evidence reviewed addresses each of the domains specified under Article 2(4) of the 1971 Convention: nicotine's dependence potential, its abuse risk, its public health and social impact, and the degree of its usefulness in medical therapy. The totality of evidence supports the need for comprehensive evaluation of nicotine within international drug control systems, taking into account its pharmacological properties, abuse liability, and population-level health impact.

Chemical identity of nicotine

Nicotine is a naturally occurring alkaloid primarily found in plants of the genus *Nicotiana*, particularly *Nicotiana tabacum*. Chemically, nicotine consists of a pyridine ring linked to a pyrrolidine ring and has the molecular formula $C_{10}H_{14}N_2$ with a molecular weight of 162.23 g/mol. The molecule is optically active and occurs predominantly as (S)-nicotine, the biologically active enantiomer found in tobacco plants.

Nicotine behaves as a weak base with a pKa of approximately 8.0, meaning that it can exist in protonated (ionized) and unprotonated (free-base) forms depending on pH (Sansone et al., 2023). This acid–base equilibrium determines nicotine volatility and membrane permeability and therefore influences how nicotine is absorbed in different delivery systems such as cigarettes, e-cigarettes and oral nicotine products (Duell et al., 2018, 2020).

In tobacco plants, nicotine is synthesized mainly in the roots and transported to the leaves where it accumulates as the dominant alkaloid. The biosynthetic pathway involves the condensation of a pyridine ring derived from nicotinic acid with a pyrrolidine ring derived from ornithine or arginine metabolism.

Free-base nicotine versus nicotine salt formulations

Nicotine used in consumer products can exist either as free-base nicotine or as nicotine salts, which differ in chemical structure and physicochemical properties. Free-base nicotine refers to the unprotonated form of nicotine, which predominates under alkaline conditions and is relatively volatile. This form was historically used in conventional cigarettes and early electronic cigarettes (Duell et al., 2020).

In contrast, nicotine salts are formed when nicotine reacts with an acid, producing a protonated form of the molecule. Organic acids commonly used to form nicotine salts include benzoic, lactic, and levulinic acids (Harvanko at al., 2020). These acids lower the pH of the formulation and convert nicotine into its protonated form, which reduces sensory irritation during inhalation and allows higher nicotine concentrations to be delivered with less throat irritation (Harvanko at al., 2020; Johnson et al., 2020).

This technological modification is not trivial: by reducing aversive sensory effects, nicotine salt formulations enable substantially higher nicotine concentrations and more efficient pulmonary uptake, thereby facilitating rapid systemic exposure and increasing addiction liability (Benowitz, 2010; Jackler & Ramamurthi, 2019).

Analytical studies show that nicotine in e-liquids can exist in both free-base and protonated forms and the relative proportions depend largely on the pH of the formulation. Free-base nicotine is more volatile and more readily diffuses across biological membranes, whereas protonated nicotine is less volatile and typically produces a smoother sensory experience during inhalation (Duell et al., 2020; Hartendorp et al., 2024). Controlled experimental studies have also demonstrated that acid additives in e-cigarettes that change nicotine from free base

to salt appeared to enhance the appeal and sensory experience of vaping (Leventhal et al., 2021).

Critically, enhanced sensory tolerability and higher delivery efficiency are closely linked to higher plasma nicotine peaks and faster brain exposure, which are key determinants of addictive potential and reinforcement behaviour (Benowitz, 2009). Moreover, rapid nicotine delivery kinetics, particularly in modern high-concentration salt-based devices, are associated with stronger sympathetic activation, which may amplify acute haemodynamic stress responses relevant to cardiovascular risk (Münzel et al., 2026; Benowitz, 2016). Thus, formulation chemistry directly translates into biological impact, linking product design to addiction trajectories and downstream cardiovascular toxicity.

Manufacturing and extraction pathways relevant to modern nicotine products

Nicotine used in commercial products may be obtained either from tobacco plant extraction or from synthetic chemical production. Traditionally, nicotine has been extracted from tobacco leaves using acid–base extraction processes, which involve converting nicotine into a water-soluble salt, separating it from plant material and then regenerating free-base nicotine through alkaline treatment and purification (Sansone et al., 2023).

The extraction process may leave trace impurities, including tobacco-specific nitrosamines and other alkaloids, depending on purification efficiency, which can contribute to the overall toxicological profile of the final product (Mallock-Ohnesorg et al., 2024).

In recent years, synthetic nicotine has been introduced as an alternative source. Synthetic nicotine is produced through chemical synthesis rather than plant extraction and may consist of either racemic mixtures of nicotine enantiomers or purified (S)-nicotine depending on the synthesis method. Analytical techniques such as chiral chromatography and isotope analysis can distinguish synthetic nicotine from tobacco-derived nicotine based on differences in enantiomer composition and impurity profiles (Berman et al., 2023).

Importantly, synthetic nicotine is often marketed as “tobacco-free,” which may create a misleading perception of reduced harm despite the fact that the pharmacologically active compound, nicotine, remains identical in its biological effects. In addition, synthetic production pathways may introduce distinct impurity profiles, including residual solvents, reaction by-products, or stereoisomeric contaminants, for which toxicological data remain limited or absent (WHO, 2023).

Modern nicotine delivery systems, including electronic cigarettes, heated tobacco products, and nicotine pouches, may therefore contain nicotine derived either from plant extraction or chemical synthesis, and the chemical form (free-base versus salt) may vary depending on the formulation design.

This heterogeneity in sourcing and formulation introduces substantial variability in nicotine pharmacokinetics, exposure levels, and potential toxicity, complicating both risk assessment and regulatory oversight.

Furthermore, the rapid evolution of synthetic nicotine and nicotine analogues (e.g., modified or "non-nicotine" compounds such as 6-methylnicotine/metatine) poses an emerging regulatory challenge, as these substances may evade existing tobacco regulations while retaining similar addictive and potentially harmful biological effects **(**WHO, 2023; Munzel et al., 2025; Dennison Himmelfarb et al., 2025).

Mechanism of action attributed to nicotine addiction at nicotinic acetylcholine receptors

Nicotine, the principal addictive component in tobacco and nicotine products, is mechanistically linked to its interaction with neuronal nicotinic acetylcholine receptors (nAChRs). nAChRs are ligand-gated ion channels composed of five transmembrane subunits. The α4β2 receptor subtype is the most common in the brain, playing a crucial role in the behavioral effects of nicotine. When nicotine binds to α4β2 nAChR, it significantly enhances the firing rate and burst firing of dopamine neurons in the brain, thereby activating the mesolimbic dopamine system. The α4β2 nAChR subunit has been identified as the principal subtype implicated in the pathogenesis of nicotine addiction. However, other nAChR subtypes also play important roles in the onset and maintenance of nicotine addiction (Jiang et al., 2025).

Beyond its role in addiction, activation of nAChRs, particularly within autonomic and peripheral neuronal networks, represents a key upstream trigger for systemic physiological responses, including sympathetic nervous system activation and downstream cardiovascular effects (Münzel et al., 2026; Benowitz, 2016).

Upon binding to nAChRs, nicotine causes conformational changes that open the receptor channel, allowing influx of cations, primarily sodium (Na^+) and calcium (Ca^{2+}), resulting in neuronal depolarization. This leads to increased neurotransmitter release across several systems, including dopamine, norepinephrine, acetylcholine, glutamate, serotonin and γ-aminobutyric acid (GABA). Chronic nicotine exposure leads to receptor desensitization and up-regulation, particularly of α4β2 receptors, which contributes to tolerance and dependence. Desensitization occurs when prolonged receptor activation causes temporary functional inactivation, while compensatory receptor up-regulation increases receptor density in the brain, reinforcing addiction cycles during repeated exposure and withdrawal (Liu et al., 2025).

Importantly, calcium influx via nAChRs is not only central to neuronal signalling but also contributes to activation of downstream redox-sensitive pathways, including mitochondrial dysfunction and reactive oxygen species (ROS) generation (Kaludercic et al., 2014).

Recent structural and molecular studies using cryo-electron microscopy have provided new insights into nicotine binding sites and receptor conformational dynamics, highlighting how different receptor subtypes contribute to the pharmacological and addictive properties of nicotine (Zhang et al., 2026).

These advances further support the concept that subtle differences in receptor subtype activation and ligand interaction may translate into distinct physiological and toxicological profiles across nicotine delivery systems.

Central nervous system stimulation

Nicotine acts as a central nervous system stimulant by activating nAChRs located in cortical, subcortical and brainstem regions involved in cognition, attention and autonomic regulation. In cortical and hippocampal circuits, nicotine enhances cholinergic and glutamatergic

signaling, which can transiently improve attention, vigilance, and information processing (Nara et al., 2023).

Nicotine also stimulates the autonomic nervous system through nAChRs located in sympathetic ganglia and the adrenal medulla, leading to release of catecholamines such as epinephrine and norepinephrine. These responses produce acute physiological effects including increased heart rate, elevated blood pressure, and enhanced cardiac contractility (Soni & Verma, 2024).

Neurochemical studies show that nicotine modulates several neurotransmitter pathways simultaneously. In addition to stimulating dopaminergic signaling, nicotine increases glutamate release and modulates GABAergic inhibition, altering excitatory–inhibitory balance in several brain circuits. These changes contribute to the stimulant effects of nicotine and to neuroadaptive processes that reinforce dependence (Kim & Picciotto, 2023).

Emerging evidence also indicates that nicotine exposure during adolescence alters neurodevelopmental processes and dopaminergic circuitry, increasing susceptibility to addiction later in life (Reynolds et al., 2025).

Reward circuitry activation

A central pharmacological mechanism underlying nicotine dependence is activation of the mesolimbic dopamine reward pathway. Nicotine stimulates nAChRs in the ventral tegmental area (VTA), increasing neuronal firing and dopamine release in the nucleus accumbens, a key component of the brain's reward circuitry (Jiang et al., 2025).

Activation of high-affinity β2-containing receptors enhances phasic dopaminergic signaling, which strengthens reward perception and reinforces repeated nicotine use (Jiang et al., 2025).

Nicotine also modulates reward circuitry indirectly by enhancing excitatory glutamatergic input to dopamine neurons while desensitizing inhibitory GABAergic interneurons. This combination amplifies dopamine release and contributes to reinforcement and addiction (Kim & Picciotto, 2023).

Recent experimental work further demonstrates that nicotine activates feedback loops within the VTA–nucleus accumbens network that regulate reward signaling and may contribute to persistent nicotine-seeking behavior (Le Borgne et al., 2025).

In addition to reward pathways, aversive circuits involving the medial habenula–interpeduncular nucleus pathway can limit nicotine intake at higher doses, providing a counterbalance to reinforcing effects (Ciscato et al., 2025).

Nicotine's effects on the amygdala represent another key neurobiological mechanism underlying dependence, particularly through modulation of emotional learning, stress reactivity and cue-induced craving. The amygdala is central to affective processing and reinforcement learning and recent neuroimaging and translational studies demonstrate that nicotine alters amygdala function and connectivity within broader addiction-related circuits. It is found that nicotine administration disrupts the neural discrimination between threat and safety, with reduced differential activation of the amygdala during fear learning and altered

connectivity with reward-related regions such as the nucleus accumbens and ventral tegmental area (Mueller et al., 2024). In addition, recent neurobiological reviews highlight the role of the amygdala in stress-induced relapse, showing that nicotine modulates amygdala-driven stress pathways and promotes reinstatement of nicotine-seeking behaviour (Wang et al., 2024). Functional imaging studies also indicate that nicotine withdrawal is associated with increased amygdala activity and altered amygdala–insula connectivity, changes that are linked to craving and relapse vulnerability (Panagopoulos et al., 2024). Together, these findings demonstrate that nicotine directly affects core limbic circuitry involved in emotional regulation and reinforcement, supporting its classification as a dependence-producing psychoactive substance (Mihov and Hurlemann, 2012).

Dose–response relationships

Nicotine exhibits complex dose–response relationships reflecting both stimulant and toxicological properties. At low to moderate doses, nicotine stimulates high-affinity nAChRs and produces central nervous system activation characterized by increased alertness, improved attention, and mild mood elevation (Kim & Picciotto, 2023).

At higher doses, nicotine activates additional receptor populations and produces broader autonomic and toxicological effects including nausea, dizziness, sweating, and vomiting. These symptoms reflect excessive stimulation of autonomic ganglia and central cholinergic pathways (Soni & Verma, 2024).

Experimental studies indicate that nicotine's reinforcing effects occur within a relatively narrow dose range and that higher doses can activate aversive neural circuits that limit drug intake (Jehl et al., 2025).

Tolerance develops rapidly due to receptor desensitization and neuroadaptive changes in dopaminergic and cholinergic signaling pathways. As tolerance increases, users often escalate nicotine intake to maintain rewarding effects, reinforcing dependence and chronic exposure.

This escalation of intake is of particular clinical relevance, as cumulative nicotine exposure increases the magnitude and persistence of sympathetic activation, oxidative stress, and endothelial dysfunction (Liu et al., 2025).

Differences in nicotine delivery kinetics across products, including conventional cigarettes, electronic nicotine delivery systems, heated tobacco products and oral nicotine products, result in different plasma nicotine profiles and receptor stimulation patterns, which may influence addiction potential and dose–response dynamics. Formulation characteristics, including nicotine salts, can increase delivery efficiency and influence addiction potential (Jackler & Ramamurthi, 2019).

Thus, pharmacokinetics, determined by product design, interact directly with pharmacodynamic mechanisms to shape both addiction trajectories and cardiovascular risk profiles.

Toxicological effects of nicotine on multiple organ systems are well documented. Toxicity arises both from nicotine itself and from additional toxicants delivered through nicotine-containing products such as conventional cigarettes, smokeless tobacco, electronic nicotine delivery systems (ENDS) and heated tobacco products. Acute exposure to nicotine produces a characteristic cholinergic toxicity syndrome involving nausea, vomiting, abdominal pain, hypersalivation, tachycardia, hypertension, tremor, dizziness and confusion. At higher doses, severe toxicity may occur, including respiratory failure, seizures, circulatory collapse, and death (Mishra et al., 2015).

Cardiovascular Toxicity

Nicotine is often mistakenly considered relatively harmless and addictive, but not causally linked to Cardiovascular Diseases (CVD). Nicotine use represents a global public health threat because nicotine-containing products such as tobacco cigarettes, e-cigarettes, shisha, heated tobacco products and oral nicotine products (for example nicotine pouches) expose both users and bystanders through mainstream smoke as well as sidestream and secondhand smoke. These exposures trigger oxidative stress and inflammation, which damage the vascular endothelium and lead to endothelial dysfunction. Persistent endothelial dysfunction promotes cardiovascular disease and ultimately contributes to hypertension, acute and chronic acute coronary syndromes, heart failure, stroke, and arrhythmia.

Cigarette smoke in particular causes cardiovascular injury through three major toxic components: oxidant chemicals and particulate matter, carbon monoxide and nicotine. Oxidant chemicals and particulate matter promote inflammation, platelet activation, thrombosis, and endothelial dysfunction. Carbon monoxide reduces oxygen availability in the blood, thereby limiting oxygen delivery to the myocardium. At the same time, nicotine activates the sympathetic nervous system, which increases heart rate, blood pressure and myocardial contractility while also causing coronary vasoconstriction. These combined effects reduce blood supply, oxygen and nutrients to the myocardium while simultaneously increasing myocardial oxygen demand. The imbalance between oxygen supply and demand results in myocardial ischaemia and infarction, which may ultimately lead to sudden death (Münzel et al., 2025).

Specifically, nicotine-induced sympathetic activation triggers β_1-adrenergic signalling, increasing renin release and angiotensin II formation, which activates vascular NADPH oxidases (NOX1/NOX2), leading to excessive generation of reactive oxygen species (ROS) (Griendling et al., 2014). Nicotine disrupts endothelial nitric oxide (NO) signalling and inducing eNOS uncoupling, resulting in reduced NO bioavailability and increased superoxide production (Deo et al., 2013). In addition, nicotine increases endothelin-1 levels, reduces prostacyclin synthesis, and impairs vasodilatory signalling, collectively shifting vascular homeostasis toward vasoconstriction, thrombosis, and inflammation (Whitehead et al., 2021).

Human studies consistently demonstrate that nicotine exposure impairs flow-mediated dilation (FMD), increases arterial stiffness, and elevates inflammatory biomarkers, all of which are predictive of future cardiovascular events (Inaba et al., 2010; Yeboah et al., 2007). Importantly, antioxidant interventions such as vitamin C have been shown to reverse nicotine-induced endothelial dysfunction, providing strong causal evidence for oxidative stress as the central mechanism (Otsuka et al., 2001; Chaumont et al., 2018).

Developmental and Neurotoxic Effects

Nicotine exposure during critical developmental periods including prenatal development, infancy and adolescence, has been associated with adverse neurodevelopmental outcomes. Experimental and epidemiological studies demonstrate that nicotine can disrupt normal brain development by altering cholinergic signaling pathways involved in neuronal proliferation, differentiation, and synaptic plasticity.

These effects are mediated through persistent alterations in neurotransmitter systems and receptor expression, leading to long-term changes in brain structure and function.

Evidence from both animal and human studies indicates that prenatal nicotine exposure can affect cognitive development, attention regulation and behavioral outcomes, potentially increasing susceptibility to neuropsychiatric disorders later in life.

Nicotine exposure during adolescence is also of major concern due to the fact that the adolescent brain remains highly plastic and vulnerable to neurochemical perturbations. Early nicotine exposure may alter neural circuits involved in reward processing and impulse control, increasing vulnerability to nicotine addiction and to addiction to alcohol and to other drugs and substances and potentially affecting cognitive development. These developmental toxicities are particularly relevant given the increasing nicotine uptake of new emerging nicotine products such as e-cigarettes and oral nicotine pouches among adolescents (McGrath-Morrow et al., 2020).

Respiratory and Systemic Toxicity

Respiratory toxicity associated with nicotine products is primarily linked to inhaled products such as cigarettes and e-cigarettes. Recent systematic reviews evaluating ENDS indicated potential associations with pulmonary inflammation, airway irritation, and increased risk of respiratory diseases including asthma and chronic obstructive pulmonary disease (Kundu et al., 2025). E-cigarette aerosols may contain toxic substances such as heavy metals, volatile organic compounds, ultrafine particles, and carbonyl compounds, which may contribute to respiratory toxicity (Kaur et al., 2025).

Notably, even nicotine-containing aerosols without combustion have been shown to induce oxidative stress and inflammatory responses in pulmonary and vascular tissues, indicating that heated (non-combusted products) are not biologically inert **(**Kuntic et al., 2020; Ito et al., 2020).

Nicotine also exerts systemic effects beyond the cardiovascular and respiratory systems. Chronic exposure has been associated with metabolic alterations, immune dysregulation, and potential effects on reproductive health. Although nicotine itself is not considered a major

carcinogen, its role in promoting tumor growth and angiogenesis has been explored in experimental studies (Benowitz, 2009).

These systemic effects further support the concept that nicotine acts as a pleiotropic biological agent influencing multiple organ systems through shared pathways of oxidative stress and inflammation.

Nicotine and Cancer

It is well recognized from numerous sources that using tobacco causes cancer—approximately one-third of all cancers. What is less recognized is the impact of nicotine intake on the development and progression of cancers, and how it can affect cancer treatments and outcomes/survival (U.S. Department of Health and Human Services, 2014).

Most human cells have nicotinic acetylcholine receptors (nAChRs) on their cellular membrane. For a long time, nAChRs were thought to be solely related to the neurological systems of the body. However, for the past few decades, increasing research has identified these nAChRs on other somatic cells, their subtypes and their functional impact on intracellular signal transduction pathways (Warren & Singh, 2013; Singh et al., 2011).

Nicotine is not a classical genotoxic carcinogen but acts as a tumour promoter through activation of nAChRs and β-adrenergic signalling pathways (Schuller et al., 2009). These receptor-mediated processes initiate intracellular signalling cascades that regulate key pathways involved in tumour biology, including increased cellular proliferation, inhibition of apoptosis, enhanced angiogenesis, tumour cell migration, metastasis, and reduced responsiveness to therapy (Singh et al., 2011; Warren & Singh, 2013). These effects raise concerns regarding continued nicotine exposure, including through non-combustible nicotine products, in individuals with active malignancy.

The nAChR is composed of 5 subunits, mostly of alpha (1–10) and beta (1–4) subunits. Although alpha7 is most commonly thought to be involved with neurotransmissions, it is also critical for trans-membrane cellular communications in the cancer cell realm. However, other combinations are also involved, and their activity and utility remain areas of active investigation.

Thus, nicotine can be considered a co-carcinogen—an agent not carcinogenic alone, but that potentiates the effect of a known carcinogen—because by itself it does not damage DNA and does not create DNA adducts that can cause mutations. That said, its metabolites, NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and NNN (N'-nitrosonornicotine), are derived from nicotine through the tobacco curing or smoking/combustion process. Nicotine, NNK and NNN also interact with nAChRs, with varying sensitivity depending on the receptor subunit mixtures, and depending on the nAChR, result in a myriad of intracellular signal transduction effects.

In addition, beta-adrenergic receptors are also active in supporting survival of cancer cells, and this appears to be in response to the presence of nicotine or NNK and their stimulation of noradrenaline release (Warren & Singh, 2013; Singh et al., 2011).

Studies have demonstrated that nicotine usage decreases the utility of chemotherapy and/or radiation during cancer treatment. These observations have been identified both *in vivo* and *in vitro* (Singh et al., 2011; Warren et al., 2012). In a recently published paper, persistent smoking after a diagnosis for lung cancer suggested that it may be a more important factor than anatomical staging for prognosis. Perhaps a significant factor is the nicotine content within that persistent smoking (Eng et al., 2025).

"Moreover, the direct role of nicotine alone on several aspects of tumorigenesis raises the need to revisit the potential tumour-promoting effects of nicotine-replacement therapy (Singh et al., 2011)."

Poisoning Risk

The increasing availability of highly concentrated nicotine formulations, particularly in refill liquids and synthetic nicotine products, has significantly increased the risk of accidental and intentional poisoning.

Nicotine poisoning represents an important acute toxicological concern, particularly with the increased availability of concentrated nicotine liquids used in e-cigarettes and refill products. De-identified poison center data across eight EU Member States reporting on e-cigarette liquid exposure incidents showed that, of the 223 e-liquid exposure incidents recorded, 64.7% were unintentional exposures, ranging from 48.4% among adults aged ≥19 years to 100.0% among children aged 0–5 years ($p < 0.05$). The most frequent route of exposure was ingestion (73.5%), while 55.2% experienced any clinical symptoms, including nausea (16.6%), vomiting (11.1%), and dizziness (9.0%). 57.8% of the cases were treated at the residence or on-site (Vardavas et al., 2021).

Similar poison control data indicate increasing reports of accidental ingestion or dermal exposure, particularly among children. Symptoms of nicotine poisoning may include nausea, vomiting, excessive salivation, sweating, confusion, seizures, and in severe cases respiratory failure. Cases of fatal poisoning have been reported following ingestion of high-concentration nicotine liquids or intentional self-poisoning (Hua &Talbot, 2016).

Additionally, recent clinical evidence found that modern oral nicotine products, particularly nicotine pouches, can result in acute nicotine toxicity under conditions of typical use. A case report described a 21-year-old male who developed neurological symptoms, including confusion and altered mental status, following repeated use of high-dose nicotine pouches over a 12-hour period, requiring hospital evaluation (Kent et al., 2024). Importantly, toxicity occurred through cumulative exposure rather than a single excessive dose, reflecting real-world patterns of repeated use and self-titration. Surveillance and epidemiological data have documented adverse effects associated with nicotine pouch exposure, including nausea, vomiting, dizziness, and cardiovascular symptoms, particularly among younger populations (Park-Lee et al., 2024; U.S. Food and Drug Administration, 2023). Poison center data further indicate that oral nicotine products can result in clinically significant toxicity, especially

following accidental or high-dose exposure (Gummin et al., 2023). These findings suggest that high-dose oral nicotine products can achieve systemic nicotine exposure sufficient to produce acute toxic effects and reinforce their abuse potential (Benowitz & Helen, 2021; Lunell et al., 2020). This profile contrasts with regulated nicotine replacement therapies, which are designed to deliver nicotine more slowly and at controlled doses to minimize adverse effects (World Health Organization, 2024; Hartmann-Boyce et al., 2018).

Pregnancy and neonatal effects

Prenatal exposure to nicotine is associated with a wide range of adverse pregnancy and neonatal outcomes, reflecting nicotine's ability to cross the placenta and directly affect fetal development. Nicotine enters fetal circulation and accumulates in fetal tissues, including the brain, where it can disrupt normal neurodevelopment through activation of nicotinic acetylcholine receptors (England et al., 2015; Bruin et al., 2010). Epidemiological and clinical evidence indicates that maternal nicotine exposure, whether through all nicotine and tobacco products, is associated with increased risks of low birth weight, preterm birth, impaired lung development and alterations in brain development that may affect cognition and behaviour later in life (U.S. Surgeon General, 2020; World Health Organization, 2024). Experimental and human studies further demonstrate that prenatal nicotine exposure can lead to long-term dysregulation of neurotransmitter systems and increased susceptibility to addiction and neurobehavioral disorders in offspring (Slotkin, 2004; Spindel and McEvoy, 2016). A 2024 systematic review concluded that vaping during pregnancy poses biological risks to fetal development, including potential effects on lung and neurodevelopment (Ussher et al., 2024). More recent meta-analyses report that maternal e-cigarette use is associated with significantly increased risks of preterm birth and low birth weight, with pooled estimates suggesting approximately 40% higher risk of preterm birth and nearly 50% higher risk of low birth weight compared with non-use and even greater risks among dual users of cigarettes and e-cigarettes (Vallée et al., 2025; Sukhato et al., 2025). Earlier systematic evidence also indicates associations with reduced neonatal growth and increased neonatal morbidity (Pereira et al., 2022). Together, these findings demonstrate that nicotine itself, including when delivered through modern products such as e-cigarettes, contributes directly to developmental toxicity and represents a significant risk factor for adverse maternal and child health outcomes.

Environmental Exposure

Environmental exposure to nicotine occurs through second-hand smoke, third-hand smoke residues and environmental contamination from tobacco product waste. Second-hand smoke exposure remains a major source of involuntary nicotine exposure and is associated with increased risks of cardiovascular disease, respiratory disease and adverse pregnancy outcomes. Third-hand smoke, residual nicotine and tobacco chemicals that persist on surfaces and dust, may also contribute to chronic low-level exposure in indoor environments (U.S. Department of Health and Human Services, 2014).

Environmental contamination from discarded tobacco products and nicotine product waste is increasingly recognized as a public health and environmental issue. Cigarette butts, for example, contain residual nicotine and other toxic chemicals that can contaminate soil and aquatic ecosystems. Studies have demonstrated that nicotine leached from cigarette waste can be toxic to aquatic organisms and contribute to environmental pollution (World Health Organization, 2017).

Tobacco cultivation itself also contributes substantially to environmental degradation and population-level exposure risks. Occupational exposure among agricultural workers is significant, including "green tobacco sickness," a form of acute nicotine poisoning resulting from dermal absorption during handling of wet tobacco leaves (McBride et al., 1998). It is worth mentioning that, in the past, nicotine has been used as a broad-spectrum insecticide due to its neurotoxic action on nicotinic acetylcholine receptors. However, its environmental toxicity has raised concerns, particularly regarding effects on non-target species such as pollinators. Contemporary evidence on nicotine-related compounds (including neonicotinoids derived from nicotine chemistry) demonstrates significant harmful effects on biodiversity, especially bees and other pollinators, including increased mortality and disruption of reproductive and ecological functions (Mamy et al., 2025; Thompson et al., 2020).

Environmental persistence of nicotine and associated toxicants further extends exposure beyond active users, contributing to involuntary health risks and environmental contamination.

Chapter 04 — Dependence & Abuse Potential

The 1988 US Surgeon General's Report on the Health Consequences of Smoking focused on nicotine addiction (U.S. Department of Health and Human Services, 1988). The report compiled and reviewed evidence from several lines of inquiry and made strong conclusions concerning the role of nicotine in development and maintenance of addiction to tobacco use, as summarized in the foreword to the Report:

"Scientists in the field of drug addiction now agree that nicotine, the principal pharmacologic agent that is common to all forms of tobacco, is a powerfully addicting drug... After carefully examining the available evidence, this Report concludes that:

- Cigarettes and other forms of tobacco are addicting.
- Nicotine is the drug in tobacco that causes addiction
- The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine (U.S. Department of Health and Human Services, 1988)."
- Importantly, nicotine addiction is not merely a behavioural disorder but a chronic exposure pathway that sustains long-term biological injury. Through repeated use, dependence leads to sustained nicotine exposure and increased health risk (Münzel et al., 2026).

Since this landmark report of the Surgeon General Report 1988, the neurobiological evidence supporting treating nicotine as an addictive drug has strengthened further. In particular, the impact of nicotine exposure on the developing brain has gained greater attention, with multiple adverse outcomes such as greater vulnerability to developing addiction of great concern (Castro et al., 2023). Of critical relevance is the development of new formulations of nicotine products that have been developed and marketed as non-therapeutic products. These new products include electronic nicotine delivery systems/ENDS ('e-cigarettes' or 'nicotine vaping products') and products that are placed in the mouth to deliver nicotine through the oral mucosa. Prior to the advent of ENDS and their mass marketing as non-therapeutic nicotine products, most of the research on the addictiveness of nicotine was based on nicotine delivered in tobacco products or in nicotine replacement therapies (NRT), which were intended to reduce nicotine withdrawal symptoms without a high risk of consumers developing dependence on them.

A wide range of non-therapeutic nicotine products are now marketed and sold illegally in many countries. Nicotine delivery methods include via inhalation (e.g., electronic nicotine delivery systems/ENDS) with nicotine uptake via aerosol droplets deposited throughout the respiratory tract and lungs and oral products that facilitate absorption via the oral mucosa through direct contact (e.g., nicotine pouches, gum, lozenge, gummies), (Jackson et al., 2025; Borowiecki et al., 2024).

An analysis of the global market share of different nicotine-containing products between 2007 and 2021 demonstrated that the overall market share made up of non-conventional nicotine products, grew particularly since 2016, with ENDS increasing market share to 2.5% of the overall non-therapeutic nicotine product market by 2021 and oral nicotine products, such as nicotine pouches making up 0.3% of the market (Liu & Filippidis, 2024). This indicates that increasing importance of these new products within the context of the overall nicotine product market.

Non-therapeutic nicotine products can contain nicotine extracted from tobacco plants or synthetically produced nicotine. They are also produced in a wide range of flavours, nicotine content and formulations that can influence nicotine pharmacokinetics, such as by altering the pH (Felicione et al., 2026; Al-Otaibi & Althobiani, 2025). Differences such as freebase compared to nicotine salt-based formulations can also impact how the products are used, with nicotine salt formulations facilitating higher nicotine doses. The wide variability in products, which has changed over time may have led to changes in abuse potential because these factors can influence pharmacokinetics, consumer attractiveness and acceptability among different populations, and patterns of use.

Several factors influence the dependence potential of nicotine products, including the total nicotine exposure, peak plasma dose and speed of absorption. An in-depth review of these mechanisms is covered in the 2010 US Surgeon General's Report, (U.S. Department of Health and Human Services, 2010).

Rapid nicotine delivery to the brain, particularly via inhalation, produces strong reinforcement by synchronizing pharmacokinetics with reward circuitry activation. This rapid delivery enhances reinforcement and addiction potential (Benowitz, 2016).

Previously, tobacco cigarettes have been the nicotine-containing product with the greatest dependence potential due to the rapid peak nicotine blood levels produced via lung inhalation (Fant et al., 1999). While slightly slower to reach peak concentration, oral snuff also produces relatively fast delivery, high peak levels and high total nicotine exposure. In contrast, nicotine replacement therapies (NRT) are slower to reach peak concentration, and do not reach the high peak concentration and total nicotine exposure as these tobacco products (U.S. Department of Health and Human Services, 2010). These characteristics of NRT are associated with only partial suppression of nicotine withdrawal symptoms among people stopping smoking and lower dependence risk (abuse liability). In contrast, the range of non-therapeutic nicotine products that are now marketed legally and sold illegally in many countries have nicotine pharmacokinetic profiles that more closely mimic tobacco products (cigarettes, oral snuff) than NRT, as described below.

Electronic Nicotine Delivery Systems (ENDS), which aerosolise nicotine in a carrier fluid for inhalation commenced with rudimentary products that were characterised by low powered devices and modest nicotine delivery (Leong & Samin, 2025). However, the technology rapidly

developed into a wide spectrum of products, with the most commercially successful being the JUUL pod device and subsequent products that incorporate key features of JUUL in their design, particularly the use of nicotine salts rather than base nicotine (Cho et al., 2024).

As the ENDS market has grown, they have become the dominant nicotine product used by youth in multiple countries (Raad et al., 2025; Gentzke et al., 2020).

Clinical studies have demonstrated that ad libitum rather than standardised puffing regimes are critical in accurate evaluation of the abuse liability of ENDS because participants who use ENDS in more naturalistic ways alter their puffing behaviour to achieve more efficient nicotine delivery (Cho et al., 2024; Benowitz et al., 2025), that can approximate that achieved from tobacco cigarettes(Benowitz et al., 2025; Gades et al., 2022).

Clinical studies have demonstrated that ENDS with higher nicotine formulations lead to higher peak and total blood nicotine levels (Gades et al., 2022), more effectively reduced nicotine cravings than lower nicotine doses, a nicotine form by dose interaction was observed, such that high strength nicotine salt formulations led to more intense puffing topography, higher nicotine intake and were rated more positively by participants (Cho et al., 2024). These are indications of greater abuse liability.

A national survey of adolescents and young adults (ages 13 to 24 years) recruited from an online panel in the USA measured loss of autonomy over nicotine product use by different product types with modified versions of the Hooked on Nicotine Checklist (Lin et al., 2022). The majority of participants endorsed at least one indicator of loss of autonomy across all types of products (conventional cigarettes 91.4%; disposable ENDS 80.7%; pod-based ENDS 83.1%; mod/other ENDS 82.5%) including among participants who only used ENDS devices (disposable ENDS 72.2%; pod-based ENDS 73.6%; mod/other ENDS 79.0%), (Lin et al., 2022). This study demonstrates that ENDS use is associated with symptoms of dependence among youth and young adults.

Analysis of cross-sectional survey data collected from 14 to 18 year old US high school students participating in the National Youth Tobacco Surveys between 2014 and 2023 found changes in symptoms of nicotine dependence reported over time among youth who used ENDS, with reporting craving ENDS and wanting to use ENDS within 30 minutes of waking were higher from 2018 to 2023 compared to between 2014 and 2017, suggesting that ENDS have become more dependence-forming after 2017 (Jackson et al., 2025). This corresponds with the period following the introduction of high dose nicotine salt-based ENDS, such as JUUL.

In a cross-sectional school survey conducted in the Netherlands, 35% had ever used a nicotine or tobacco product, 80% of whom had initiated nicotine use with ENDS, 18% with tobacco cigarettes and 2% with nicotine pouches. Among students who used nicotine in the past year,

41% self-identified as being addicted to nicotine and 60% had made a past-year quit attempt (77% of which were unsuccessful), (Raad et al., 2025).

ENDS and other nicotine products that are marketed as non-therapeutic products typically are designed to maximise consumer attractiveness including a range of flavours, attractive packaging and advertising that may increase experimentation among youth (Borowiecki et al., 2024). In combination with efficient nicotine delivery, these products are likely to have much greater dependence risk than nicotine replacement therapy products approved as medicines. A systematic review of 104 studies that examined the role of nicotine and flavour in dependence potential and appeal of ENDS among adults concluded that higher nicotine concentration and greater variety of flavours were associated with higher dependence potential (Gades et al., 2022). Survey research among adults found use of liquids with higher nicotine concentration via ENDS were associated with greater cigarette craving reduction (among those who were quitting smoking), higher satisfaction ratings and longer duration of use (Gades et al., 2022). In clinical trials, ENDS with higher nicotine doses were a better substitute for cigarettes than those with lower doses (fewer cigarettes smoked, lower exhaled carbon monoxide readings, and higher smoking abstinence levels). Survey research found that use of sweet-flavoured ENDS increased over time with tobacco flavour decreasing in popularity, suggesting that flavoured products have greater abuse potential (Gades et al., 2022). Laboratory studies have found young adults who use ENDS found fruit and menthol-flavoured ENDS more appealing than tobacco flavoured-ENDS and also that consumers rated use of ENDS in their usual flavour to be more satisfying than other flavoured ENDS. Non-tobacco flavoured ENDS (e.g., cherry) are also valued higher than unflavoured or tobacco-flavoured ENDS. Flavour (e.g., strawberry, cherry) also appears to influence how ENDS are used, with more and longer puffs that resulted in higher total nicotine exposure and higher peak concentration in some studies. Clinical trials with adults who smoke have found mixed results regarding flavours and substitutability of ENDS for cigarettes, with some finding no difference in withdrawal symptoms or cravings associated with flavour. Among adolescents, use of ENDS in non-tobacco flavours is associated with continuation of use, while use of cooling flavours is associated with greater intensity of use (Villanueva-Blasco et al., 2025). Hence, the reinforcing effect of flavours may differ by age and smoking experience, with sweet or cooling flavours potentially reducing the aversiveness of nicotine use among youth who do not smoke (Gades et al., 2022).

Many people who use ENDS find cessation difficult, providing key evidence of dependence formation. Several randomised clinical trials of ENDS-cessation interventions have been conducted, demonstrating varying degrees of effectiveness and a need for more high-quality evidence (Heshmati et al., 2025; Butler AR et al., 2025).

Nicotine pouches are a relatively new entrant to the nicotine product market and are similar to Swedish snus. Most nicotine pouch products are marketed as consumer products rather than tobacco cessation medicines. In some markets they are known as “white snus”, denoting their similarity to Swedish snus and marketed as an alternative to traditional snus (Carlsson et al.,

2025). Nicotine pouches can contain either nicotine extracted from tobacco plants or synthetically produced nicotine (Felicione et al., 2026; Zamarripa et al., 2025) and hence may contain one or both of two nicotine stereoisomers (S- and R-nicotine), (Zamarripa et al., 2025). They are produced in a wide range of doses with differences in ingredients, and moisture content, that can impact nicotine absorption, by altering parameters such as pH (Felicione et al., 2026; Al-Otaibi & Althobiani, 2025; Zamarripa et al., 2025). Nicotine pouches are marketed in a range of flavours, with flavours cited as a reason for use in survey data. Nicotine content across studies have ranged from 1.29 mg per pouch to 47.5 mg per pouch (Zamarripa et al., 2025).

In addition to variations in nicotine concentration and formulation, some manufacturers have introduced product technologies specifically designed to enhance nicotine delivery. Recent WHO analyses describe nicotine pouch products incorporating features such as “pearls” or “capsules” that are marketed as increasing the speed and intensity of nicotine absorption and accelerating nicotine dissolution, illustrating ongoing product innovation aimed at optimizing nicotine delivery and user satisfaction (WHO, 2026)

A systematic review of seven clinical studies (two independent and five tobacco industry studies) found that the time to reaching peak nicotine concentration is slower from pouches (20-65 minutes) than from cigarettes (5-8 minutes), and more similar to oral snuff (Heshmati et al., 2025). The peak blood nicotine concentration and total nicotine exposure produced from nicotine pouches can exceed that from cigarettes, for higher dose formulations (>8.0mg), (Zamarripa et al., 2025; Heshmati et al., 2025).

These findings challenge the perception of oral nicotine products as lower-risk alternatives, as high-dose formulations can achieve systemic exposures comparable to or exceeding conventional cigarettes.

There was variability in nicotine pharmacokinetics among pouches with the same reported dose but in different flavours. Flavoured nicotine pouches produced higher Cmax and total nicotine exposure than unflavoured nicotine pouches. High freebase nicotine pouches produced higher greater Cmax and total nicotine exposure than low freebase nicotine pouches. The review authors noted that the results from the independent studies were similar to those from tobacco industry funded studies. The form of nicotine isomer may also impact nicotine pharmacokinetics with one study finding higher plasma concentrations associated with nicotine pouches containing >99% S-nicotine compared to ones containing 50:50 S- and R-nicotine. Subjective measures associated with abuse liability, such as ‘drug liking’, ‘pleasant drug effect’ and ‘intention to use again were associated with nicotine pouch use in clinical studies. Nicotine pouches also suppressed urges to smoke, and cravings, albeit less than smoking ‘own-brand’ cigarette. A limitation of the current literature is that most clinical studies are industry funded (Zamarripa et al., 2025).

There are limited studies of the epidemiology of nicotine pouch use, with most surveys based on small samples and cross-sectional designs only. However, market data and survey research indicate that nicotine pouch use is increasing in several countries (Zamarripa et al., 2025; Brose et al., 2026). Between 2023 and 2024, a national survey of 10th and 12th grade students in the US noted an increase in past 30 day nicotine pouch use (from 0.2% to 0.9%), (Han et al., 2025). Nicotine pouch use has increased in Great Britain, with 1% of adults and 1.2% of youth reporting current use (Brose et al., 2026). Survey data from a sample of 118 adults reporting past 30 day nicotine pouch use found the sample demonstrated a significant level of mean nicotine dependence using a standardised test for smokeless tobacco dependence (Zamarripa et al., 2025; Dowd et al., 2024).

Dual and poly product use is a notable feature of the changing nicotine product market Zamarripa et al., 2025; Ali et al., 2016). Between 2023 and 2024 in the US among participants in the National Youth Tobacco Survey, dual use of both pouches and ENDS in the past 30 days increased from 1.1% to 1.7% (Han et al., 2024). Analysis of five waves of cross-sectional data collected from 16-19 year olds in the US between 2019 and 2021 observed an increase in oral nicotine product use over the time period (3.5% to 4.1%) oral nicotine product use was associated with past 30 day use of other nicotine products, including cigarettes (AOR=2.18, 95% CI=19.37, 40.88), ENDS (AOR=4.27, 95% CI=3.02, 6.04), and smokeless tobacco (AOR=28.14, 95% CI=19.37, 40.88), (Schneller et al., 2023). Among adult samples, nicotine pouch use is associated with smokeless tobacco use, cigarettes, and ENDS (Zamarripa et al., 2025; Dowd et al.,2024). Among Dutch students in a cross-sectional survey who had used nicotine products in the past year, 70% reported dual use of ENDS and tobacco cigarettes (Raad et al., 2025). A systematic review of 16 original studies examined patterns of transition between ENDS, conventional cigarettes and dual use of both found dual use was associated with maintenance of smoking (Hamoud et al., 2024).

Dual and poly-use patterns are particularly concerning from a public health perspective, as they sustain nicotine dependence while preventing cessation, thereby maintaining cumulative exposure and associated disease risk.

Hence, how different non-tobacco nicotine containing products are used in combination with each other and also with conventional tobacco products is relevant to evaluating their potential to lead to nicotine dependence formation and maintenance.

Overall, the scientific literature on modern non-therapeutic nicotine products marketed as alternatives to tobacco cigarettes is still evolving. However, there is already sufficient evidence to demonstrate that these products can deliver nicotine more efficiently and at higher doses than approved medicinal nicotine replacement therapies, often approximating the pharmacokinetic profile of tobacco cigarettes. Emerging data on patterns of use, including the development of dependence and withdrawal symptoms upon cessation, are consistent with these pharmacokinetic characteristics. Importantly, nicotine dependence should not be viewed solely as a behavioural disorder but as a primary driver of sustained biological exposure. The

pharmacokinetic properties of modern nicotine products—characterised by rapid delivery, high peak plasma concentrations, and enhanced tolerability—promote persistent use and increase cumulative dose. This sustained exposure increases cumulative health risk over time. Accordingly, addiction and toxicity are not separate phenomena but intrinsically connected components of nicotine's overall health impact.

Chapter 05 — Therapeutic Use and Medical Applications

Despite nicotine's well-established dependence-producing properties, it is widely used for therapeutic purposes, mainly for the treatment of tobacco dependence through nicotine replacement therapy (NRT). NRT therapy aims to reduce withdrawal symptoms and cravings and prevent relapse by delivering nicotine in controlled doses (World Health Organization, 2024).

Importantly, the therapeutic rationale for NRT is based on harm reduction and controlled dosing. NRT provides lower and more gradual systemic nicotine exposure compared with conventional cigarettes, thereby reducing addiction reinforcement and limiting acute physiological stress responses (Benowitz, 2016).

Depending on the country, there are several NRT formulations available such as transdermal patches, chewing gum, lozenges, sublingual tablets, oral sprays, inhalers, and nasal sprays. The above-mentioned NRT formulations are authorized in most WHO Member States either as prescribed medications or over-the-counter depending on national regulation. The WHO clinical treatment guideline for tobacco cessation published in 2024 identifies NRT as a first-line pharmacotherapy and recommends its availability as part of comprehensive cessation services (World Health Organization, 2024).

These formulations are specifically designed to avoid rapid nicotine delivery to the brain, resulting in lower peak plasma concentrations and reduced abuse liability compared with inhaled nicotine products (Benowitz et al., 2009).

The WHO highlights that NRTs should be distinguished from consumer nicotine products such as e-cigarettes, nicotine pouches and heated tobacco products due to the fact that they are evaluated for efficacy, safety and dose delivery under medicinal regulatory pathways ((World Health Organization, 2024; WHO Study Group on Tobacco Product Regulation, 2021).

This distinction is critical, as non-therapeutic nicotine products are often engineered to maximise nicotine delivery efficiency, sensory appeal and user satisfaction, thereby increasing dependence potential and cumulative exposure. In contrast, NRT is intended for time-limited use within a clinical context, with the goal of tapering and ultimately eliminating nicotine exposure. Even at therapeutic doses, nicotine can exert pharmacological effects including sympathetic activation, haemodynamic changes, and potential endothelial dysfunction (Münzel et al., 2026, 2025; Thomas et al., 2025). Accordingly, the benefit–risk profile of NRT is favourable primarily because it replaces a substantially more harmful exposure. From a public health perspective, this distinction underscores a key principle: therapeutic nicotine use within a controlled cessation framework differs fundamentally from chronic exposure through consumer nicotine products designed for sustained use.

Approved Therapeutic Indications

Smoking Cessation

The most recent Cochrane systematic review evaluating different doses, durations, and formulations of NRT included 63 randomized controlled trials. Evidence showed high-certainty evidence that using combination NRT versus single-form NRT and 4 mg versus 2 mg nicotine gum can increase the chances of successfully quitting smoking. In addition, 21 mg patches resulted in higher quit rates than 14 mg (24-hour) patches and using 25 mg patches resulted in higher quit rates than using 15 mg (16-hour) patches. The use of a fast-acting form of NRT, such as gum or lozenge, resulted in similar quit rates to nicotine patches (Lindson et al., 2019). These findings underscore that the efficacy of NRT is closely linked to achieving sufficient nicotine substitution to suppress withdrawal, highlighting the central role of nicotine pharmacokinetics in both dependence and cessation.

Another systematic review which included 133 studies also confirmed that NRT products significantly increase smoking cessation rates compared with placebo or no treatment. Across pooled analyses, NRT increased the rate of quitting by 50% to 60%, regardless of setting, and further research is very unlikely to change our confidence in the estimate of the effect. Combination NRT—typically a long-acting NRT (transdermal patch) combined with a short-acting product such as gum, lozenge, spray or inhaler demonstrates superior efficacy compared with NRT monotherapy use, increasing sustained cessation rates by approximately 20–25% (Hartmann-Boyce et al., 2018). Recent meta-analyses also confirm that combination NRT performs similarly to or slightly below varenicline in long-term abstinence outcomes and remains highly effective and broadly applicable because of its safety profile and wide availability (Cahill et al., 2013).

Importantly, the effectiveness of combination NRT reflects its ability to approximate nicotine delivery patterns sufficient to prevent withdrawal while avoiding the rapid, high-peak exposure associated with combustible or inhaled nicotine products (Benowitz et al., 2016).

The safety profile of approved NRT products is well established. The WHO clinical treatment guideline for tobacco cessation in adults concluded that the balance of benefits against harms favours NRT on the basis of moderate to large benefits (NRT versus placebo/no NRT, NNT: 12–45 for one additional long-term abstinence depending on level of baseline behavioural support) and small harms (the most common adverse events with NRT include hiccups, jaw pain, sore throat, mouth ulcers, gastrointestinal disturbance and local irritation, while more severe adverse events such as increased risk of chest pains and heart palpitations were uncommon), (World Health Organization, 2024).

NRT also plays an important role in relapse prevention and smoking reduction where immediate complete abstinence is not achieved. Some clinical guidelines support NRT for gradual reduction before quit attempts, particularly in highly dependent smokers unwilling to stop immediately. This broader therapeutic use reflects the flexibility of nicotine substitution approaches in clinical practice (National Institute for Health and Care Excellence, 2023).

From a clinical perspective, this approach is best understood as a transitional strategy aimed at reducing cumulative exposure and facilitating eventual cessation, rather than as a long-term maintenance therapy.

Investigational and Non-Approved Medical Uses

Several studies have investigated the potential therapeutic effects of nicotine in a range of neurological and psychiatric conditions, including Parkinson's disease, Alzheimer's disease, and attention-deficit/hyperactivity disorder (Miditana et al., 2025; Centner et al., 2020). While some studies have suggested possible benefits, the overall evidence remains inconclusive and no major regulatory authority has approved nicotine for these indications (Miditana et al., 2025; Newhouse et al., 2012).

These exploratory findings are primarily based on nicotine's modulatory effects on cholinergic neurotransmission; however, such central nervous system effects occur in parallel with systemic physiological responses, including sympathetic activation and haemodynamic changes (Benowitz, 2016).

Systematic reviews conclude that any potential benefits in these contexts are outweighed by concerns regarding dependence, cardiovascular effects, and the availability of alternative treatments with more favorable risk–benefit profiles (Dautzenberg et al., 2021; Benowitz, 2016).

Importantly, the same pharmacological mechanisms that may underlie potential therapeutic effects, namely receptor activation and neurotransmitter modulation, also contribute to addiction, cardiovascular stress, and long-term toxicity. In addition, chronic nicotine exposure is associated with activation of oxidative and inflammatory pathways, which may counteract or outweigh any potential neuroprotective effects (Münzel et al., 2026).

Taken together, the current evidence does not support the use of nicotine as a therapeutic agent outside of regulated cessation contexts, and its use for investigational indications should be approached with caution.

Regulatory Status and Oversight

Regulatory agencies such as the U.S. Food and Drug Administration and the European Medicines Agency consider NRTs as regulated medicinal products, which are subject to pharmaceutical manufacturing standards, dose limits, labeling requirements and post-marketing surveillance. They have consistently emphasized that NRT products are intended for short- to medium-term use as part of smoking cessation efforts and not for indefinite nicotine maintenance (U.S. Food and Drug Administration, 2026; European Medicines Agency, 2009).

This regulatory framework reflects a risk–benefit assessment in which controlled, time-limited nicotine exposure is considered acceptable when it replaces substantially more harmful

exposures such as conventional cigarettes. However, it also implicitly acknowledges that nicotine itself is not biologically inert and that prolonged or uncontrolled exposure carries potential health risks.

Importantly, therapeutic nicotine products such as NRTs differ from consumer nicotine products in several respects, including slower systemic absorption, lower peak plasma nicotine concentrations and reduced abuse liability due to their slower rate of nicotine delivery. These pharmacokinetic characteristics contribute to their regulatory approval despite nicotine's known dependence liability (Benowitz, 2009).

In contrast, many non-therapeutic nicotine products are designed to optimise rapid nicotine delivery, sensory appeal, and user satisfaction, features that increase abuse liability and cumulative exposure. This divergence highlights a fundamental regulatory asymmetry: while medicinal nicotine is tightly controlled, consumer nicotine products often evolve rapidly and may fall outside traditional pharmaceutical regulatory frameworks.

The continuing medical exemption of nicotine therefore rests on a distinction between substance and formulation. Nicotine itself remains pharmacologically active and dependence-producing, but in approved NRT formulations it is delivered under conditions specifically designed to minimize abuse liability while maximizing therapeutic benefit (Benowitz, 2009).

From a scientific perspective, this distinction underscores that risk is determined not only by the substance itself but by its mode of delivery, pharmacokinetics and patterns of use. Accordingly, regulatory approaches that focus solely on product category rather than on nicotine exposure and delivery characteristics may underestimate the health risks associated with emerging nicotine products. This has important implications for public health policy, as the increasing diversity of nicotine formulations, including synthetic nicotine and high-concentration products, challenges existing regulatory paradigms.

Conventional cigarettes

Globally, approximately 1.20 billion people aged 15 years and older were current users of one or more tobacco products, with conventional cigarettes the most dominant form of use. There is a substantial decline from the 1.379 billion in 2000, but this change is largely driven by reductions in some regions and progress is uneven and dependent on sustained tobacco-control efforts. The global adult tobacco use prevalence remains approximately 20%, with men disproportionately affected (male current tobacco users aged 15 years and older totalled 997 million, and female users aged 15 years and older totalled 206 million), (World Health Organization, 2024). Cigarette smoking is the most common form of tobacco use worldwide and there is no safe level of exposure to tobacco smoke (World Health Organization fact sheet, 2024).

As the nicotine product landscape evolves, distinguishing between product categories alone may underestimate the true burden of exposure, particularly in the context of increasing use of non-combustible nicotine products.

ENDS / E-Cigarettes

As presented in the WHO global tobacco trends report, more than 100 million people worldwide currently use electronic nicotine delivery systems (ENDS), including at least 86 million people aged 15 years and older (53 million men and 34 million women) and ≥15 million adolescents aged 13–15 years. Adolescents in countries with available data were on average nine times more likely than adults to vape, highlighting a major shift in nicotine initiation pathways (World Health Organization, 2024).

This shift represents a fundamental change in the epidemiology of nicotine use, with non-combustible products increasingly serving as the primary entry point into nicotine exposure, particularly among youth. Unlike traditional patterns in which nicotine dependence typically followed conventional cigarettes use, current trends indicate that many adolescents initiate nicotine use directly through ENDS, often without prior cigarette smoking. In addition, the high prevalence of ENDS use among adolescents reflects the combined impact of product design, flavouring, marketing, and rapid nicotine delivery technologies, which together increase product appeal and dependence potential. Importantly, this epidemiological shift may translate into a delayed but substantial future burden of cardiovascular and metabolic disease, as early-life nicotine exposure establishes long-term biological risk trajectories (Münzel et al., 2026).

Heated Tobacco Products (HTPs)

A systematic review and meta-analysis on the global prevalence of heated tobacco product use revealed that HTP use has increased since their introduction after 2015. The lifetime HTP use prevalence between 2015–2022 is estimated at 4.87%, with current use around 1.5% globally. Meta-regression showed higher current HTP use in the Western Pacific Region (3.80%)

compared with the European Region (1.40%) and the Americas (0.81%). Current global use is higher for males (3.45%) compared to females (1.82%), while adolescents had higher lifetime experimentation with HTPs (5.25%) than adults (2.45%), (Sun et al., 2023).

Although current global prevalence of HTPs remains lower than that of conventional cigarettes and electronic nicotine delivery systems, their rapid increase in uptake since introduction reflects a growing and evolving segment of the nicotine market (World Health Organization, 2023; Kim et al., 2020). HTPs are frequently marketed as reduced-risk alternatives to cigarettes; however, evidence indicates that their use commonly occurs alongside other nicotine products rather than as complete substitutes (Glantz, 2020; Tabuchi et al., 2018). Dual and poly-use patterns involving HTPs, cigarettes and ENDS are increasingly reported, potentially sustaining nicotine dependence and cumulative exposure rather than reducing it (Gallus et al., 2021).

Smokeless Tobacco (Including Snus)

Smokeless tobacco (ST) use varies considerably across geographic regions, age groups and gender demographics. The patterns of use are shaped by a combination of cultural traditions, socioeconomic determinants and differences in national regulatory and public health frameworks. The WHO South-East Asia Region, including countries such as India and Bangladesh, accounts for more than 80% of all global ST users. Use is particularly widespread in South Asia, where it is deeply embedded in social and cultural practices. In India alone, it is estimated that approximately 200 million individuals use smokeless tobacco (Mehrotra et al., 2026).

Smokeless tobacco use is also prevalent in several African countries. In Sudan, Toombak, a traditional oral smokeless tobacco product prepared from Nicotiana rustica, is widely used. Toombak is characterized by high nicotine content and exceptionally high concentrations of tobacco-specific nitrosamines (TSNAs), potent carcinogens that have been associated with a markedly increased risk of oral cancer among long-term users. This example highlights the substantial variability in nicotine delivery and toxicant exposure across smokeless tobacco products globally and underscores the importance of considering regional product characteristics when assessing the public health impact of nicotine-containing products (Sami et al., 2023).

This high prevalence represents a substantial and often under-recognized source of global nicotine exposure, particularly in regions where public health surveillance has traditionally focused more on smoking than on smokeless forms of use.

Although less common in Western countries, smokeless tobacco remains a public concern in the United States, especially among young males and in rural areas. Within Europe, Scandinavian countries and especially Sweden, represent a distinct epidemiological context, where the use of snus, a form of oral smokeless tobacco, is culturally established. It should be distinguished from the newer category of oral nicotine pouches, which are typically tobacco-free products that may contain either tobacco-derived or synthetic nicotine (Siddiqi et al., 2020).

Snus and other smokeless tobacco products are sometimes promoted as lower-risk alternatives to smoking; however, they still deliver substantial doses of nicotine and sustain dependence. From a biological perspective, nicotine exposure from smokeless tobacco continues to activate sympathetic, oxidative, and inflammatory pathways associated with cardiovascular disease (Münzel et al., 2026).

In general, men have higher rates of use than women, except in some regions such as Bangladesh, Indonesia and Thailand where female prevalence is equal or higher. ST use is also more prevalent in lower-income and rural communities (Mehrotra et al., 2026).

These demographic patterns highlight important health equity concerns, as vulnerable populations may experience disproportionate exposure and associated disease burden. Importantly, long-term use of smokeless tobacco is associated with increased risks of cardiovascular disease, oral cancer, and other chronic conditions, underscoring that non-combustible nicotine use is not without significant health consequences.

Oral Nicotine Pouches

Population-based surveys conducted in North America, Europe, and Oceania (Canada, England, United States, New Zealand) demonstrate increasing awareness and use of tobacco-free oral nicotine pouches between 2022 and 2024. Past-30-day use among adolescents ranged between 0.8% and 2.5%, while prevalence among young adults reached up to 7.9% in some surveys. These products are frequently used by individuals who also use cigarettes or e-cigarettes (Reid et al., 2025).

Self-reported national survey data demonstrate a high prevalence of oral nicotine use in Sweden. According to the Public Health Agency of Sweden, approximately 22% of adult men report daily snus use, while survey-based data from the Swedish Council for Information on Alcohol and Other Drugs (CAN) indicate that around 26% of men report current (past-30-day) use (Public Health Agency of Sweden) . Long-term epidemiological analyses further show that snus use among men has remained consistently high, at approximately 25–30% over recent decades (Sjodin et al., 2024), with even higher prevalence observed in younger male populations (Ermann et al., 2024).

Although current prevalence remains lower than for other nicotine products, the rapid increase in awareness and uptake indicates that oral nicotine pouches represent a growing segment of the nicotine market (World Health Organization, 2023; Robichaud et al., 2020). These products are frequently used in addition to, rather than instead of, other nicotine products, contributing to dual and poly-use patterns that sustain dependence and cumulative exposure (Czaplicki et al., 2021). Oral nicotine pouches can deliver high doses of nicotine, with some formulations exceeding those of traditional smokeless tobacco products, raising concerns regarding addiction potential and systemic exposure (Mallock et al., 2024). Their discreet use, absence of combustion, and wide range of flavours may increase acceptability among youth and non-smokers, potentially facilitating initiation of nicotine use (Park-Lee et al., 2024; Marynak et al., 2021). Furthermore, the classification of these products as "tobacco-free" may create a misleading perception of reduced harm (Robichaud et al., 2020). Furthermore, the

classification of these products as “tobacco-free” may create a misleading perception of reduced harm, despite continued nicotine exposure and its associated biological effects (Robichaud et al., 2020; Patel et al., 2023).

Epidemiology of Nicotine Products in Youth

Global Burden

Around 10% of the global population of youth aged 13–15 years (>40 million) were estimated to use one or more tobacco-containing products (excluding e-cigarettes and nicotine pouches). The highest prevalence was recorded in the WHO European Region (11.6%), followed by the WHO Eastern Mediterranean Region (11.0%) and the WHO Western Pacific Region (10.5%), (World Health Organization, 2024).

These estimates likely underestimate total nicotine exposure among youth, as they exclude non-combustible products such as e-cigarettes and nicotine pouches, which are increasingly used in this age group. Taken together, the available data indicate that nicotine use among adolescents remains widespread globally, albeit with shifting patterns across product types.

With regards to cigarette use, it is estimated that an average of 5.1% of adolescents between 13–15 years are current cigarette users, with the highest prevalence in the WHO European Region (8.4%), followed by the Western Pacific Region (6.4%) and the Region of the Americas (5.7%). It is worth mentioning that the results of the European School Survey Project on Alcohol and Other Drugs found that, on average, 20% of mid-adolescents aged 16 years were current cigarette smokers. Iceland had the lowest prevalence among European countries (5.1%), while among the highest were Bulgaria and Italy (ESPAD Report 2019).

While cigarette smoking among youth has declined in some regions, this trend is increasingly offset by rising use of alternative nicotine products, indicating a shift rather than a reduction in overall nicotine exposure. This shift in initiation pathways, from conventional cigarettes to non-combustible nicotine products, represents a fundamental change in the epidemiology of nicotine use. Early initiation is strongly associated with greater dependence severity, longer duration of use, and higher cumulative lifetime exposure, thereby amplifying long-term cardiovascular and metabolic risk (Munzel et al., 2021). In addition, persistent alterations in acetylcholine and dopamine signaling caused by adolescent nicotine exposure may contribute to the heightened risk for psychiatric disorders including substance abuse, anxio-depressive disorders, and schizophrenia for which deficits in a large spectrum of motivational domains are highly prevalent (Reynolds et al., 2025). From a population health perspective, current patterns of youth nicotine use may translate into a substantial future burden of chronic disease, even in settings where cigarette smoking prevalence is declining.

E-cigarettes

Globally, the prevalence of current e-cigarette use among adolescents aged 13–15 years has been estimated at 7.2% (~14.7 million adolescents). A comparative analysis of adult and adolescent survey data from 64 countries demonstrated a pronounced age-related disparity in

e-cigarette use, with the prevalence among adolescents aged 13–15 years on average 9 times higher than among adults. In approximately half of the countries analyzed, the ratio of adolescent to adult use was 9:1 or greater (World Health Organization, 2024).

Data from the Global Tobacco Surveillance System further illustrated this pattern: among adolescents aged 13–15 years, current e-cigarette use ranged from 8.2% to 18.4%, whereas adult prevalence in the same countries ranged from only 0.2% to 3.4% in surveys conducted in the Philippines, Romania, Ukraine and Uruguay between 2015 and 2019. In Albania, Belarus, the Dominican Republic, Guam, Morocco, Niue, Oman, the Russian Federation, and Ukraine, current e-cigarette use among adolescents aged 13–15 years was reported to be two to three times more common than conventional cigarette smoking, while in Paraguay it was approximately four times higher (Reid et al., 2025).

In several settings, e-cigarette use has overtaken conventional cigarette smoking among adolescents, indicating a profound shift in nicotine consumption patterns rather than a simple decline in tobacco use. This transition suggests that nicotine dependence is being established through new delivery systems, potentially sustaining or even expanding the overall burden of addiction.

Results of the ITC survey in Canada showed an increasing trend of e-cigarette use between 2017 and 2022, as the number of 16–19-year-olds reporting current e-cigarette use doubled (Hammond et al., 2023). In England, prevalence among secondary school students predominantly aged 11–15 years rose steadily between 2014 and 2021, before stabilizing between 2021 and 2023 at approximately 9%. By comparison, current cigarette smoking prevalence in the same age group in 2023 was around 3%, indicating that vaping prevalence was approximately three times higher than smoking (NHS England Digital, 2024).

Finally, results from the 2019 ESPAD European School Survey showed particularly high prevalence among 15–16-year-olds, with Lithuania, Monaco, and Poland each reporting current e-cigarette use prevalence of 30% or higher (ESPAD, 2020).

Such high prevalence levels indicate that in some populations, e-cigarette use has become a normative behaviour among adolescents, raising concerns about normalization of nicotine use in younger generations. Given that early nicotine exposure is associated with long-term neurobiological changes and increased addiction vulnerability, these patterns may translate into prolonged lifetime exposure and increased future risk of cardiovascular and metabolic disease (Reynolds et al., 2025; Münzel et al., 2026).

Heated Tobacco Products (HTPs)

A systematic review and meta-analysis of Sun et al. (2023), conducted across 42 countries of all WHO regions from 2015 to 2022, highlighted that the estimated prevalence of HTP use by the general population aged ≥9 years was 4.9% (lifetime), 1.5% (current) and 0.8% (daily) during that period. Within the duration of the study, an increase of 10.48% was observed in the WHO Western Pacific Region and 1.2% in the WHO European Region (Sun et al., 2023).

Although overall prevalence remains lower than that of conventional cigarettes and e-cigarettes, the observed increases indicate that HTPs represent a rapidly expanding segment of the nicotine market. The particularly strong growth in the Western Pacific Region reflects targeted market penetration and product positioning as reduced-risk alternatives, which may influence user perception and uptake. Importantly, HTP use frequently occurs in combination with other nicotine products, particularly conventional cigarettes, rather than replacing them entirely. Such dual-use patterns may sustain nicotine dependence and cumulative exposure, thereby limiting potential reductions in health risk at the population level. From a biological perspective, HTPs continue to deliver nicotine efficiently and expose users to a range of harmful constituents, maintaining activation of pathways associated with cardiovascular and metabolic disease (Münzel et al., 2026). Furthermore, the relatively recent introduction of HTPs means that long-term epidemiological data are lacking, raising concerns that current prevalence estimates may not yet reflect their full future disease burden.

Smokeless Tobacco Products (Including Snus)

Based on nationally representative school surveys conducted between 2014 and 2024 in 129 countries, covering approximately 66% of WHO Member States and 73% of the global population aged 13–15 years, an estimated 3.4% of adolescents in this age group reported current use of smokeless tobacco products. The highest estimated prevalence was observed in the WHO African Region and the WHO South-East Asia Region, where prevalence reached 4.2% in both regions. However, in the African Region, survey coverage included only 47% of the regional population in this age group, meaning that the current estimate should be interpreted cautiously (World Health Organization, 2024).

These data indicate that smokeless tobacco use remains a significant and geographically concentrated source of nicotine exposure among adolescents, particularly in regions where cultural and social factors support its use. Importantly, smokeless tobacco use is often underrepresented in global tobacco surveillance, which may lead to underestimation of total nicotine exposure in affected populations.

Recent epidemiological evidence indicates that snus use among adolescents is primarily concentrated in Nordic countries, where it represents a major component of youth nicotine consumption. In Sweden, national surveillance data show substantial prevalence among adolescents: approximately 13% of boys and 9% of girls aged 13 years report snus use, increasing to around 31% of boys and 27% of girls by age 15, indicating a marked rise during mid-adolescence (Public Health Agency of Sweden, 2024). In other Nordic countries, youth use of smokeless nicotine products, including snus, has also increased. In Denmark, surveys indicate that the use of smokeless nicotine products among adolescents rose from approximately 2% in 2010 to more than 11% by 2021(Vibjerg, 2023).

These steep increases during adolescence highlight the role of smokeless tobacco—particularly snus, as an early initiation product for nicotine use in certain populations. While often perceived as a lower-risk alternative to smoking, snus delivers substantial nicotine doses and can establish strong dependence, thereby sustaining long-term exposure. From a population

health perspective, this pattern suggests a shift in nicotine use modalities rather than a reduction in overall exposure.

Outside Scandinavia, snus use among adolescents is considerably less common but still present in some countries. In the United States, nationally representative youth surveys indicate that approximately 662,000 middle and high-school students had ever used snus in 2020, corresponding to an estimated prevalence of about 3.5% among high-school students and 1.0% among middle-school students (Dai & Leventhal, 2023).

Although prevalence outside Scandinavia remains comparatively low, the presence of snus use among youth in multiple regions indicates potential for further expansion, particularly as product availability and marketing increase. Given that early nicotine exposure is associated with long-term addiction and increased cardiometabolic risk, even relatively low prevalence levels may translate into meaningful future disease burden (Munzel et al., 2021).

Oral Nicotine Pouches

Data on use of nicotine pouches are lacking for many countries. Recent cross-national surveys conducted between 2022 and 2024 in Canada, the United States, England and New Zealand provide recent prevalence estimates on nicotine pouch use. These studies reported that approximately 5% of youth (16–19 years old) had ever used nicotine pouches in Canada, the United States, and New Zealand, and about 10% in England, while current (past-30-day) use ranged between 1.6% and 4.0% across these countries, with the highest prevalence observed in England (Reid et al., 2025).

Although prevalence remains lower than for e-cigarettes, these data indicate rapid growth in awareness and uptake, suggesting that nicotine pouches represent an emerging and expanding category of nicotine products among youth. The absence of data in many regions further raises the possibility that current estimates underestimate the true global burden of use.

European adolescent studies also suggest increasing experimentation with nicotine pouches. A survey of adolescents aged 16–17 years reported a lifetime prevalence of approximately 5.4%, with higher prevalence among boys (6.3%) than girls (3.5%). In this study, lifetime use increased substantially with age, with 15.2% of boys and 10.3% of girls aged 16–17 reporting having used nicotine pouches at least once (Hanewinkel et al., 2025). In a nationally representative survey conducted in the Netherlands in 2020, awareness of nicotine pouches among adolescents aged 13–17 years was reported by 9.1% of respondents; however, actual use remained very limited, with only 0.3% reporting ever having tried a nicotine pouch and no respondents indicating current use (Havermans et al. 2021).

These findings suggest that nicotine pouch use follows a trajectory of increasing awareness, experimentation, and subsequent uptake, consistent with patterns previously observed for e-cigarettes. The increase in use with age during adolescence highlights the vulnerability of this developmental period to initiation and progression of nicotine dependence.

In Great Britain, data from the Action on Smoking and Health Smokefree Great Britain Youth Survey 2024 among young people aged 11–18 years showed that 3.3% had ever used nicotine pouches, while 1.2% reported current use at the time of the survey (Brose et al., 2026).

In the National Youth Tobacco Survey in the USA, the prevalence of ever use of nicotine pouches by middle- and high-school students (11–18 years) was 1.9% in 2021, which rose significantly to 3.5% in 2024. The prevalence of nicotine pouch use in the past 30 days by middle- and high-school students increased significantly, from 0.8% to 1.9% between 2021 and 2024 (U.S. Food and Drug Administration, 2025).

Overall, the available epidemiological evidence indicates that nicotine pouch use among adolescents remains less prevalent than e-cigarette use or traditional cigarettes, but there is evidence of rapid growth in awareness, experimentation and early adoption among youth in several countries, particularly in Europe and North America. In addition, nicotine pouch use among adolescents frequently occurs in the context of dual or poly-nicotine product use, especially among individuals who already use e-cigarettes or other tobacco products (Public Health Agency of Sweden, 2024).

Dual and poly-use patterns are of particular concern, as they sustain nicotine dependence and increase cumulative exposure rather than replacing other sources of nicotine. Oral nicotine pouches can deliver substantial doses of nicotine, and their discreet use, flavouring, and "tobacco-free" positioning may enhance acceptability among youth and non-smokers. From a public health perspective, this combination of high-dose delivery, ease of use, and increasing uptake suggests that nicotine pouches may contribute to a new wave of nicotine initiation and sustained exposure. Given the established links between early nicotine exposure, long-term addiction, and cardiometabolic disease, even modest increases in prevalence may translate into a meaningful future health burden (Munzel et al., 2026).

Other Nicotine Products

Recently, a range of commercially marketed oral nicotine products, including nicotine gums, lozenges, gummies, mints, candies, and toothpicks—has entered several consumer markets, particularly in the United States, with much of their promotion occurring through online retail and digital marketing channels (Gaiha et al., 2023; Ling et al., 2023; Unger et al., 2022).

In the United States, data from 2024 indicate that 3.1% of middle and high-school students aged 11–18 years reported ever using at least one of these nicotine products, while 1.2% reported current use at the time of the survey (Jamal et al., 2024).

Global Burden of Nicotine Products Use (Mortality, Morbidity, Public Health Burden)

Recent global burden estimates confirm that nicotine-containing products remain one of the largest contributors to preventable morbidity and mortality worldwide. According to the most recent Global Burden of Disease analyses, tobacco exposure caused approximately 7.36 million deaths globally in 2023 and more than 200 million disability-adjusted life years (DALYs), mainly through cardiovascular disease, cancers, chronic respiratory diseases and metabolic

disorders. Conventional cigarettes remains the dominant contributor to this burden while smokeless tobacco also contributes substantially, especially through oral cancers and cardiovascular disease in South-East Asia (Morgan et al., 2025).

Although long-term mortality data for newer nicotine products such as e-cigarettes, heated tobacco products (HTPs) and nicotine pouches remain limited, emerging evidence indicates that these products may contribute to cardiovascular and respiratory morbidity and sustain nicotine dependence, particularly in younger populations (World Health Organization, 2024; Morgan et al., 2025).

The absence of long-term epidemiological data should not be interpreted as absence of risk, but rather reflects the relatively recent introduction of these products and the long latency of chronic disease development.

Given their ability to deliver nicotine efficiently and promote sustained use, these products are likely to contribute to future disease burden, particularly through early-life initiation and prolonged exposure.

There are substantial differentiations of the burden across the WHO regions. The South-East Asia Region (SEAR) accounts for approximately 2.4 million tobacco-attributable deaths annually, representing one of the highest regional mortality burdens globally, largely driven by widespread cigarette smoking and smokeless tobacco use. In India alone, smokeless tobacco is estimated to contribute to more than 350,000 deaths annually, particularly through oral cancer, ischemic heart disease, and stroke. The Western Pacific Region (WPR) contributes an estimated 2.7 million tobacco-attributable deaths each year, with China alone accounting for more than 2 million smoking-related deaths annually, making it the single largest national contributor to global tobacco mortality (World Health Organization, 2024; Morgan et al., 2025).

These regional patterns highlight that the burden of nicotine-containing products is shaped not only by prevalence but also by product type, patterns of use, and socioeconomic context.

In the African Region (AFR), tobacco-attributable mortality remains comparatively lower in absolute terms, with approximately 146,000 deaths annually, but current epidemiological trends indicate rising smoking prevalence in several countries, particularly among younger populations and urban communities (Ilesanmi et al., 2026). In the Eastern Mediterranean Region (EMR), tobacco causes approximately 429,000 deaths annually, with smoking contributing substantially to cardiovascular disease, chronic respiratory disease, and multiple cancers (Sultan et al., 2024).

These trends suggest that, in the absence of effective prevention strategies, regions with currently lower burden may experience substantial increases in nicotine-related disease in the coming decades.

In the Region of the Americas (AMR), smoking prevalence has declined substantially over the past two decades because of stronger tobacco-control policies. However, tobacco use continues

to contribute significantly to cardiovascular disease, lung cancer, and chronic obstructive pulmonary disease, while the rapid uptake of e-cigarettes and oral nicotine products among adolescents and young adults has introduced new public-health concerns with renormalization of tobacco and nicotine product use. (World Health Organization, 2024; Centers for Disease Control and Prevention, 2024).

The European Region (EUR) continues to have one of the highest prevalences of tobacco use globally. According to the most recent Eurobarometer, 24% of adults in the European Union currently use tobacco products, while 3% report current e-cigarette use and 2% heated tobacco product use. Tobacco remains the leading avoidable cause of death in Europe, responsible for approximately 700,000 deaths annually in the European Union alone, with about half of long-term smokers dying prematurely (European Commission, 2023).

The coexistence of multiple nicotine product categories within populations underscores the importance of assessing total nicotine exposure rather than individual product use in isolation.

Taken together, the global burden of nicotine-containing products reflects not only the legacy of conventional cigarettes, but also an evolving landscape of nicotine exposure in which new products, early initiation, and sustained dependence may shape future patterns of disease.

Conclusions

The evidence presented in this critical review demonstrates that nicotine is a pharmacologically active substance with well-established dependence-producing properties and a direct role in multiple pathophysiological processes, including cardiovascular injury, developmental toxicity, and systemic biological effects (Benowitz, 2009; Hukkanen et al., 2005; Leventhal et al., 2021; Munzel et al., 2026).

The conclusions reached by the World Health Organization (WHO) Expert Committee on Drug Dependence in the mid-1990s were based on the scientific evidence and product landscape available at that time. Critically, that assessment relied on implicit pharmacokinetic assumptions, particularly the absence of non-combustible delivery systems capable of producing rapid and high-intensity central nervous system exposure (World Health Organization, 1999; Benowitz, 2009; Hukkanen et al., 2005).

These assumptions no longer apply.

Modern nicotine products have fundamentally altered nicotine pharmacokinetics and exposure patterns. Evidence demonstrates that:

- Nicotine can now be delivered with rapid central nervous system penetration comparable to conventional cigarettes (Benowitz et al., 2021; Hajek et al., 2020)
- Peak plasma concentrations and total systemic exposure are sufficient to produce strong reinforcing and dependence-producing effects (Helen et al., 2016; Yingst et al., 2019)
- Product design features, including nicotine salts and formulation engineering, enhance repeated dosing and sustained exposure (Zamarripa et al., 2025; Leventhal et al., 2021; Gades et al., 2022)

These developments directly challenge the pharmacokinetic threshold concept underlying the 1996 non-scheduling decision.

Furthermore, nicotine is now widely available in purified, concentrated and readily deliverable forms. Unlike traditional tobacco products, modern nicotine delivery systems provide direct access to the psychoactive substance without the need for combustion or complex processing. This aligns with established precedents in international drug control, where the availability and extractability of a psychoactive principle have been considered relevant factors in scheduling decisions (United Nations, 1961; WHO Expert Committee on Drug Dependence, 1992).

At the population level, the increasing prevalence and diversification of nicotine products, particularly among adolescents and young adults, indicate a substantial and evolving public health burden (World Health Organization, 2024).

Patterns of dual and poly-use further sustain nicotine exposure and increase cumulative risk.

Importantly, the distinction between therapeutic and non-therapeutic nicotine use remains critical. Licensed nicotine replacement therapies, characterised by controlled dosing and slower pharmacokinetics, are designed to reduce dependence and should remain exempt under established ECDD practice (World Health Organization, 2024).

In contrast, non-therapeutic nicotine products are increasingly engineered to maximise delivery efficiency, user acceptability, and repeated exposure, thereby enhancing dependence potential and population-level risk.

In light of these considerations, the totality of current evidence supports the conclusion that nicotine, as delivered by contemporary consumer products, meets criteria that were not fulfilled under the conditions evaluated in 1996.

Accordingly, a re-assessment of nicotine under the framework of the 1971 Convention is scientifically justified and warranted.

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