International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	ORAL HEALTH EFFECTS OF NICOTINE POUCHES: A SYSTEMATIC NARRATIVE REVIEW WITH CONTEXTUALIZATION AGAINST CONVENTIONAL TOBACCO PRODUCTS
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5569
RECEIVED	14 April 2026
ACCEPTED	18 June 2026
PUBLISHED	30 June 2026
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ORAL HEALTH EFFECTS OF NICOTINE POUCHES: A SYSTEMATIC NARRATIVE REVIEW WITH CONTEXTUALIZATION AGAINST CONVENTIONAL TOBACCO PRODUCTS

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ABSTRACT

Background: Nicotine pouches are tobacco-free oral nicotine delivery products placed in the oral vestibule without combustion or tobacco leaf contact. Despite accelerating global market expansion and the 2025 U.S. Food and Drug Administration (FDA) marketing authorization, their oral health consequences remain poorly characterized.
Objective: This systematic narrative review synthesizes available clinical and mechanistic evidence on the oral health effects of nicotine pouches across four domains: oral mucosal changes, periodontal status, dental caries, and oral cancer risk.
Methods: A systematic search of PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, Embase, and Google Scholar was conducted (last updated March 2026). Ten eligible studies published between 2021 and 2026 were identified and appraised using design-appropriate quality tools. Evidence was synthesized narratively across four clinical and mechanistic domains.
Results: Evidence consistently documents localized gingival recession and leukoplakia at vestibular pouch-placement sites, with severity appearing lower than traditional snus. Periodontal clinical data are absent, though mechanistic evidence for nicotine-driven periodontal injury is robust. Nicotine promotes Streptococcus mutans virulence, induces oral microbiome dysbiosis, and impairs salivary function. No epidemiological data on oral cancer incidence in nicotine pouch users exist; however, mechanistic evidence demonstrates multi-pathway oncogenic potential of nicotine independently of tobacco-specific nitrosamines.
Conclusions: Nicotine pouches are not orally safe. Available evidence suggests a tentative harm-reduction gradient relative to cigarettes for mucosal outcomes when data are contextualized indirectly, but direct clinical comparisons between nicotine pouch users and cigarette smokers are virtually absent, and critical evidence gaps persist across all four domains. Long-term independent prospective studies are urgently required.

KEYWORDS

Nicotine Pouches, Oral Health, Oral Mucosa, Periodontal Disease, Tobacco Harm Reduction, Oral Carcinogenesis, Narrative Synthesis

CITATION

Jacek Kowalski, Dominika Julia Kozdroń, Michalina Weronika Nieścioruk, Paulina Szczepańska, Dominika Dutkiewicz, Alia Echtay Yarbou, Rami Mallah, Adrian Mikołajuk. (2026) Oral Health Effects of Nicotine Pouches: a Systematic Narrative Review with Contextualization Against Conventional Tobacco Products. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5569

Introduction

Tobacco use is one of the leading preventable causes of premature death and disability globally. Conventional cigarette smoking is causally associated with a spectrum of oral diseases: chronic periodontitis, accelerated alveolar bone destruction, impaired wound healing, elevated dental caries susceptibility, oral leukoplakia, and oral squamous cell carcinoma (OSCC) [1]. The International Agency for Research on Cancer (IARC) classifies tobacco smoking as a Group 1 human carcinogen, with oral cavity cancer risk elevated approximately 4.65-fold in smokers relative to never-smokers [2]. At the periodontal level, meta-analytic data demonstrate an 85% increase in periodontitis risk among smokers compared to non-smokers (RR = 1.845; 95% CI: 1.5–2.2), an effect attributable to both the systemic immunosuppressive action of nicotine and its local vasoconstrictive effects on gingival perfusion [3]. The magnitude of this oral health burden has driven sustained public health interest in lower-risk alternatives to combustible tobacco.

Over the past decade, a new category of tobacco-free oral nicotine delivery products — the nicotine pouch — has emerged as one of the fastest-growing segments of the global nicotine market. Nicotine pouches are small, teabag-like sachets typically measuring 8–14 mm in length, containing synthetic or tobacco-derived nicotine embedded in a matrix of plant-based cellulose fibers, water, flavoring agents, pH-adjusting salts (commonly sodium carbonate or bicarbonate), and humectants [4]. They are placed in the oral vestibule between the gum and upper or lower lip for periods of 20–60 minutes, during which nicotine is absorbed transorally without combustion, smoke inhalation, or tobacco leaf contact [4]. Available nicotine

concentrations range from 1.5 mg to 8.0 mg per pouch, with some products reaching 11–17.5 mg, generating peak plasma nicotine concentrations broadly comparable to those achieved by conventional cigarettes [4].

The global nicotine pouch market has expanded at a compound annual growth rate of 30–40% between 2019 and 2024, with projections suggesting continued double-digit growth through the late 2020s [5]. The principal commercial brands — ZYN (Swedish Match/Philip Morris International), VELO (British American Tobacco), on! (Altria), and Nordic Spirit — are now distributed across North America, Western Europe, and increasingly across emerging markets in Africa and Southeast Asia. Notably, use is highest among young adult males aged 18–34 years with limited prior tobacco history [4], raising concerns that pouches may function as a gateway product for nicotine-naive individuals rather than as a harm-reduction tool for existing smokers. This trajectory culminated in January 2025, when the U.S. FDA granted marketing authorization for ten ZYN variants under the premarket tobacco product application (PMTA) pathway — the first such authorization for any tobacco-free nicotine pouch in the United States [6]. The decision was grounded in comparative toxicological profiling and pharmacokinetic data, but critically was not premised on prospective clinical evidence of oral health safety, underscoring the urgency of independent outcome research.

The proposed risk-reduction rationale for nicotine pouches rests on the absence of combustion products and the elimination of tobacco-specific nitrosamines (TSNAs) — including NNN, NNK, NAB, and NAT — that are abundant in cured tobacco leaf and are established oral carcinogens [7]. Traditional Scandinavian snus, which shares several product characteristics with nicotine pouches, is associated with localized oral mucosal lesions, gingival recession, and a modestly elevated risk of oral and pancreatic cancer in the Swedish cohort literature [7]. However, the absence of tobacco-derived carcinogens does not equate to oral biological inertness. Prolonged direct contact of a pH-elevated, nicotine-saturated substrate with the oral mucosa creates conditions for chemical and mechanical tissue injury [8], and nicotine itself exerts direct cellular effects in oral tissues — including pro-proliferative, anti-apoptotic, and epigenetic actions — through binding to nicotinic acetylcholine receptors (nAChRs) expressed on oral keratinocytes, gingival fibroblasts, and periodontal ligament cells [9, 10]. These properties challenge the assumption, embedded in both regulatory frameworks and consumer messaging, that oral safety can be inferred from the removal of tobacco leaf.

Despite the epidemiological and biological importance of nicotine pouch safety, the evidence base on their oral health consequences remains critically sparse. The only prior systematic review on this topic identified merely three eligible primary studies, all rated at high risk of bias [11], and no synthesis has yet addressed mucosal integrity, periodontal status, dental caries risk, and oral oncological risk within a single framework. This review was designed to fill that gap: we synthesize all available clinical and mechanistic evidence on the oral health effects of nicotine pouches, place the findings in the context of the established oral disease literature, and identify priority areas for future research and clinical guidance.

Methodology

Study Design and Search Strategy

This systematic narrative review synthesizes peer-reviewed scientific evidence published primarily between 2010 and March 2026, examining the oral health consequences of nicotine pouch use and their comparison with conventional cigarette smoking. A targeted systematic literature search was conducted across six databases: PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, Embase, and Google Scholar. The search strategy combined the following keywords: "nicotine pouch”, "tobacco-free pouch”, "white snus”, ”ZYN”, ”VELO", "on!", "nicotine sachet”, "oral health", "oral mucosa”, “periodontal", “gingival", "dental caries”, "oral cancer”, “leukoplakia", "oral lesion”, “salivary", "oral microbiome”, “cigarette", “tobacco", “smoking".

Reference lists of all included studies and relevant systematic reviews were manually screened for additional eligible records. Grey literature, including FDA PMTA submissions and WHO tobacco product reports, was searched non-systematically to provide regulatory context. The methodological approach was designed to integrate findings across a hierarchy of evidence — from molecular mechanisms to large-scale epidemiological associations — covering four primary evidence categories: controlled clinical studies, observational cohort and cross-sectional studies, case series and case reports, and narrative or critical reviews providing primary descriptive data.

Eligibility Criteria

Studies were included if they: (1) involved adult participants aged ≥18 years; (2) reported exposure to tobacco-free nicotine pouches of any brand or nicotine strength; (3) assessed at least one oral health outcome — mucosal changes, periodontal indices, dental caries, or oral cancer markers; (4) were published in English between January 2010 and March 2026; and (5) were available as full-text, peer-reviewed articles. Studies were excluded if they involved only in vitro or animal models without human clinical data, reported no oral health outcome, or were conference abstracts without full peer-reviewed text. In vitro and animal studies were therefore excluded as primary sources from the systematic search; however, mechanistic literature identified through reference screening of included studies was incorporated to contextualise clinical findings within each domain. Given the emergent and poorly documented nature of the topic, case reports and case series were explicitly retained. Narrative and critical reviews were included if they provided extractable primary descriptive data not available elsewhere. It is acknowledged that direct head-to-head clinical comparisons between nicotine pouch users and conventional cigarette smokers are virtually absent from the current literature; accordingly, contextualization against cigarette smoking data is based on evidence from independent, disease-specific systematic reviews and meta-analyses rather than from within-study comparisons.

Data Extraction and Quality Assessment

Titles and abstracts were screened independently by two reviewers using Rayyan (Qatar Computing Research Institute, Doha, Qatar), with disagreements resolved by consensus or referral to a third reviewer. Data extraction captured: study design, country, sample size, participant demographics, product brand and nicotine strength, exposure duration, comparison group, oral health outcomes, diagnostic instruments, primary findings, and funding source. Study quality was assessed using design-appropriate validated appraisal tools. Potential conflicts of interest arising from tobacco industry funding or investigator affiliation were recorded explicitly and incorporated into result interpretation.

Analytic Approach

Given the substantial heterogeneity in study designs, exposure definitions, and outcome measures across eligible studies, and the inclusion of mechanistic and review literature alongside primary clinical data, a formal meta-analysis was not conducted and a narrative synthesis approach was methodologically appropriate. A thematic narrative synthesis was employed to organize evidence into four primary domains: oral mucosal integrity, periodontal status, dental caries and oral microbiome, and oral cancer risk. Within each domain, clinical findings were contextualised alongside mechanistic evidence to provide an integrated biological interpretation. Given the near-complete absence of direct head-to-head clinical studies comparing nicotine pouch users with cigarette smokers, contextualization against conventional cigarette smoking was based on disease-specific systematic reviews and meta-analyses addressing cigarette-associated oral pathology (periodontitis, oral cancer, caries, microbiome dysbiosis) as independent reference benchmarks, rather than from within-study direct comparisons. This approach constitutes an indirect comparative framework and its limitations are discussed explicitly.

Results

Study Selection and Characteristics

The systematic search yielded 1,247 records before deduplication. After removal of 400 duplicates, 847 records underwent title and abstract screening; 805 were excluded (not concerning nicotine pouches specifically, n = 312; focus on electronic nicotine delivery systems (ENDS) without nicotine pouch data, n = 201; no oral health outcome reported, n = 189; preclinical or in vitro design, n = 103). Forty-two full-text articles were assessed for eligibility, of which 10 met all inclusion criteria. The most common full-text exclusion reasons were: smokeless tobacco products other than nicotine pouches as sole exposure (n = 14), absence of extractable oral health data (n = 11), and non-English language (n = 4). Included studies comprised two controlled clinical studies, two observational cohort or cross-sectional studies, three case series or case reports, and three narrative or critical reviews. Countries of origin were Sweden, the United States, the United Kingdom, Latvia, and one multi-country collaboration; publication years ranged from 2021 to 2026. Four studies had declared or identifiable tobacco industry funding or CoEHAR (Centre for Excellence in the Acceleration of Harm Reduction) affiliation. Study characteristics are summarised in Table 1.

Table 1. Characteristics of included studies.

Study (year)	Design	Product / Exposure	Duration	CoI
Alkhatib (2025) [12]	Case series	ZYN/VELO, daily, 11–18 months	11–18 months	No CoI
Miluna-Meldere et al. (2024) [13]	Case series + histopathology	Various NP, frequency NR	NR	No CoI
La Rosa et al. (2025) [14]	Pilot observational	Novel NP technology	4 weeks	CoEHAR affil.
Alizadehgharib et al. (2022) [15]	Controlled clinical	Swedish snus → NP transition	6 weeks	No CoI
Liu et al. (2025) [16]	Cross-sectional	on! pouches vs cigarettes	Retrospective	Industry-funded
Rungraungrayabkul et al. (2024) [11]	Systematic review	Various NP	Varied	No CoI
La Rosa et al. (2024) [7]	Critical review	ENDS and NP	N/A	CoEHAR affil.
Bogdanska et al. (2025) [5]	Narrative review	Smokeless tobacco incl. NP	N/A	No CoI
Zamarripa et al. (2025) [4]	Comprehensive review	NP (all aspects)	N/A	No CoI
Agbor & Azodo (2026) [8]	Narrative review	NP	N/A	No CoI

*Note. NP = nicotine pouch; NR = not reported; CoI = conflict of interest; CoEHAR = Centre for Excellence in the Acceleration of Harm Reduction. *Conflict of interest declared or identified through institutional affiliation.*

Oral Mucosal Integrity

Vestibular mucosal changes at the pouch placement site represent the most consistently documented oral health outcome across included studies. Lesions are spatially confined to the labial or buccal mucosa immediately underlying the habitual placement zone, with sharp margins corresponding to the pouch contact area and no involvement of non-contact sites. This anatomical specificity strongly implicates local chemical and mechanical insult as the primary pathogenetic mechanism, rather than systemic nicotine exposure.

Two clinical case reports (Alkhatib, 2025) documented gingival recession and leukoplakia in otherwise healthy daily nicotine pouch users following 11 and 18 months of use respectively, with both patients referred for mucosal surveillance and advised to discontinue [12]. In contrast, a four-week pilot observational study reported that 87% of participants experienced no new mucosal changes [14]; however, this study was affiliated with CoEHAR and its findings should be interpreted with caution. Across all studies reporting mucosal symptoms, the most common user-reported complaints were localized mucosal changes (48%), oral soreness or burning at the placement site (37%), and jaw or masticatory discomfort (1%) [16].

The only histopathological characterization of nicotine pouch-associated mucosal lesions to date was provided by Miluna-Meldere et al. (2024), whose Latvian case series of eight users demonstrated parakeratotic, acanthotic epithelium with thickened stratum spinosum, intraepithelial edema, and a chronic mononuclear subepithelial infiltrate [13]. The histomorphological pattern was consistent with smokeless tobacco-induced lesions (‘tobacco pouch keratosis’), but crucially, no dysplastic epithelial changes — nuclear pleomorphism, loss of polarity, or abnormal mitotic figures — were identified in any specimen. The authors appropriately cautioned that the absence of dysplasia in a short-term case series cannot exclude malignant transformation risk over longer exposure periods.

The strongest comparative clinical evidence comes from Alizadehgharib et al. (2022), the only controlled study addressing mucosal outcomes, in which 60 Swedish snus users transitioned to a tobacco-free nicotine pouch over six weeks [15]. Mucosal lesion prevalence declined from 90% at baseline to 70% at follow-up, with complete resolution of severe-grade lesions in all affected participants. This improvement was attributed to removal of the tobacco substrate and its associated chemical irritants and TSNAs. However, the six-week timeframe is insufficient to assess chronic or oncogenic mucosal changes, and the absence of a non-tobacco-using control group prevents absolute risk quantification.

Taken together, the available evidence supports a tentative harm-reduction gradient for mucosal outcomes (cigarettes > traditional snus > nicotine pouches). However, this hierarchy rests on a very limited evidence base, is derived primarily from short-term observations, and does not address long-term oncogenic potential.

Periodontal Status

Direct clinical evidence on periodontal outcomes in nicotine pouch users is virtually absent. Among included studies, only Alkhatib (2025) reported any periodontal-related data, documenting gingival recession localized to placement sites without standardized probing depth, clinical attachment level, bleeding-on-probing, or bone level measurements [12]. No included study assessed full periodontal indices in nicotine pouch users as a primary outcome.

This clinical void contrasts with a robust mechanistic literature demonstrating that nicotine, at concentrations achievable during pouch use, drives periodontal pathology through multiple receptor-mediated pathways. Nicotine upregulates cyclooxygenase-2 (COX-2) in periodontal ligament fibroblasts, amplifying local tissue inflammation [17], while its metabolite nornicotine increases the receptor for advanced glycation end products (RAGE) expression fourfold in periodontal ligament cells, driving nuclear factor kappa-B (NF-κB)-dependent pro-inflammatory cytokine cascades [18]. In rodent models, nicotine combined with Porphyromonas gingivalis lipopolysaccharide suppresses osteogenic differentiation genes, impairing the regenerative capacity of periodontal tissues [19]. The resulting cytokine milieu — elevated interleukin-1β (IL-1β), IL-6, and tumour necrosis factor-α (TNF-α) with suppressed IL-10 — is consistent with the inflammatory profile seen in established periodontitis [20]. These mechanisms operate independently of tobacco combustion products and are therefore fully applicable to nicotine pouch exposure.

A specific clinical concern is the vasoconstriction-mediated suppression of bleeding on probing [21]. Nicotine-induced reduction in gingival perfusion may suppress BOP even in the presence of active periodontal inflammation, creating a deceptively benign clinical presentation that risks delaying diagnosis. This masking effect means that conventional clinical screening may underestimate periodontal disease burden in nicotine pouch users.

For conventional cigarettes, meta-analytic data confirm an 85% elevated risk of periodontitis compared to non-smokers (RR = 1.845; 95% CI: 1.5–2.2) [3], establishing the scale of periodontal harm attributable to nicotine-containing products. For nicotine pouches specifically, a network meta-analysis of peri-implant outcomes confirmed significantly worse tissue parameters for all nicotine-containing product users relative to non-users [22], providing indirect evidence that pouch-associated nicotine exposure is not periodontally neutral.

Prospective periodontal studies in nicotine pouch users, incorporating full-mouth probing, radiographic bone assessment, and inflammatory biomarker profiling, are urgently needed to translate the existing mechanistic evidence into clinical risk estimates.

Dental Caries and Oral Microbiome

No prospective clinical study examining dental caries rates in nicotine pouch users was identified. Nevertheless, converging mechanistic and microbiological evidence from in vitro, in vivo, and observational studies consistently implicates nicotine as a cariogenic agent through three complementary pathways: enhancement of Streptococcus mutans virulence, broad oral microbiome dysbiosis, and impairment of salivary protective function.

Regarding the cariogenic microorganism S. mutans, multiple studies demonstrate that nicotine at concentrations achievable in oral fluid during pouch use significantly enhances its virulence: increasing lactate production and acidogenic potential [23], promoting biofilm biomass and extracellular polysaccharide synthesis [24], and selectively favouring S. mutans growth over commensal Streptococcus sanguinis in dual-

species biofilm models [25]. These in vitro findings are supported by an in vivo rat caries model in which oral nicotine administration significantly increased both the frequency and severity of carious lesions [26].

Beyond the S. mutans axis, nicotine drives broader compositional disruption of the oral microbiome. Studies in electronic cigarette users — whose oral nicotine exposure shares the same pharmacological mechanism as nicotine pouches — demonstrate significantly altered microbial beta-diversity, with enrichment of Prevotella and Veillonella and depletion of health-associated Streptococcus taxa [27]. A longitudinal cohort study further confirmed elevated Firmicutes-to-Proteobacteria ratios and reduced alpha-diversity across nicotine product users, with findings stable over a four-month follow-up period [28]. The clinical significance of this dysbiosis lies in the shift towards an acid-tolerant, periodontopathogenic microbiome profile that predisposes to both caries and periodontal disease.

Salivary dysfunction constitutes a third cariogenic pathway. Systematic review data from ENDS users report statistically significant reductions in unstimulated salivary flow rate, pH, and bicarbonate buffering capacity compared with non-users [29]. Given that nicotine is the primary shared pharmacological agent, analogous salivary effects are biologically plausible in nicotine pouch users, though direct salivary data in this population are lacking.

The convergence of these three pathways — S. mutans virulence enhancement, microbiome dysbiosis, and salivary hypofunction — constitutes a mechanistically coherent and clinically testable framework for cariogenesis in nicotine pouch users. Prospective clinical studies incorporating standardized caries indices, salivary analysis, and microbiome profiling are required to determine whether this mechanistic risk translates into measurable clinical outcomes.

Oral Cancer Risk

No epidemiological study on oral cancer incidence or malignant transformation in nicotine pouch users has been published. This is the most critical evidence gap in the field, reflecting the product category's short commercial history relative to the decades-long latency of tobacco-associated carcinogenesis. Mechanistic evidence, however, identifies multiple convergent oncogenic pathways through which nicotine, independently of TSNAs, may promote malignant transformation in oral tissues.

At the cellular level, nicotine activates pro-proliferative and anti-apoptotic signalling in oral epithelial and OSCC cells through nAChRs. Activation of the Ras/Raf-1/MEK1/ERK and PI3K/Akt/mTOR cascades accelerates cell cycle progression, upregulates anti-apoptotic proteins, and confers resistance to cytotoxic agents [9]. Nicotine additionally induces epithelial-mesenchymal transition, enhancing the invasive potential of oral epithelial cells [9].

At the epigenetic level, prolonged nicotine exposure drives promoter hypermethylation of tumour suppressor genes, global histone modification changes, and mitochondrial oxidative stress accumulation — collectively generating a cellular environment permissive to malignant transformation [10].

These mechanisms acquire particular clinical relevance in the context of oral leukoplakia — a lesion directly documented at nicotine pouch placement sites in included studies [12, 13]. Nicotine selectively suppresses apoptosis in dysplastic keratinocytes via the α7nAChR/Prx1 axis, conferring a survival advantage to premalignant cell populations that is not observed in healthy epithelium [30]. Further mediators of nicotine-driven leukoplakia progression have been identified within the Prx1 interactome [31]. In vivo evidence confirms a genotoxic stress response to oral nicotine exposure, with upregulation of p53 and deoxyribonucleic acid (DNA) repair genes [32], while nicotine also disrupts physiological apoptotic surveillance in non-dysplastic tissue by inhibiting nitric oxide-induced cell death [33]. Together, these findings suggest that nicotine pouches may both initiate and promote the malignant progression of placement-site leukoplakia.

For conventional cigarettes, a meta-analysis of 15 case-control studies established a 4.65-fold increased risk of oral cancer (OR = 4.65; 95% CI: 3.19–6.77) [2]. The corresponding risk for nicotine pouches cannot yet be quantified. However, the documented generation of oral leukoplakia — which carries a malignant transformation rate of approximately 2.0–3.5% over five years in the general population [8] — combined with the multi-pathway oncogenic activity of nicotine reviewed above, provides biologically grounded reason for oncological vigilance in this population.

Discussion

The Harm-Reduction Gradient: Real but Incomplete

The most consistent finding across included studies is that nicotine pouches produce localized vestibular mucosal changes of apparently lower severity than traditional snus or conventional cigarettes, supporting a tentative harm-reduction gradient. This gradient is biologically plausible: the removal of tobacco leaf eliminates the principal source of TSNAs, polycyclic aromatic hydrocarbons (PAHs), and direct mucosal chemical irritants, and the transition from snus to nicotine pouches was associated with measurable lesion regression in the only controlled clinical study available [15].

However, interpreting this gradient as evidence of oral safety requires two assumptions that current data cannot support. First, it assumes that lesion severity tracks with oncogenic risk — an assumption unsubstantiated by any long-term follow-up data for nicotine pouches. Second, it assumes that the absence of TSNAs eliminates carcinogenic potential, whereas the mechanistic evidence reviewed here demonstrates that nicotine itself exerts pro-proliferative, anti-apoptotic, and epigenetically destabilizing actions in oral epithelial tissues independently of tobacco-derived carcinogens [9, 10]. The harm-reduction gradient is therefore a real but partial finding: it addresses mucosal irritation, but not oncological risk.

Nicotine as the Primary Oral Toxicant

A unifying theme across all four evidence domains is that nicotine — the component retained in tobacco-free pouches — is itself sufficient to drive oral pathology through receptor-mediated mechanisms that operate independently of combustion or tobacco leaf contact. At the mucosal level, nicotine maintains a direct chemical irritant effect through pH-elevated substrate contact [8]. In the periodontium, nicotine drives inflammation, impairs osteogenic regeneration, and suppresses the clinical signal of disease through vasoconstriction [17, 18, 19, 20, 21]. In the cariogenic and microbiome domain, nicotine enhances S. mutans virulence and disrupts the oral microbial community in ways that favour pathogenic over commensal species [23, 24, 25, 26]. In oral epithelial tissues, nicotine activates oncogenic signalling cascades and selectively promotes the survival of premalignant cells [9, 10, 30].

This convergence across four domains has an important regulatory implication: toxicological safety assessments based on the absence of TSNAs and PAHs address only a subset of the biological risk. The FDA's 2025 PMTA authorization of ZYN pouches was appropriately grounded in comparative toxicology, but was not designed to constitute a determination of oral health safety. Given that the median latency from carcinogen exposure to OSCC diagnosis is approximately 20–30 years, and nicotine pouches have existed at meaningful market scale for less than a decade, the current absence of clinical oncological data reflects follow-up duration rather than demonstrated safety.

Evidence Quality and Conflicts of Interest

The evidence base synthesized in this review is not only sparse but systematically compromised by conflicts of interest. Four of the ten included studies carried declared or identifiable tobacco industry funding or CoEHAR affiliation — a research centre with documented industry ties. This proportion is consistent with the broader pattern in tobacco harm-reduction literature, in which industry-affiliated studies systematically report more favourable safety conclusions than independent research. The two studies reporting the most reassuring mucosal findings (La Rosa 2025 [14]; Liu 2025 [16]) both carried industry affiliations and moderate risk of bias ratings, limiting the weight that can be placed on their conclusions.

Additional methodological limitations include: the largest primary clinical study comprised only 60 participants followed for six weeks; exposure characterization was heterogeneous across studies; and mechanistic evidence is predominantly from in vitro and rodent models. The indirect comparative framework employed here — benchmarking nicotine pouch data against independent literature on cigarette-associated oral disease — further limits the strength of harm-differential conclusions. Independent, prospective, industry-unaffiliated research is the highest priority for the field.

Clinical and Regulatory Implications

For oral health professionals, the available evidence supports several practice-level conclusions that do not require resolution of the outstanding research questions. Patients using nicotine pouches should undergo regular oral examination with systematic attention to vestibular mucosal integrity at the habitual placement site; any persistent keratotic lesion warrants histopathological assessment. Full periodontal charting should be performed, with awareness that BOP suppression may underestimate disease severity. Formal caries risk assessment, salivary function evaluation, and appropriate preventive protocols should be incorporated into routine care for this patient group.

For regulators and public health bodies, the evidence underscores that marketing authorization based on comparative toxicology does not substitute for prospective clinical outcome data. The gateway use pattern — highest prevalence among young adult males with no prior tobacco history [4] — means that a population with no pre-existing oral disease burden is accumulating decades of nicotine pouch exposure in the absence of any long-term safety data. Mandating post-market surveillance studies with standardized oral health endpoints as a condition of continued marketing authorization represents the most proportionate regulatory response to this evidence gap.

Conclusions

The available evidence supports a tentative harm-reduction gradient for oral mucosal outcomes: nicotine pouches produce less severe vestibular lesions than snus or cigarettes, and the transition from snus to pouches is associated with measurable mucosal improvement in the short term. This is a genuine, if modest, toxicological advantage. It should not, however, be mistaken for safety. The gradient applies to mucosal irritation only; it says nothing about periodontal disease, caries, or oncological risk — domains for which clinical data in nicotine pouch users are either absent or severely limited.

The thread connecting all four domains is nicotine itself. Independently of tobacco combustion products or TSNAs, nicotine drives periodontal inflammation and suppresses the clinical signs of disease, enhances cariogenic microbiota and impairs salivary defence, and activates pro-proliferative and anti-apoptotic pathways in oral epithelial cells — including, with particular concern, in the premalignant keratinocytes found at the same vestibular sites where pouches generate leukoplakia. The product's tobacco-free identity does not neutralise these mechanisms.

These conclusions rest on a limited and partially compromised evidence base. Primary studies are small and short-term, and a disproportionate share of available data originates from industry-affiliated investigators. Independent long-term research is not merely desirable — it is the precondition for any evidence-based position on nicotine pouch safety.

Until that evidence exists, oral health professionals should treat nicotine pouch users as a population at uncharacterised risk: examining vestibular mucosa systematically, interpreting BOP results with awareness of nicotine-induced masking, assessing caries risk formally, and biopsying any persistent placement-site lesion. The nicotine pouch market is growing fastest among young adults with no prior tobacco history and potentially decades of future exposure. The urgency of independent prospective research is proportional to that scale.

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