Metal Allergy: Palladium

33

Joris Muris and Cees J. Kleverlaan

33.1 Introduction

Palladium (Pd) was discovered by William Hyde Wollaston in 1803 and named after the asteroid Pallas. Soon, it became clear that this metal had very interesting chemical properties. It had a great ability to absorb hydrogen (up to 900 times its own volume) and was therefore used as a catalyst in many (de)hydrogenation reactions. Today, Pd chemistry is still of great interest: in 2010 the Nobel Prize in chemistry was awarded to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for Pd-catalysed cross-coupling in organic synthesis. Pd is widely used in chemical, electronic, and especially automotive industries as a catalyst [1], which taken together accounts for approximately 88.8% of the total Pd demand worldwide in 2013 (Table 33.1). Still, human exposure to Pd is mainly through contact with jewellery and dental appliances, which account for 4.0 and 5.3% of the total demand, respectively. There was demand for 15.9 tonnes of Pd for the dental industry worldwide in 2013 (Johnson & Matthey: www.platinum.matthey.com).

Table 33.1 Palladium demand in tonnes for dental industry in various areas of the world

	2004	2009	2013
Europe	2.5	2.0	2.3
Japan	16.2	9.2	6.4
USA	7.3	8.1	6.7
China	0.2	–	–
Rest of the world	0.3	0.5	0.5
Total	26.4	19.8	15.9

Source: www.platinum.matthey.com

33.2 Bioactivity of Palladium

Pd is a group 10 metal in the periodic table and has close chemical resemblance with nickel (Ni) and platinum (Pt). The latter two metals have interesting bioactive properties. The metal Ni and its alloys are known for adverse reactions, especially allergic contact dermatitis, while Pt salts are well known in cancer treatment. As expected, there is cross-reactivity between Ni and Pd for allergic contact dermatitis, and broad spectrum organometallic Pd compounds are currently being explored as a possible cancer treatment [2]. Pd exists as a pure metal, alloy, inorganic salt, and organometallic compound. The pure metal and alloy can release ions and react to inorganic salts or organometallic compounds depending on the local environment. The synthetic inorganic salts or organometallic compounds are frequently used in catalysis. Pd and its compounds have a very low to moderate threshold for acute oral toxicity: about 200 to >4000 mg kg^{-1} body weight

J. Muris • C.J. Kleverlaan (✉)
Department of Dental Materials Science, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
e-mail: c.kleverlaan@acta.nl

© Springer International Publishing AG, part of Springer Nature 2018
J.K. Chen, J.P. Thyssen (eds.), *Metal Allergy*, https://doi.org/10.1007/978-3-319-58503-1_33

depending on the solubility of the Pd compound used [3–5]. However, intravenous administration results in much higher toxicity (6 mg kg^{-1} body weight) [4].

33.3 Palladium Release

Considerable amounts of Pd are released from dental alloys in in vitro and in vivo studies [6–11]. As explained before, this release is influenced by the composition and microstructure of the alloy and the surrounding environment [11]. Pd-containing dental alloys were reported to release up to 33.7 μg/cm^2/week of metal ions in a corrosive test solution [12]. Precious dental alloys can be divided into two major groups: gold (Au)-based and Pd-based and Pd-based alloys can be subdivided into silver (Ag) and copper (Cu) alloys (Table 33.2).

Measurable levels of Pd and other components of dental alloys are found in saliva and oral mucosa cells, which is consistent with release of Pd from dental appliances [8, 13, 14]. Also, samples of serum and urine of patients with Pd monosensitization were found to have significantly elevated concentrations of Pd, with the highest in urine, suggesting a predominantly renal excretion of Pd. Amounts in serum were, however, not significant [13]. These levels were shown to return to normal values when the appliances were removed from the oral cavity, along with a remission of symptoms. Levels of released Pd from dental appliances correlated to oral clinical symptoms and to skin sensitization to Pd. Also, specific induction of IFN-γ responses in peripheral blood mononuclear cells (PBMC) was detected in Pd-sensitized individuals [13].

33.4 Adverse Reactions Towards Palladium

The first report on Pd allergy (1955) describes a 35-year-old housewife who suffered from contact dermatitis on her left fourth finger, on which she wore a 90 wt% Pd-containing wedding ring [15]. In 1969, a case of contact allergy to Pd was reported by a chemist working with noble metal salts, including $Na_{(2?)}PdCl_4$ [16]. Occupational exposure to Pd is infrequent but may also occur in dental technicians, miners, and workers in the electronics and chemical industries [1, 9, 17].

Although Pd has been used in dental alloys for almost a century [18], its wide-scale use started in the 1970s due to increasing gold prices [19]. Shortly thereafter, Pd allergies emerged in the literature more frequently [19]. The first report on Pd allergies from dental alloys was documented by two Dutch researchers, van Ketel and Nieboer [20].

Japan has long been the largest Pd-consuming region for dental applications, followed by North America and then Europe, although Japan's demand has decreased substantially in the last years (Table 33.1). Interestingly, Pd allergy prevalence seems to be distributed similarly, that is, 7–24% in Japan [21, 22], 8.5–13.3% in the USA [23–25], and 4.9 (Germany)–11.7% (Spain) [26, 27] in Western Europe. In Europe, much more data is available, and there are considerable variations between Northern and Southern European

Table 33.2 Sub-classification of the Pd-based dental alloys based on weight percentage according to the American Dental Association (ADA)

Classification	Percentage of noble metals	Subgroups	Most important components
High-noble	≥60% Au + Pt + Pd (>40% Au)	Au-based alloys	Au-Pt Au-Pd
		Pd-based alloys	Pd-Au (>40Au)
Noble	≥25% Au + Pt + Pd	Pd-based alloys	Pd-Au (<40Au) Pd-Ag Pd-Cu
		Ag-based alloys	Ag-Pd

countries [17]. Several extensive studies (including between 542 and 4446 patients) described the difference in prevalence between gender in dermatitis patients: 17.1% vs. 3.1% in Spain; 14.8% vs. 2.5% in Turkey; 14.9% vs. 3.2% in Minnesota, USA; and 6.7% vs. 2.3% in Italy for women and men, respectively [26, 28–30]. Most reports on Pd allergy are related to dental alloys and oral disease [20, 31–44]. This clearly shows the importance of dental alloys as the main source of exposure.

Until the introduction of a new test allergen for use in patch testing, the prevalence of Pd monosensitization ranged from 0.2% [17] to 1.6%, while the prevalence of Pd sensitization in association with Ni sensitization was 13.0% [13]. The salt normally used in epicutaneous patch testing for diagnosis of Pd allergy was, until 2007, Pd chloride, $PdCl_2$ (1–2% in petrolatum or in water), which forms an oligomeric or polygomeric structure with water, accounting for a very poor solubility of this salt. As such, skin penetration, of which epicutaneous patch testing highly depends, might be impaired and thus results in false negatives. Sodium tetrachloropalladate, Na_2PdCl_4, at 3%, was shown to be a much more accurate test allergen for epicutaneous patch testing, mainly due to its solubility in water and monomeric structure [45–47]. In fact, the results of patch testing with this new test salt showed much higher rates of Pd sensitization, which meant that previously Pd sensitization possibly had been largely underestimated (Fig. 33.1). A multicentre study in Europe, where 3% Na_2PdCl_4 was used, showed that prevalence of Pd monosensitization increased from 1.6% to 4.2% and that Pd sensitization prevalence increased from 9.3% to 18.2% among dermatitis patients [48]. Interestingly, the rate of Pd sensitization was similar to that of Ni (6–7%) [49]. Furthermore, the results of that study support the previous suggestion [50] that Pd might be a more potent sensitizer than Ni, since a formulation of the new Pd salt including fewer atoms was sufficient for elicitation and likely also sensitization [51].

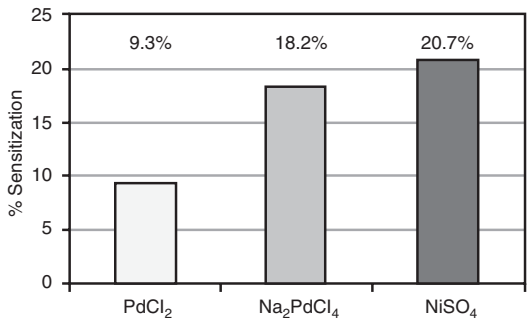

Fig. 33.1 Positive skin test results (+, ++, and +++) to 1% or 2% $PdCl_2$, 3% Na_2PdCl_4, and 5% $NiSO_4$ from a multicentre study in Europe among 1651 dermatitis patients (Data adapted from [48])

In contrast with that of Ni, Pd (mono)sensitization is not related to female sex, which relates to the different sources of exposure of the two metals [49]. The prevalence of Pd allergy is higher in female patients, because it goes together with the prevalence of Ni sensitization, which is higher in women and which relates to the contact with jewellery. Thus, different sources of exposure are expected.

Although most Pd allergy cases are related to dental alloys, a few describe clinically relevant allergic contact dermatitis to Pd [15, 16, 52, 53]. Several authors have described Pd-induced sarcoidal-type allergic contact granulomas due to body piercings [33, 54–59]. Some have discussed the relevant systemic allergic contact dermatitis to dental Pd [21, 34, 40, 60, 61]. Notably, a recent report described allergic contact gastritis due to a Pd-containing dental bridge [38]. It must be stated that patients who are allergic to Pd rarely exhibit a reaction to skin exposure to the metal [17, 62].

Despite the numerous case reports describing adverse reactions to Pd-containing dental alloys, the clinical relevance of positive patch tests to Pd is still unclear, or at least difficult to assess. One of the reasons is that the clinical picture of Pd-induced allergic contact stomatitis is ambiguous. Furthermore, it's possible that no oral lesions may be present in the case of systemic contact allergy to dental materials, as pointed out in several case reports; instead, systemic complaints or lesions could be atypical, e.g. gastritis or alopecia. Pd sensitization, as measured by positive patch tests, is frequently found in the absence of clinical relevance, both intra- and extra-orally.

Case reports showed that strongly palladium-sensitized individual appeared to have relatively mild contract dermatitis reactions [62, 63]. Furthermore, Pd allergic patients' lack of awareness of the presence of dental alloys and/or their composition complicates the evaluation of clinical relevance considerably.

Pd allergies have been estimated to be overall equally prevalent in dermatitis and oral disease patients at 7–8% (range < 1 up to 24% worldwide) [17, 21]. However, this figure is based on studies that have evaluated either dermatitis or oral disease patients. Therefore, interregional, interindividual, and inter-laboratory variation, as well as test materials used, the number of patients, and the period of testing, could skew these observations. Moreover, some investigators marked a 2+ reaction as positive, while others scored a 1+ reaction as positive, and patch test readings were done at various different time points and frequencies. Finally, because Pd is not included in standard patch test series but is rather part of specific 'metal', 'oral disease', or 'dental' screening series, it is not always clear what specific patients have been tested. Studies that compare the prevalence of dermatitis and oral disease patients are scarce, but they do indicate a higher prevalence among patients with oral disease relative to those with dermatitis. One study reported that, among 106 Pd-sensitized patients, 55.7% suffered from oral disease and 29.2% from allergic contact dermatitis [29]. An older study retrospectively comparing patients with intra-oral complaints (n = 397) to patients suffering from eczema (n = 112) showed that especially gold and Pd sensitivity were significantly increased in the dental patient group: 23% vs. 6% for gold and 8% vs. <1% for Pd [64]. Another important issue to address in this context is the cross-reactivity between nickel and Pd.

33.4.1 Cross-Reactivity to Nickel and Concomitant Reactivity to Other Metals

The relevance of a positive patch test reaction to Pd is likely compromised by potential cross-reactions to nickel, even though exclusive positive reactions to Pd are also reported continuously and appear to be more prevalent in recent years [17]. The simultaneous positive reactions of nickel and Pd are explained by (1) sensitization to both metals, (2) contamination of the Pd patch test material with traces of nickel (despite the fact that several studies have disproved this theory) [50], and (3) the fact that nickel and Pd have similar chemistry and electron arrangements, which could cause cross-reactivity at the T-cell level [65, 66]. It has also been shown that nickel and Pd form similar complexes with sulphur ligands [67], which may explain why both metals form similar metal-protein complexes as suggested by Santucci [68]. Hindsén et al. [69] provided in vivo evidence for cross-reactivity to nickel and Pd by systemic administration. They produced flare-up reactions on sites previously patch tested with nickel and Pd after oral exposure to nickel. In this study, contamination was excluded by chemical analysis.

Other metals often produce positive patch test results in Pd-sensitized patients. In Spain, researchers found concomitant reactivity to nickel (97%), cobalt (36%), and chromium (13%) [26]. These figures are similar to findings in Austria [70]. In the USA, the instance of co-sensitization to nickel was considerably less (57.0%) and was strikingly only slightly higher than that for gold (48.2%) [29]. In the latter report, co-sensitization to cobalt and chromium was measured at 37.6% and 10.2%, respectively.

33.4.2 Palladium-Induced Immune Responses

Since palladium exposure is mainly due to dental applications, exposure is mainly to the oral mucosa. Clinically, this can result in, for example, non-plaque-related gingivitis (Fig. 33.2). Even though an association was evident, in many cases, this was not always reflected by a systemic Pd-induced immune response. Apparently, not all cases of non-plaque-related gingivitis are caused by allergic pathways (Th-1 or Th-2), but rather a local innate immune response may be responsi-

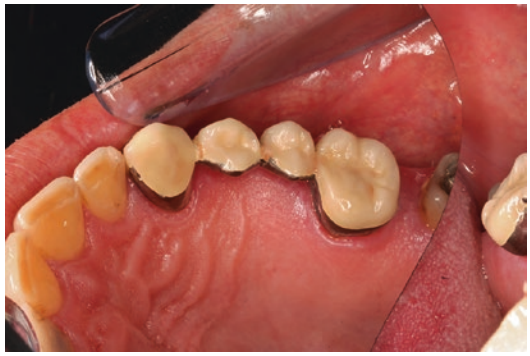

Fig. 33.2 An example of non-plaque-related gingivitis around the metal bridge

ble for the inflammation. In the human body, both Ni and Pd can directly activate the innate immune system through toll-like receptor 4 (TLR-4) [71]. This means that non-plaque-related gingivitis does not necessarily result from allergy but could simply be an innate immune response, functioning much the same way as irritant contact dermatitis/stomatitis. Innate effects were investigated by using in vitro cultures based on human monocyte-derived dendritic cells (MoDC) and THP-1 cells [72]. These cells were exposed to different metals, with and without an endotoxin (lipopolysaccharide; LPS). IL-8 production was used as a parameter for innate stimulation. The results showed that Pd and Au of the dental alloys, and especially PdCu alloys, can trigger the innate immune response. In these experiments, the innate immune response was enhanced when bacterial endotoxins, like LPS, were added to the medium.

Systemic effects of Pd were investigated in well-defined positive and negative control patients using patch test results from testing with Na_2PdCl_4 and $NiSO_4$ as the gold sttandard [73]. A lymphocyte proliferation test (LPT) and specific cytokine production profiles (Th1, IFN-γ; Th2, IL-5 and IL-13) were used to investigate the systemic effect measured by using peripheral blood mononuclear cells (PBMCs). It was found that, in contrast to IFN-γ (Th1), the Ni- and Pd-induced production of Th2 cytokines (IL-5 and IL-13) were good predictors for sensitization based on patch testing. Although the findings with regard to Th2 cytokines correspond to results of Minang et al. [74], they were in conflict with previous research that showed predominant Th1 responses in Ni-allergic patients. Pd-induced LPT showed good specificity (95%), meaning that only very few false-positive results were obtained. However, it lacked sensitivity (63%), meaning that several false-negative results were found. High specificity is especially useful in cases of a positive patch test with unclear clinical relevance. Pd-induced LPT was found to be strongly related to present exposure to Pd (e.g. the presence of Pd-based dental alloys), clinical anomalies, and even subjective complaints [75]. In cases of sensitization in the absence of exposure, the LPT is more likely to be negative. LPT could therefore be useful to differentiate between clinically relevant patch test results and irrelevant ones. Finally, positive LPT results could (further) support an indication for invasive dental replacement treatment in tricky cases.

Ultimately, the so-called 'irrelevant' positive patch test results still have some relevance, since it is clear that patients with positive patch test results to metals, regardless of possible clinical relevance, should not receive dental appliances containing these metals. It is also important to realize that a negative patch test result to a specific metal does not guarantee the ability to safely use that metal on a patient in the future, because the patient may not have been previously exposed; an allergy could still develop after patch testing. For the dermatologist and the general dental practitioner, it is important to realize that dental alloys are possible sources of metal exposure that may contribute to (metal-induced) skin disease, even in the absence of oral lesions.

References

1. Kielhorn J, Melber C, Keller D, Mangelsdorf I. Palladium--a review of exposure and effects to human health. Int J Hyg Environ Health. 2002;205(6):417–32.
2. Kapdi AR, Fairlamb IJ. Anti-cancer palladium complexes: a focus on PdX2L2, palladacycles and related complexes. Chem Soc Rev. 2014;43(13):4751–77.
3. Holbrook DJ Jr, Washington ME, Leake HB, Brubaker PE. Studies on the evaluation of the toxicity of various

salts of lead, manganese, platinum, and palladium. Environ Health Perspect. 1975;10:95–101.
4. Moore W, Hysell D, Hall L, Campbell K, Stara J. Preliminary studies on the toxicity and metabolism of palladium and platinum. Environ Health Perspect. 1975;10:63–71.
5. Phielepeit T, Legrum W, Netter KJ, Klotzer WT. Different effects of intraperitoneally and orally administered palladium chloride on the hepatic monooxygenase system of male mice. Arch Toxicol Suppl. 1989;13:357–62.
6. Cai Z, Vermilyea SG, Brantley WA. In vitro corrosion resistance of high-palladium dental casting alloys. Dent Mater. 1999;15(3):202–10.
7. Wataha JC, Craig RG, Hanks CT. The release of elements of dental casting alloys into cell-culture medium. J Dent Res. 1991;70(6):1014–8.
8. Garhammer P, Schmalz G, Hiller KA, Reitinger T. Metal content of biopsies adjacent to dental cast alloys. Clin Oral Investig. 2003;7(2):92–7.
9. Schmalz G, Garhammer P. Biological interactions of dental cast alloys with oral tissues. Dent Mater. 2002;18(5):396–406.
10. Wataha JC. Biocompatibility of dental casting alloys: a review. J Prosthet Dent. 2000;83(2):223–34.
11. Milheiro A, Muris J, Kleverlaan CJ, Feilzer AJ. Influence of shape and finishing on the corrosion of palladium-based dental alloys. J Adv Prosthodont. 2015;7(1):56–61.
12. Manaranche C, Hornberger H. A proposal for the classification of dental alloys according to their resistance to corrosion. Dent Mater. 2007;23(11):1428–37.
13. Cristaudo A, Bordignon V, Petrucci F, Caimi S, De Rocco M, Picardo M, et al. Release of palladium from biomechanical prostheses in body fluids can induce or support PD-specific IFNgamma T cell responses and the clinical setting of a palladium hypersensitivity. Int J Immunopathol Pharmacol. 2009;22(3):605–14.
14. Garhammer P, Hiller KA, Reitinger T, Schmalz G. Metal content of saliva of patients with and without metal restorations. Clin Oral Investig. 2004;8(4):238–42.
15. Sheard C. Contact dermatitis from platinum and related metals - report of a case. Arch Dermatol. 1955;71(3):357–60.
16. Munro-Ashman D, Munro DD, Hughes TH. Contact dermatitis from palladium. Trans St. Johns Hosp Dermatol Soc. 1969;55(2):196–7.
17. Faurschou A, Menne T, Johansen JD, Thyssen JP. Metal allergen of the twenty-first century-a review on exposure, epidemiology and clinical manifestations of palladium allergy. Contact Dermatitis. 2011;64(4):185–95.
18. Wise EM, Eash JT. The role of the platinum metals in dental alloys, III - the influence of platinum and palladium and heat treatment upon the microstructure and constitution of basic alloys. T Am I Min Met Eng. 1933;104:276–303.
19. Aberer W, Holub H, Strohal R, Slavicek R. Palladium in dental alloys--the dermatologists' responsibility to warn? Contact Dermatitis. 1993;28(3):163–5.
20. van Ketel WG, Niebber C. Allergy to palladium in dental alloys. Contact Dermatitis. 1981;7(6):331.
21. Hosoki M, Bando E, Asaoka K, Takeuchi H, Nishigawa K. Assessment of allergic hypersensitivity to dental materials. Biomed Mater Eng. 2009;19(1):53–61.
22. Nonaka H, Nakada T, Iijima M, Maibach HI. Metal patch test results from 1990-2009. J Dermatol. 2011;38(3):267–71.
23. Davis MD, Wang MZ, Yiannias JA, Keeling JH, Connolly SM, Richardson DM, et al. Patch testing with a large series of metal allergens: findings from more than 1000 patients in one decade at Mayo Clinic. Dermatitis. 2011;22(5):256–71.
24. Fowler JF, Hayden JM. Palladium Patch reactivity. Exog Dermatol. 2003;2:277–8.
25. Torgerson RR, Davis MD, Bruce AJ, Farmer SA, Rogers RS 3rd. Contact allergy in oral disease. J Am Acad Dermatol. 2007;57(2):315–21.
26. Bordel-Gomez M, Miranda-Romero A, Castrodeza-Sanz J. Isolated and concurrent prevalence of sensitization to transition metals in a Spanish population. J Eur Acad Dermatol Venereol. 2008;22:1452.
27. Raap U, Stiesch M, Reh H, Kapp A, Werfel T. Investigation of contact allergy to dental metals in 206 patients. Contact Dermatitis. 2009;60(6):339–43.
28. Akasya-Hillenbrand E, Ozkaya-Bayazit E. Patch test results in 542 patients with suspected contact dermatitis in Turkey. Contact Dermatitis. 2002;46(1):17–23.
29. Durosaro O, el- Azhary RA. A 10-year retrospective study on palladium sensitivity. Dermatitis. 2009;20(4):208–13.
30. Larese Filon F, Uderzo D, Bagnato E. Sensitization to palladium chloride: a 10-year evaluation. Am J Contact Dermat. 2003;14(2):78–81.
31. Downey D. Contact mucositis due to palladium. Contact Dermatitis. 1989;21(1):54.
32. Downey D. Porphyria induced by palladium-copper dental prostheses: a clinical report. J Prosthet Dent. 1992;67(1):5–6.
33. Fernandez-Acenero MJ, Fernandez-Lopez P. Granulomatous contact dermatitis to palladium following ear piercing. Indian J Dermatol Venereol Leprol. 2008;74(6):651–2.
34. Hanafusa T, Yoshioka E, Azukizawa H, Itoi S, Tani M, Kira M, et al. Systemic allergic contact dermatitis to palladium inlay manifesting as annular erythema. Eur J Dermatol. 2012;22(5):697–8.
35. Koch P, Baum HP. Contact stomatitis due to palladium and platinum in dental alloys. Contact Dermatitis. 1996;34(4):253–7.
36. Mizoguchi S, Setoyama M, Kanzaki T. Linear lichen planus in the region of the mandibular nerve caused by an allergy to palladium in dental metals. Dermatology. 1998;196(2):268–70.

37. Namikoshi T. Case of oral lichen planus due to dental metal allergy. Nihon Hotetsu Shika Gakkai Zasshi. 2006;50(3):461–3.
38. Pfohler C, Korner R, Vogt T, Muller CS. Contact allergic gastritis: an underdiagnosed entity? BMJ Case Rep. 2012;2012:bcr2012006916.
39. Pigatto PD, Feilzer AJ, Valentine-Thon E, Zerboni R, Guzzi G. Burning mouth syndrome associated with palladium allergy? Eur J Dermatol. 2008;18(3):356–7.
40. Van Loon LA, Nieboer C, Van Ketel WG. A case of local and systemic disorders caused by palladium hypersensitivity. Ned Tijdschr Tandheelkd. 1982;89(2):50–1.
41. Hansen PA, West LA. Allergic reaction following insertion of a Pd-Cu-Au fixed partial denture: a clinical report. J Prosthodont. 1997;6(2):144–8.
42. Kutting B, Brehler R. Clinically relevant solitary palladium allergy. Hautarzt. 1994;45(3):176–8.
43. Garau V, Masala MG, Cortis MC, Pittau R. Contact stomatitis due to palladium in dental alloys: a clinical report. J Prosthet Dent. 2005;93(4):318–20.
44. Feilzer AJ. Complaints caused by palladium-containing alloys. Ned Tijdschr Tandheelkd. 1997;104(12):475–6.
45. Feilzer AJ, Laeijendecker R, Kleverlaan CJ, van Schendel P, Muris J. Facial eczema because of orthodontic fixed retainer wires. Contact Dermatitis. 2008;59(2):118–20.
46. Muris J, Feilzer AJ, Rustemeyer T, Kleverlaan CJ. Palladium allergy prevalence is underestimated because of an inadequate test allergen. Contact Dermatitis. 2011;65(1):62.
47. Muris J, Kleverlaan CJ, Rustemeyer T, von Blomberg ME, van Hoogstraten IMW, Feilzer AJ, et al. Sodium tetrachloropalladate for diagnosing palladium sensitization. Contact Dermatitis. 2012;67(2):94–100.
48. Muris J, Goossens A, Goncalo M, Bircher AJ, Gimenez-Arnau A, Foti C, et al. Sensitization to palladium in Europe. Contact Dermatitis. 2015;72(1):11–9.
49. Muris J, Goossens A, Goncalo M, Bircher AJ, Gimenez-Arnau A, Foti C, et al. Sensitization to palladium and nickel in Europe and the relationship with oral disease and dental alloys. Contact Dermatitis. 2015;72(5):286–96.
50. Wahlberg JE, Boman AS. Cross-reactivity to palladium and nickel studied in the guinea pig. Acta Derm Venereol. 1992;72(2):95–7.
51. Muris J. Palladium allergy in relation to dentistry. University of Amsterdam. 2015.
52. Bircher AJ, Stern WB. Allergic contact dermatitis from "titanium" spectacle frames. Contact Dermatitis. 2001;45(4):244–5.
53. Suhonen R, Kanerva L. Allergic contact dermatitis caused by palladium on titanium spectacle frames. Contact Dermatitis. 2001;44(4):257–8.
54. Gonzalez-Perez R, Ruiz-Carrillo G, Soloeta R. Sarcoid-type allergic contact granuloma caused by earrings in a boy. Actas Dermosifiliogr. 2012;103(1):73–4.
55. Thijs L, Deraedt K, Goossens A. Granuloma possibly induced by palladium after ear piercing. Dermatitis. 2008;19(5):E26–9.
56. Goossens A, De Swerdt A, De Coninck K, Snauwaert JE, Dedeurwaerder M, De Bonte M. Allergic contact granuloma due to palladium following ear piercing. Contact Dermatitis. 2006;55(6):338–41.
57. Casper C, Groth W, Hunzelmann N. Sarcoidal-type allergic contact granuloma: a rare complication of ear piercing. Am J Dermatopathol. 2004;26(1):59–62.
58. Jappe U, Bonnekoh B, Gollnick H. Persistent granulomatous contact dermatitis due to palladium body-piercing ornaments. Contact Dermatitis. 1999;40(2):111–2.
59. Blum R, Baum HP, Ponnighaus JM, Kowalzick L. Sarcoidal allergic contact dermatitis due to palladium following ear piercing. Hautarzt. 2003;54(2):160–2.
60. Fernandez-Redondo V, Gomez-Centeno P, Toribio J. Chronic urticaria from a dental bridge. Contact Dermatitis. 1998;38(3):178–9.
61. Katoh N, Hirano S, Kishimoto S, Yasuno H. Dermal contact dermatitis caused by allergy to palladium. Contact Dermatitis. 1999;40(4):226–7.
62. Thyssen JP, Johansen JD, Jellesen MS, Menne T. Provocation test with metallic palladium in a palladium-allergic patient. Contact Dermatitis. 2011;65(5):304–6.
63. Tillman C, Engfeldt M, Hindsen M, Bruze M. Usage test with palladium-coated earrings in patients with contact allergy to palladium and nickel. Contact Dermatitis. 2013;69(5):288–95.
64. Marcusson JA. Contact allergies to nickel sulfate, gold sodium thiosulfate and palladium chloride in patients claiming side-effects from dental alloy components. Contact Dermatitis. 1996;34(5):320–3.
65. Moulon C, Vollmer J, Weltzien HU. Characterization of processing requirements and metal cross-reactivities in T cell clones from patients with allergic contact dermatitis to nickel. Eur J Immunol. 1995;25(12):3308–15.
66. Pistoor FH, Kapsenberg ML, Bos JD, Meinardi MM, von Blomberg ME, Scheper RJ. Cross-reactivity of human nickel-reactive T-lymphocyte clones with copper and palladium. J Invest Dermatol. 1995;105(1):92–5.
67. Sellmann D, Prechtel W, Knoch F, Moll M. Transition-metal complexes with sulfur ligands 0.94. Synthesis and reactivity of nickel, palladium, and platinum complexes with the thiolate carbene ligand S2c2--x-ray structure determinations of [Ni(Pme3)(S2c)], [Ni(Pph3)(S2c)], [Ni(Sc)2], [Pt(Pme3)(S2c)], and (S2co)2. Inorg Chem. 1993;32(5):538–46.
68. Santucci B, Cristaudo A, Cannistraci C, Picardo M. Interaction of palladium ions with the skin. Exp Dermatol. 1995;4(4 Pt 1):207–10.

69. Hindsen M, Spiren A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. Contact Dermatitis. 2005;53(1):2–8.
70. Kranke B, Aberer W. Multiple sensitivities to metals. Contact Dermatitis. 1996;34(3):225.
71. Rachmawati D, Bontkes HJ, Verstege MI, Muris J, von Blomberg BM, Scheper RJ, et al. Transition metal sensing by Toll-like receptor-4: next to nickel, cobalt and palladium are potent human dendritic cell stimulators. Contact Dermatitis. 2013;68(6):331–8.
72. Rachmawati D, von Blomberg BM, Kleverlaan CJ, Scheper RJ, van Hoogstraten IM. Immunostimulatory capacity of dental casting alloys on endotoxin responsiveness. J Prosthet Dent. 2016;117:677.
73. Muris J, Feilzer AJ, Kleverlaan CJ, Rustemeyer T, van Hoogstraten IM, Scheper RJ, et al. Palladium-induced Th2 cytokine responses reflect skin test reactivity. Allergy. 2012;67(12):1605–8.
74. Minang JT, Arestrom I, Troye-Blomberg M, Lundeberg L, Ahlborg N. Nickel, cobalt, chromium, palladium and gold induce a mixed Th1- and Th2-type cytokine response in vitro in subjects with contact allergy to the respective metals. Clin Exp Immunol. 2006;146(3):417–26.
75. Muris J, Scheper RJ, Kleverlaan CJ, Rustemeyer T, van Hoogstraten IM, von Blomberg ME, et al. Palladium-based dental alloys are associated with oral disease and palladium-induced immune responses. Contact Dermatitis. 2014;71(2):82–91.