The incidence of nickel-induced allergic contact dermatitis is rising. In the 1990s, the European Union passed the Nickel Directive limiting the weekly allowable release of nickel from products. However, similar legislation has yet to be adopted in the United States. This article reviews the burden of nickel sensitivity and initiatives in place to combat this growing problem.

HISTORICAL PERSPECTIVE

As early as the 1600s, a dark red ore with a distinct green coating became a notable source of irritation for copper miners in Saxony, Germany. Believing that the dark red substance was an ore of copper, they continued mining it. As the ore was causing ailments, the miners turned to folklore and adopted a belief that it was protected by goblins. This ultimately led to the naming of the ore as “kupfernichel,” translating to “goblin’s copper.” It was not until the mid-1750s, that Swedish chemist Axel Cronstedt discovered the true nature of kupfernichel (nickel arsenide) and through experiments on magnetism realized the isolation of a new element. Since then, because of its relatively low cost and unique properties such as malleability and anti-corrosive nature, nickel has been used in a large variety of fields.

After World War II, nickel was commonly included in costume jewelry. Jewelry and piercings have thereafter become major sources of nickel exposure for the general population, and thus, a major source for nickel sensitization. Interestingly, meteorites are one of the principal sources of nickel in the world. Metal bead artifact-jewelry made from meteorites has been found in Egyptian graves dating back to as early as 5000 BC, and wedging rings made from the 1836 Namibian Gibeon-meteorite have been reported to cause nickel allergic contact dermatitis (ACD). The common practice of jewelry use in females among various cultural groups around the world has resulted in a much higher rate of nickel sensitization among females than males.

In 1981, Peltonen wrote a commentary about the problem of nickel sensitivity in which she described the significant importance of nickel over the prior 20 to 30 years, now — 34 years later, nickel is still ranking first in the list of allergens. Peltonen noted that nickel sensitivity was surprisingly common among the US population as gathered through epidemiologic studies. In 1978, 1,158 volunteers were tested with 2.5% nickel sulfate in order to find the underlying prevalence of nickel sensitivity. The study found that 9% of the subjects were sensitized. By recent counts, that number has almost tripled. Additionally, Peltonen reported the significant association between atopy, nickel sensitivity and hand eczema. Some patients with an underlying nickel dermatitis do not present in a clinically obvious fashion, but rather with hand or other types of eczema. In fact, nickel sensitivity is a much wider problem as Peltonen alarmingly and poignantly pointed out over 30 years ago: “half of the subjects sensitized to nickel have never consulted a doctor because of their nickel dermatitis; still fewer have visited a dermatologist.”

THE HIDDEN NICKEL DERMATITIS

While nickel dermatitis is commonly associated with a localized reaction, as
many as 50% of children with nickel-induced ACD can present with more diffuse reactions — known as idopathic. Clinically, idopathic nickel dermatitis appears as pruritic papules in non-exposed sites, such as on the extremities and upper trunk. In the idopathic-type of response, areas that may not in fact have had direct contact with nickel can potentially generate a response secondary to autosensitization from immune cells circulating in the body. Unfortunately, as discussed, this type of a reaction has the potential to be misdiagnosed as an eczema (such as atopic dermatitis [AD]), due to its diffuse nature and its common involvement of the upper arms, thighs, knees and elbows. Furthermore, as a side note, “children with AD may experience an exacerbation of their atopic pruritus secondary to comorbid nickel ACD.” Recent evidence indicates that patients with AD have a genetic mutation that allows nickel to more easily penetrate the upper epidermis allowing easier exposure to the immune system. At this time, we do not know the number of children who suffer from nickel dermatitis, and are placed on systemic immunosuppressive therapy for what is thought to be “atopic disease,” rather than being accurately identified and treated with allergen avoidance for ACD. As Peltonen so clearly articulated over 30 years ago, large population studies, including those cases never seen at dermatologic clinics, are needed.

INTERNATIONAL INITIATIVES

Although there are products available to test various materials for nickel, the source of nickel ACD is often obvious; for example, neck or earlobe dermatitis from use of costume jewelry, the periumbilical area from contact with a belt buckle or pants snap, or the unilateral facial dermatitis from the cellular phone (Table). With the rising nickel sensitization and ACD, the Danish Ministry of the Environment passed legislation in 1992 to regulate the amount of nickel released from products with prolonged skin contact in an effort to decrease the rates of sensitization to nickel. This limitation on nickel release to less than 0.5 µg/cm² per week helped to decrease rates of sensitization among Danish children age 0 to 18 years from 24.8% to 9.2% between 1985 and 1998, respectively. In 1994, the European Union (EU) recognized this dramatic decrease in morbidity and enacted the Nickel Directive legislation. This legislation limited the weekly allowable release of nickel to less than 0.5 µg/cm². A 2004 amendment further reduced the weekly allowable release of nickel from [ear ring (piercing)] posts placed after piercing to 0.02 mg/cm². These initiatives have not only resulted in decreases in sensitization rates, but have greatly reduced both the indirect and direct societal costs of nickel dermatitis — saving a reported $2 billion US dollars over a 20-year period. Nevertheless, nickel ACD continues to be problematic even in the EU as increasing numbers of recognized cases in younger children without a history of piercing continue to be reported. Thus, other sources of nickel exposures need to be investigated and ultimately reductions of exposure in a broader scope may be necessary. Moreover, analyses of the mechanisms for and timing of nickel release from metals may provide more information on certain safer materials or practices for nickel-containing items.

THE STATE OF REGULATION IN THE UNITED STATES

Despite regulations in Europe with proven clinical outcome success, similar legislation has yet to be adopted in the United States, even in the face of similar nickel sensitization rates to those seen in Europe in the mid-1980s. For example, the most recent North American Contact Dermatitis Group (NACDG) 2005–2012 data demonstrates that 25.6% of 883 children patch tested had a clinically relevant response to nickel. In order to prevent early exposure to nickel and consequently decrease the rates of nickel contact allergy, US initiatives are needed to limit the quantity of nickel released from products with prolonged skin contact. “Approximately 10 years ago, representatives from the Nickel Development Institute and the Nickel Producers Environmental Research Association met with the Consumer Product Safety Commission (CSPC) urging the US adoption of legislation similar to the 1994 European Nickel Directive, which is now included in the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals.” In fact “The CPSC shared concerns over the need for limiting nickel release from articles that would come in direct and prolonged contact with the skin, but could not commit to action at that time.” Thus, the US not only lacks legislation regulating prevalent products such as piercing equipment and jewelry posts, but also common children-directed merchandise and clothing. In a recent study, Jensen et al indicated that over half the toys containing metal in the US contain nickel. Furthermore, there are increasing reports of potential sources of nickel in cell phones, iPads, laptops and other electronic devices, including the rapidly expanding market of portable wearable health-oriented computing devices.

In 2009, the Journal of the American Academy of Dermatology published an article on the need for an EU-like Nickel Directive to limit the maximum allow-
able release of nickel from products with prolonged skin contact in the United States, consistent with the concentrations mandated in Europe. Based on the fact that approximately 35.8% of the North American patch–test female patients under the age of 18 were reported to have nickel contact allergy in the United States, the authors discussed that a Nickel Directive in the United States could dramatically lower the burden of ACD from nickel both through national legislation and public health education. Nevertheless, since nickel cases are widely underreported and potentially remain undiagnosed, a better definition of the hidden nickel epidemic must exist in order to have an accurate “before and after” understanding of the population in the context of any governmental legislation.

**US MONITORING: TIP OF THE ICEBERG**

In 1939, Bonnevie proposed the first standard series of 21 epicutaneous patch test antigens in the United States showing nickel to be a prominent allergen. Even 76 years later, nickel remains at the top of the sensitizer chart. A review of the literature by Loma Linda University (LLU) researchers resulted in the identification of 611 confirmed cases of clinically relevant nickel dermatitis in US children published between 1986 and 2014 in the public medical domain from over 200 provider/centers (eg, ranging from large groups such as the Mayo Clinic and the NACDG to case series and single case reports). Furthermore, the literature review revealed that despite the previous perception that contact dermatitis in children was less prevalent than in adults (which we now know to be a false assumption due to representational underreporting), pediatric patch testing is being performed by a wide range of practitioners from allergists, dentists and general dermatologists to pediatric dermatologists, family medicine and occupational medicine providers. Nevertheless, the peer-reviewed literature is incomplete with some states reporting only 1 case, while other states completely missing valuable reported data regarding pediatric nickel ACD (Figure 1).

As part of the LLU Contact Dermatitis Registry project recruitment effort, LLU investigators reached out to medical practices within states which had reported <2 pediatric cases of nickel ACD in the peer-reviewed literature to offer information on the study. This process canvassed private–individual practitioners, group practices and academic institutions, and included providers of various backgrounds — physicians, physician assistants (PAs) and registered nurse practitioners (NPs). The findings confirmed that, although a significant amount of nickel dermatitis in children is being clinically seen, the majority of the providers stated that these cases have remained unpublished. Practitioners also noted that confirmatory patch testing is not always performed because the “nickel source was obvious.”

To identify who the clinicians are that are providing pediatric patch test services, in November 2014, LLU launched the Pediatric Contact Dermatitis Registry study (Institutional Review Board approval #5140151). The first part of the study surveys for clinical providers (physicians, PAs, NPs) nationwide to identify those offering patch test services to children. The second part of the study is a registry for practitioners to report their de-identified pediatric ACD cases into a centralized, confidential, secure, online system (Figure 2). The registry project is building upon the groundwork laid by the first 2 pivotal North American studies on pediatric ACD which combined reported patch test results for a total of 456 affected children, from 18 patch testers, over an average of 5.3 years. Their findings equaled to an average of 5 children being patch tested per year — a clear depiction of wide underreporting. However, of the 456 children screened, 124 (27%) had confirmed sensitization to nickel. Thus, despite the small sample size, these studies unanimously point to the significant nickel allergy in tested children in the United States/North America and to the need for preventive intervention.

The use of unregulated jewelry, specifically in ear piercings in children, significantly increases the lifetime risk of nickel, cobalt and likely potassium dichromate allergy. Thus, a legislative public health regulation limiting the maximum allowable release of nickel from products with prolonged skin contact at the concentra-
tions mandated in Europe — 0.5 µg/cm²/week, and body piercing post assemblies to 0.2 µg/cm²/week, in addition to a public awareness campaign of the risks of piercing practices, is needed.

The Nickel Allergy Alliance (NAA), a groundswell subcommittee of Registry providers and other interested parties, has formed to track the growing number of confirmed nickel dermatitis cases and serve as a voice for those concerned with the increasing prevalence of nickel allergy in the United States. In February 2015, the ACDS and the NAA co-endorsed a resolution recommending that the American Academy of Dermatology Patient Safety and Quality Committee Issue a Health Advisory Regarding the high sensitization rates to nickel in the United States and for mandatory national nickel directive to regulate the allowable release of nickel (for a Europe-like nickel safety regulation).

LEARNING FROM OUR PAST, DEFINING THE PRESENT AND FOCUSING ON THE FUTURE

In 2001, in response to rising rates of severe allergic reactions to para-phenylenediamine (PPD)-laced temporary tattoos, the FDA launched a reporting hotline to provide consumer ease of reporting of such events (MedWatch, 800-332-1088).27 The number of cases continued to rise, and in 2006, Dermatitis named PPD as Allegen of the Year to heighten awareness in both the professional and public sectors.28 In 2008, the American Contact Dermatitis Society and the American Academy of Dermatology jointly advised a ban on the practice of using PPD-enhanced henna tattoos. This collective effort toward change has resulted in a visible reduction in reported pediatric PPD-temporary tattoo cases after the advisory.29

A similar consumer hotline for outbreaks of nickel ACD would likewise provide invaluable evidence on the true prevalence of nickel dermatitis in the United States. Correspondingly, the collaborative research underway through the LLU pediatric registry hopes to address Peltonen’s mission statement that: “Large population studies, including also those cases never seen at dermatologic clinics, are therefore needed to clarify the still controversial problems of relations between atopy and nickel sensitivity, as well as the frequency and clinical picture of hand eczema coexisting with nickel sensitivity.”41

In the last 3 decades, nickel dermatitis rates have dramatically risen heightening the public health issue,30 signaling that, as in Europe in the 1990s, the time for legislation allowing regulation in the United States has come. As in many other instances, manufacturers may act ahead of legislation by voluntarily mandating that their products adhere to the guidelines set forth by the EU, as has already been accomplished by Levi Strauss,31 and more recently Apple Inc.32 Clinicians and consumers have the right to demand protective safety legislation and company compliance with directives, for “regulation is a toothless tiger if compliance is not appropriately checked and enforced.”15 Primary prevention of nickel dermatitis stems from accurate surveillance and timely legislation. With an infrastructure in place that validates the burden of nickel allergy in children, healthcare providers will be able to shape sound healthcare policy. However, as in Denmark and the EU, the journey requires a collaborative effort on the part of health professionals, consumers, manufacturers and lawmakers.

Dr. Jacob is an associate professor of dermatology at Loma Linda University in Loma Linda, CA.

Ms. Goldenberg is a medical student at the University of California San Diego in La Jolla, CA.

Dr. Silverberg is a clinical professor of dermatology at Mount Sinai, chief of pediatric dermatology at Mount Sinai Health System and director of pediatric and adolescent dermatology in the department of dermatology at Mt. Sinai St. Luke’s-Roosevelt Hospital Center, all in New York, NY.

Dr. Fonacier is a professor of clinical medicine at the State University of New York at Stony Brook and head of Aley & Training Program Director at Winthrop University Hospital in Mineola, NY.

Dr. Brod is a clinical professor of dermatology at the University of Pennsylvania, Perelman School of Medicine in Philadelphia, PA.

Dr. Usatine is professor of Family and Community Medicine, Dermatology and Cutaneous Surgery and medical director of the Skin Clinic at University of Texas Health Science Center San Antonio, all in San Antonio, TX.

Dr. Sidbury is an associate professor in the department of pediatrics and chief of the division of dermatology at the University of Washington School of Medicine - Seattle Children’s Hospital in Seattle, WA.

Dr. Young is president of Yankton Medical Clinic, PC, located in Yankton, SD, and an associate clinical professor of dermatology at the University of South Dakota in Vermillion, SD.

Dr. Fransway is with Associates in Dermatology in Fort Myers, FL.

Dr. Silverberg is an assistant professor in the departments of dermatology, preventive medicine and medical social sciences at Northwestern University Feinberg School of Medicine in Chicago, IL.

Dr. Yan is an associate professor of pediatrics and dermatology at the Perelman School of Medicine and chief of pediatric dermatology at Children’s Hospital of Philadelphia, both in Philadelphia, PA.

Dr. Pelletier is head of Pediatric Dermatology of Maine and head of pediatric dermatology at Eastern Maine Medical Center, both in Bangor, ME.

Disclosure: Dr. Jacob received an American Contact Dermatitis Society Mid-Career Development Award for information technology and research design training in development of the Pediatric Contact Dermatitis Registry Project. The Pediatric Contact Dermatitis Registry Project is funded in part by a Society for Pediatric Dermatology Pilot Project Grant. She has served as an independent investigator on the safety and efficacy of T.R.U.E. Test™ (Smart Practice; Phoenix, AZ) panels 1.1, 2.1 and 3.1 in children and adolescents, Pediatric Research Equity Act (PREA-1) trial and now serves as an investigator on PREA. She has served as a consultant for Johnson & Johnson.

Dr. Silverberg has served as a consultant for Johnson & Johnson.

Dr. Fonacier received research and educational grants (made to Winthrop University Hospital) from Genentech, Baxter and Merck and is in the Speaker’s Bureau of Baxter. She is currently on the Board of Directors of the Joint Council of Allergy, Asthma and Immunology and is chair of the Work Group of the Joint Task Force on practice parameter. Working on Update on Contact Dermatitis, a Practice Parameter.

Dr. Fransway is emeritus member of the North American Contact Dermatitis Group.

Ms. Goldenberg, and Drs. Brod, Usatine, Sidbury, Young, Silverberg, Yan and Pelletier report no relevant financial relationships.

References