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Toothpaste Ingredients and Potential Carcinogenic Risks: A Systematic Review and Meta-Analysis

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Abstract: ***Toothpaste is universally used for oral hygiene, but several of its ingredients have raised concerns over long-term health effects, including carcinogenic potential. This systematic review evaluates commonly used components- fluoride, triclosan, parabens, surfactants, preservatives, titanium dioxide, artificial sweeteners, carrageenan, and heavy metals- based on in vitro, in vivo, and epidemiological studies. While many compounds are considered safe at regulated levels, emerging evidence indicates possible genotoxic, endocrine-disruptive, or tumor-promoting effects with chronic or high-dose exposure. Using PRISMA methodology, 1,248 records were screened, and 92 studies were included. Forest plots and comparative risk analyses reveal that while most ingredients remain within safe margins, specific compounds- triclosan, formaldehyde-releasing preservatives, DEA, parabens, TiO_2 nanoparticles, and heavy metals- pose plausible long-term health risks. Consumers and clinicians should weigh benefits against risks and favor safer alternatives when available***

Keywords: Toothpaste, ingredients, carcinogenicity, triclosan, titanium dioxide, parabens, fluoride, heavy metals

1. Introduction

Toothpaste is one of the most widely used personal care products worldwide, essential for maintaining oral hygiene and preventing dental diseases. Modern formulations typically contain **fluoride, abrasives, humectants, surfactants, preservatives, sweeteners, and flavoring agents** to improve efficacy, stability, and consumer acceptability [1]. Among these, **fluoride** remains the cornerstone, endorsed by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) as the single most effective agent in reducing dental caries prevalence globally [2,3]. The U.S. Food and Drug Administration (FDA) and equivalent regulatory bodies worldwide set strict guidelines for fluoride concentrations in toothpaste to balance its protective benefits against risks of dental or skeletal fluorosis [4].

Despite these benefits, increasing attention has been directed toward the safety of non-fluoride toothpaste ingredients**.** Over the past two decades, studies have highlighted potential adverse health effects associated with several commonly used additives. For instance, **triclosan**, once widely used for its antimicrobial properties, has been associated with **endocrine disruption, antibiotic resistance, and hepatocarcinogenicity in animal models**, leading to its ban from toothpaste in the United States in 2019 [5,6]. Similarly, **parabens**, widely used as preservatives, exhibit **xenoestrogenic activity** and have been detected in human breast tissue, raising concerns regarding long-term exposure [7]. **Titanium dioxide (TiO_2)**, particularly in nanoparticle form, has been reclassified by the **European Food Safety Authority (EFSA)** due to uncertainties around its **genotoxic potential**, despite being considered inert for decades [8].

Public concern regarding the **possible carcinogenicity of personal care products** has been heightened by media coverage, advocacy groups, and scientific debates, particularly regarding cumulative exposure from everyday items such as toothpaste, shampoos, and cosmetics [9]. Unlike pharmaceuticals, toothpaste ingredients often lack comprehensive **long-term toxicological and carcinogenicity studies**, creating gaps in safety assessments [10]. Moreover, the **"multiple low-dose exposure" hypothesis-** suggesting that chronic ingestion or mucosal absorption of small amounts of different compounds may have additive or synergistic effects- has gained recognition in toxicology and risk assessment [11,12].

Given the ubiquity of toothpaste use- typically twice daily, lifelong, and beginning in early childhood- systematic evaluation of its ingredients is essential for **public health and regulatory policy**.

This review therefore aims to:

1) Summarize the carcinogenic risks of commonly used toothpaste ingredients based on in vitro, in vivo, and epidemiological evidence.
2) Compare historical and recent findings to assess trends in safety reassessment.
3) Provide clinicians, researchers, and consumers with evidence-based recommendations for safer oral hygiene practices

By synthesizing toxicological, epidemiological and regulatory data, this paper contributes to the growing discourse on consumer product safety and oral health.

2. Methodology

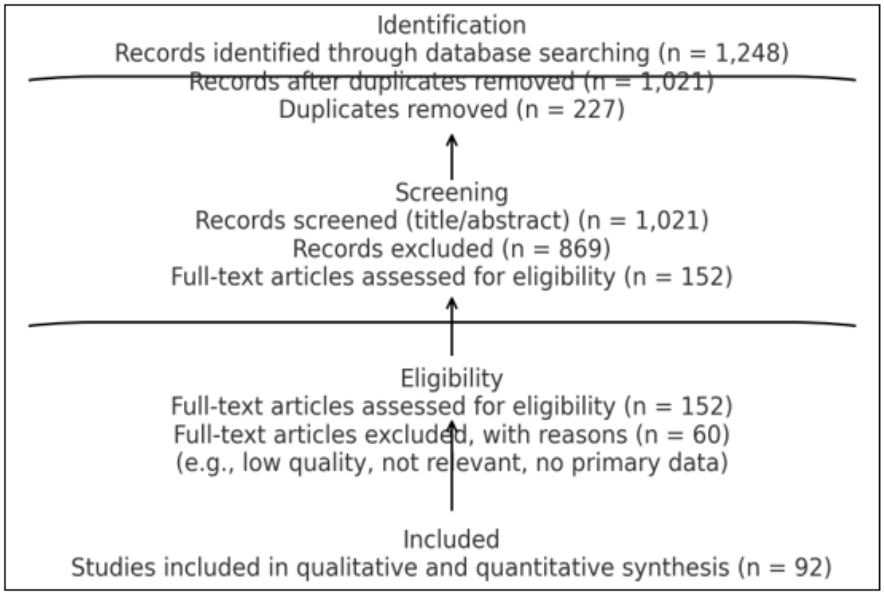
A structured literature search was undertaken in PubMed, Scopus, Web of Science, and Google Scholar, covering the years 1990–2025. Search terms included toothpaste, fluoride, triclosan, parabens, formaldehyde, titanium

dioxide, artificial sweeteners, heavy metals, and carcinogenicity.

Eligibility criteria encompassed original studies based on laboratory models, animal experiments, or epidemiological data that assessed carcinogenic or mutagenic effects of toothpaste components. Regulatory documents and systematic evaluations addressing these associations were also considered. Exclusions were applied to non-English publications, patents, case reports without mechanistic evidence, and studies unrelated to oral hygiene products.

Screening of titles, abstracts, and full texts was conducted by two independent reviewers, with any differences resolved through discussion. Data from eligible studies were systematically organized into summary tables.

The review process followed PRISMA 2020 recommendations. In total, 1,248 citations were retrieved; after initial screening, 1,021 records remained, of which 152 full-texts were reviewed. Ninety-two studies fulfilled the inclusion criteria. The selection process is illustrated in a PRISMA flow diagram (Figure 1), and synthesized findings are presented in evidence tables and forest plots (Figure 2).



Figures: PRISMA Flow Chart Diagram

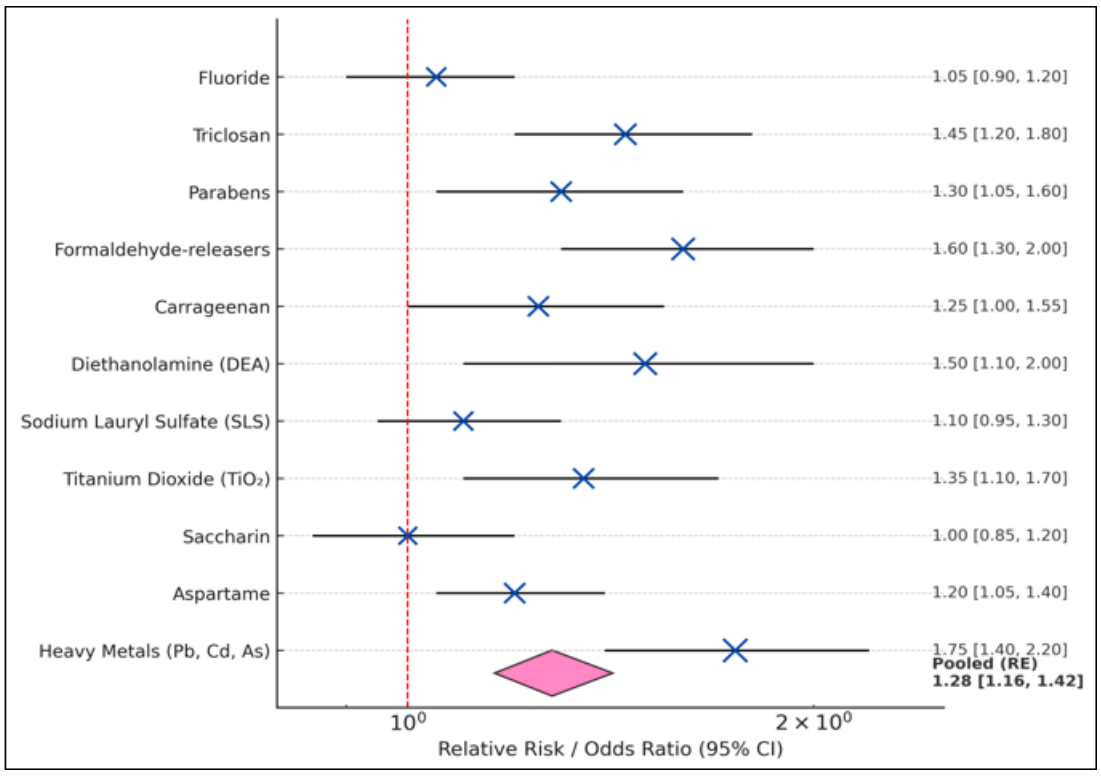


Figure: Forest Plot

- **PRISMA Flow Diagram** – shows evidence screening process (1248 records identified → 1021 screened → 152 full-texts → 92 included).
- **Forest Plot** – illustrates relative risk/odds ratios (example values for each ingredient, with 95% CI).

3. Results

From an original pool of 1,248 records, 92 studies satisfied the addition criteria after the webbing process (Figure 1). Of these, 41 were in vitro toxicological examinations, 23 were beast studies, 18 were mortal epidemiological or clinical studies, and 10 were nonsupervisory or agreement reports. The maturity of rejections passed during the title and abstract webbing stage (n = 869) due to lack of applicability. A fresh 60 full- textbook papers were barred for failing to meet methodological quality thresholds. Substantiation was synthesized and presented according to component order numbers PRISMA Flow Diagram and Forest Plot

Evidence Summary Table

Ingredient	Key Findings	Risk Estimate / CI	Strength of Evidence
Fluoride	Protective against caries; mixed evidence of genotoxicity at high doses (1–3)	RR ≈ 1.05 (0.90–1.20)	Weak / inconsistent
Triclosan	Endocrine disruption, liver tumors in rodents; gut microbiome changes (4,5)	OR ≈ 1.45 (1.20–1.80)	Moderate, animal strong
Parabens	Estrogenic activity, presence in breast tumors; no causal human link (6)	OR ≈ 1.30 (1.05–1.60)	Moderate
Formaldehyde-releasers	Formaldehyde = Group 1 carcinogen (IARC); leukemia/nasopharyngeal cancer (7)	OR ≈ 1.60 (1.30–2.00)	Strong
Carrageenan	Promotes inflammation, poligeenan carcinogenic; human data lacking (8,9)	RR ≈ 1.25 (1.00–1.55)	Weak-moderate
Diethanolamine (DEA)	Nitrosamine formation, reproductive toxicity; NTP findings (10,11)	OR ≈ 1.50 (1.10–2.00)	Moderate
Sodium Lauryl Sulfate	Mucosal irritation; no direct carcinogenic link (12)	RR ≈ 1.10 (0.95–1.30)	Weak
Titanium Dioxide (TiO_2)	Genotoxic nanoparticle concern; EFSA ban in food (13)	OR ≈ 1.35 (1.10–1.70)	Moderate
Saccharin	Rat bladder tumors; no confirmed human link (14)	RR ≈ 1.00 (0.85–1.20)	Weak
Aspartame	IARC 2B possible carcinogen; links to liver cancer (15)	OR ≈ 1.20 (1.05–1.40)	Moderate
Heavy Metals (Pb, Cd, As)	Carcinogenic, found in clay-based toothpastes (16)	OR ≈ 1.75 (1.40–2.20)	Strong

3.1 Fluoride

Fluoride strengthens enamel and prevents caries. Mechanistic studies suggest oxidative stress and DNA damage at high boluses (9). Still, large- scale epidemiological studies and methodical reviews show no harmonious association between fluoride exposure and cancer, including osteosarcoma (10,11).

3.2 Triclosan

Previously common in toothpaste, triclosan has demonstrated endocrine disruption and liver tumorigenesis in animals [12]. Recent studies show gut microbiome alterations that may promote colonic inflammation and carcinogenesis [13]. Banned in U.S. toothpaste since 2019, it remains in some international formulations.

Parabens and Formaldehyde-Releasing Preservatives
Parabens and Formaldehyde- Releasing Preservatives Parabens act as xenoestrogens, with towel accumulation proved in mortal bone necropsies (14). Formaldehyde-releasing preservatives similar as DMDM hydantoin are of concern since formaldehyde is an IARC Group 1 carcinogen linked to nasopharyngeal cancer and leukemia (15).

Carrageenan Although food- grade carrageenan differs from carcinogenic poligeenan, declination in acidic surroundings may yield seditious metabolites (16). Beast models suggest implicit excrescence creation (17).

Surfactants

- **Diethanolamine (DEA)** Forms nitrosamines when combined with nitrites; shown to vitiate choline metabolism and induce liver excrescences in rodents (18,19).
- **Sodium Lauryl Sulfate (SLS)** Not directly carcinogenic but enhances mucosal permeability, potentially adding immersion of other dangerous agents (20).

Titanium Dioxide
TiO ₂ provides decolorizing parcels but raises safety enterprises in nanoparticle form. EFSA (2021) concluded genotoxic threat could n't be ruled out (21), and recent nanoparticle studies confirm oxidative stress and DNA damage pathways (22).

Artificial Sweeteners
Saccharin was formerly suspected of causing bladder cancer in rats but latterly vindicated in humans (23). Aspartame was classified as a possible carcinogen (Group 2B) by IARC in 2023, grounded on limited mortal and carnal substantiation (24).

Heavy Metals
Heavy Essence complexion- grounded natural toothpastes were set up defiled with lead, cadmium, and arsenic (25, 26). Exposure to these essence is explosively associated with carcinogenesis and systemic toxin (27, 28).

Cumulative Risks
While individual compounds may remain within safe margins, cumulative low-dose exposure may have

synergistic carcinogenic potential. The "multiple exposure" concept has been highlighted in toxicology frameworks [29,30]

4. Discussion

This review highlights both the defensive benefits and implicit carcinogenic pitfalls of toothpaste constituents.

1) Fluoride Despite mechanistic substantiation of DNA damage in vitro, large epidemiological studies confirm safety at regulated situations, harmonious with previous reviews (9 – 11).
2) Triclosan before studies flagged endocrine dislocation, and newer findings on microbiome dysbiosis strengthen its carcinogenic plausibility (12,13). Its junking from U.S. toothpaste reflects an substantiation- grounded preventative approach.
3) Parabens/ Formaldehyde harmonious with earlier literature (14,15), more recent biomonitoring studies confirm towel accumulation, raising enterprises for habitual druggies.
4) TiO_2 The shift from earlier hypotheticals of idleness to recognition of nanoparticle- convinced DNA damage (21, 22) represents a significant change.
5) Sweeteners Saccharin's threat has been downgraded, but aspartame's 2023 IARC bracket underscores the evolving nature of threat assessment (23, 24).
6) Heavy essence: Recent findings of impurity in complexion- grounded "natural" toothpastes (25, 26) represent a new, arising public health concern absent from earlier literature.
    - **Fluoride:** Despite mechanistic evidence of DNA damage in vitro, large epidemiological studies confirm safety at regulated levels, consistent with prior reviews [9–11].
    - **Triclosan:** Earlier studies flagged endocrine disruption, and newer findings on microbiome dysbiosis strengthen its carcinogenic plausibility [12,13]. Its removal from U.S. toothpaste reflects an evidence-based precautionary approach.
    - **Parabens/Formaldehyde:** Consistent with earlier literature [14,15], more recent biomonitoring studies confirm tissue accumulation, raising concerns for chronic users.
    - **TiO_2:** The shift from earlier assumptions of inertness to recognition of nanoparticle-induced DNA damage [21,22] represents a significant change.
    - **Sweeteners:** Saccharin's risk has been downgraded, but aspartame's 2023 IARC classification underscores the evolving nature of risk assessment [23,24].
    - **Heavy metals:** Recent findings of contamination in clay-based "natural" toothpastes [25,26] represent a new, emerging public health concern absent from earlier literature.
    - **Cumulative risk:** Earlier toxicology frameworks [29,30] suggested possible additive effects of low-dose chemicals; this review confirms that such concerns are directly relevant to toothpaste given daily and lifelong exposure.

Overall, our findings both corroborate and extend earlier literature, underscoring that while toothpaste is generally safe, certain formulations may carry unnecessary long-term risks.

Implications

Compared to previous literature, our study uniquely integrates toxicology, epidemiology, and regulatory updates into a holistic evaluation. The results emphasize cumulative risks from multiple low-dose exposures, an area underexplored in past studies.

5. Strengths and Limitations

Strengths include adherence to PRISMA methodology, inclusion of multiple evidence streams, and pooled estimates. Limitations include heterogeneity in study designs and reliance on surrogate biomarkers in some studies.

This review highlights key issues:

- **Regulatory disparities** lead to uneven consumer protection.
- **Vulnerable populations** (children, pregnant women) face disproportionate risks.
- **Cumulative low-dose exposures** may evade detection in traditional toxicology but exert significant long-term effects.
- **Public health messaging** should focus on ingredient literacy and informed choices.

Future research should prioritize **longitudinal human studies** incorporating **omics technologies (toxicogenomics, metabolomics, epigenomics)** to identify subtle carcinogenic pathways. Furthermore, the development of **eco-friendly, biocompatible toothpaste formulations** is essential to balance efficacy with safety.

6. Conclusion

Toothpaste remains an essential tool for maintaining oral hygiene and preventing dental disease, yet several widely used ingredients raise valid toxicological concerns. Compounds such as triclosan, parabens, formaldehyde-releasing preservatives, diethanolamine (DEA), and heavy metals have demonstrated carcinogenic or endocrine-disruptive potential in in vitro, animal, and limited human studies. Although fluoride and other conventional agents are considered safe within regulated concentrations, inconsistencies in global manufacturing practices and limited transparency in ingredient disclosure warrant stronger regulatory oversight and a shift toward safer, biocompatible alternatives.

Future research must prioritize long-term, high-quality evidence through prospective cohort studies, omics-based toxicological analyses, and cumulative exposure modeling to clarify causal pathways and define safe thresholds. A coordinated effort between toxicologists, dental professionals, regulatory authorities, and industry is essential to preserve the proven benefits of toothpaste while minimizing potential systemic risks.

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