

Nickel Allergy in Adults in the US: 1962 to 2015

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Abstract: Although a significant number of nickel dermatitis cases are seen clinically, most cases are neither patch-tested nor captured in the literature, allowing for a prospering hidden nickel epidemic. We present a qualitative review utilizing the public medical library of peer-reviewed US adult nickel dermatitis cases with the goal of identifying regional variations and trends. Between 1962 and 2015, 18,251 adult patients were reported to be sensitized to nickel. The number of articles has exponentially increased over the past 5.5 decades as 4.3% of total cases were reported between the 1960s and 1990s, 31.3% between 2000 and 2009, and 64.3% were reported between 2010 and 2015. Geographically, 27 US states have had at least 1 reported case of adult nickel dermatitis. Rising rates of US nickel dermatitis noted in our findings further highlight the need for medical professionals, legislators, and manufacturers to advocate for regulation of nickel-containing items.

For 53 years, nickel has been unparalleled as the most common allergen documented in patch-tested US patients of all ages.¹ Recently, the North American Contact Dermatitis Group (NACDG) reported that detection of nickel allergy had increased in North American patch-tested patients between 1992 and 2015.¹ In this time interval, the NACDG patch tested 25,626 patients and demonstrated a steady increase in nickel sensitivity from 14.5% in 1992 to 18.8% in 2004 ($P < 0.0001$).¹ Most notably, this increase over the last 12 years involved a significant prevalence in women.² Traditionally, this trend has been attributed to a female predominance in the practice of ear piercing. However, cultural practices have evolved, with increased male participation in piercing practices, leading possibly to higher nickel sensitization rates in the future.³ Of note, in stainless steel, nickel may be tightly bound to other metal disallowing its release, underscoring the important point that it is the products with substantial free-nickel release which are the major culprits in sensitization.

In 1994, The European Union (EU) Nickel Directive led to the regulation of nickel release in products targeted for the skin. Subsequent reduced environmental exposures in Europe

have led to decreased rates of sensitization after regulation.^{4,5} Furthermore, in Europe, lower numbers of children with nickel contact sensitization are now being reported (9.2%), compared with much higher rates in the United States (28.1%).^{2,6} Specifically, women who had their ears pierced after regulatory intervention in Denmark demonstrated a significantly lower prevalence rate of nickel sensitization and dermatitis when compared with women who were ear pierced before the regulations.^{4,7} However, continued high rates of nickel allergy remain possibly due to continued excessive nickel exposures in unregulated consumer products.^{8,9}

Occupational sources seem to be a lower source of overall sensitization, but occupational dermatitis contributes significantly to the associated cost of nickel allergy (especially in the context of hand eczema).¹⁰ The estimated annual societal cost per patient with occupational hand eczema in Germany is €8799 (US \$9575)—similar to the cost of patients with psoriasis and atopic dermatitis.¹¹ The majority of the cost was found to be related to productivity loss resulting from disability.¹¹ As the lifetime prevalence of hand eczema in the general population is estimated to be 15%,¹² the extrapolated societal costs would be staggering.

However, in the United States, nickel regulation continues to be stagnant, resulting in continued increases in sensitization.¹ Although a significant number of nickel dermatitis cases are being evaluated clinically, most of these cases are clinically straightforward—these patients are not patch tested or seemingly captured in the literature. Thus, despite being commonly seen in the clinical setting, nickel dermatitis reports within the peer-reviewed sector remain limited.

We present the results of an in-depth literature review of the peer-reviewed adult nickel dermatitis cases published within the United States. We aimed to identify regional variations and

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TABLE 1. Study Inclusion Criteria

Adult population (>19 y)
Patients treated within the United States
Nickel sensitivity reported
Text in English language

trends in reporting cases of nickel dermatitis, sources of nickel sensitization, and the significance of occupational exposures.

METHODS

A comprehensive review of the available literature on nickel contact dermatitis was performed via the public medical library (March 2015 PubMed search term: *contact dermatitis*, *ACD*, *allergic contact dermatitis*, *allergy* and *nickel*, and *United States*, *US*, or *America*; Table 1, Fig. 1), filtered to “human studies,” in “English language.” Additional articles were obtained by using the “related articles” function in MEDLINE, by searching associated references within articles, and via expert knowledge of study authors. Articles were filtered by study population; only studies pertaining to US adults were included. Non–United States–based population studies and publications in other than English language were excluded. Screened articles were evaluated for source of nickel exposure, number of cases, and geographic location of cases. The frequency of nickel allergy reports and type of health field reporting the cases were noted. The correlation between nickel dermatitis reports and time was evaluated via 2-sided Pearson correlation analysis with SPSS software (v 22; SPSS, Inc, Chicago, Ill).

RESULTS

Between 1962 and 2015, there were 74 articles published in peer review literature reporting cases of nickel sensitivity in US adults

(Table 2). In total, 18,251 US adult patients were reported to be sensitized to nickel and evaluated for contact dermatitis. Five articles were found to report occupational exposures to nickel.^{15,26,30,72,73} Occupational sources included items such as a stethoscope,³⁰ chalk,²⁶ and a military-issued lanyard chain from an identification neck tag (aka “dog tag”).⁷² The most commonly reported nonoccupational sources were Essure contraceptive micro-inserts (15 cases) and Amplatz septal occluders for atrial septal defects (12 cases; Table 2).

The patients were evaluated by 24 different health fields, including dermatology, periodontology, family medicine, and cardiology. Notably, 44 (58.6%) of the 75 articles, which include 18,096 (99.1%) of the 18,251 patch test–evaluated patients, were published by a provider in the field of dermatology. Analyzing the articles by decade, the frequency of published articles on nickel sensitivity has continuously increased (Table 3, Fig. 2). Between 1960 and 1970, only 1 article was published; however, in the 1980s, a total of 10 articles were published, and that number nearly doubled in the 2000s. In the last 5 years, 30 articles have been published. There is a significant correlation between time and reported number of published nickel dermatitis cases ($r = 0.798$, $P = 0.057$).

When the nickel dermatitis cases are represented geographically (based on author zip code), 27 US states have had at least 1 reported case of adult nickel dermatitis. The top 6 states with the most author origins are Ohio (13), California (11), New York (9), Massachusetts (7), Minnesota (6), and Wisconsin (6) (Fig. 3).

DISCUSSION

Our extensive literature review of the public medical database identified 18,251 confirmed cases of US adults reported to be sensitized to nickel between the years 1962 to 2015.

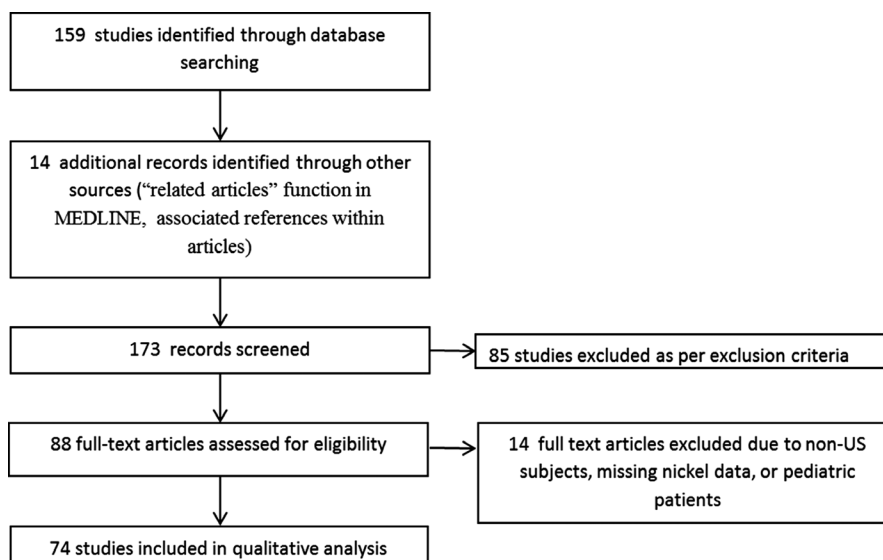

Figure 1. Study design.

TABLE 2. Published Cases of Nickel-Sensitive Adults in the United States

Year of Publication	Author	Patients (N = 18,251)	Source of Nickel	Occupational (n = 5)	Evaluating Health Field
1962	Epstein ¹³	1	Unknown		Dermatology
1979	Fisher ¹⁴	2	Ankle screws		Dermatology
1983	Gochfeld ¹⁵	1	Nickel residue on clothing	Yes	Occupational medicine
1984	Olerud et al ¹⁶	1	Hemodialysis		Dermatology
1984	Kalkwarf ¹⁷	1	Esthetic dental crowns		Dentistry
1985	Laufer and Laufer ¹⁸	1	Jewelry		Pediatrics
1985	Strauss and Eggleston ¹⁹	1	Dental alloy		Dentistry
1987	Lamster et al ²⁰	2	Nonprecious alloy crowns		Dermatology
1988	Fransway and Winkelmann ²¹	2	Various	Unknown	Dentistry
1989	Dunlap et al ²²	1	Orthodontic wire		Dermatology
1989	Storrs et al ²³	109	Various	Unknown	Dentistry
1989	TRUE test team ²⁴	21	Various	Unknown	Dermatology
1990	Barnett ²⁵	1	Jewelry		Dermatology
1991	Fisher ²⁶	1	Chalk	Yes	Dermatology
1992	Klein and Fowler ²⁷	1	Disulfiram		Dermatology
1992	Guyuron and Lasa ²⁸	1	Surgical grade stainless steel		Plastic surgery
1993	Fisher ²⁹	1	Jewelry		Dermatology
1993	Bischof ³⁰	1	Stethoscope	Yes	Family medicine
1993	Latta et al ³¹	1	Denture		Dentistry
1994	Lyzak et al ³²	1	Dental alloys		Dentistry
1995	Bruce and Hall ³³	1	Dental alloys		Dentistry
1997	Houck et al ³⁴	1	Necklace		Dermatology
1998	Prue et al ³⁵	571	Various	Unknown	Dermatology
1998	Morris ³⁶	39	Various		Dermatology
1999	Albert et al ³⁷	162	Various	Unknown	Dermatology
2001	Elston ³⁸	1	Eyeglasses frame		Dermatology
2001	Scalf et al ³⁹	8	Various	Unknown	Dermatology
2002	Cervený and Brodell ⁴⁰	1	Jean button		Internal medicine
2004	Weinstein et al ⁴¹	1	Wristwatch strap and metal clasp		Dermatology
2004	Singh et al ⁴²	1	Amplatzer septal occluder		Cardiology
2005	Lai et al ⁴³	1	Amplatzer patent foramen ovale (PFO) occluder device		Cardiology
2005	Wetter et al ⁴⁴	186	Various	Unknown	Dermatology
2005	Mohammad et al ⁴⁵	10	Various	Unknown	Dermatology
2006	Lu and Dunnick ⁴⁶	1	Jean button, jewelry		Dermatology
2006	Veremis-Ley et al ⁴⁷	11	Various	Unknown	Dermatology
2007	Kosboth et al ⁴⁸	1	Eyeglasses frame		Rheumatology, dermatology
2007	Khan et al ⁴⁹	1	Nitinol biliary stent		Gastroenterology
2007	Torgerson et al ⁵⁰	40	Various	Unknown	Dermatology
2008	Nguyen et al ⁵¹	4571	Various	Unknown	Dermatology
2008	Rietschel et al ^{1*}	905	Various	Unknown	Dermatology
2009	Prasarn et al ⁵²	1	Metal femoral bone plate		Orthopedic surgery
2009	Rabkin et al ⁵³	1	Amplatzer PFO occluder		Cardiothoracic surgery
2009	Zug et al ⁵⁴	841	Various	Unknown	Dermatology
2009	Landeck et al ⁵⁵	104	Various	Unknown	Dermatology
2010	Szyfelbein Masterpol et al ⁵⁶	1	Flavorings in toothpaste and mouthwash; spices in food		Dermatology
2010	Rajpara and Feldman ⁵⁷	1	Cell phone		Dermatology
2010	Gipson et al ⁵⁸	92	Various	Unknown	Dermatology

(Continued on next page)

TABLE 2. (Continued)

Year of Publication	Author	Patients (N = 18,251)	Source of Nickel	Occupational (n = 5)	Evaluating Health Field
2010	Nedorost and Babineau ⁵⁹	1149	Various	Unknown	Dermatology
2010	Yoo et al ⁶⁰	57	Various	Unknown	Dermatology
2010	Landeck et al ⁶¹	1235	Various	Unknown	Dermatology
2010	Bhate et al ⁶²	2	Various		Dermatology
2011	Al-Safi et al ⁶³	1	Essure microinserts		Obstetrics/gynecology
2011	Fasoldt and Tieu ⁶⁴	1	Cell phone		Family medicine
2011	Suárez et al ⁶⁵	1	Cell phone		Dermatology
2011	Silvestri et al ⁶⁶	1	Peanut butter		Dermatology
2011	Zurawin and Zurawin ⁶⁷	13	Essure microinserts		Obstetrics/gynecology
2011	Verma and Tobis ⁶⁸	7	Patent foramen ovale closure device		Interventional cardiology
2011	Davis et al ⁶⁹	250	Various	Unknown	Dermatology
2011	Aneja et al ⁷⁰	1	Nuss procedure—stainless steel alloy bar		Dermatology
2012	Obert et al ⁷¹	1	Nuss procedure—stainless steel alloy bar		Radiology, internal medicine, surgery
2012	Dever et al ⁷²	1	Dog tag/ID chain	Yes	Dermatology
2012	Caero and Cohen ⁷³	1	Violin chin rest bracket	Yes	Dermatology
2012	Warshaw et al ⁷⁴	4844	Various	Unknown	Dermatology
2012	Hession and Scheinman ⁷⁵	7	Various	Unknown	Dermatology
2013	Jain et al ⁷⁶	1	Atrial septal defect closure device		Cardiology
2013	Warshaw et al ⁷⁷	666	Various	Unknown	Dermatology
2013	Fransway et al ⁷⁸	984	Various	Unknown	Dermatology
2014	Conely and Polcari ⁷⁹	1	Watch, ring, and belt buckle		Dermatology
2014	Rizvi et al ⁸⁰	1	Amplatzer patent foramen ovale device		Cardiology
2014	Zhubrak and Bar-David ⁸¹	1	Stainless steel screws (14% nickel)		Podiatry
2014	Morshedi and Kinney ⁸²	1	Inferior vena cava filter		Radiology
2014	Goldthwaite et al ⁸³	1	Essure intratubal microinserts		Obstetrics/gynecology
2014	Wentworth et al ⁸⁴	537	Various	Unknown	Dermatology
2015	Warshaw et al ⁸⁵	781	Various	Unknown	Dermatology

*Only 2002–2003 data were included to avoid double inclusion of patients from other dates, which are reported in Nguyen et al.⁵¹

The breakdown of nickel reported cases by decades showed a continued rise in the number of published cases and nickel-sensitized individuals. Our data demonstrated an exponential increase in reported nickel sensitization within the past few decades, as 4.3% of total cases were reported between the 1960s and 1990s, 31.3% were reported from 2000 and 2009, and 64.3% were reported from 2010 and 2015. This trend may be simply explained by an increase in reporting and publication rate; however, changing patterns of consumer exposure to nickel may also play a role. A particular development of the 21st century is the mass availability and use of personal electronic devices with unregulated nickel content. Cell phones, tablets, and laptops have been reported to be positive for nickel and other metals.^{86–92} As 90% of Americans report ownership of a cellphone,⁹³ potential exposure to electronic devices with reported nickel content is widespread.⁸⁶ This trend is especially

apparent among children, as tablets and computers are often used for educational activities both at home and at school, possibly leading to continued future rises in nickel sensitization rates.⁸⁶

TABLE 3. Published US Reports of Nickel Sensitivity by Decade

Decade	No. Published Articles	Nickel Sensitive Patients (N = 18,251)	Pearson Correlation
1960–1969	1	1	$r = 0.798$
1970–1979	1	2	$P = 0.057$
1980–1989	10	140	
1990–1999	13	782	
2000–2009	19	6686	
2010–2015*	30	10,640	

*The last period is only 5 years.

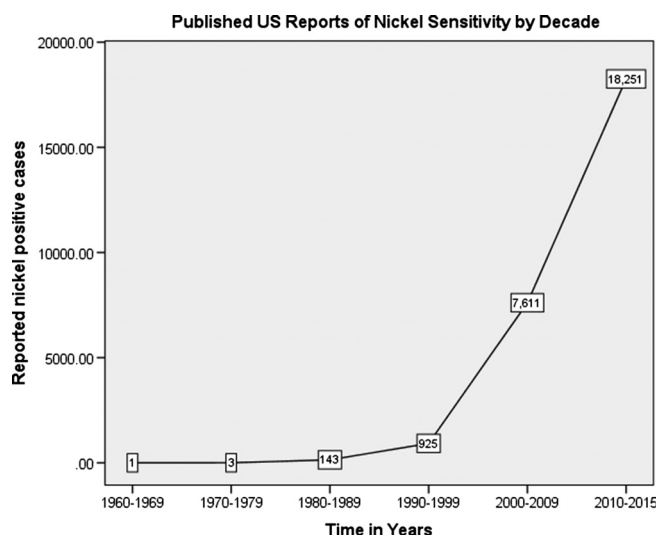


Figure 2. Line graph of published US reports of nickel sensitivity by decade.

Although routine environmental exposure accounts for the lion's share of nickel sensitization, risk of occupational nickel exposure is still present. In our review, only 5 articles focused on occupational nickel dermatitis, suggesting a potential under-reporting of occupational cases in the United States when compared with available data worldwide. International reports of occupational nickel dermatitis range from 12% to 30.7% of all cases.^{94–97} In Britain, of 368 patients with nickel dermatitis, 22.8% had occupational exposure—hairdressers, retail clerks, caterers, domestic cleaners, and metalworkers.⁹⁴ Data from occupational surveillance reporting in the United Kingdom showed that of 1190 cases of occupational contact dermatitis, 195 (36%) had nickel as the relevant allergen.⁹⁸ An analysis of 565 handheld tools in Sweden found that 27% were positive for nickel content.⁹⁹ In

Denmark, a review of nickel sensitization among hairdressers reported that the prevalence of nickel allergy was lower among younger hairdressers in comparison to older hairdressers, a possible reflection of the EU Nickel Directive, which limited nickel content in tools.¹⁰⁰ Thus, as the United States has not initiated any nickel regulations, the lack of US occupational nickel reports in peer-reviewed literature seemingly “hides” the underlying risk for nickel exposure in the US workforce.

Of note, 13 of the reported nickel cases were due to an implantable device, and one listed a food item. Systemic nickel allergy syndrome is a generalized reaction to nickel among nickel-sensitized patients via extracutaneous sources—oral, intravenous, endovascular, subcutaneous, intradermal, intramuscular, intranasal, subconjunctival, dental, intrauterine, and arthroplastic.^{101–104} Systemic nickel allergy syndrome pathophysiology is complex as it involves both Th1 and Th2 responses.¹⁰⁴ Systemic nickel allergy syndrome may present as a worsening of allergic contact dermatitis (ACD), atopic dermatitis, and potentially with extracutaneous symptoms (gastrointestinal, respiratory, and neurological).¹⁰⁵

Notably, the foods with the highest nickel content (>100 µg/serving) include sunflower seeds, oat-based cereals, beans, and chocolate.¹⁰⁴ Low nickel diets, as well as oral desensitization regimens, and removal of implanted devices have been used as treatments.¹⁰⁴ Although our study did not address symptoms or treatment, our results may help indicate that a wide population with extracutaneous nickel exposure may be at risk for systemic nickel allergy syndrome, deserving specific in-depth investigation.

In our review, most identified nickel dermatitis cases were reported by dermatologists, as they are often at the front line of ACD diagnosis. Nevertheless, the multidisciplinary medical backgrounds of the nickel reports from fields of podiatry to gynecology and cardiology represent both the diversity of nickel dermatitis presentation and wide range of nickel exposure source. Furthermore, the geographic depiction of nickel cases

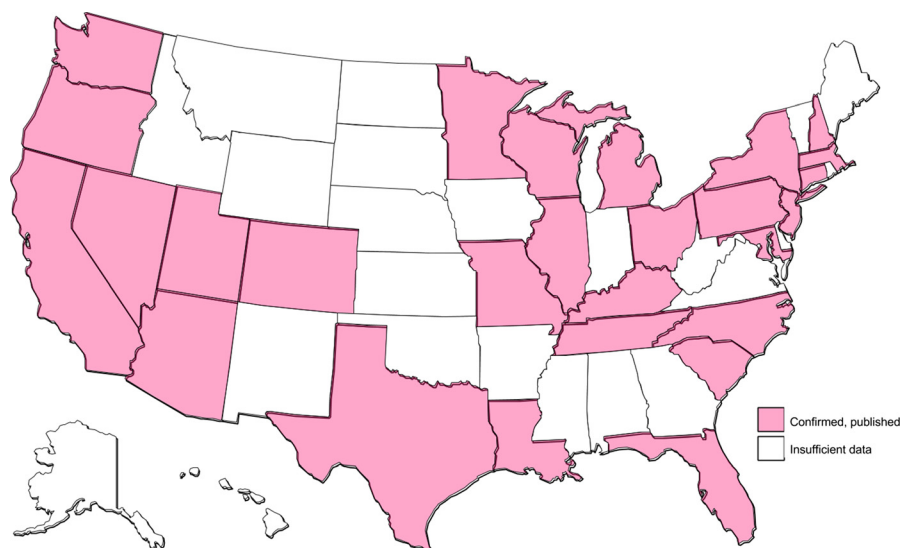


Figure 3. Map of nickel dermatitis cases in adult US patients published in peer-reviewed literature between 1962 and 2015.

throughout the United States depicts a true borderless epidemic of nickel dermatitis.

Our qualitative review has several limitations. Underreporting of nickel dermatitis in peer review literature, relevant articles with incomplete data, and undiagnosed/unreported cases may have led to an underestimation of the true frequency of nickel ACD in the United States. In addition, because the NACDG data sources are not clearly established, some of our findings may have duplicate inclusions of patients resulting in a higher total frequency of nickel dermatitis than truly exists.

CONCLUSIONS

Rising rates of US nickel ACD noted in our data further highlight the need for medical professionals, legislators, and manufacturers to advocate for regulation of nickel-containing items. In 1994, the EU passed the Nickel Directive legislation, prohibiting trade with products releasing more than 0.5 $\mu\text{g}/\text{cm}^2$ per week of free nickel.⁸ Thereafter, multiple studies demonstrated a general decrease in nickel sensitization. In a Danish schoolgirl population, it was found that 17.1% of the girls with ears pierced before implementation of the nickel exposure regulation demonstrated a positive nickel patch test versus only 3.9% of the girls with ears pierced mainly after regulation implementation.⁴ In Germany, nickel sensitization decreased over a 9-year period from 36.7% to 25.8% among women younger than 30 years.⁹ Despite these positive outcomes, the United States has not adopted similar legislation and has left the burden of increasing nickel ACD to patients and physicians.

To support passage of legislation in the United States, national epidemiologic evidence of the nickel epidemic is necessary, especially in regards to occupationally associated cases. In February 2015, the Nickel Allergy Alliance formed as a groundswell subcommittee of the Loma Linda University Provider Registry Study (institutional review board approval number 5140151) specifically to focus on nickel dermatitis awareness and legislative change. These initiatives can serve as springboards to unite medical specialists to develop more thorough research, raise public awareness, and gain national support for legislative change.

“Nickel is with you and does things for you from the time you get up in the morning until you go to sleep at night.”¹⁰⁶ This 1960s “*Romance of Nickel*” brochure quote is as true today, as nickel continues to be ubiquitous in our environment. Unless a multi-disciplinary effort is made toward legislative change, nickel’s wrath will continue to befall the US population for generations to come.

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