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Nickel Ion Release from Orthodontic Archwires: A Narrative Review of Experimental and Clinical Studies

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ABSTRACT

Nickel-containing archwires, especially those fabricated from nickel-titanium (NiTi) and stainless steel (SS), are essential in fixed orthodontic therapy due to their favorable mechanical characteristics. Nonetheless, concerns persist regarding nickel-induced hypersensitivity, cytotoxic effects, and the release of metal ions, particularly nickel. This narrative review examines contemporary evidence on nickel release from orthodontic archwires, extending previous systematic reviews by evaluating both laboratory (in vitro) and clinical (in vivo) investigations under diverse environmental conditions. Searches were conducted in Web of Science, Scopus, and PubMed for studies addressing the association between nickel ion release from nickel-containing archwires and environmental factors. Evidence indicates that although metal ions are released during short-term orthodontic treatment, the concentrations generally remain below harmful thresholds, with release rates influenced by factors such as pH, corrosion, duration of treatment, and environmental conditions. Long-term studies are limited and are typically confined to either in vitro or in vivo settings, rarely both. To clarify causal relationships in metal ion release, monitoring ions such as nickel in vivo is crucial, and further research is needed to evaluate their long-term effects. Additionally, collaboration among clinicians, researchers, and regulatory authorities is essential to formulate evidence-based guidelines for the selection of orthodontic materials, emphasizing patient safety and the mitigation of metal ion risks.

Keywords: Orthodontic appliances, Artificial saliva, In vivo, In vitro, Nickel release, Nickel-containing archwires

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Introduction

Nickel exposure at elevated levels can lead to diverse health issues [1]. Historically, fatal cases were reported from nickel carbonyl exposure, and by the 1930s, nickel was recognized as a common cause of contact dermatitis. Occupational exposure was also linked to increased lung and nasal cancer rates [2, 3]. In 2008, Gillette highlighted nickel as the "Allergen of the Year," emphasizing a continued rise in nickel hypersensitivity [4, 5]. Nickel is additionally classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC), although there is no direct evidence connecting nickel released from orthodontic appliances to cancer in treated patients [6].

The majority of nickel produced globally is used in stainless steel and nickel-based alloys [7], which are integral to medical devices, including orthodontic archwires. Archwires are essential components in fixed orthodontic therapy, facilitating controlled tooth movement and forming the foundation of treatment [8]. Despite innovations in materials and techniques, no single archwire type is ideal for every treatment phase [9]. Commonly used archwires include nickel-titanium (NiTi) alloys, sometimes alloyed with copper, and stainless steel (SS) wires.

The nickel content in these wires varies considerably. NiTi wires can contain over 50% nickel, while copper-nickel-titanium variants usually have slightly less, and SS wires contain roughly 8% nickel [10-12]. SS wires are easier to manipulate and generally less allergenic due to their chromium content (12–13%), which forms a protective oxide layer against corrosion [13]. However, SS wires are more rigid and less flexible, often requiring additional clinical adjustments [14, 15].

NiTi archwires offer high elasticity, shape memory, and resistance to permanent deformation. Although they may deform permanently at high temperatures, low-temperature strains are reversible upon reheating [16]. Yet, the nickel content raises concerns about cytotoxic, allergic, and potentially mutagenic effects, prompting questions about their overall biocompatibility [17].

Long-term orthodontic treatment can affect both titanium and SS wires through changes in oral pH and fluoride exposure. While the phenomenon of orthodontic appliance corrosion is established, its clinical and health implications remain underexplored. Existing evidence indicates that metal ion release occurs during treatment, but at levels far below those normally ingested in the diet, highlighting the need for further in vivo studies to evaluate clinical significance [18, 19]. Allergic reactions in orthodontic patients can occur for multiple reasons, including nickel sensitization, with some studies showing higher prevalence in female patients [11, 20, 21].

The introduction of NiTi alloys led to focused biocompatibility research. For instance, Wever *et al.* [22] combined in vitro and in vivo approaches, concluding that NiTi alloys demonstrate good short-term biocompatibility due to minimal ion release and strong corrosion resistance. Recent studies over the past decade support these conclusions, showing that nickel ion release from brackets and wires in patients' saliva remains below toxic thresholds and typically declines after an initial peak [23].

Allergic reactions to nickel released from nickel-containing alloys

Although NiTi alloys are generally considered safe, nickel released from these materials can still provoke undesirable biological responses. In orthodontics, allergic reactions are typically similar to type IV (delayed-type) hypersensitivity, arising from immune system sensitization to nickel ions [24, 25]. This process occurs in two phases: the first, sensitization, involves the immune system recognizing nickel ions and generating memory T-cells, and the second, elicitation, is triggered by subsequent exposure, prompting the release of inflammatory mediators like cytokines. The resulting localized inflammation can manifest extra-orally as contact dermatitis, presenting with swelling, redness, or, in severe cases, oral ulceration. Other metals found in orthodontic devices, including chromium, cobalt, copper, titanium, and silver, can also induce allergic reactions [11]. Beyond classic type IV responses, nickel released from fixed orthodontic appliances may trigger reactions in both the oral cavity and distant body sites, as described by Di Spirito *et al.* [26].

Interest in metal ion release from orthodontic archwires has grown in recent years. Although the concentrations of released ions are considerably lower than those encountered in a typical diet, understanding the complex interactions between alloy properties, environmental factors, and individual patient susceptibility remains challenging [27-29]. Nickel is recognized as the leading cause of metal-induced allergic contact dermatitis, responsible for more allergic reactions than all other metals combined [30].

Influence of saliva and other environmental factors on nickel release

Environmental factors, particularly saliva, play a significant role in the release of nickel from orthodontic devices. Brackets, bands, and archwires are continuously exposed to fluctuating oral conditions, including changes in pH (often influenced by diet), temperature variations, mechanical stresses, and the inherent susceptibility of alloys to corrosion [31]. Several studies [29, 32, 33] have simulated oral conditions by immersing nickel-containing archwires in artificial saliva for durations corresponding to common treatment periods. These studies demonstrate a measurable increase in nickel levels in saliva and serum following the placement of fixed appliances [34].

Despite this, research consistently shows that metal ion concentrations remain far below harmful thresholds, with permissible levels in drinking water exceeding those measured in saliva from orthodontic patients [35]. Surface passivation layers composed of chromium and titanium oxides help limit corrosion and slow ion release, though these protective layers can degrade due to mechanical wear, polishing, or acidic conditions [13]. Additional strategies to reduce nickel release include applying surface coatings to orthodontic devices [36, 37].

Interestingly, exposure to electromagnetic radiation, such as radiofrequencies from mobile phones, has been associated with increased nickel release from archwires [38, 39]. Mortazavi *et al.* [38] recommend further research into the effects of radiofrequencies from other devices, including Wi-Fi routers. Rajendran *et al.* [39] also found that using earphones reduces the phone's impact on nickel release, suggesting proximity to electronic devices may enhance ion liberation.

Earlier systematic reviews by Mikulewicz and Chojnacka (2009, 2010) [31, 35] evaluated both in vitro and in vivo studies of metal ion release from orthodontic appliances, concluding that short-term appliance use does not result in toxic nickel exposure. However, data on long-term exposure were limited and required further investigation. A 2019 meta-analysis by Imani *et al.* [40] similarly reported low nickel release, which may even induce oral tolerance in early treatment stages, but emphasized the need for studies with larger, more ethnically diverse populations and controlled saliva composition.

The present review seeks to summarize the current understanding of nickel release, highlight novel findings since prior systematic reviews, and provide recommendations for future research. The included studies are categorized into in vitro and in vivo groups, examining how various environmental and material factors influence nickel ion release from orthodontic archwires.

Scope and sources of reviewed literature

This review provides a detailed summary of current research examining nickel ion release from commonly used orthodontic archwires, specifically stainless steel (SS) and nickel-titanium (NiTi) alloys. The discussion covers a variety of wire types, including SS CrNi, thermally activated (martensitic) NiTi and CuNiTi, as well as superelastic (austenitic) NiTi wires, reflecting the materials most frequently employed in modern orthodontic practice.

To gather pertinent studies, a focused literature search was carried out across Web of Science (WoS), Scopus, and PubMed. Keywords included terms such as "nickel ion release," "nickel content dynamics," "stainless steel orthodontic archwires," "nickel-titanium archwires," "in vitro," and "in vivo." Articles were selected according to these criteria: (1) they investigated nickel-containing archwires (SS or NiTi); (2) they assessed nickel release under laboratory (in vitro) or clinical (in vivo) conditions; and (3) they explored environmental factors—such as pH or other conditions—that could influence ion release.

Unlike a systematic review, this study did not adhere to rigid, protocol-driven inclusion rules. Instead, it adopted a narrative approach, aiming to synthesize available evidence, highlight key trends, and provide insights into the variables that affect nickel ion release from orthodontic materials.

Studies failing to meet these parameters were excluded from analysis **(Figure 1)**, ensuring the review maintained focus on the most relevant research while still offering a broad understanding of nickel release dynamics in orthodontic practice.

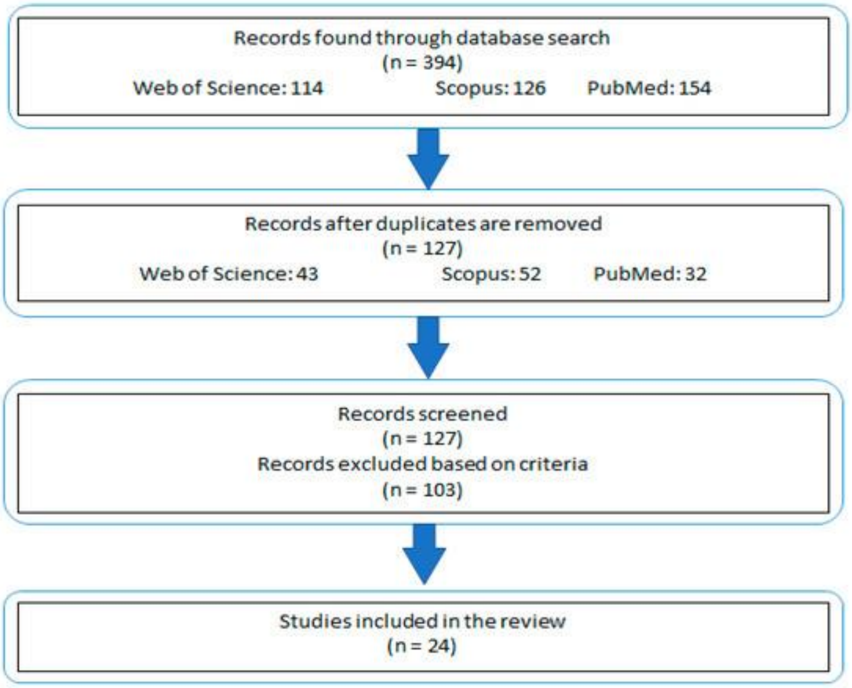

Figure 1. Schematic representation of the study selection and exclusion process

Key findings from the literature

To quantify metal ion release from orthodontic archwires, atomic absorption spectrometry (AAS) and atomic emission spectroscopy (AES) are most frequently employed due to their ability to analyze small sample volumes. Scanning electron microscopy coupled with energy-dispersive spectroscopy (SEM/EDS) is commonly used to examine surface elemental composition and identify localized morphological changes in specific areas of the samples.

In vitro studies of nickel-containing archwires

In vitro research on nickel-containing archwires often uses artificial saliva to replicate the oral environment. **Table 1** summarizes the composition of artificial saliva used across the reviewed studies. Many investigations focus on the effects of artificial saliva on nickel ion release over defined time periods.

Cioffi *et al.* [41] examined pseudoelastic NiTi archwires under simulated physiological conditions, incorporating stress and fluoridated media. Their findings indicated that nickel ions were not released during stress-induced austenite-to-martensite transformations, suggesting that the NiTi surface remains stable under tensile stress. However, prolonged fluoride exposure significantly increased ion release, highlighting the need for further investigation into the short-term effects of fluorides.

Pastor *et al.* [42] studied commonly used archwires immersed in various mouthwashes in 2023. Results demonstrated that mouthwash exposure elevated nickel release, which could trigger hypersensitivity in susceptible patients. The authors emphasized caution when using mouthwashes during orthodontic treatment.

Mirjalili *et al.* [18] conducted in vitro tests using artificial saliva to explore localized corrosion and the effects of pre-passivation treatments through potentiodynamic and potentiostatic polarization. They reported that NiTi did not undergo pitting corrosion, while SS showed minor improvements from pre-passivation. Furthermore, artificial crevices did not influence corrosion in fluoridated media, and pre-passivation positively affected pitting resistance in both alloys.

Didovic *et al.* [43] investigated NiTi wires along with SS brackets, bands, and ligatures. Their analysis revealed that different manufacturing processes led to variations in surface morphology. As-received SS bands and brackets showed pitting corrosion, while adhesive coatings formed on SS brackets and ligatures during immersion. Protective oxide layers were absent across all components, and salt precipitation, mainly potassium chloride (KCl), was observed. SS bands released considerably more ions than other components, likely due to welding during manufacturing, and surface roughness did not correlate with ion release.

Ganidis *et al.* [44] immersed SS, NiTi, and CuNiTi wires in artificial saliva and analyzed ion leachates. Chromium (Cr) and nickel (Ni) dominated after 30 days, with maximum release occurring at pH 3.5. Regardless of material type or aging conditions, released ion levels remained below typical daily dietary intake.

Laird *et al.* [45] assessed five archwires in buffer solutions with varying pH levels. Their findings indicated that nickel release increased over time and decreased at higher pH, with coated wires consistently exhibiting lower ion release than uncoated ones.

Osmani *et al.* [46] evaluated six archwire types (NiTi, coated NiTi, SS, nickel-free SS, CoCr, and TMA) in artificial saliva under different pH conditions. NiTi released more Ti and Ni than coated NiTi, SS released more Fe, Cr, and Ni than nickel-free SS, and CoCr leached high Co and smaller amounts of Cr, Ni, and Mo compared to TMA. Overall, ion release was lower at pH 6.6 and for hypoallergenic alloys compared to standard dental alloys.

Al-Jammal *et al.* [47] investigated NiCr alloys in artificial saliva at four pH levels. Using AAS, they found that Ni and Cr release peaked at pH 2.5 across all immersion times, with nickel released in larger quantities than chromium. The study concluded that acidic conditions enhance metal ion release, with nickel being released more readily than chromium.

Chikhale *et al.* [48] compared metal ion release from titanium-molybdenum (TMA) and nickel-titanium (NiTi) archwires by immersing them in artificial saliva. The study revealed that NiTi wires emitted higher levels of nickel, whereas TMA wires released greater amounts of titanium. Importantly, the measured ion concentrations remained within safe limits for clinical use.

In a study by Aiswareya *et al.* [29], both NiTi and stainless steel (SS) wires were paired with SS and ceramic brackets and immersed in artificial saliva to evaluate nickel and chromium ion release. Ion concentrations were quantified using flame atomic absorption spectroscopy (FAAS), and cytotoxicity was tested on HeLa cells. Results indicated that wires attached to SS brackets released significantly more nickel and chromium, while comparisons between the wires themselves did not show meaningful differences in ion release.

The influence of saliva pH on ion release was highlighted by Kao *et al.* [49], who investigated fluoride-corroded extracts from SS and heat-activated NiTi wires on human osteosarcoma (U2OS) cells. Exposure to saliva at different pH levels revealed that fluoride-containing environments could pose cytotoxic risks, emphasizing the need for careful consideration during orthodontic treatment. Similarly, Senkutvan *et al.* [33] assessed four types of archwires—NiTi, SS, CuNiTi, and ion-implanted NiTi—immersed in artificial saliva. Nickel release declined over time and remained below levels likely to induce allergic reactions, confirming the clinical safety of these wires even under acidic conditions.

Table 1. Formulations of Artificial Saliva Used in Reviewed Studies

Artificial Saliva Composition	References
Phosphate-buffered saline (PBS), pH 4.6	[41]
PBS with 0.001% sodium fluoride (NaF), pH 4.8	[41]
PBS with 0.01% NaF, pH 5.0	[41]
PBS with 0.1% NaF, pH 5.6	[41]
Sodium chloride (0.844 mg), potassium chloride (1.2 mg), anhydrous calcium chloride (0.146 mg), magnesium chloride hexahydrate (0.052 mg), dipotassium phosphate (0.34 mg), 70% sorbitol solution (60 mg), methyl paraben (2 mg), hydroxyethyl cellulose (3.5 mg)	[48], [30], [17]
Sodium chloride (0.4 g), potassium chloride (1.21 g), sodium hypophosphate (0.78 g), sodium sulfide (0.005 g), urea (1 g), distilled and deionized water (1000 mL)	[33], [29]
Neutral solution: 1.5 mM calcium (Ca), 0.9 mM phosphorus (P), 20 mM Tris buffer, 150 mM potassium chloride, pH 7.0; Acidic solution: 2 mM Ca, 2 mM P, 74 mM acetate buffer, pH 4.3	[32]
Potassium chloride (0.4 g), sodium chloride (0.4 g), calcium chloride dihydrate (0.906 g), sodium dihydrogen phosphate dihydrate (0.69 g), sodium sulfide nonahydrate (0.005 g), urea (1 g)	[18]
Sodium chloride (0.84 mg/100 mL), potassium chloride (1.2 mg/100 mL), magnesium chloride (0.052 mg/100 mL), calcium chloride (0.146 mg/100 mL), potassium dihydrogen phosphate (0.34 mg/100 mL), 70% sorbitol solution (60 mL), hydroxyethyl cellulose (3.5 mg/100 mL)	[49]
Potassium chloride (1.5 g/L), sodium bicarbonate (1.5 g/L), potassium thiocyanate (0.5 g/L), lactic acid (0.9 g/L)	[37], [42], [46]
Dipotassium phosphate (7.69 g), potassium dihydrogen phosphate (2.46 g), sodium chloride (5.3 g), potassium chloride (9.3 g) in 1000 mL distilled water	[47]

Sodium chloride (NaCl); potassium chloride (KCl); monosodium phosphate (NaH_2PO_4); water (H_2O); sodium sulfide (Na_2S); urea ($CO(NH_2)_2$); calcium chloride ($CaCl_2$); sodium bicarbonate ($NaHCO_3$); potassium thiocyanate (KSCN).

In vivo, the oral environment is dynamic, and saliva flow can significantly influence the release of metal ions from orthodontic wires. To simulate this, Mikulewicz *et al.* [50] designed a thermostatically controlled glass reactor that maintained a continuous flow of artificial saliva and assessed nickel release from stainless steel (SS) archwires. Their results confirmed that nickel levels remained far below toxic limits, supporting the clinical safety of SS wires.

Patient oral hygiene routines also impact ion release. Jamilian *et al.* [30] investigated SS and round NiTi wires submerged in three solutions—Oral B®, OrthoKin®, and artificial saliva—and observed that ion release increased over time. Among the solutions, artificial saliva caused the least metal emission, and SS wires generally released ions more slowly than NiTi. Mirhashemi *et al.* [51] similarly reported that mouthwashes affected metal release differently, with Listerine causing the highest release and Oral B® the lowest.

Zubaidy and Hamdany [52] evaluated whether magnetically treated water (MTW) could influence nickel release from SS wires. They found that MTW significantly reduced nickel emission compared to mouthwashes, suggesting it could be a safer oral rinse during orthodontic treatment. Additionally, Erwansyah *et al.* [53] showed that Salacca zalacca (snake fruit) extract at 300 ppm could inhibit nickel release from SS wires, indicating a possible protective effect.

Table 2 summarizes key in vitro studies, listing archwire types, brand names, analyzed ions, exposure times, and evaluation methods. Wire geometry also plays a role in ion release: Azizi *et al.* [17] found that rectangular NiTi wires released more ions than round wires, especially during the first hour of immersion, emphasizing that wire shape influences metal leaching.

Although most in vitro findings indicate ion release remains within safety thresholds, evaluating cytotoxicity is essential. Dugo *et al.* [54] tested metal eluates from NiTi and SS appliances—including archwires, brackets, bands, and ligatures—on CAL 27 (lingual epithelium), HepG2 (liver), CaCo-2 (colon), and AGS (stomach carcinoma) cells. CAL 27 cells were highly sensitive, while CaCo-2 showed the greatest resistance. ROS production was observed in HepG2 and AGS cells, with higher concentrations sometimes reducing ROS levels compared to lower concentrations. Minor genotoxic effects and pro-oxidative DNA damage were associated with Cr, Mn, and Al, but these effects were insufficient to overwhelm normal cellular defenses. Statistical analyses highlighted that Fe, Cr, Mn, and Al contributed most to cytotoxicity, while Mn and Cr were mainly responsible for hydroxyl radical formation and DNA strand breaks, and Fe and Ni promoted ROS.

Finally, Thiyagarajan *et al.* [55] assessed NiTi, SS, and CuNiTi wires using electrochemical techniques after three days in artificial saliva. Their findings indicated that NiTi and CuNiTi displayed superior corrosion resistance relative to SS, and nickel release was minimal. The study underscored that saliva can modify corrosion behavior, but overall, the risk of harmful nickel release from these wires is very low.

In vivo studies on nickel-containing archwires

This section reviews clinical investigations that assessed nickel release from orthodontic archwires over treatment periods ranging from one week to eighteen months. Studies are presented according to treatment duration, ending with two analyses addressing the statistical behavior of nickel ion release. **Table 3** provides a summary of these studies, including archwire composition, brand, measured ions, clinical exposure times, and evaluation techniques.

Orthodontic devices containing nickel have been widely studied due to their potential to trigger hypersensitivity and release metal ions into the oral environment. Ghazal *et al.* [56] examined the surface characteristics and nickel emission of superelastic and heat-activated NiTi wires after 30 days in patients' mouths. Both wire types released similar nickel amounts, but superelastic wires exhibited rougher surfaces. Interestingly, wires tested after retrieval released fewer ions in artificial saliva, suggesting that nickel leaching may decrease over time despite surface alterations caused by clinical use.

Ibañez *et al.* [57] analyzed metal ion release over time in heat-activated NiTi and stainless steel (SS) wires and explored its relationship with salivary pH. Metal release reached a peak but remained within safe levels. Salivary pH dropped during the first three months of treatment but returned to alkaline levels after six months, indicating that the oral environment may adjust to the presence of orthodontic appliances.

Almasry *et al.* [58] investigated nickel release from round thermoactive NiTi wires during the first two months of use. They observed a modest increase in nickel concentration, yet levels remained below established safety limits, supporting the general biocompatibility of these wires in early treatment stages.

Bass *et al.* [59] explored nickel sensitization in patients with known allergies who received SS and NiTi archwires. Of 29 participants, five females were initially sensitive to nickel, and two additional patients developed sensitivity during treatment. The results suggested a higher risk of nickel hypersensitivity in female patients, though overall oral health was minimally affected by the orthodontic appliances.

Lages *et al.* [60] measured salivary metal levels in patients using either metal or esthetic orthodontic appliances (SS brackets with heat-activated NiTi wires). Their retrospective study found no significant differences in nickel levels between control subjects and patients with metal appliances or between esthetic and control groups. However, nickel concentrations were influenced by the type of appliance, emphasizing that material selection plays a role in regulating metal ion exposure.

Amini *et al.* [61] compared saliva from patients with fixed orthodontic appliances (NiTi and SS archwires with SS brackets and bands) to that of their same-gender siblings without orthodontic treatment. Nickel levels were significantly higher in patients, while chromium concentrations showed no significant difference. The study concluded that fixed appliances can increase salivary metal ions, highlighting the importance of monitoring patient exposure throughout treatment.

Below is a paraphrased version of the table, presented in table form, summarizing the general overview of nickel-containing archwires and methods used in the reviewed in vitro studies. The content has been rephrased while maintaining the structure and key details.

Table 2. Summary of Nickel-Containing Archwires and Analytical Methods in In Vitro Studies

Material	Brand and Manufacturer	Ions Analyzed	Test Medium	Exposure Duration	Analytical Techniques	Reference
NiTi	Nitinol N Memory-Metalle (0.5 × 0.5 mm), Nitinol S Memory-Metalle foil (0.05 and 1 mm) (GmbH, Weil am Rhein, Germany); Sentalloy standard (0.46 × 0.46 mm), Neo Sentalloy standard (0.46 × 0.63 mm) (GAC International Inc., Bohemia, NY, USA)	Ni	Fluoridated and non-fluoridated artificial saliva	7 days	Thin layer activation, X-ray photoelectron spectroscopy	[41]
NiTi	Round (0.020 in) and rectangular (0.016 × 0.016 in) NiTi archwires (Ortho Technology, Tampa, FL, USA)	Ni, Ti	Artificial saliva	1 h, 24 h, 7 days, 21 days	Inductively coupled plasma atomic emission spectrometry	[17]
NiTi, TiMo	NiTi (17 × 25 in), TMA (17 × 25 in) (Modern Orthodontics, Ludhiana, India)	Ni, Ti	Artificial saliva	90 days	Atomic absorption spectrometry	[48]
SS, NiTi, TiMo	SS (American Orthodontics, Sheboygan, WI, USA); NiTi (Neo Sentalloy, GAC, West Columbia, USA); TiMo (Beta Blue, Highland Metals, Bangkok, Thailand)	Ni, Ti	Unspecified mouthwashes	1 day, 4 days, 7 days, 14 days	Inductively coupled plasma mass spectrometry, Scanning electron microscopy	[43]
NiTi, CuNiTi	NiTi Memory Wire (0.016 in), Damon Optimal-Force Cu Ni-Ti (0.016 in), Tanzo Cu NiTi (0.016 in) (American Orthodontics); Flexy NiTi Cu (0.016 in) (Orthometric)	Ni, Cu	Neutral and acidic solutions	7 days	Graphite furnace atomic absorption spectrometry, Inductively coupled plasma atomic emission spectrometry	[32]
NiTi, Coated NiTi, SS, Ni-free SS, CoCr, TMA	BioForce Sentalloy, High Aesthetic (Dentsply GAC, New York, NY, USA); Remanium, Noninium, Elgiloy, Rematitan Special (Dentaurum, Ispringen, Germany)	Ni, Ti	Artificial saliva	3 days, 7 days, 14 days, 28 days	Inductively coupled plasma mass spectrometry	[46]
NiTi, CuNiTi, SS	Not specified	Ni	Artificial saliva	3 days	Cyclic voltammetry, Electrochemical impedance spectroscopy, Polarization (Tafel) plot	[55]

NiTi, Esthetic wires, SS	NiTi (0.019 × 0.025 in, Ormco, Glendora, CA, USA); FLI wire, Iconix (American Orthodontics, Sheboygan, WI, USA); Bio-Active RC (GC Orthodontics, TOMY Inc., Fuchu City, Tokyo); SS (3M Unitek, St. Paul, MN, USA)	Ni, Cr	Buffer solutions (pH 4, 5.5, 7)	4 weeks, 13 weeks	Inductively coupled plasma mass spectrometry	[45]
NiTi, SS	Rematitan® LITE ideal arches (0.43 × 0.64 mm, Dentaurum, PA, USA)	Fe, Ni, Cr, Mn, Al, Ti, Cu	Artificial saliva	3 days, 7 days, 14 days	Scanning electron microscopy with energy dispersive spectroscopy, Inductively coupled plasma mass spectrometry	[42]
NiTi, SS	SS Upper 016 Form III (0.016 × 0.016), NiTi Form I Upper 016 (0.016 × 0.016), Tanzo® Copper NiTi (0.016 × 0.016), Tru-Arch® UM (0.016 × 0.016), Tru-Arch® CuNiTi 35 °C UL (0.016 × 0.022) (Ormco)	Ni, Mn, Cr, Mo, Ti	Artificial saliva	7 days, 30 days	Inductively coupled plasma optical emission spectrometry	[44]
NiTi, SS	SS (0.010/0.014/0.016 × 0.022 in), Heat-activated Nitinol (0.016/0.016 × 0.022 in) (3M Unitek, Monrovia, CA, USA)	Ni, Ti, Cr	Artificial saliva	1 h, 24 h	Atomic absorption method	[49]
NiTi, SS	NiTi, SS, Ion-implanted NiTi, Copper NiTi (0.016 × 0.022 in) (American Orthodontics, Sheboygan, WI, USA; GAC International, Bohemia, NY, USA; Ormco)	Ni	Artificial saliva	7 days, 14 days, 21 days	Atomic absorption method	[33]
NiTi, SS	SS, NiTi rectangular archwires (0.017 × 0.025 in) (Ormco)	Ni, Cr	Artificial saliva	7 days, 14 days, 1 month	Flame atomic absorption spectrometry	[29]
NiTi, SS	Nitinol (0.4 mm, Dentaurum, Germany); SS304 (0.4 mm, Tiger Ortho, Boston, MA, USA)	Ni, Ti, Cr, Mo, Mn	Fusayama–Meyer solution	Not specified	Potentiodynamic and potentiostatic polarizations, Energy dispersive X-ray, Atomic adsorption spectroscopy	[18]
NiTi, SS	SS, NiTi (0.018 in diameter, American Orthodontics, Sheboygan, WI, USA)	Ni, Cr	Oral B®, Orthokin®, Artificial saliva (SaliLube®, Sinphar Pharmaceutical	1 h, 6 h, 24 h, 7 days	Atomic absorption method	[30]

			Co., Ltd., Taipei, Taiwan)			
NiTi, SS	Not specified	Ni, Cr	Oral B®, Oral B® 3D White Luxe, Listerine, Listerine Advanced White	1 h, 6 h, 24 h, 168 h	Atomic absorption spectroscopy	[51]
SS	Not specified	Ni, Cr	Snakefruit extract (Salacca zalacca)	24 h	Atomic absorption spectrophotometry	[50]
SS	SS archwires (0.016 × 0.022 in, Dentaurum, Germany)	Ni	Magnetically treated water, OrthoKin®	24 h, 2 weeks, 4 weeks	Scanning electron microscopy, Atomic absorption spectrometry	[52]
NiCr (alloy)	Not specified	Ni, Cr	Artificial saliva	12 days, 24 days, 36 days	Atomic absorption spectroscopy	[47]

Nickel-Titanium (NiTi); nickel-titanium with coating (coated NiTi); copper nickel-titanium (CuNiTi); stainless steel (SS); nickel-chromium (NiCr); nickel-free stainless steel (Ni-free SS); titan-molybdenum (TiMo); cobalt-chromium (CoCr); titanium-molybdenum alloy (TMA); days (d); inches (in).

Table 3. Summary of Nickel-Containing Archwires and Analytical Methods in Reviewed In Vivo Studies

Material	**Brand and Manufacturer**	**Ions Studied**	**Study Environment**	**Exposure Duration**	**Analytical Methods**	**References**
NiTi	NiTi Force I® 0.019 × 0.025 in, Therma-Ti Lite® 0.019 × 0.025 in (American Orthodontics, Sheboygan, WI, USA)	Ni	Oral environment	1 month	Scanning electron microscopy, Atomic force microscopy, Atomic absorption spectrophotometry	[56]
NiTi, CuNiTi	Superelastic NiTi 0.016 × 0.022 in, Heat-activated NiTi 0.016 × 0.022 in, Heat-activated CuNiTi 0.016 × 0.022 in	Ni	Oral environment	6 weeks, 8 weeks	Energy dispersive X-ray, Dynamic modeling	[62]
NiTi, Rh-coated NiTi, SS	Heat-activated nitinol archwire (Abzil, São José do Rio Preto, SP, Brazil), Rhodium-coated nitinol 0.014 in (BioActive, Crystal 3D, São Carlos, SP, Brazil)	Ni, Cr, Fe, Cu	Oral environment	1–6 months	Total reflection X-ray fluorescence	[60]
NiTi, SS	Not specified	Not specified	Oral environment	3 months	Nickel patch, Gingival index, Plaque index, Intraoral photographs	[59]
NiTi, SS	Ni–Ti heat-activated wires 0.016 in, Stainless steel wires 0.016 × 0.022 in (3M™ Unitek™)	Ni, Ti	Oral environment	1 month	Coupled plasma optical emission spectroscopy, Scanning electron microscopy	[57]
NiTi, SS	Round thermoactive archwires 0.016 in (Equire Thermo-Aktive, Dentaurum, Germany)	Ni	Oral environment	7 days, 1 month, 2 months	Atomic absorption spectrophotometry	[58]
NiTi, SS	Stainless steel CrNi, Superelastic NiTi, Thermodynamic heat-activated NiTi, CuNiTi,	Ni	Oral environment	6 weeks, 8 weeks	Scanning electron microscopy with energy dispersive spectroscopy, Dynamic modeling	[63]

	TriTanium™, Bio-active™					
NiTi, SS	Pre-adjusted roth stainless steel brackets 0.018 in (Discovery, Dentaurum, Pforzheim, Germany), Stainless steel bands (Unitek/3M, Monrovia, CA, USA), Nitinol (Ormco Corporation, Orange, CA, USA), Stainless steel archwires (Remantium, Dentaurum)	Ni, Cr	Oral environment	12–18 months	Atomic absorption spectrophotometry	[61]

Nickel-Titanium (NiTi); nickel-titanium with coating (coated NiTi); copper nickel-titanium (CuNiTi); stainless steel (SS); nickel-chromium (NiCr).

Statistical analyses have been conducted to evaluate how nickel content in various nickel-containing orthodontic archwires changes with clinical use and to offer guidance on recommended durations of application [62, 63].

In a 2019 study [62], researchers examined austenitic NiTi, heat-activated NiTi, and heat-activated CuNiTi wires. The wires were categorized into four groups: autoclaved as-received (S0), untreated as-received (S1), used intraorally for up to six weeks (S2), and used intraorally for over eight weeks (S3). Nickel levels were assessed at multiple visually distinct sites along each wire, using both global averages across all areas and localized measurements focused on the most corroded regions. While the overall global measurements did not show significant differences among groups, localized data revealed notable changes between S1, S2, and S3. Based on these localized observations, the authors proposed a model describing nickel release dynamics; however, they cautioned that the model serves as a general framework, and clinicians should interpret it in the context of individual patient factors.

Building upon this, a 2025 study [63] included the same NiTi wire types and added stainless steel (SS) and multi-force wires. Archwires were categorized as as-received, used intraorally for up to six weeks, and used for over eight weeks. The results indicated that each alloy type displays distinct patterns of nickel release influenced by both material composition and oral environmental conditions. Wires such as SS-CrNi, heat-activated NiTi with copper (HA-NiTi-Cu), and TriTanium™ demonstrated sufficient stability for long-term use, while superelastic NiTi, heat-activated NiTi without copper (HA-NiTi), and Bio-Active™ showed higher nickel release, suggesting their use is more appropriate for shorter treatment periods. The authors emphasized that these recommendations are generalized, and patient-specific considerations remain essential.

Together, these studies illustrate that orthodontic appliances containing nickel can release metal ions and may contribute to sensitization, particularly in female patients. Despite this, released nickel levels generally stay within safe limits. Factors such as surface roughness, wire type, and length of clinical use affect the extent of release. While nickel hypersensitivity is a potential concern, careful material selection combined with monitoring can reduce risk, allowing orthodontic treatments to remain safe for most patients.

Additional influences on nickel release include fluoride exposure, pH fluctuations, immersion duration, saliva composition, oral hygiene routines, dietary factors, and wire geometry. These variables can impact both the degree of ion release and clinical safety, highlighting their importance when selecting orthodontic materials.

Key insights from the literature

The 24 studies reviewed, primarily from recent years, provide a comprehensive view of nickel release from nickel-containing orthodontic appliances, with emphasis on NiTi archwires (with and without copper) and SS archwires. These are among the most frequently used in fixed orthodontic treatments, and understanding their behavior is critical for patient safety and biocompatibility. Over time, research has evolved from initial concerns about NiTi biocompatibility to a more detailed understanding of the multiple factors that influence nickel ion release in both laboratory and clinical settings.

Biocompatibility and short-term safety of NiTi alloys

The research by Wever *et al.* [22] played a pivotal role in demonstrating that nickel-titanium (NiTi) alloys, widely used in orthodontic archwires, are biocompatible in the short term. Their combined in vitro and in vivo investigations revealed that NiTi exhibits low cytotoxicity, minimal potential for sensitization, and strong corrosion resistance, making it suitable for clinical use. Supporting these conclusions, Kovac *et al.* [64] confirmed that ion release from NiTi wires and stainless steel (SS) brackets remains below recommended daily intake limits, even over extended periods. However, the fact that higher concentrations of nickel were detected in debris compared to artificial saliva indicates that localized accumulation, such as food debris enriched with nickel ions, could provoke hypersensitivity reactions in susceptible patients. Matusiewicz [65] further emphasized that metallic debris generated by corrosion in intraoral conditions can build up over time, particularly in patients with poor oral hygiene, which is relevant for assessing overall biocompatibility.

While in vitro studies generally show that the amount of metal ions released, including nickel, does not reach harmful levels, these experiments cannot fully replicate the complex intraoral environment of individual patients, and should therefore be interpreted as indicative rather than definitive. In vivo investigations complement these findings, showing that nickel-containing archwires release ions at levels generally considered safe, but can still induce sensitization, especially among females. Careful selection of materials and regular monitoring remain crucial for minimizing potential risks and ensuring orthodontic treatment safety.

Impact of fluorides, saliva, and pH on nickel release

Fluoride exposure is a major factor influencing nickel ion release. Studies by Cioffi *et al.* [40] and Mirjalili *et al.* [18] indicated that NiTi archwires resist tensile stress-induced phase transformation, yet prolonged contact with fluoridated media increases nickel release, which is clinically relevant due to the widespread use of fluoride-containing dental products during orthodontic care. Kao *et al.* [49] highlighted potential cytotoxic effects of fluoride corrosion extracts in acidic conditions, underscoring the need for caution with acidic fluoride agents in patients with NiTi wires. Conversely, Zubaidy and Hamdany [52] demonstrated that magnetically treated water can reduce nickel release compared to conventional mouthwashes, suggesting a potential preventive measure.

Saliva dynamics further influence nickel release. Mikulewicz *et al.* [50] created a thermostatically controlled flow reactor to simulate oral conditions and found that nickel release from SS archwires remained well below toxic thresholds, highlighting the importance of mimicking intraoral conditions in laboratory studies. Additionally, research by Senkutvan *et al.* [33] and Ibañez *et al.* [57] revealed that nickel release increases in acidic environments but decreases over time, remaining within safe limits, suggesting adaptive responses in the oral cavity. Osmani *et al.* [46] supported these findings, showing that higher pH levels reduce metal ion release, confirming that acidic conditions promote greater nickel leaching **(Figure 2)**.

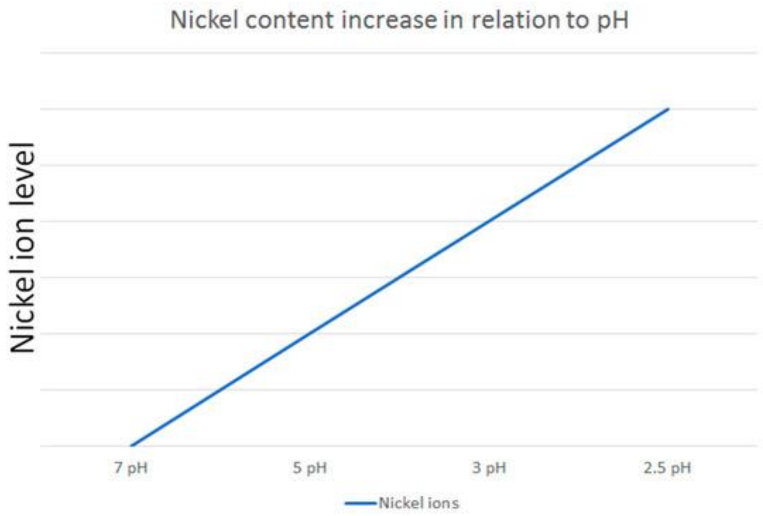

Figure 2. A visual representation showing the variation of nickel ion release at different pH levels, as reported in the reviewed studies

Influence of wire characteristics and material choice on nickel release

The release of nickel ions from orthodontic archwires is strongly affected by the surface properties and geometric shape of the wires. Studies by Didovic *et al.* [42] and Aiswareya *et al.* [29] revealed that variations in manufacturing techniques and surface roughness can significantly alter ion leaching, with stainless steel (SS) bands tending to release more nickel than nickel-titanium (NiTi) wires due to welding processes. Azizi *et al.* [17] further demonstrated that rectangular NiTi wires release more nickel than round wires, suggesting that wire design should be factored in when treating patients with nickel sensitivity.

Material selection also plays a decisive role in managing nickel exposure. Research by Lages *et al.* [60] indicated minimal differences in salivary nickel levels between patients using metal versus esthetic fixed appliances, implying that esthetic options could be safer for susceptible individuals. In contrast, Bass *et al.* [59] highlighted that nickel sensitivity is more common in females and may be aggravated by orthodontic devices, underlining the importance of individualized material choice and monitoring.

Clinical recommendations and future perspectives

Predictive models proposed in studies [62, 63] offer guidance for anticipating nickel release patterns, helping clinicians tailor treatment according to patient susceptibility. Based on current evidence, the following recommendations can be made:

- SS CrNi (stainless steel chromium–nickel): Stable over extended periods, suitable for long-term treatment.
- NiTi Superelastic: Best for short-term use (approximately 4–6 weeks) due to higher initial nickel release; long-term use may increase sensitization risk.
- Heat-Activated NiTi (without copper): Appropriate for 6–8 weeks; replacement may be needed for prolonged treatment.
- Heat-Activated NiTi (with copper): Steadier nickel release allows for longer treatment periods.
- TriTanium™: Nickel release stabilizes over time, supporting long-term application.
- Bio-Active™: Effective for short- to medium-term use; may require replacement for extended treatment.

Nickel release is influenced by multiple factors, including exposure to fluoride, oral pH, immersion time, saliva composition, oral hygiene products, diet, and wire design. Careful assessment of these variables is essential for safe clinical practice.

Future research should prioritize long-term in vivo studies to evaluate cumulative nickel exposure, the development of corrosion-resistant materials with lower ion release, and strategies to mitigate nickel exposure through natural protective agents like snake fruit extract [53] or enhanced surface treatments such as pre-passivation [18].

Conclusion

This review, by design, is limited in scope and should not be taken as universally definitive. Evidence from the examined studies consistently indicates that nickel-containing orthodontic archwires release nickel ions both in laboratory and clinical settings. Although these amounts typically remain below toxic thresholds, they still present a potential risk for inducing nickel sensitization or allergic reactions in previously unaffected individuals.

When selecting archwires, clinicians should consider multiple factors, including the patient's oral pH, saliva flow and composition, wire geometry, hygiene practices, dietary habits, and any preexisting metal allergies. Short-term use of these materials is generally safe; however, continuous monitoring is recommended to identify any emerging sensitivity. While the release of nickel from stainless steel (SS) and nickel-titanium (NiTi) wires over short durations is well-documented, data on long-term exposure—especially studies combining in vitro and in vivo conditions—are limited. Additional investigations are needed to better understand the effects of prolonged nickel exposure and to strengthen clinical safety protocols.

In-depth in vivo assessments should examine not only the total concentration of nickel (Ni) and chromium (Cr) but also their chemical states, oxidation levels, and potential interactions with biological molecules. Advances in trace element analysis are crucial to detect and characterize ions at extremely low concentrations, from subnanogram to picogram levels.

Ultimately, improving patient safety will require close collaboration between clinicians, researchers, and regulatory authorities. Establishing evidence-based guidelines for orthodontic materials, informed by rigorous monitoring of metal ion release, will help minimize health risks while ensuring effective orthodontic care.

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