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Original Research Article

Metal contact allergies and dental amalgam in risk factor-negative oral cavity cancer

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Abstract – Background: Oral cavity cancer (OCC) is increasing in prevalence in younger patients without a history of tobacco or alcohol use. Emerging evidence suggests that chronic inflammation and intraoral metal allergies, such as those related to dental amalgam, may play a role in OCC pathogenesis, particularly in risk-factor negative populations. **Objectives:** (1) To determine the incidence of dental amalgam and metal allergies in OCC patients with and without traditional risk factors and, (2) To determine if there is an association between dental amalgam, allergies, and OCC laterality. **Materials and Methods:** Prospective cohort study from February 11, 2021 to May 31, 2023. Patients with OCC were tested for contact allergies to 45 metals found in dental amalgam. Patient demographics, OCC tumor characteristics, risk factors, presence of dental amalgam, and results from allergy testing were collected via chart review. Associations between metal allergies, dental amalgam, and OCC laterality were determined. **Results:** A total of 38 OCC patients underwent metal allergy testing and were included. Eighteen patients had a positive metal allergy, 90% of whom were female. Thirty (79%) patients had dental amalgam. Regardless of metal allergy status, patients with unilateral dental amalgam were significantly more likely to have an adjacent OCC ($p = 0.006$). **Conclusions:** Metal allergies are more prevalent in women with OCC. Regardless of metal allergy status, the presence of dental amalgam appears to be associated with an increased risk of the development of an adjacent OCC.

Introduction

Oral cavity cancer (OCC) is the most common malignancy in the head and neck and an important cause of morbidity and mortality globally [1,2]. While primarily regarded as a disease affecting men with a significant tobacco and alcohol history in their fifth to seventh decade of life, there has been an increase in incidence of OCC, particularly in young adults under 45 years of age [1–3]. This subset accounts for approximately 5% of patients with head and neck squamous cell carcinoma (HNSCC) and appears to be a distinct clinical entity, as they lack significant exposure to typical risk factors [3]. Despite intense investigation, a direct cause has yet to be identified [4,5].

Recent evidence supports the critical role of inflammation in tumor formation and progression. Tumor-associated macrophages (TAMs) are a major component of inflammatory infiltrates that mediate the process, resulting in oxidative stress and irreversible DNA damage that promotes tumorigenesis [6]. The link between chronic inflammation and OCC is well-established in the literature. Individuals with predisposing oral inflammatory conditions, including poor oral health, recurrent physical trauma, and chemical irritation, have been shown to be at a significantly higher risk of developing OCC [7–9]. Few studies, however, have investigated the relationship between allergies and OCC. Intraoral contact allergies to dental amalgam can lead to stomatitis, or inflammation of the oral mucosa [10]. In a study of 65 patients with oral squamous cell carcinoma (OSCC), patch testing revealed one-third were allergic to at least one metal adjacent to their cancer site [11]. While this finding supports the probable connection between allergies and OCC, tobacco and alcohol use were not excluded. Consequently, it is difficult to appreciate the true impact of metal allergies in this population.

Given the historically commonplace practice of using metal alloys as a component of dental fillings and its potential carcinogenic effects, further exploration of the relationship between intraoral metal allergies and the development of OCC is warranted, particularly in young, risk factor negative patients. The objective of this study is: (1) To determine the incidence of dental amalgam and metal allergies in OCC

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patients with and without traditional risk factors and (2) To determine if there is an association between dental amalgam, allergies, and OCC laterality.

Methods

This study was a single institution prospective study of OCC patients who had surgical resection of their primary tumor and underwent allergy testing between February 1, 2021 and May 31, 2023. All procedures were performed in compliance with relevant laws and institutional guidelines. Approval for this study was obtained from the Institutional Review Board at the University of Utah on November 14, 2010 (IRB: 00045048).

All patients seen for OCC over this period at our institution's head and neck surgical oncology clinic were screened. Patients were offered allergy testing and included in this study if they were over age 18 years, diagnosed with a primary OCC treated with surgery, and were risk factor negative (defined as those without a history of alcohol or tobacco use, or if they had quit any substance use at least 20 years prior to diagnosis). Patients were excluded if they were risk factor positive or did not undergo allergy testing.

Patients were screened for allergies to metals used in dental prosthetics, and components of oral antimicrobials and toothpaste, including flavoring, preservatives, synthetic polymers, coloring and detergents (Supplemental Fig. 1). Two dermatologists (R.D., D.P.) evaluated for contact allergies to a comprehensive list of 45 different metals found in dental restoration by performing skin prick testing (to detect type I hypersensitivity reactions) and patch testing (to detect type IV hypersensitivity reactions) (Supplemental Fig. 1). Skin prick testing was performed to capture more patients with possible allergy and test for intraoral allergies. T-cells that cause chronic mucositis or dermatitis migrate in the tissues and bloodstream, often causing inflammation far from the original contact. Thus, if an intraoral metal allergy exists, the skin will react when tested [12–14]. The first read was performed after 48 hours and a final read was performed after 72 to 96 hours. Positive reactions were indicated by erythema, raised, and blistering skin at the application site of the offending allergen. This was further categorized as weakly positive, strongly positive, or extremely positive based on the severity of the reaction. A positive skin test suggested a patient may be allergic to a particular substance.

Data from electronic medical records was collected on patient demographics, laterality of OCC, stage, adjuvant treatment, history of recurrence and/or second primary with associated laterality, tobacco and alcohol use, presence of dental amalgam, and results from allergy testing. Statistical analysis was performed using Stata version 16 software for Windows. Chi-squared test was used for univariate analysis of categorical variables, and Student's *T*-test was used for univariate analysis of continuous variables. Significant differences were determined by p-value <0.05. Patients included in the study were divided into two groups based on the presence or absence of allergies to dental amalgam. Associations between the groups were evaluated based on the laterality of OCC, the presence of adjacent dental amalgam, and positive allergy to metal(s) and associated preservatives.

Results

Demographics and baseline characteristics

A total of 38 patients were included in this study (Tab. I). All patients underwent allergy testing post-operatively, with a median time of 21 months between surgery and testing. Patients were stratified by the presence or absence of metal allergy. There were 18 (47%) patients with a confirmed metal allergy and 20 (53%) patients without (non-allergy group). The metal allergy group had twice as many females as the non-allergy group ($p < 0.01$). The median age was 60.5 years in the allergy group and 62.5 years in the non-allergy group ($p = 0.29$). Dental amalgam was present in 30 (79%) patients and the rate was similar between the two cohorts ($n = 14$, 78% metal allergy versus $n = 16$, 80%; $p = 0.12$).

Both groups had a similar number of patients with a history of systemic inflammatory diseases and oral inflammatory conditions ($p > 0.05$). There were no patients with a history of immunosuppression. With regard to systemic autoimmune conditions, there were two patients with psoriasis, one with rheumatoid arthritis, and one with Sjogren's disease.

The rates of tobacco and alcohol use were consistent between both cohorts ($p > 0.05$), the majority of which were never users of either substance ($n = 34$, 89% never used tobacco; $n = 25$, 66% never used alcohol). Additionally, the presence of dental amalgam, systemic comorbidities, predisposing oral lesions, co-existing allergies, and histologic findings of the primary tumor were similar between the allergy and non-allergy groups ($p > 0.05$) (Tab. I). In both groups, most patients had a primary tumor stage of 2 or less ($n = 13$, 72% allergy group versus $n = 16$, 80% non-allergy group; $p = 0.62$) (Tab. I). Few patients had a recurrence or second primary in both the allergy and non-allergy groups ($n = 11$, 30% and $n = 8$, 21%, respectively; $p > 0.05$). The rates of radiation and systemic therapy were low for both cohorts ($n = 8$, 21%, $n = 4$, 11%, respectively; $p > 0.05$). Excluding patients without dental amalgam did not affect baseline characteristics. Metal allergies were predominantly to nickel, gold, and palladium (Tab. II).

Laterality of dental amalgam & OCC – stratified by metal allergy status and tobacco/alcohol use

While more patients with unilateral dental amalgam and an adjacent OCC were positive for metal allergies ($n = 6$, 30%), this finding was not significantly different from the number of patients without metal allergies and an ipsilateral OCC ($n = 4$, 22%; $p = 0.35$) (Fig. 1). There was a similar proportion of patients with bilateral dental amalgam in both cohorts ($n = 8$, 40% allergy group versus $n = 11$, 61% non-allergy group; $p > 0.05$) (Fig. 1). The only patient with dental amalgam contralateral to their primary tumor did not have a metal allergy (Fig. 1).

Table I. Comparison of patient baseline characteristics and risk factors; stratified by metal allergy status. Baseline characteristics include patient demographic data, presence of dental amalgam, behavioral risk factors, history of oral, allergic, or inflammatory conditions, tumor characteristics including stage, history of recurrence or secondary primary, and treatment modality.

Characteristic	Metal Allergy Yes n = 18 (%)	Metal Allergy No n = 20 (%)	p-value*
Gender			
Male	2 (11)	11 (55)	<.01
Female	16 (89)	9 (45)	
Age*	60.5 (24)	62.5 (28)	0.29
Dental Amalgam			
Yes	14 (78)	16 (80)	
No	1 (6)	4 (20)	0.12
Unknown	3 (16)	0	
Systemic Inflammatory Disorders†	6 (33)	5 (25)	0.72
Oral Inflammatory Conditions††	11 (61)	15 (75)	0.49
Other Allergies	12 (67)	11 (55)	0.52
Tobacco Use			
Current	0 (0)	3 (15)	
Former	0 (0)	1 (5)	0.16
Never	18 (100)	16 (80)	
Alcohol Use			
Current	3 (17)	8 (40)	
Former	0	2 (10)	0.07
Never	15 (83)	10 (50)	
Histologic Diagnosis			
Squamous Cell Carcinoma	15 (75)	14 (78)	
High Grade Dysplasia	4 (20)	2 (11)	0.74
Verrucous Carcinoma	1 (5)	2 (11)	
Primary Tumor Staging			
Stage ≤2†	13 (72)	16 (80)	0.62
Stage ≥3	2 (11)	3 (15)	
Unknown	3 (17)	1 (5)	
Recurrent Tumor	5 (28)	6 (30)	0.58
Secondary Primary	5 (28)	3 (15)	0.44
Radiation Therapy	4 (22)	4 (20)	0.59
Systemic Therapy	2 (11)	2 (10)	0.66

* p-values for categorical data determined by Chi-squared test or Fisher's exact test, and p-values for continuous data determined by Student's T test. Continuous data presented as group median with interquartile range (IQR) in parentheses. Significance assigned if $p<0.05$.
† Systemic conditions include type 2 diabetes, chronic kidney disease, reflux esophagitis, systemic inflammatory disorders (psoriasis, Sjogren's disease), and skin conditions (epidermolysis bullosa, prior squamous cell carcinoma).
†† Oral lesions include oral lichen planus, leukoplakia, gingivitis, periodontitis, and carcinoma *in situ*.
Ω Includes patients with T2, T1, or high grade dysplasia.
n = number of patients.

Similarly, when patients with a history of tobacco or alcohol use were excluded, 27% in the allergy group and 10% in the non-allergy group had amalgam on the ipsilateral side ($p = 0.31$) (Fig. 2). Again, there was no statistical difference in the proportion of patients with bilateral dental amalgam in either group ($n = 7$, 47% allergy group versus $n = 8$, 80% non-allergy group; $p > 0.05$) (Fig. 2).

Laterality of dental amalgam & OCC – observed vs. expected

When evaluating patients with unilateral dental amalgam regardless of metal allergy status, all but 1 had an adjacent OCC and this finding was significant ($n = 10$, 91% ipsilateral OCC versus $n = 1$, 9% contralateral OCC; $p = 0.006$) (Fig. 3).

Table II. Positive results for allergies to specific agents. Lists rate of allergies to metals, agents used in dental work, and toothpaste components.

Metals	n = 38 (%)
Any metal	18 (47)
Palladium	6 (16)
Aluminum	1 (3)
Gold	5 (13)
Nickel	9 (24)
Copper	1 (3)
Rhodium	1 (3)
Titanium	1 (3)
Zinc	1 (3)
Agents used in dental work	
Dental prosthetic components	7 (18)
Antibiotics	2 (5)
Toothpaste components	
Polymer structure/synthesis	4 (11)
Flavoring	10 (26)
Preservatives	9 (24)
Detergent	3 (8)

n = number of patients.

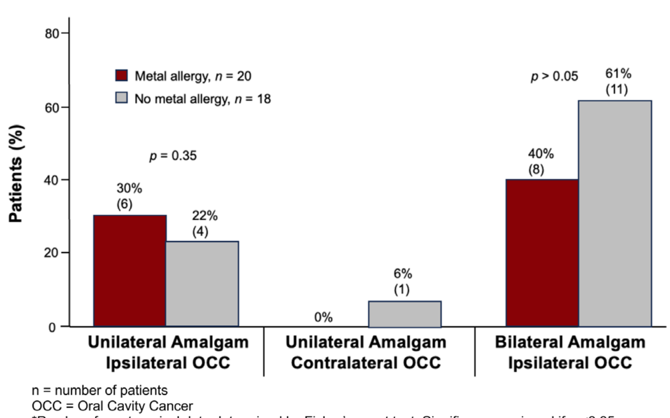

Fig. 1. Laterality of dental amalgam & OCC among all patients, stratified by metal allergy status. There was no significant difference

Discussion

The incidence of OCC in young adults has been increasing with no identifiable cause [3]. Our understanding of the effects of longstanding oral inflammation on the development of OCC is evolving and has been a major focal point of head and neck cancer research. More recently, atopy has been recognized as a mediator of chronic inflammation. Chronic allergic inflammation in patients with atopic diseases is associated with alterations to the protective barrier function of the affected epithelia and increased susceptibility to infection [15]. In the oral cavity, contact allergies can produce a localized mucosal inflammatory disorder known as contact stomatitis [10]. The presence of dental amalgam can be a source of contact stomatitis and predispose to OCC in individuals with metal allergies. However, there is limited data investigating the relationship between metal allergies and OCC with even fewer studies that exclude tobacco or alcohol use. To date, this is the largest cohort study in the literature investigating allergies to dental amalgam in risk factor negative OCC patients.

Given the rising population of risk factor negative OCC patients and routine use of amalgam in dental restoration, this study sought to determine the incidence of metal contact allergies and presence of dental amalgam adjacent to OCC sites in patients with and without traditional risk factors. Thus, OCC patients who were predominantly non-tobacco and non-alcohol users were intentionally selected for inclusion. It is worth noting that there was a disproportionately higher number of female patients in this study compared to males. Furthermore, the majority of patients were diagnosed with stage 2 or lower OCC. These findings are congruent with the literature. Harris et al conducted a retrospective review on 78 young adults diagnosed with head and neck cancer. When stratified by risk factors, patients who were never smokers and/or never drinkers tended to be female and have stage T1 disease [16]. This further supports the notion that other underlying factors are likely at play in the development of early onset OCC.

Systemic and oral inflammatory conditions have also been investigated as a potential risk factor for OCC. Patients with chronic inflammatory disorders, such as Crohn disease, systemic lupus erythematosus, and diabetes mellitus are at an increased risk for OCC [17–19]. The presence of systemic inflammatory disorders was accounted for in this study and the majority of patients did not have a related condition. We also evaluated for the presence of other oral inflammatory diseases, including oral lichen planus, leukoplakia, and periodontal disease. While over half of the patients did have a predisposing oral condition, the rates were similar for both the metal allergic and non-allergic cohorts.

In the present series, allergy testing revealed almost 50% of patients to be allergic to at least one metal. This is much higher than the general population, with reported rates of metal hypersensitivity ranging from 10% to 17% [20]. It is possible that the addition of skin prick testing may have picked up more allergy than if skin patch testing alone was performed. A similar study conducted by Weber *et al* demonstrated 29% of OCC patients had metal allergies compared to 21% in the control (non-cancer) group [11]. Another possible explanation for the increased rate of allergies in OCC patients is that the development of cancer may increase sensitization to allergens due to local destruction of epithelium, resulting in loss of a protective barrier [15]. Finally, in evaluation of 10,061 patients who underwent patch-testing of relevant oral allergens from 2001 to 2004 by the North American Contact Dermatitis Group, only 2% of patients had reactions limited to the lip. In addition to being immediately adjacent to the oral

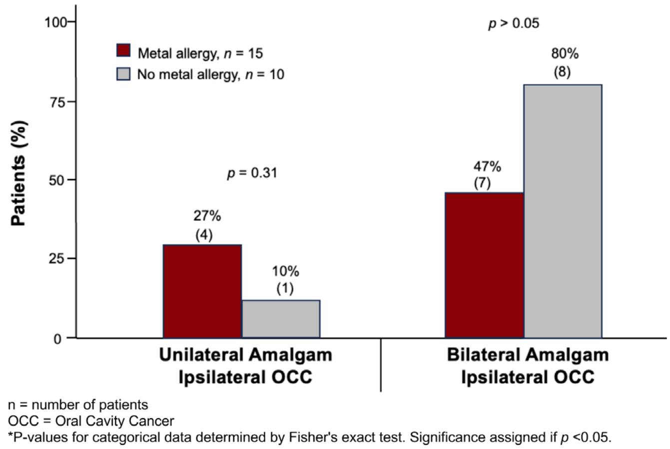

Fig. 2. Laterality of dental amalgam & OCC among non-smoking/non-drinking patients, stratified by metal allergy status. There was no difference rate of metal allergies in the unilateral and bilateral dental amalgam cohorts among non-smoking/non-drinking patients with OCC.

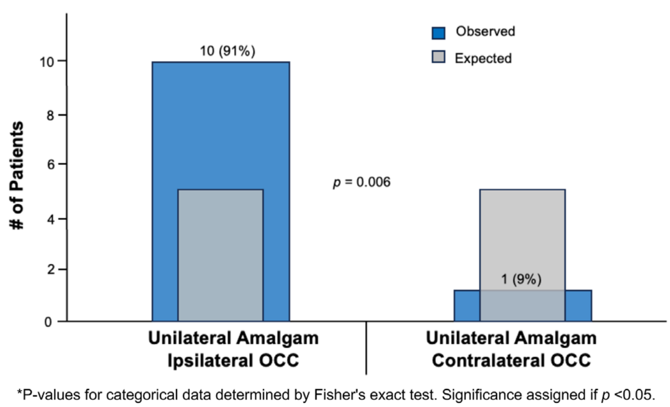

Fig. 3. Unilateral amalgam & OCC laterality, observed versus expected. Patients with unilateral dental amalgam were significantly more likely to have an adjacent OCC.

mucosa, the lip is thought to be even more susceptible to allergy and thus, serves as a reasonable comparison site [21].

Dental amalgam is a mixture of predominantly mercury mixed with silver, tin, and copper, which were all tested for in this study [22]. We identified nickel, followed by palladium and gold as the most common metal allergies. Although not typically found in dental amalgam, it should be noted that these other metals, especially palladium, are often used in other forms of dental restoration, including crowns and bridges. While we did not identify allergies to the specific metals most commonly found in dental amalgam, Hougeir et al. reported substantially higher rates of metal allergies consistent with amalgam components in a similar pilot study [23]. These differences in observations could be due to our addition of skin prick testing and the fact that metals create irritant reactions that are difficult to read and often overcalled as an allergic reaction in those less experienced with metal allergy testing. Interestingly, we noted a female preponderance to metal allergies. This finding is consistent with other studies and further supports the trend that women with OCC tend to be risk factor negative and at increased risk for metal allergies [11].

When assessing for OCC laterality, 91% of patients were found to have dental amalgam on the same side as their cancer. This was observed regardless of the patient's metal allergy status, as patients with and without metal allergies were equally likely to develop OCC ipsilateral to the side of their dental amalgam. Given the prevalence of amalgam in the general population ranges from 4% to 69%, this is a significant finding [22]. While it is unknown whether the association between dental amalgam and ipsilateral OCC is related to dental caries or inflammation that the amalgam was used to treat, there are multiple plausible explanations. Prior trauma from dental amalgam fillings and longstanding physical contact between metal and oral mucosa could lead to chronic irritation/inflammation, as oral trauma has been shown to be associated with OCC. Non-smoking individuals and those who wore dentures have been found to be significantly more likely to develop carcinoma at sites of recurrent trauma [8]. Alternatively, the dentition in regions of dental amalgam is presumably subpar with a history of underlying infection and periodontal disease prior to being addressed with metal fillings. Patients with periodontitis, a chronic inflammatory disease of the gingiva, have been found to be at greater risk of developing OCC than those who maintain good oral hygiene [7]. Thus, poor oral health could serve as a nidus for an occult chronic inflammatory state and subsequently OCC. It is also possible that the development of OCC is multifactorial, and the presence of dental amalgam is indicative of longstanding poor oral hygiene, prior dental trauma, and a history of periodontal disease all contributing to chronic inflammation.

Despite the trend away from dental amalgam to composite resins, there is still a significant proportion of the United States population with dental amalgam. The prevalence of dental amalgam in the general population increases with age, with nearly 23% in individuals 16 to 19 years old to 57% in adults over the age of 20 [22]. Reported rates of amalgam restorations appear to be similar between genders across all age groups [22]. Many of these patients may be at an increased risk for OCC. Importantly, pretesting for metal allergies does not predict future sensitization. Placement of any dental or orthopedic metal puts a person at risk of sensitization, even if they have been previously tested, and can lead to a false sense of security. Prevention through avoidance and use of epoxy resin as an alternative material have been advocated. In 2020, the FDA recommended avoiding dental amalgam restorations in certain groups, including patients with known heightened sensitivity to mercury or other components of dental amalgam [24]. There has not been a strict recommendation to remove dental amalgam in asymptomatic individuals due to the risks involved, including loss of healthy tooth structure and temporary exposure to mercury vapor during removal [24]. However, OCC patients without classic risk factors may warrant metal allergy testing to elucidate the possibility of an occult inflammatory reaction. Furthermore, although a strong recommendation cannot be made for removal of amalgam should an allergy be present, this could be considered in patients without other obvious risk factors.

There were several limitations to this study. One limitation is the presence of bilateral dental amalgam in over a third of our cohort, which does overinflate the proportion of patients who appear to have an adjacent tumor. Another limitation is the absence of a control group to determine the actual prevalence of dental amalgam and intraoral metal allergies in the general population. Although this is the largest known study evaluating contact allergies to dental amalgam in risk factor negative OCC patients, the sample size is small and may have precluded identification of a meaningful difference in metal allergy status in patients with dental amalgam adjacent to their OCC. Additionally, there was insufficient documentation on the presence and location of dental amalgam on a number of patients, which also limited our ability to include them in our calculations. For the patients who were included, it would be informative to have data on oral hygiene, history of periodontal disease, dental procedures performed in addition to dental restoration, and frequency of dental hygiene visits, to determine what role, if any, these factors may have in the development of OCC.

Conclusion

Metal allergies are more prevalent in women with OCC. Regardless of metal allergy status, patients with dental amalgam may be at an increased risk of developing an adjacent OCC. Routine use of metal alloys for dental fillings has fallen out of favor but is still prevalent in older populations. In female and risk factor negative individuals, we recommend the use of epoxy resin as an alternative for dental restoration, as this may serve as a preventative measure against the development of chronic inflammation and OCC.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability statement

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions, as they contain information that could compromise patient confidentiality. Data were obtained from patient medical records at the University of Utah Huntsman Cancer Institute following IRB approval.

Author contribution statement

V. Husmann: Conceptualization, Methodology, Data Curation, Formal Analysis, Investigation, Visualization, Writing – Original Draft, Writing – Review & Editing, Validation, Project Administration. N. Bellamkonda: Data Curation, Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing. C. Nielson: Data Curation, Formal Analysis, Investigation. V. Sahni: Resources. R. deShazo: Investigation, Resources, Writing – Review & Editing. D. Powell: Investigation, Resources. Z. Hopkins: Resources, Writing – Review & Editing. S. Drejet: Resources. J. Hunt: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Funding Acquisition.

Ethics approval

This study received ethical approval from the Institutional Review Board at the University of Utah on November 14, 2010 under IRB: 00045048.

Informed consent

Written informed consent was obtained from all patients and/or families.

Supplementary material

Supplemental Figure 1. Comprehensive list of tested allergens. Categories of allergens tested include metals, dental prosthetics, antibiotics, flavoring, preservatives, synthetic polymers, and detergents.

The Supplementary Material is available at https://www.jomos.org/10.1051/mbcb/2025030/olm.

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