

Original Article

Liberation of Nickel Ions from Orthodontic Archwires with Nickel Content: A Narrative Synthesis of Laboratory and Clinical Investigations

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ABSTRACT

Nickel-based orthodontic archwires—particularly those composed of nickel-titanium (NiTi) and stainless steel (SS)—are essential components in fixed orthodontic systems due to their favorable mechanical performance. Nonetheless, apprehensions persist regarding nickel-related hypersensitivity, cytotoxicity, and ion emission. This narrative review investigates current evidence concerning nickel ion release from orthodontic materials, expanding on earlier systematic reviews by assessing both *in vitro* and *in vivo* experiments under diverse environmental scenarios. Searches were conducted in PubMed, Scopus, and Web of Science databases to identify studies evaluating the correlation between environmental factors and nickel ion release from nickel-containing archwires. Findings demonstrate that metal ion emission occurs in the early phases of treatment but typically remains below toxic limits, with factors like pH, corrosion rate, treatment duration, and environmental exposure influencing the extent of release. However, long-term investigations remain limited and are generally confined to either *in vitro* or *in vivo* contexts rather than combining both. To clarify causal associations regarding metal ion emission, *in vivo* tracking of nickel and other ions is essential, along with further exploration of chronic effects. Additionally, collaboration among clinicians, scientists, and regulatory agencies is crucial for formulating evidence-based standards in orthodontic material selection, ensuring patient safety while minimizing ion exposure risks.

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

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Introduction

Excessive exposure to nickel can result in multiple adverse health outcomes [1]. Fatalities linked to nickel carbonyl exposure have been reported, and by the 1930s, nickel had been acknowledged as a cause of contact dermatitis. Moreover, increased incidences of nasal and pulmonary cancers were recorded in occupational settings with nickel exposure [2, 3]. In 2008, Gillette designated nickel as the “Allergen of the Year” [4], noting a continued rise in nickel

hypersensitivity cases. These developments heightened scientific interest in the biological impact of nickel [5]. Nickel is also listed by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen, although no definitive association has been established between nickel released from orthodontic devices and cancer formation in patients [6].

Most nickel production serves in fabricating stainless steel and nickel alloys [7], extensively utilized in medical and dental applications, particularly in orthodontic archwires. Such wires are indispensable for producing controlled tooth movement and form the

backbone of orthodontic therapy [8]. Although innovative materials and techniques have evolved, no single wire type is optimal for all treatment stages [9]. Commonly employed varieties include NiTi alloys—sometimes modified with copper—and SS (stainless steel).

These materials are favored for their mechanical efficiency; however, NiTi wires typically comprise over 50% nickel, copper–nickel–titanium alloys contain under 50%, and SS wires generally possess about 8% nickel [10–12]. SS wires are simpler to manipulate and exhibit lower allergenic potential compared with NiTi types. Their 12–13% chromium composition forms a protective chromium oxide film that inhibits oxygen penetration and corrosion [13]. Nevertheless, SS wires tend to be stiffer and less elastic, often requiring more frequent clinical adjustments [14, 15].

Conversely, NiTi archwires exhibit exceptional elasticity, shape memory, and deformation resistance. Although exposure to elevated temperatures may induce irreversible distortion, deformation occurring at lower temperatures can be reversed through reheating [16]. Despite these advantages, the presence of nickel raises concerns regarding the potential cytotoxic, allergenic, and mutagenic effects of NiTi alloys, challenging their overall biocompatibility [17].

Long-term orthodontic treatment can negatively influence titanium and stainless-steel (SS) archwires due to shifts in pH and fluoride concentration. Although the corrosion of orthodontic components is a well-documented phenomenon, its implications for treatment efficacy and patient well-being remain insufficiently understood. Current findings indicate that metal ions are released during orthodontic procedures, though at levels far below those typically ingested through a daily diet. To gain deeper insights, further investigations under clinically relevant conditions are necessary [18, 19]. Orthodontic patients may also develop allergic responses from multiple causes, including nickel exposure [11, 20]. Supporting this, Zigante *et al.* [21] reported that sensitization to nickel and titanium occurs more frequently among female subjects.

The introduction of nickel–titanium (NiTi) alloys into orthodontics raised questions regarding their biological safety, prompting numerous evaluations. Wever *et al.* [22] conducted comprehensive *in vitro* and *in vivo* tests assessing NiTi's compatibility, revealing that these alloys exhibit strong short-term biocompatibility due to their minimal ion release and high corrosion resistance. Consequently, NiTi alloys were deemed safe for clinical application. Similar outcomes have been

consistently observed over the past decade, showing that nickel ion levels in saliva from orthodontic components remain below toxic limits and even decline after an initial peak [23].

Allergic reactions to nickel released from nickel-containing alloys

The aforementioned results do not imply that nickel emitted from NiTi alloys is entirely harmless. Nickel hypersensitivity, resembling a type IV (delayed) immune response, may still develop in susceptible individuals [24, 25]. This immune process unfolds in two stages: sensitization, where immune cells recognize nickel ions and produce memory T-cells, followed by elicitation, in which re-exposure triggers cytokine release, causing local inflammation. Clinically, this may present as extra-oral contact dermatitis, swelling, erythema, or, in severe instances, oral ulceration. Ions from metals such as chromium, cobalt, copper, titanium, and silver may provoke similar effects [11]. In addition to delayed hypersensitivity reactions, nickel discharge from fixed appliances may lead to other localized or distant reactions, as highlighted by Di Spirito *et al.* [26].

Recent years have seen a rise in studies exploring metal ion release during orthodontic therapy. Although ion concentrations remain markedly below dietary intake levels, the multifactorial relationship between alloy properties, oral environment, and patient-specific variables remains complex and incompletely defined [27–29]. Notably, nickel stands as the primary cause of metal-related allergic contact dermatitis, responsible for more hypersensitivity cases than any other metal combined [30].

Influence of saliva and other environmental factors on nickel release

The role of saliva and other oral environmental factors is significant in determining the extent of nickel ion release during orthodontic therapy. Orthodontic components—brackets, bands, and archwires—are continually subjected to fluctuating pH levels, temperature changes, mechanical stress, and corrosive exposure [31]. Several investigations [29, 32, 33] have simulated these oral conditions by immersing nickel-based wires in artificial saliva for durations reflecting real treatment periods. These studies show elevated nickel concentrations in saliva and serum following appliance placement [34]. Nonetheless, most findings confirm that ion levels remain well below toxic thresholds, and allowable concentrations of metals in drinking water are considerably higher than those measured in saliva, implying lower relative exposure from orthodontic devices [35].

This reduced ion release is attributed to the formation of passive oxide layers, primarily consisting of chromium and titanium oxides, which serve as corrosion barriers. However, these layers may deteriorate due to mechanical wear, surface finishing, or reduced pH [13]. Applying protective coatings to orthodontic components has also been suggested as a strategy to further minimize nickel emission [36, 37]. Interestingly, several studies [38, 39] have linked exposure to mobile phone radiofrequency radiation with increased nickel ion release from orthodontic wires. Mortazavi *et al.* [38] emphasized the need for more studies to assess how electromagnetic emissions from other electronic devices, such as Wi-Fi routers, might influence this effect. Rajendran *et al.* [39] further observed that using earphones while operating mobile phones can significantly lessen this phenomenon, suggesting that device proximity may play a key role in ion emission.

Systematic reviews conducted by Mikulewicz and Chojnacka [31, 35] synthesized findings from in vitro and in vivo studies, concluding that short-term appliance use does not produce toxic nickel or metal ion levels. However, long-term exposure effects were not adequately investigated at the time. Later, a meta-analysis by Imani *et al.* [40] confirmed the presence of trace nickel release capable of inducing early oral tolerance, but also emphasized the necessity for further research with larger, ethnically diverse samples and better control of saliva-related variables.

This review seeks to summarize advances in understanding nickel ion release, highlight developments since earlier systematic reviews, and propose directions for future research. The following studies were organized into two main categories—in vitro and in vivo—to analyze how various environmental conditions influence nickel ion release from nickel-based orthodontic archwires.

Scope and Sources of Reviewed Literature

This narrative review seeks to deliver a broad summary of the existing research on the emission of nickel ions from stainless steel (SS) and nickel–titanium (NiTi) orthodontic wires. These alloys—covering SS CrNi, thermoactive (martensitic) NiTi and CuNiTi, and superelastic (austenitic) NiTi wires—represent the main categories of materials commonly used in fixed orthodontic procedures.

To capture a comprehensive yet focused set of studies, a targeted literature search was performed without applying the strict methodology typical of systematic reviews. The primary databases consulted were PubMed, Scopus, and Web of Science (WoS). Search phrases included “nickel ion emission,” “nickel concentration variation,” “stainless steel orthodontic wires,” “nickel–titanium wires,” “in vivo,” and “in vitro.”

The articles selected for inclusion met the following requirements:

- (a) investigations had to involve nickel-containing wires composed of stainless steel or nickel–titanium;
- (b) both in vitro and in vivo evaluations of nickel release were acceptable;
- (c) research examining environmental influences such as pH changes or any other factor affecting nickel ion discharge was included.

Although a defined approach guided study selection, it did not follow the rigid structure of a systematic review. Instead, it aimed to summarize the current body of knowledge through a narrative synthesis, offering interpretive insights into the variables that govern nickel release from orthodontic materials.

Publications failing to meet the specified inclusion parameters were omitted from the analysis (**Figure 1**). This process maintained both focus and inclusivity, ensuring that the most relevant findings were retained for discussion.

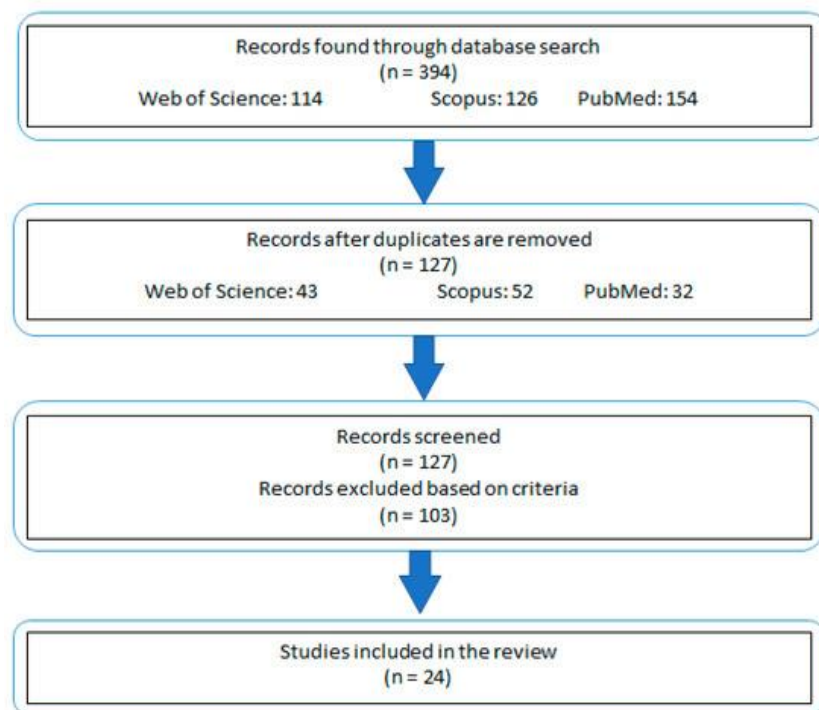


Figure 1. Diagram illustrating the process of selecting and excluding studies

Key findings from the literature

For the quantification of released ions, atomic absorption spectrometry (AAS) and atomic emission spectroscopy (AES) are most frequently employed, given their precision in detecting trace elements within small-volume samples. Scanning electron microscopy with energy-dispersive spectroscopy (SEM/EDS) is additionally utilized to assess surface composition and to visualize microstructural alterations on examined materials.

In Vitro analyses of nickel-containing archwires

Most in vitro investigations replicate oral conditions using artificial saliva as the immersion medium. **Table 1** summarizes the formulations used across reviewed experiments.

Many in vitro works assess the behavior of nickel-containing wires when immersed in artificial saliva for controlled periods. For instance, Cioffi *et al.* [41] studied pseudoelastic NiTi wires in fluoride-enriched artificial saliva to explore the combined impact of stress and chemical environment. Their results showed no nickel ion release during the stress-induced transition between austenite and martensite phases, suggesting good surface stability under load. However, extended fluoride exposure significantly elevated ion discharge, leading to the recommendation for further short-term fluoride studies.

Expanding on this topic, Pastor *et al.* [42] investigated various orthodontic wires immersed in multiple

commercial mouth rinses. Their findings indicated that mouthwash exposure increased nickel liberation, which may trigger allergic reactions in predisposed individuals. Consequently, they advised caution in the use of mouth rinses during active orthodontic therapy. Similarly, Mirjalili *et al.* [18] immersed archwires in artificial saliva and used potentiodynamic and potentiostatic methods to assess localized corrosion and the benefits of pre-passivation. They observed that NiTi displayed no pitting corrosion in artificial saliva, while stainless steel showed only minor improvement. Artificial crevice simulation did not influence corrosion in fluoridated media, but pre-passivation substantially enhanced corrosion resistance in both alloys.

In another experiment, Didovic *et al.* [43] examined NiTi wires along with SS brackets, bands, and ligatures. They found that manufacturing techniques produced distinct surface textures among these components. SS bands and brackets exhibited early pitting corrosion in their unprocessed state. During immersion, adhesive films developed on brackets and ligatures, yet no protective oxide coatings appeared. Precipitation of potassium chloride (KCl) crystals was also detected. Among all components, SS bands released the highest ion quantities—mainly attributed to the welding process—while surface roughness was not directly associated with ion release intensity.

Using the same approach, Ganidis *et al.* [44] evaluated SS, NiTi, and CuNiTi orthodontic wires immersed in artificial saliva. Analysis of the solutions revealed

enrichment with chromium (Cr) and nickel (Ni) ions after 30 days of exposure, especially under lower pH conditions. The peak ion release occurred at pH 3.5. Despite variations in pH, alloy composition, or duration, the concentrations of released metals remained far below normal dietary intake levels.

Laird *et al.* [45] investigated five distinct archwire types placed in buffered media with varying acidity levels. Their findings indicated that as immersion time increased, the average amount of nickel ions released rose correspondingly, while a reduction in pH led to greater ion liberation. Wires with surface coatings emitted noticeably fewer ions than uncoated ones.

In a comparable experiment, Osmani *et al.* [46] assessed six orthodontic alloys—nickel–titanium (NiTi), coated NiTi, stainless steel (SS), nickel-free SS, cobalt–chromium (CoCr), and titanium–molybdenum (TMA)—in artificial saliva under different pH values. Ion concentrations were recorded after each exposure interval. Their data revealed that NiTi released more nickel (Ni) and titanium (Ti) compared to coated NiTi, while conventional SS emitted greater quantities of iron (Fe), chromium (Cr), and Ni than its nickel-free version. The CoCr wires produced high cobalt (Co) but lower Cr, Ni, and molybdenum (Mo), whereas TMA mainly discharged Mo and Ti. Overall, alloys tested at pH 6.6 and hypoallergenic versions showed the least metal release compared to conventional types.

The influence of acidity on ion discharge was further examined by Al-Jammal *et al.* [47] using nickel–chromium (NiCr) alloy samples. Specimens were separated into four groups according to the artificial saliva's pH, and metal concentrations were quantified by atomic absorption spectroscopy (AAS). The study revealed the greatest release of Ni and Cr ions at pH 2.5 for all immersion periods, with nickel levels

consistently exceeding chromium. The authors concluded that the lower the pH, the higher the metal leaching, and that nickel is more readily released than chromium.

For a comparison between materials, Chikhale *et al.* [48] submerged titanium–molybdenum (TMA) and nickel–titanium (NiTi) wires in artificial saliva. Nickel ion levels were higher for NiTi, while TMA released greater quantities of titanium. Nevertheless, none of the measured metal concentrations surpassed recommended safety thresholds.

A separate experiment by Aiswareya *et al.* [29] included both wires and brackets. Stainless steel (SS) and nickel–titanium (NiTi) wires were combined with either SS or ceramic brackets, then immersed in artificial saliva. Using flame atomic absorption spectrometry (FAAS), the researchers determined the amounts of Ni and Cr released and assessed cytotoxicity on HeLa cells. Assemblies involving SS brackets exhibited significantly greater metal ion discharge, though no meaningful differences were observed between the wire types alone.

The relationship between pH variation and cytotoxicity was also studied by Kao *et al.* [49], who analyzed fluoride corrosion extracts from SS and heat-activated NiTi wires exposed to different pH conditions. These extracts were tested on human osteosarcoma (U2OS) cells. The authors observed potential cytotoxic effects from fluoride-rich media, recommending cautious use of such products during orthodontic therapy. Similarly, Senkutvan *et al.* [33] investigated nickel ion release from NiTi, SS, CuNiTi, and ion-implanted NiTi wires in artificial saliva. Nickel concentrations declined with time and remained below allergenic levels. They concluded that although acidic solutions promote ion discharge, all tested wires are clinically safe.

Table 1. Components of artificial saliva used in the reviewed studies

Artificial Saliva Formula	Cited Works
Buffered saline solution, pH 4.6	[41]
Buffered saline with 0.001% NaF, pH 4.8	
Buffered saline with 0.01% NaF, pH 5	
Buffered saline with 0.1% NaF, pH 5.6	
Sodium chloride 0.844 mg, Potassium chloride 1.2 mg, Anhydrous calcium chloride 0.146 mg, Magnesium chloride hydrate 0.052 mg, Dipotassium phosphate 0.34 mg, 70% Sorbitol blend 60 mg, Methyl paraben 2 mg, Cellulose derivative 3.5 mg	[48], [30], [17]
Sodium chloride 0.4 g, Potassium chloride 1.21 g, Sodium phosphate 0.78 g, Sodium sulfide 0.005 g, Urea 1 g, Purified and deionized water 1000 mL	[33], [29]
Neutral blend: 1.5 mM Calcium, 0.9 mM Phosphorus, 20 mM Tris buffer, 150 mM Potassium chloride, pH 7.0	[32]
Acidic blend: 2 mM Calcium, 2 mM Phosphorus, 74 mM acetate buffer, pH 4.3	[18]
Potassium chloride 0.4 g, Sodium chloride 0.4 g, Hydrated calcium chloride 0.906 g, Hydrated sodium phosphate 0.69 g, Hydrated sodium sulfide 0.005 g, Urea 1 g	
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), Monopotassium phosphate (0.34 mg/100 mL), 70% Sorbitol blend 60 mL, Cellulose derivative (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, Monopotassium phosphate 2.46 g, Sodium chloride 5.3 g, Potassium chloride 9.3 g, mixed in 1000 mL purified water	[47]

NaCl (sodium chloride); KCl (potassium chloride); NaH₂PO₄ (monosodium phosphate); H₂O (water); Na₂S (sodium sulfide); CO(NH₂)₂ (urea); CaCl₂ (calcium chloride); NaHCO₃ (sodium bicarbonate); KSCN (potassium thiocyanate).

Saliva within the oral cavity under in vivo conditions is constantly circulating rather than static—an essential aspect often overlooked. To better replicate this reality, Mikulewicz *et al.* [50] designed a thermostatically controlled glass apparatus that maintained a continuous flow of artificial saliva, simulating intraoral dynamics, to evaluate nickel ion emission from stainless steel (SS) archwires. Their analysis confirmed that total nickel output remained far below toxic thresholds, supporting the biocompatibility of SS materials.

Another variable that notably affects ion emission from nickel-based orthodontic wires involves patients' use of oral hygiene agents. Addressing this, Jamilian *et al.* [30] assessed nickel and chromium release from SS and round NiTi wires soaked in three media—Oral B®, OrthoKin®, and artificial saliva. Ion concentrations increased progressively with immersion duration, though artificial saliva showed the lowest values overall. SS wires released ions more slowly than NiTi counterparts.

In a similar context, Mirhashemi *et al.* [51] examined multiple mouthwash formulations and observed that **Listerine** produced the highest degree of ion liberation, whereas Oral B® resulted in the least.

The impact of magnetically treated water (MTW) was explored by Zubaidy and Hamdany [52], who compared it to conventional mouthwash exposure for SS archwires. MTW significantly reduced nickel discharge relative to the control group, leading the authors to propose MTW as a safer adjunct for patients undergoing orthodontic therapy.

Beyond mouth rinses, certain consumable substances can also influence corrosion. Erwansyah *et al.* [53] discovered that snake fruit extract (*Salacca zalacca*), particularly at 300 ppm, suppressed nickel ion release from SS wires, indicating a potential inhibitory or protective effect.

Table 2 outlines the general parameters of the in vitro studies discussed, including wire composition, commercial brand, ions detected, immersion duration, and post-exposure analytical techniques.

Since the cross-sectional design of an archwire is an important clinical choice, Azizi *et al.* [17] evaluated whether geometry influences ion liberation. Comparing round and rectangular NiTi wires, they found the rectangular variant emitted significantly higher ion concentrations, especially within the initial hour of artificial saliva exposure. The researchers

concluded that wire shape can influence ion dynamics under simulated intraoral conditions.

Although numerous experiments have indicated that released metal quantities remain below hazardous limits, evaluating potential cytotoxicity at the cellular level remains vital. Dugo *et al.* [54] explored this by testing eluates from NiTi and SS orthodontic assemblies (including archwires, brackets, bands, and ligatures) on four cell lines: CAL 27 (oral epithelial), HepG2 (hepatic), CaCo-2 (colon), and AGS (gastric carcinoma). The majority of samples exerted cytotoxic effects on CAL 27 cells across all exposure durations, while CaCo-2 cells were comparatively resistant. All eluates induced reactive oxygen species (ROS) formation in AGS and HepG2 cells; interestingly, higher concentrations (2×) reduced ROS levels relative to lower exposures. Slight genotoxic and oxidative effects were attributed to the presence of Cr, Mn, and Al, but these did not exceed the body's defense capacity. Statistical analyses linked Fe, Cr, Mn, and Al to the observed cytotoxicity, with Mn and Cr notably contributing to hydroxyl radical formation and single-strand DNA breaks, while Fe and Ni mainly drove ROS generation.

A more recent investigation by Thiagarajan *et al.* [55] employed electrochemical analyses to measure corrosion and nickel release rates from NiTi, SS, and CuNiTi archwires immersed in artificial saliva for three days. Findings indicated that NiTi and CuNiTi exhibited higher corrosion resistance compared to SS, with negligible nickel emission overall. The authors concluded that the presence of saliva itself can influence the corrosion stability of orthodontic alloys.

In Vivo studies of Ni-containing archwires

The in vivo segment of this review covers research on nickel-based archwires used clinically over treatment periods ranging from 7 days to 18 months. The studies are arranged according to the longest reported duration, concluding with two that statistically examined nickel release kinetics. **Table 3** summarizes wire types, brands, examined ions, treatment duration, and analytical procedures.

Because nickel-containing orthodontic components can trigger allergic sensitization and metal discharge, numerous investigations have focused on these effects. To better understand the release mechanism, Ghazal *et al.* [56] evaluated surface topography and nickel ion

emission in superelastic and heat-activated NiTi wires. Both wire types released comparable nickel quantities after 30 days in clinical use, but superelastic wires exhibited greater surface roughness, which increased over time. Nevertheless, when the retrieved wires were later immersed in artificial saliva, nickel output declined, suggesting a reduction in release potential with prolonged intraoral exposure.

Ibañez *et al.* [57] explored how time and salivary pH interact with metal ion release from heat-activated NiTi and SS archwires. Ion concentrations peaked within acceptable biocompatibility limits, while saliva pH dropped to acidic values after three months but rebounded toward alkalinity by six months, implying that although orthodontic devices temporarily alter oral chemistry, adaptive mechanisms eventually restore equilibrium.

Almasry *et al.* [58] monitored nickel ion discharge from circular thermoactive NiTi archwires during the initial two months of orthodontic application. A minor rise in nickel concentration was detected, yet values remained well within biologically acceptable ranges. Their findings reaffirm that while trace nickel emission occurs during treatment, such levels rarely surpass toxic thresholds.

In an earlier report, Bass *et al.* [59] explored how stainless steel (SS) and nickel-titanium (NiTi) archwires might influence nickel hypersensitivity, particularly in predisposed individuals. Among 29 participants, five females exhibited nickel sensitivity

prior to therapy, while two more developed allergic responses during treatment. They concluded that nickel reactivity appears predominantly among women and, although orthodontic components have limited impact on general oral health, they may occasionally provoke allergic sensitization.

Lages *et al.* [60] further examined metal exposure by analyzing salivary ion concentrations, including nickel, among users of both metal and esthetic orthodontic systems employing SS brackets and heat-activated NiTi wires. Their retrospective cohort comparison showed no major differences in nickel levels between control subjects and those wearing either metallic or esthetic appliances. However, variations in ion levels were influenced by appliance composition, highlighting that material choice affects metal release. In a related study, Amini *et al.* [61] assessed whether metal ion content in saliva differs between orthodontic patients and their untreated siblings of the same sex. The experimental group wore fixed systems using NiTi and SS archwires with stainless-steel components for brackets and bands, while the control group remained appliance-free. Saliva samples were collected from both. The results showed significantly greater nickel (Ni) concentrations in treated individuals compared with their controls, whereas chromium (Cr) differences were not statistically meaningful. Within the limits of in vivo analysis, the authors concluded that fixed orthodontic devices elevate salivary metal ion accumulation.

Table 2. Overview of nickel-based archwires and techniques applied in the in vitro evaluations

Alloy Category	Item and Producer	Elements Examined	Testing Medium	Contact Period	Detection Method	Citation
NiTi	Nitinol N Memory-Metalle 0.5 × 0.5 mm (GmbH, Weil am Rhein, Germany)	Ni	Artificial oral fluid (fluoridated and non-fluoridated)	7 d	Surface layer activation, Photoelectron X-ray analysis	[41]
	Nitinol S Memory-Metalle foil 0.05 and 1 mm (GmbH, Weil am Rhein, Germany)					
	Sentalloy standard 0.46 × 0.46 mm (GAC International Inc., Bohemia, NY, USA) Neo Sentalloy standard 0.46 × 0.63 mm (GAC International Inc., Bohemia, NY, USA)					
NiTi	Circular and rectangular NiTi wires 0.020 in circular and 0.016 × 0.016 in rectangular (Ortho Technology, Tampa, FL, USA)	Ni, Ti	Artificial oral fluid	1 h, 24 h, 7 d, 21 d	Plasma-based atomic emission analysis	[17]
NiTi, TiMo	NiTi wire 17 × 25 in, TMA wire 17 × 25 in	Ni, Ti	Artificial oral fluid	90 d	Atomic absorption detection	[48]

(Modern Orthodontics, Ludhiana, India)						
SS, NiTi, TiMo	Stainless Steel (American Orthodontics, Sheboygan, WI, USA) NiTi (Neo Sentalloy, GAC, West Columbia, USA) TiMo (Beta Blue, Highland Metals, Bangkok, Thailand)	Ni, Ti	Oral rinse solutions (brands not detailed)	1 d, 4 d, 7 d, 14 d	Plasma mass analysis, Microscopic surface imaging	[43]
NiTi, CuNiTi	Ni Titanium Memory Wire 0.016 in (American Orthodontics) Damon Optimal-Force Cu Ni-Ti 0.016 in (Ormco) Tanzo Cu NiTi 0.016 in (American Orthodontics) Flexy NiTi Cu 0.016 in (Orthometric)	Ni, Cu	Neutral and acidic media	7 d	Graphite furnace atomic detection, Plasma emission spectrometry	[32]
NiTi, Coated NiTi, SS, Ni-free SS, CoCr, TMA	BioForce Sentalloy (Dentsply GAC, New York, NY, USA) High Aesthetic (Dentsply GAC, New York, NY, USA) Remanium (Dentaurum, Ispringen, Germany) Noninium (Dentaurum, Ispringen, Germany) Elgiloy (Dentaurum, Ispringen, Germany) Rematitan Special (Dentaurum, Ispringen, Germany)	Ni, Ti	Artificial oral fluid	3 d, 7 d, 14 d, 28 d	Plasma mass detection	[46]
NiTi, CuNiTi, SS	N/A	Ni	Artificial oral fluid	3 d	Voltammetric cycling, Impedance-based electrochemical analysis, Tafel polarization plot	[55]
NiTi, Esthetic Wires, SS	NiTi 0.019 × 0.025 in (Ormco, Glendora, CA, USA) FLI wire 0.019 × 0.025 in (Rocky Mountain Orthodontics, Denver, CO, USA) Iconix 0.019 × 0.025 in (American Orthodontics, Sheboygan, WI, USA) Bio-Active RC 0.019 × 0.025 in (GC Orthodontics, TOMY Inc., Fuchu City, Tokyo) SS 0.019 × 0.025 in (3M Unitek, St. Paul, MN, USA)	Ni, Cr	pH-adjusted buffer media (pH 4, 5.5, 7)	4 wks, 13 wks	Plasma mass detection	[45]
NiTi, SS	Rematitan® LITE ideal arches 0.43 × 0.64 mm (Dentaurum, PA, USA)	Fe, Ni, Cr, Mn, Al, Ti, Cu	Artificial oral fluid	3 d, 7 d, 14 d	Surface imaging with energy dispersive analysis, Plasma mass detection	[42]
NiTi, SS	SS Upper 016 Form III 0.016 × 0.016, NiTi Form I Upper 016 0.016 × 0.016, Tanzo® Copper	Ni, Mn, Cr, Mo, Ti	Artificial oral fluid	7 d, 30 d	Optical plasma emission analysis	[44]

	Nickel Titanium Low Wire Upper 016 0.016 × 0.016, Tru-Arch® UM 0.016 × 0.016 (Ormco), Tru-Arch® CuNiTi 35 °C UL 0.016 × 0.022 (Ormco)					
NiTi, SS	Stainless Steel (Fe-18Cr-8Ni) 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 oral fluid	1 h, 24 h	Atomic absorption technique	[49]
NiTi, SS	NiTi 0.016 × 0.022 in, Stainless Steel 0.016 × 0.022 in (American Orthodontics, Sheboygan, WI, USA), Ion-implanted NiTi 0.016 × 0.022 in (GAC International, Bohemia, NY, USA), Copper NiTi 0.016 × 0.022 in (Ormco)	Ni	Artificial oral fluid	7 d, 14 d, 21 d	Atomic absorption technique	[33]
NiTi, SS	SS rectangular wires 0.017 × 0.025 in, NiTi rectangular wires 0.017 × 0.025 in (Ormco)	Ni, Cr	Artificial oral fluid	7 d, 14 d, 1 mo	Flame-based atomic absorption analysis	[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 medium	N/A	Polarization tests (potentiodynamic and potentiostatic), X-ray energy dispersive analysis, Atomic adsorption technique	[18]
NiTi, SS	Stainless Steel 0.018 in diameter, NiTi 0.018 in diameter (American Orthodontics, Sheboygan, WI, USA)	Ni, Cr	Oral B®, Orthokin®, Artificial oral fluid (SaliLube®, Sinphar Pharmaceutical Co., Ltd., Taipei, Taiwan)	1 h, 6 h, 24 h, 7 d	Atomic absorption technique	[30]
NiTi, SS	N/A	Ni, Cr	Oral B®, Oral B® 3D White Luxe, Listerine, Listerine Advanced White	1 h, 6 h, 24 h, 168 h	Atomic absorption technique	[51]
SS	N/A	Ni, Cr	Snakefruit extract (Salacca zalacca)	24 h	Atomic absorption photometric analysis	[50]
SS	Stainless Steel wires 0.016 × 0.022 in (Dentaurum, Germany)	Ni	Magnetically processed water, OrthoKin®	24 h, 2 wks, 4 wks	Surface imaging microscopy, Atomic absorption technique	[52]
NiCr (alloy)	N/A	Ni, Cr	Artificial oral fluid	12 d, 24 d, 36 d	Atomic absorption technique	[47]

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

Table 3. Overview of nickel-containing archwires and testing methods used in in vivo assessments

Alloy Type	Product and Producer	Elements Investigated	Testing Environment	Contact Duration	Evaluation Technique	Citation
NiTi	NiTi Force I® 0.019 × 0.025 in (American	Ni	Intraoral setting	1 mo	Surface imaging microscopy, Atomic force analysis,	[56]

	Orthodontics, Sheboygan, WI, USA) Therma-Ti Lite® 0.019 × 0.025 in (American Orthodontics, Sheboygan, WI, USA)				Atomic absorption spectrometry	
NiTi, CuNiTi	Superelastic NiTi 0.016 × 0.022 in Thermally activated NiTi 0.016 × 0.022 in Thermally activated CuNiTi 0.016 × 0.022 in	Ni	Intraoral setting	6 wks, 8 wks	X-ray energy dispersive analysis, Computational modeling	[62]
NiTi, Rh- coated NiTi, SS	Thermally activated nitinol wire (Abzil, São José do Rio Preto, SP, Brazil) Thermally activated nitinol wire with rhodium coating 0.014 in (BioActive, Crystal 3D, São Carlos, SP, Brazil)	Ni, Cr, Fe, Cu	Intraoral setting	1–6 mo	Total reflection X- ray fluorescence method	[60]
NiTi, SS	N/A	N/A	Intraoral setting	3 mo	Nickel sensitivity patch, Gingival health index, Plaque accumulation index, Oral imaging	[59]
NiTi, SS	Heat-activated Ni–Ti wires 0.016 in (3M™ Unitek™ mark) Stainless steel wires 0.016 × 0.022 in (3M™ Unitek™ mark)	Ni, Ti	Intraoral setting	1 mo	Plasma optical emission analysis, Electron surface microscopy	[57]
NiTi, SS	Circular thermoactive wires 0.016 in (Equire Thermo-Aktive, Dentaurum, Germany)	Ni	Intraoral setting	7 d, 1 mo, 2 mo	Atomic absorption spectrometry	[58]
NiTi, SS	Stainless steel CrNi Superelastic NiTi Thermodynamic heat- activated NiTi Thermodynamic heat- activated CuNiTi TriTanium™ Bio-active™	Ni	Intraoral setting	6 wks, 8 wks	Surface microscopy with energy dispersive analysis, Computational modeling	[63]
NiTi, SS	Pre-adjusted roth stainless steel brackets 0.018 in (Discovery, Dentaurum, Pforzheim, Germany) Stainless steel orthodontic bands (Unitek/3M, Monrovia, CA, USA) Nitinol (Ormco Corporation, Orange, CA, USA) Stainless steel wires (Remanium; Dentaurum)	Ni, Cr	Intraoral setting	12–18 mo	Atomic absorption spectrometry	[61]

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

To interpret nickel release variation after intraoral exposure, several investigations analyzed compositional changes and suggested appropriate clinical durations for different wire categories [62, 63].

In 2019, study [62] statistically evaluated austenitic NiTi, heat-activated NiTi, and CuNiTi wires. Samples were separated into four groups: autoclaved as-received (S0), as-received (S1), used up to six weeks

(S2), and used beyond eight weeks (S3). Distinct surface regions were examined to determine nickel distribution. Quantification involved both overall mean (global) and localized (highly corroded) surface evaluations. Global data revealed no significant variations between S0–S1 or S1–S2/S3, whereas localized analysis demonstrated clear statistical differences among S1, S2, and S3. Using these findings, a model was developed to describe nickel variation over time. The authors stressed, however, that it should be applied as a general reference only, since clinical outcomes depend on patient-specific conditions.

A 2025 investigation [63] expanded upon this framework by adding stainless steel (SS) and multi-force wires. Specimens were divided into three categories: unused, used for ≤ 6 weeks, and used for > 8 weeks. Results showed each alloy exhibited distinct nickel emission behavior, influenced by its microstructure and surrounding oral environment. The analysis identified SS-CrNi, heat-activated NiTi with copper (HA-NiTi-Cu), and TriTanium™ as the most stable and suitable for extended treatment. In contrast, superelastic NiTi, heat-activated NiTi without copper (HA-NiTi), and Bio-Active™ demonstrated higher nickel liberation, making them more appropriate for short- to mid-term applications. The researchers cautioned that these patterns provide general guidance only, as patient factors ultimately dictate wire longevity.

Collectively, the research indicates that orthodontic devices, especially those incorporating nickel, have the potential to release metal ions, which can occasionally trigger sensitization, particularly in female patients. Still, the quantity of nickel emitted typically remains below hazardous levels. The degree of release is influenced by several factors, including surface texture, type of appliance, and duration of use. While nickel hypersensitivity continues to be a relevant concern, selecting appropriate materials and maintaining careful monitoring allows most patients to undergo orthodontic treatment safely.

Several variables affect nickel ion release, including exposure to fluoride, salivary pH, time of exposure, saliva flow and composition, oral hygiene products, dietary habits, and the geometry of the archwire. These factors are critical when evaluating clinical safety and determining the optimal materials for orthodontic therapy.

Literature-Based Insights

The 24 studies analyzed in this review, predominantly from recent years, offer a thorough perspective on

nickel release from orthodontic appliances containing nickel, focusing on nickel-titanium (NiTi) archwires (with or without copper) and stainless steel (SS) archwires. These wires are widely used in fixed orthodontic approaches and carry major implications for patient safety and biocompatibility. Research has progressed from initial concerns about the safety of NiTi alloys to a more nuanced understanding of how multiple factors influence nickel ion emission both in vitro and in vivo.

Biocompatibility and immediate safety of NiTi

The study by Wever *et al.* [22] was instrumental in establishing that NiTi alloys, commonly used for orthodontic archwires, demonstrate good short-term biocompatibility. Their combined in vitro and in vivo tests showed low cytotoxicity, minimal risk of sensitization, and strong resistance to corrosion, confirming their clinical suitability. Kovac *et al.* [64] reinforced these findings, reporting that NiTi archwires and SS brackets release ions below recommended daily intake limits, even after extended exposure.

Localized accumulation of metal debris, often embedded in trapped food particles, can result in higher concentrations than measured in artificial saliva, which may contribute to hypersensitivity in susceptible individuals. Matusiewicz [65] reviewed studies demonstrating that archwires exposed to oral conditions, simulated or natural, undergo corrosion that releases metal debris over time, particularly in patients with suboptimal oral hygiene.

While in vitro studies generally confirm that metal ion release remains below harmful levels, these models cannot fully replicate individual oral environments. Thus, in vivo studies are essential, as they not only verify that nickel-containing archwires release ions at safe levels, but also reveal a higher incidence of sensitization among females. Proper selection of wire materials and consistent monitoring can mitigate these risks, ensuring safe orthodontic treatment for most patients.

Effects of fluoride, pH, and saliva dynamics

Fluoride exposure has emerged as a key determinant of nickel release. Cioffi *et al.* [40] and Mirjalili *et al.* [18] demonstrated that while NiTi wires resist tensile stress-induced phase transformations, prolonged contact with fluoridated solutions significantly increases ion release. This is clinically important, as orthodontic patients frequently use fluoride-containing oral hygiene products.

Kao *et al.* [49] highlighted that fluoride corrosion extracts at low pH can be cytotoxic, emphasizing caution with acidic fluoride agents in patients using

NiTi archwires. In contrast, Zubaidy and Hamdany [52] reported that magnetically treated water may limit nickel release, offering a potential safer alternative to conventional mouthwashes.

The dynamic nature of saliva further complicates nickel emission. Mikulewicz *et al.* [50] developed a thermostatic flow system to simulate real oral conditions and found that nickel release from SS archwires stayed well below toxic levels. This underscores the importance of replicating physiological conditions in in vitro experiments.

Studies by Senkutvan *et al.* [33] and Ibañez *et al.* [57] demonstrated that although acidic conditions initially increase nickel release, levels decline over time and remain within safe limits, suggesting the oral environment may adjust to the presence of archwires. Osmani *et al.* [46] further support that higher pH conditions generally reduce ion release, whereas acidic environments amplify it (**Figure 2**).

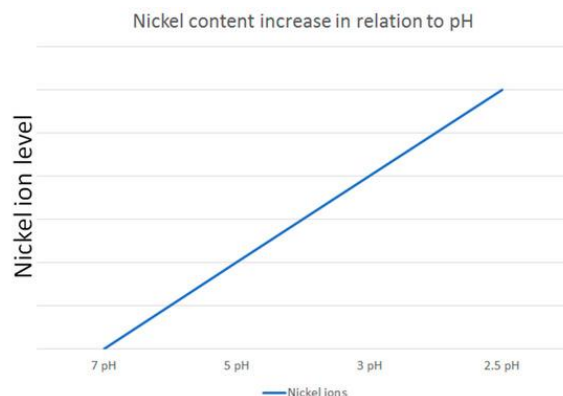


Figure 2. Example illustrating nickel ion release variations as a function of pH, based on reviewed studies

Influence of surface characteristics, wire geometry, and material choice

Surface characteristics and the geometry of orthodontic wires are major determinants of nickel ion emission. Research by Didovic *et al.* [42] and Aiswareya *et al.* [29] demonstrated that both surface roughness and manufacturing methods have a marked impact on ion discharge, with stainless steel (SS) components exhibiting higher nickel release than nickel-titanium (NiTi) ones, largely due to the effects of welding. In another study, Azizi *et al.* [17] showed that rectangular NiTi wires emit more ions than circular ones, indicating that wire configuration should be an essential consideration when treating patients prone to nickel hypersensitivity.

Material selection in orthodontics is equally critical for limiting nickel ion leakage. Findings by Lages *et al.* [60] reported no substantial differences in nickel

concentration between users of metallic and esthetic fixed appliances, suggesting that esthetic systems could be suitable for nickel-sensitive individuals. However, Bass *et al.* [59] observed that nickel hypersensitivity occurs more frequently in females and might be intensified by orthodontic therapy, underscoring the importance of personalized material selection and continuous monitoring.

Clinical significance and future prospects

Predictive models, such as those proposed in studies [62, 63], may serve as valuable tools for clinicians to forecast nickel release patterns and tailor treatment based on patient-specific sensitivity. From the collective research, the following recommendations are outlined for each wire category:

- **SS CrNi (stainless steel chromium–nickel):** Ideal for prolonged treatments, as nickel emission stabilizes after the initial phase. Suitable for therapies extending several months.
- **NiTi Superelastic:** Most appropriate for short durations of 4–6 weeks, when initial nickel release contributes to steady force application; extended use may raise sensitization concerns.
- **Heat-Activated NiTi (without copper):** Recommended for 6–8 weeks of use due to its high early ion release; replacement is suggested afterward to ensure nickel stability.
- **Heat-Activated NiTi (with copper):** Effective for extended treatments over several months, given its gradual and plateauing release rate that minimizes nickel overexposure.
- **TriTanium™:** Well-suited for long-term applications, as nickel output stabilizes with time, ensuring safety in multi-month treatments.
- **Bio-Active™:** Appropriate for short- to mid-term therapy (up to 4–6 weeks); the initial ion burst can aid in early tooth movement but may necessitate replacement for extended use.

The reviewed literature confirms that nickel release is strongly influenced by variables such as fluoride contact, pH, exposure duration, saliva chemistry, oral care products, dietary intake, and wire structure. These parameters directly impact clinical safety and guide material choice, emphasizing careful evaluation during treatment planning.

Future investigations should emphasize long-term in vivo experiments to elucidate cumulative nickel exposure over complete treatment periods. Moreover, innovation in corrosion-resistant materials and alloys with minimized ion emission can enhance patient protection. Studies exploring natural corrosion inhibitors, such as snake fruit extract [53], and

improved surface modification strategies, like pre-passivation [18], present promising pathways for reducing nickel discharge.

Concluding Remarks

Given its design, this review is inherently limited and not universally generalizable; thus, findings should be interpreted in context.

Evidence consistently indicates that nickel-containing archwires emit measurable ions both in vivo and in vitro. Although the daily exposure remains well below toxic levels, the possibility of sensitization or allergic response in previously unaffected patients necessitates vigilance. Material choice should integrate considerations such as oral pH, saliva dynamics, wire geometry, hygiene practices, individual allergies, and diet. While short-term use of SS and NiTi wires is generally safe, ongoing patient assessment remains crucial to detect emerging sensitivities.

Despite ample data on short-term ion release, the scarcity of long-term combined in vitro–in vivo studies limits understanding of chronic exposure outcomes. Additional research is essential to refine clinical safety frameworks and assess extended exposure effects.

To accurately determine cause–effect relationships in metal ion liberation, in vivo tracking of nickel (Ni) and chromium (Cr) ions is vital. Evaluations should go beyond total ion measurement to encompass oxidation state, chemical species, and organometallic profiles. Progress in trace metal detection techniques—capable of differentiating ionic species at subnanogram to picogram levels—is indispensable.

Lastly, collaboration among dental professionals, material scientists, and regulatory authorities is crucial to establish evidence-based guidelines for orthodontic materials. Such initiatives should prioritize minimizing patient risk and addressing concerns related to metallic ion release.

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