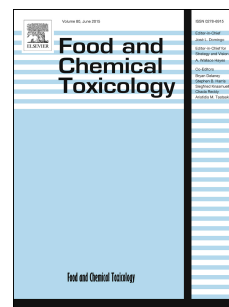


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Nan An, Selma Pourzal, Stefano Luccioli, Stanislav Vukmanović



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EFFECTS OF DIET ON SKIN SENSITIZATION BY NICKEL, POISON IVY, AND SESQUITERPENE LACTONES¹

Nan An*, Selma Pourzal*, Stefano Luccioli[#] and Stanislav Vukmanović

*These authors have contributed equally

Authors' affiliations: Cosmetics Division

Office of Cosmetics and Colors (OCAC)

Center for Food Safety and Applied Nutrition (CFSAN)

Food and Drug Administration (FDA)

and

[#] Office of Compliance (OC)

Center for Food Safety and Applied Nutrition (CFSAN)

Food and Drug Administration (FDA)

Corresponding author: Stanislav Vukmanović, Cosmetics Division, Office of Cosmetics and Colors, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 4300 River Road, College Park, MD 20740, Tel: 240-402-2829

ORCID numbers: Nan An: 0000-0001-8962-9320; Selma Pourzal: 0000-0002-6059-6761; Stanislav Vukmanovic: 0000-0003-3547-8349

¹Abbreviations: ACD- allergic contact dermatitis; SL- sesquiterpene lactone

ABSTRACT

Skin contact or exposure to sensitizers often occurs as a consequence of occupational exposures (e.g. poison ivy in forestry), wearing jewelry (e.g. nickel), or use of cosmetics (e.g. fragrances). However, many of the known skin sensitizers or their chemical variants are also consumed orally through foods or other sources. Since oral exposure to antigenic substances can lead to tolerance, consumption of sensitizers may impact the development and potency of skin sensitization, especially if the sensitizer is consumed early in life, prior to the first skin contact. To address this issue, we have reviewed human clinical and epidemiological literature relevant to this subject and evaluate whether early oral exposures to relevant sensitizers, or their chemical variants, are associated with reduced prevalence of skin sensitization to three main allergic sensitizers – nickel, urushiols of poison ivy, and sesquiterpene lactones of chrysanthemum and other plants.

Key words: allergic contact dermatitis; nickel; oral tolerance; sesquiterpene lactones; skin sensitization; urushiol; T cells

INTRODUCTION

Allergic contact dermatitis (ACD) is a delayed type (type IV) hypersensitivity (DTH) reaction that develops after skin encounters chemicals called “sensitizers”^{1,2}. Skin sensitizers, also referred to as “allergens” (these two terms are used interchangeably), engage in molecular interactions contributing to formation of novel antigenic determinants that stimulate the immune system of the skin³. Upon subsequent encounter(s) with the same compound, a reaction develops in the skin, characterized by migration of the primed T cells to the area of the skin in direct contact with the sensitizer. The resulting local immune response causes clinical symptoms of rash, blisters, wheals, urticaria, pruritis, and burning skin that usually develop 24-72 hours following re-exposure^{1,2}. Currently, more than 4000 chemicals able to induce ACD have been identified⁴, and the list is growing⁵. Contact dermatitis affects 72.3 million people and imposes a burden of US\$2.191 billion in direct and indirect costs per year⁶. In addition to the condition localized to the skin, systemic re-exposure to sensitizers (percutaneous, transmucosal, oral, intravenous, intramuscular, or inhalational) can result in rare cases of systemic contact dermatitis^{7,8}.

Individuals may become exposed to skin sensitizers through occupational activities. For example, agriculture and forestry professionals are often affected by poison ivy dermatitis⁹. This form of dermatitis has the highest prevalence among all skin sensitizers, with as many as 50-75% of the US population sensitive to poison ivy or to other related plants, such as, including poison oak or poison sumac. Mango pickers^{10,11} and cashew processing facility workers¹² are known to develop skin contact allergies to mango or cashew, respectively. Similarly, “bulb dermatitis” (sensitivity to tulips and its relative plants) is known to be a problem in the florist industry¹³, allergic responses to onion and garlic

can be found in caterers ¹⁴, and sensitivity to lavender occurs mostly among massage and aromatherapy professionals ¹⁵.

Other sources of sensitizers are objects people wear, such as clothes or jewelry. Allergies to clothing most frequently involve dyes [e.g. p-aminoazobenzene, p-phenylenediamine (PPD), or mostly dark (black or blue) varieties of disperse colors]¹⁶, rubber ¹⁷, and textile fibers such as wool and silk ¹⁸. Contact dermatitis to textiles is more associated with personal clothing items than with occupational wear ¹⁶, although the lines between the two may become blurred, as exemplified by recent reports of sensitivity reactions of American Airlines employees after introduction of their new uniforms ¹⁹. Another important “clothing” allergen is nickel. Interestingly, nickel allergy was initially (in the first half of the 20th century) observed mainly in plating industry workers ²⁰. However, consumer-based sensitivity to nickel emerged in the second half of the century after reports of skin eruptions at the sites of stocking suspenders belt buckles, jeans buttons and zippers. With increasing popularity of ear piercing and the spread of nickel-plated jewelry towards the end of the last century, nickel became one of the most prominent allergen sensitizers ²⁰. It was declared allergen of the year in 2008 by the American Contact Dermatitis Society. Other examples of clothing-related sensitizers have been described. Chromium, which is used for tanning in leather production and is a recognized source of dermatologic allergies to wearing leather shoes ²¹.

Sensitizers can also be found in personal care products, especially cosmetics, or topically applied medications. Use of sensitization-promoting compounds and botanical extracts in cosmetics production continues to grow ²²⁻²⁵. Topically applied medications, such as benzocaine and other anesthetics, corticosteroids, and neomycin, can also induce skin sensitization ²⁶. Some topical agent sensitizers, such

as those found in ultraviolet filters, may be classified as medications or cosmetics, depending on regulatory jurisdiction ²³.

Sensitizers that cause dermatitis through skin contact exposure can also be intentionally or inadvertently present in various foods, drugs, or other orally consumed substances. Some important foods that are sensitizers include mango, cashew, and garlic. However, possible oral exposure is less obvious for some other sensitizers. For example, metals such as nickel, are abundantly found in soil and can be taken up by growing vegetables. Thus, exposure to nickel may be widely represented in food, with higher levels reported in soybeans, nuts, cocoa, and chocolate ²⁷. Furthermore, many fragrances and flavors have a botanical origin and thus, can be consumed by way of supplements or other dietary products. Perhaps the most common in this respect is cinnamic aldehyde extracted from the bark of cinnamon trees and used as a flavoring agent in foods and toothpastes ²⁸. Many fragrance compounds found in tree-derived Balsam of Peru (eugenol, isoeugenol, cinnamic aldehyde, cinnamic alcohol, benzyl cinnamate, and vanillin) are used in a variety of foods and spices ²⁹. In fact, of the 26 fragrance compounds designated by the European Directive as allergens, 18 are present in natural products that can be consumed orally ³⁰. In addition, other allergens used in cosmetics production are natural extracts that are also consumed orally, including, but not limited to, lavender ³¹, chamomile ³², and chrysanthemum ³³. Chemical sensitizers in drugs or other oral agents don't necessarily need to be applied dermally to cause adverse reactions to skin. Some agents taken orally or parenterally can cause various forms of systemic contact dermatitis ³⁴, which is outside of the scope of the present review.

Given that early oral exposure to antigenic substances often leads to immunological tolerance, a logical next question follows: "Can oral consumption of skin sensitizers impact the sensitization and/or

reactivity potential of these sensitizers through skin?" We will explore answers to this question by reviewing relevant research for three skin sensitizers: nickel, urushiol of poison ivy, and sesquiterpene lactones (SLs) of chrysanthemum and other plants. These examples were chosen since the relationship between dietary intake of these sensitizers and skin sensitization rates has been explored previously and reported in the literature, and because each differently illustrates how antigenic structural diversity and complexity may play a role in cross-sensitization and subsequent oral and developmental tolerance. This review will focus on human clinical and epidemiological research involving oral introduction of skin sensitizers as potential tolerogens. It excludes animal studies and human research using parenteral routes of antigen loading.

ORAL TOLERANCE

The immune system of the gut is thought to be a tolerogenic environment, in that antigens introduced orally are generally believed to induce tolerance³⁵. Everyday consumption of food constantly exposes hosts to innocuous antigens. Immunological reaction of these antigens would not only be a waste of energy for the immune system but could also lead to immune reactions to foods that would prevent further consumption. Physical properties of the gastrointestinal tract (low pH, peptidase activity) to a certain degree prevent immunization to foods by leading to antigen destruction. However, sufficient amounts of antigens retain their antigenic forms, and physiologic mechanisms exist that lead to tolerance induction³⁶. The tolerogenic factors of the oral route are thought to include 1) IL-10 producing dendritic cells; 2) TGF β -producing T cells; 3) presence of regulatory FoxP3⁺ T cells; and 4) presence of retinoic acid in the gut environment³⁵. Overall, an enormous body of literature supports the concept of oral tolerance as the "most common means by which the individual becomes immunologically tolerant"

³⁷. In recent years, a form of oral tolerance, called sublingual immunotherapy, has gained attention in clinical settings as safe and effective approach of desensitization to food, hay fever and other allergens ³⁸⁻⁴².

Intrinsic to the concept of oral tolerance is that introduction of antigens through the oral route by default leads to tolerance, while introduction through other entry points, e.g. skin, leads to immunization ^{35,43,44}. Based on this, it is likely that oral application of skin sensitizers could lead to tolerance ⁴⁵. Achieving tolerance, however, depends on multiple factors, many of which are still unclear but likely involve activation of the innate and adaptive immune systems. As a result, there may be exceptions where the end result of oral exposure is immunization rather than tolerance. A useful example is the development of food allergies. Since allergies to food occur only in a subset of individuals, it can be argued that food allergies represent a genetically transmitted failure of a mechanism that was designed to induce tolerance ⁴³. Another example of immunization occurring after oral exposure is oral vaccination ⁴⁶. The best known of these vaccines is the oral polio vaccine, which has been the pillar of global polio eradication ⁴⁷. Oral vaccines are immunogenic because microorganisms found in these vaccines activate the innate immune system. This may also be true for chemical sensitizers which engage Toll Like Receptors (TLRs), NOD like receptors (NLRs), Keap1, TRP1, and the aryl hydrocarbon receptor ⁴⁸⁻⁵⁰. Immunization may also occur in humans following apparently innocuous consumption of food. This is exemplified by antibodies made in response to antigens of the ABO blood group when the immune system encounters the "missing" ABO blood group antigens in foods or in microorganisms. This happens at an early age because sugars identical, or very similar, to the ABO blood group antigens are found throughout nature. The most frequently cited example, but not the only one, is the role of intestinal flora *E. Coli* in promoting development of antibodies specific for blood group B

^{51,52}. Furthermore, so-called “edible” vaccines are being developed, where plants are created to express molecules from infectious agents ⁵³. The microbial molecules in the context of plant food are devoid of the usual microbial context (pathogen-associated molecular patterns) that stimulate the innate immune system. Nevertheless, the plant vaccination is expected to induce immune responses following plant consumption.

The above examples suggest that oral antigenic exposure does not exclusively lead to tolerance and under certain conditions may induce immune responses. One important factor contributing to the outcome of oral antigen exposure is the state of specific immunity before the antigen is introduced. It is easier to induce tolerance in naïve than in allergic individuals, and this statement applies to oral as well as parenteral, attempts to induce hyposensitization ⁵⁴. Another factor influencing the induction of oral tolerance is the age of the individual. The older the individual, the more difficult it is to induce tolerance ³⁶. Overall, the mechanisms of immunity versus tolerance induction following oral antigenic exposure are complex and not very easy to predict and/or control. However, exceptions to the tolerogenic role of the gut-associated immune system may explain certain conflicting results in the literature.

DEVELOPMENTAL TOLERANCE

Neonates, infants, and children up to five years of age respond to a variety of antigens less efficiently than adults ⁵⁵⁻⁵⁹. The lower immune responsiveness is partly due to incompletely developed mechanisms of immune defense and inflammatory responses ⁵⁹⁻⁶⁴, and to active mechanisms of tolerance induction, (e.g. clonal deletion/inactivation and the development of regulatory mechanisms) ⁶⁵⁻⁶⁸. Besides self-tissues, the

same mechanisms appear to operate to induce tolerance to commensal microflora⁶⁹⁻⁷¹ that colonize skin and mucosa immediately after birth⁷².

The concept of tolerance induction following antigen introduction before the immune system is fully developed was first suggested by Burnet and Fenner⁷³, and subsequently confirmed through experiments by Billingham, Brent, and Medawar⁷⁴. They found that mice and chickens failed to raise immune responses as adults to antigens that were first introduced during their fetal life. The transition of the immune system from an immature, non-responsive state to a mature, responsive state is gradual. Incrementally increasing levels of responsiveness were observed in late fetal, neonatal, and early post-neonatal life stages of animals⁷⁵. Many subsequent experimental approaches focused on models of introducing tissue antigens during the embryonic or neonatal periods⁷⁶ or models of neonatal thymectomy, which induces a variety of autoimmune conditions, due to prevention of regulatory T cell development that otherwise occurs several days after birth⁷⁷. Consequently, the literature is replete with references to neonatal tolerance. However, the term “neonatal” has also been used for animals beyond the neonatal age⁷⁸. Because of that, as well as the fact that tolerance can be established beyond the neonatal period, the term “developmental” may better describe this tolerance process.

The concept that exposure early in life could lead to lifelong immunological tolerance to specific foreign antigens has spurred interest in exploring the potential of developmental tolerance for therapeutic purposes. Perhaps the best known and most developed example is the recent recommendation to introduce peanut diet early in childhood, based on experimental observations of lower incidence of peanut allergies in high-risk children exposed to peanuts early in life versus those exposed later⁷⁹⁻⁸¹. Although allergy to peanuts develops mostly due to type I hypersensitivity (IgE-mediated) response, which differs from the type IV hypersensitivity (cell-mediated) responses seen with skin sensitizers, the

concept of developmental tolerance applies to many distinct types of effector immune responses, including immunoglobulin G responses in treatment of hemophilia⁸², cellular immune responses in graft rejection⁸³, or type IV responses in autoimmunity⁸⁴.

Neonatal and/or infantile exposure to antigen does not always lead to tolerance but can induce immunity⁸⁵, as exemplified by vaccination of newborns and small infants as immune protection against severe infections. However, vaccines are acknowledged to be less efficient in neonates than in adults, and vaccine formulations adapted for the immature neonatal immune system are actively being explored^{86,87}. This would suggest that early life exposure to antigens may preferentially lead to tolerance rather than immunity. The question, then, is whether the same concept holds for very early exposure to skin sensitizers, due to the fact that they are not necessarily antigens but participate in antigen formation in a more or less indirect manner³. To address this question, we explored the literature for publications in which dietary exposure to skin sensitizers (or their variants) was documented in early childhood and compared to prevalence of sensitization.

NICKEL

Sources. Nickel is a ubiquitous metal found in soil, water, and air. Nickel is used worldwide in the manufacture of steel because of its strength and resistance to oxidation, as well as part of multimetal alloys (with cobalt, palladium, iron, titanium, vanadium, and magnesium). These alloys are used for manufacturing of everyday items, such as jewelry, eyeglass frames, watchbands, belt buckles, snaps, and coins⁸⁸. The alloys are also used in production of medical and orthodontics devices, such as replacement

surgery implants, dentures, orthodontic wires, braces, bridges, or crowns⁸⁹. Nickel is commonly present in foods and beverages, and consequently is consumed daily. Some foods are richer in nickel content than others; for example, fruits and vegetables on average contain four times the levels found in meats and other foods of animal origin⁹⁰. Estimates of daily intake of nickel can be made from Total Diet Study (Market Basket), Duplicate Portion Technique, Dietary Records, and these estimates range from 128 to 388 μg per day (Table 1).

Table 1. Summary of daily dietary nickel intake, levels of nickel in urine, and nickel allergy rates in the general populations of some countries.

Country	Dietary nickel intake ($\mu\text{g}/\text{day}$)				Biomonitoring of nickel in urine ($\mu\text{g}/\text{L}$)				Nickel allergy in general population			
	Year	Study population (n) ^a	Geographic region	Average nickel intake	Year	Study population (n) ^a	Geographic region	Average urinary Ni	Year	Study population (n) ^a	Geographic region	Prevalence (%)
Norway	n/a	n/a	n/a	n/a	1994-1995	1204	Northern Norway	1.2 ^{91,92}	1994-1995	1767	Northern Norway	18.4% ^{93,94}
Italy	1996 ^b ; 2004	432-1978	Northern Italy	388 ^{95,96}	1990	878	Northern Italy	0.9 ^{97,98}	2008; 2011	546	Bergamo (northern Italy)	16.4% ⁹⁹
Germany	1990; 1997	56-294	Northeast, East-central	135 ^{100,101}	1989 ^a	123	Not reported (Erlangen/Southeast)	0.9 ¹⁰²	2008; 2011	1024	Central, Southwest	13.9% ⁹⁹
Denmark	1982; 2003	1837-4433	Nationwide	168 ¹⁰³⁻¹⁰⁶	1997	118	Southwest of Copenhagen	1.1 ^{97,107}	1990; 1998	469-567	Copenhagen (county)	8.8% ^{108,109}

							(MONICA)					
Russia	n/a	n/a	n/a	n/a	1994- 1995	1029	Western Russia	3.6 ⁹²	1994- 1995	873	Northwest Russia	5.9% ¹¹⁰
USA	1978; 1984	Not reported	Nationwide	140 27,100,111	1972; 1986	34-50	Connecticut	2.1 ^{112,113}	1978	1158	California	5.8% ¹¹⁴
Finland	1975; 1981	Not reported	Not reported	128 ^{100,115}	1987	299	Not reported (Helsinki)	4.8 ¹¹⁶	1976- 1977	980	Turku (Southwest)	4.5% ¹¹⁷
France	1998; 2009	1474-1918	Paris-Lyon, Nationwide	135 ^{103,118-} 120	2008- 2010	1910	Northern France	2.7 ¹²¹	1985 ^a	3207	Not reported (Northern France?)	4.2% ¹²²

^a The two numbers, when present, refer to the lowest and the highest number of study participants in multiple studies.

^b Year when this study was performed was not specifically disclosed in the publication. Year of publication is provided instead.

Contact dermatitis induction. Nickel is one of the most common causes of ACD, which disproportionately affects women; estimates of nickel allergy prevalence among patch-tested patients in Western Europe and North America range between 17% and 25% in women and 3% to 8% in men^{20,88,123}. Higher rates found in females are usually explained by higher exposure, as adult females are more likely to wear jewelry or undergo ear piercing^{124,125}. Additional support for this notion is the fact that sex differences in prevalence are not seen in children who do not commonly wear jewelry¹²⁶. Sensitization to nickel has been reported from use of orthodontic and/or medical devices (e.g. hip replacement, intraarterial shunts, and others), and can present additional health issues in individuals with already compromised health^{89,127,128}. Other consumer-related nickel allergies may develop due to use of cosmetics, clothing, household products, music instruments (e.g. trumpet and violin), and, more recently, cellular phones⁸⁹. Although more prevalent in the early 20th century, nickel allergies originating from occupational activities today represent a minority of sensitization cases, amounting to 20-30% of total nickel allergies^{129,130}.

With regard to the mechanism of sensitization, nickel binds human Toll Like Receptor 4 (TLR4)¹³¹, an innate immune receptor that promotes proinflammatory responses. Nevertheless, not all humans develop nickel sensitization, which depends on formation of highly defined coordinated complexes with various proteins, including peptide/HLA complexes^{132,133}. Interestingly, nickel can relatively easily transfer between different protein carriers, suggesting that likely more than one “antigen” is involved in promoting sensitization to nickel.

Immunological cross-sensitivity. Contact dermatitis to several metals, such as cobalt¹³⁴⁻¹³⁶, copper¹³⁶⁻¹³⁹, and palladium^{136,140,141}, frequently occurs concurrently with sensitivity to nickel. Interestingly, palladium

and cobalt, in addition to nickel, can bind to TLR4 and activate the innate immune system¹⁴². Copper, too, can activate innate immunity, albeit to a lesser degree and apparently not through TLR4.

Alloys used in the manufacture of various products contain the metals listed above, and it is still unclear whether sensitization to these other metals is a consequence of cross-reactivity of nickel-specific T cells or represents concomitant immunization to different antigens (e.g. nickel-modified and cobalt-modified antigens). Cross-sensitization and/or reactivity between metals may be inferred by observations of new flares or reactions at skin sites previously challenged with palladium after oral challenge with nickel¹⁴⁰. T cell clones isolated from patients with allergies to various metals have been studied^{143,144}. Because T cell clones are derived from a single cell precursor, their potential reactivity to more than one antigen strongly suggests cross-reactivity. These studies have revealed four types of clones: 1) reactive to nickel alone; 2) reactive to nickel and copper; 3) reactive to nickel and palladium; and 4) reactive to nickel, copper, and palladium. Thus, cross-reactivity appears to occur between nickel and copper and/or palladium, but not cobalt.

Developmental (oral) tolerance to nickel. If oral exposure to nickel from an early age or before skin sensitization occurs has potential to cause tolerance induction, then one might predict an inverse correlation between levels of nickel dietary intake and nickel sensitization rates. Because of observed differences in nickel dietary intake between certain countries, comparison of intake numbers with sensitization rates in those countries were reviewed and compared (Table 1). However, there are limitations with this approach. First, nickel levels in food can vary significantly, depending on the levels in soil and water, climate, and season⁹⁰. Second, there are also individual variations in gastrointestinal absorption and metabolism of nickel¹⁴⁵. Consequently, calculations of daily nickel intake may not

accurately predict the actual levels of nickel in the human body. To circumvent this problem, we searched for human biomonitoring data performed in various countries. Nickel levels measured in urine of healthy individuals were found more frequently than levels measured in blood. Comparison of dietary nickel intake and urinary nickel levels did not directly correlate ($p=0.1$; data not shown), suggesting potential involvement of the above-mentioned variations.

Another limitation is that sensitization rates are usually reported relative to the total patch-tested patient population, which is sometimes confined to a single or several medical centers. The population tested, therefore, may be skewed based on the spectrum of contact sensitivity in the locality,

accessibility to health centers that perform patch-testing, local differences in occupational hazards, and other factors. Exact sensitization rates among general populations are not frequently reported; however, these studies have been conducted in some countries, and comparisons of urinary nickel levels to sensitization rates in the general populations of these countries, where both sets of data are available, are shown in Table 1.

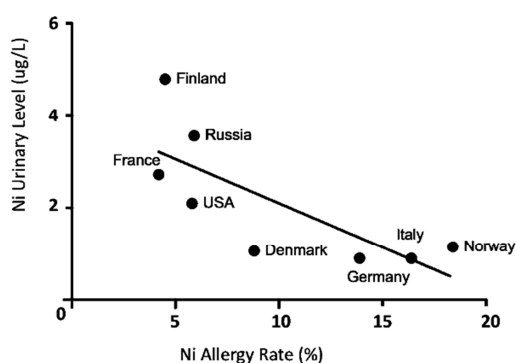


Figure 1. Correlation between urinary nickel levels and sensitization rates in the general populations of indicated countries. The data used for this analysis was taken from Table 1. Pearson correlation coefficient (r) of -0.75 ($p = 0.03$) suggests a statistically significant correlation between the two parameters.

Based on the aforementioned sets of data, there is an apparent inverse correlation between the mean nickel levels in urine and the nickel sensitization rates in the general population by country (Fig. 1). This correlation ($r = -0.75$) is statistically significant ($p = 0.03$). Although this finding suggests that higher levels of nickel present in human bodies may lead to reduced susceptibility to sensitization, some caveats are associated with this type of analysis that need to be considered. Biomonitoring and patch-tests may not be perfectly matched with respect to time and/or place of performance. Also, there may be alternate, non-oral routes of exposure that may positively or negatively impact prevalence of nickel sensitization. For example, increased concentrations of nickel in ambient air have been reported to be associated with increased levels of urinary nickel concentrations and higher prevalence of nickel sensitization¹⁴⁶⁻¹⁴⁸. In contrast, parenteral introduction of nickel through repeated patch-testing appears to reduce nickel sensitization rates¹⁴⁹.

Another set of observations linking possible tolerance from oral nickel exposure and decreased sensitization rates to nickel is related to the effects of wearing nickel-containing orthodontic braces on nickel sensitization. Some studies, summarized in Table 2, indicated that wearing nickel-releasing dental braces is associated with reduced prevalence of nickel sensitization, provided that braces were worn before the occurrence of a sensitizing event (e.g. ear piercing). Even though nickel intake by this route is not a part of the intended diet, released nickel from the braces is likely swallowed and, hence, contributes to the diet. Daily intake of nickel due to release from braces is about five- to ten-fold lower than through food and drink¹⁵⁰⁻¹⁵². Thus, the lower levels of ingested nickel due to release from braces may have a more potent tolerizing effect. One possible explanation is that braces release nickel at a

relatively constant rate, while the amounts of nickel ingested through food may fluctuate. The immune system responds more readily to changes in antigenic load ¹⁵³, whereas constant release of antigen preferentially promotes regulatory T cell development ¹⁵⁴. Another explanation is that nickel may be absorbed from the gastrointestinal tract better on an empty stomach (27% of ingested nickel) than after a meal (0.7%)¹⁵⁵, suggesting that more nickel may reach the host's immune system from braces than from the dietary intake. Finally, it is theoretically possible that anatomic sites (oral versus gastrointestinal mucosa) of nickel absorption may play a role, although evidence of the presence of immunosuppressive milieu throughout the gastrointestinal tract ³⁵ and the induction of oral tolerance in experimental animals when oral mucosa is bypassed ¹⁵⁶ argue against this possibility. It remains to be seen whether any of these possibilities can explain the effect of braces-derived nickel on nickel skin sensitization rates.

Table 2: Effects of orthodontic braces worn by females before or after ear piercing on rates of contact allergy to nickel.^a

Neither braces nor piercing	Braces without piercing	Braces before piercing	Piercing without braces	Piercing before braces	Country/Reference
3/41 (7.3%)	1/6 (16.7%)	9/36 (25.0%)	NA ^b	13/36 ^c (36.1%)	Northern Ireland ¹⁵⁷
NA ^b	NA ^b	0/17 (0%)	NA ^b	50/143 (35.0%)	Finland ^d ¹⁵⁸
3/66 (4.5%)	1/46 (2.2%)	1/48 (2.1%)	45/308 (14.6%)	31/138 (22.5%)	Denmark ¹⁵⁹
3/56 (5.4%)	1/28 (3.6%)	27/108 (25%)	203/517 (39.3%)	32/73 (43.8%)	Several ^e ¹⁶⁰

24/912 (2.6%)	17/692 (2.5%)	28/353 (7.9%)	185/1382 (13.4%)	156/875 (17.8%)	Sweden ¹⁶¹
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^aData are shown as the number of patients with positive patch test for nickel versus the total number of patients (percentage included in the parenthesis).

^bNA: Data not available.

^cThere is an apparent typo in the paper. Reported patient numbers were 13 (positive patch test) and 26 (total) which gives a 50% rate. Nevertheless, indicated rate was 36%. Given that the rate of 36% was used throughout the manuscript, we assumed that total number of patients was 36 (which gives rate of 36%), and not 26.

^dData shown only for females wearing fixed appliances.

^eStudy was performed in nine dermatology clinics located in Amsterdam, Barcelona, Belfast, Hellerup, High Wycombe, Leuven, London, Oulu, and Roskilde.

Lastly, support for tolerance induction by nickel oral exposure emerged as an accidental occurrence that developed in the region where Norway borders Russia. Nickel refineries in two Russian cities of Nikel and Zapolyarny created extensive local nickel pollution which did not spread to the neighboring Norwegian region of Sør-Varanger. Levels of nickel in tap water studied in 1994 and 1995 in Zapolyarny and Nikel were respectively 34-fold and 68-fold higher than in Sør-Varanger⁹². The higher levels of nickel in drinking water also resulted in 3-to-6-fold higher levels of nickel found in urine of residents of these two Russian cities compared to Sør-Varanger⁹². Because factories were built in 1940¹⁶², great

majority of the study subjects (18-69 years old) were either exposed to high nickel levels from birth or from early childhood. Subsequent comparison of nickel sensitization by patch-testing revealed significantly lower rates of nickel sensitization in females living in Nikel/Zapolyarny (7.2%) relative to those living in Sør-Varanger (27.5%). These sensitization rates were different despite similar (~85%) sensitizing exposure by ear piercing ¹¹⁰.

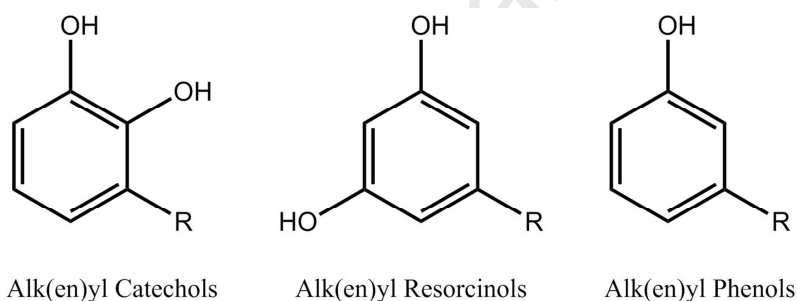
Conclusions. Review of available evidence from human data suggests that early oral exposure to relatively high or persistent amounts of nickel in the environment may lead to immunological tolerance, thus reducing the prevalence of nickel sensitization. The strength of evidence is based mostly on indirect observational data. Controlled oral nickel challenge studies are still needed to account for potential confounding factors, such as non-oral nickel exposures, geographic differences in nickel availability, variations in concentrations of nickel in products, and other factors. Although evidence of immunological cross-reactivity between nickel and some other metals such as copper/palladium is available, studies examining cross-tolerance between these metals are currently not available.

URUSHIOL

Sources and chemical composition. Urushiol is a sensitizer responsible for inducing poison ivy (*Toxicodendron radicans*) dermatitis. Although the name *Rhus radicans* has also been used to describe poison ivy in the literature, it has been suggested that this name is not correct because poison ivy and its relatives (genus *Toxicodendron*) represent distinct developmental lineage from the genus *Rhus* ¹⁶³. The word urushiol is Japanese in origin and means the sap of the lacquer tree ¹⁶⁴. The Japanese lacquer tree

(*Toxicodendron vernicifluum*) is in the same family (Anacardiaceae) with poison ivy (*Toxicodendron radicans*), as well as with a number of other plants that produce urushiol. These include poison oak (*Toxicodendron pubescens* or *Toxicodendron toxicarium* - eastern version; *Toxicodendron diversilobum* - western version), poison sumac (*Toxicodendron vernix*), mango (*Mangifera indica*) and cashew nuts (*Anacardium occidentale*)^{9,164,165}. Urushiol from each of these plants is chemically distinct yet very similar in structure, consisting of a mixture of various alk(en)yl catechols and/or alk(en)yl resorcinols and/or alk(en)yl phenols (Table 3). These compounds are composed of catechol (benzene ring with hydroxyl groups at positions 1 and 2), resorcinol (benzene ring with hydroxyl groups at positions 1 and 3) or phenol (benzene ring with hydroxyl group at position 1) ring and an aliphatic side chain of various lengths linked at catechol/phenol position 3 or resorcinol position 5 (Fig. 2).

Figure 2. Chemical structures of various components of urushiols. The R fatty acid side chain can vary in length and number of unsaturated bonds.



Poison ivy urushiol consists of pentadecyl catechol, pentadecenyl catechol, pentadecadienyl catechol and pentadecatrienyl catechol^{166,167}. In addition to these compounds with 15 carbon side chains, smaller amounts of several 17 carbon side chain compounds have been identified¹⁶⁸. Major components of the lacquer tree urushiol include two chemicals found in the poison ivy urushiol (pentadecyl catechol and pentadecenyl catechol), as well as some other alkenyl catechol species that differ only in the number and position of unsaturated bonds from the other two major compounds of poison ivy urushiol¹⁶⁹. Poison oak urushiol consists of three components with longer (17 carbons) side chains¹⁷⁰, while poison

sumac urushiol is more similar to that of poison ivy¹⁷¹. Major components of mango urushiol are heptadecenyl resorcinol, heptadecadienyl resorcinol and pentadecyl resorcinol¹⁷². Urushiol components of cashew nuts are for the most part slight chemical modifications of the structures described so far. Thus, besides pentadecyl resorcinol (also called cardol), methylated cardol, cardanol (different from cardol by having only one hydroxyl group at the benzene ring- in effect phenol), and anacardic acid (carboxylated cardanol) are found¹⁷³. It should be pointed out that chemical mixtures described in this paragraph are referred to as urushiols in some^{9,164}, but not all literature. In other publications chemical mixtures containing resorcinols are usually referred to as alk(en)yl resorcinols^{165,172,174,175}, while an attempt has been noted of calling the mango-derived mixture “mangol”¹⁷⁶. The name “urushiol” in these publications is reserved only for products of the *Toxicodendron* genus.

Contact dermatitis induction. Plants from *Toxicodendron*, *Mangifera* and *Anacardium* genera can induce contact dermatitis¹⁷⁷. The disease may develop from occupational and recreational activity but also from food consumption as well. Occupational skin-associated disease development is most frequently associated with poison ivy dermatitis that occurs amongst forest or agriculture professionals⁹. Sensitization to mango and cashew nuts is much rarer^{178,179}. For cashew nuts, contact dermatitis occurs more frequently among workers in docks and cashew processing facilities¹². Consuming cashew nuts induces dermatitis less frequently because urushiol is concentrated in the oily nutshell liquid which is usually removed before consumption¹⁸⁰; however, dermatitis can be triggered by contaminating nutshell pieces and cashew shell oil extract stains¹⁸¹, or shell oil contamination of cashew nut butter¹⁸². In contrast to cashews, mango dermatitis occurs more frequently due to fruit consumption¹⁷⁹ and rarely due to occupational activity, such as among mango pickers^{10,11}. Dermatitis may develop after consuming

the skin as well as the pulp (flesh) ¹⁸³⁻¹⁸⁵. The mango skin was found to contain about ten-fold more alk(en)yl resorcinols than the flesh ¹⁷², and is the primary cause of sensitization ^{178,179}.

Table 3. Plant species specific urushiol composition..

Plant name	Plant family/ genus	Urushiol composition ^a	Ring structure (catechol-C, resorcinol-R, or phenol-P)	Aliphatic side chain length ^b	Unsaturated bonds in aliphatic side chain ^c	Reference
Poison ivy (<i>Toxicodendron radicans</i>)	Anacardiaceae/ Toxicodendron	pentadecyl catechol (3%)	C	15	0	166,167
		pentadecenyl catechol (15%)	C	15	1	
		pentadecadienyl catechol (60%)	C	15	2	
		pentadecatrienyl catechol (22%)	C	15	3	
		heptadecadienyl catechol ^d	C	17	2	168
		heptadecatrienyl catechol ^d	C	17	3	
		heptadecatetraenyl catechol ^d	C	17	4	
Japanese lacquer tree (<i>Toxicodendron verniciifluum</i>)	Anacardiaceae/ Toxicodendron	pentadecyl catechol (4.5%)	C	15	0	169
		pentadecenyl catechol (15%)	C	15	1	
		pentadecadienyl catechol (10.9%)	C	15	2	
		pentadecatrienyl catechol (64.7%)	C	15	3	
		heptadecenyl catechol (1.5%)	C	17	1	

		heptadecadienyl catechol (1.8)	C	17	2	
Poison oak (<i>Toxicodendron pubescens</i>)	Anacardiaceae/ Toxicodendron	pentadecyl catechol (3-22%)	C	15	0	171
		pentadecenyl catechol (1-8%)	C	15	1	
		pentadecadienyl catechol (0-3%)	C	15	2	
		pentadecatrienyl catechol (0-1%)	C	15	3	
		heptadecyl catechol (0-2%)	C	17	0	
		heptadecenyl catechol (6-11%)	C	17	1	
		heptadecadienyl catechol (19-25%)	C	17	2	
		heptadecatrienyl catechol (35-63%)	C	17	3	
		heptadecatetraenyl catechol (0-1%)	C	17	4	
Poison sumac (<i>Toxicodendron vernix</i>)	Anacardiaceae/ Toxicodendron	pentadecyl catechol (15%)	C	15	0	171
		pentadecenyl catechol (41%)	C	15	1	
		pentadecadienyl catechol (33%)	C	15	2	
		pentadecatrienyl catechol (11%)	C	15	3	
Mango (<i>Mangifera indica</i>)	Anacardiaceae/ Mangifera	pentadecyl resorcinol (6%)	R	15	0	172,176
		pentadecenyl resorcinol (2%)	R	15	1	
		heptadecyl resorcinol (1%)	R	17	0	
		heptadecenyl resorcinol (53%)	R	17	1	

		heptadecadienyl resorcinol (33%)	R	17	2	
		heptadecatrienyl resorcinol (2%)	R	17	3	
		nonadecadecenyl resorcinol (2%)	R	19	1	
		nonadecadienyl resorcinol (1%)	R	19	2	
Cashew (<i>Anacardium occidentale</i>)	Anacardiaceae/ Anacardium	pentadec((di/tri)en)yl resorcinol (aka cardol) (15-20%)	R	15	0-3 ^d	173
		2-methyl cardol (1.7-2.6%)	methylated R	15	0-3 ^d	
		pentadecyl phenol (aka cardanol) (1-9%)	P	15	0-3 ^d	
		anacardic acid (74-77%)	carboxylated P	15	0-3 ^d	
Ginkgo (<i>Ginkgo biloba</i>)	Ginkgoaceae/ Ginkgo	anacardic acid: 6-[tridecanyl] salicylic acid (7.5%)	carboxylated P	13	0	186
		anacardic acid: 6-[8'(Z)-pentadecenyl] salicylic acid (43.2%)	carboxylated P	15	1	
		anacardic acid: 6-[10'(Z)-heptadecenyl] salicylic acid (10.2%)	carboxylated P	17	1	
		bilobol (5-pentadecenylresorcinol) (9.8%)	R	15	1	
		Cardanol: 3-[pentadecenyl] phenol	P	15	1	

		(1.4%)				
		Cardanol: 3-[heptadecenyl] phenol (<1%)	P	17	1	
<i>(Philodendron scandens)</i>	Araceae/ Philodendron	heptadecadienyl resorcinol (50%)	R	17	2	¹⁶⁵
		heneicosatetraenyl resorcinol (25%)	R	21	4	
		tricosatetraenyl resorcinol (15%)	R	23	4	
		pentacosatetraenyl resorcinol (10%)	R	25	4	
<i>(Grevillea banksia)</i>	Proteaceae/ Grevillea	undecyl resorcinol (3%)	R	11	0	¹⁸⁷
		tridecyl resorcinol (30%)	R	13	0	
		pentadecyl resorcinol (7%)	R	15	0	
		pentadecenyl resorcinol (60%)	R	15	1	

^a The percentage indicated in parenthesis represents fraction of the particular compound found in the urushiol of the species.

^b The length of the aliphatic side chain may be important for immunologic cross-reactivity ¹⁸⁸.

^c The number of unsaturated bonds is provided to account for different names of compounds with same aromatic ring and same carbon atom numbers in the aliphatic chain.

^d The exact content of specific chemicals with indicated numbers of unsaturated bonds was not determined.

Immunological cross-sensitivity. Longstanding epidemiological and clinical observations have suggested a certain degree of immune cross-reactivity among urushiols^{189,190}. Thus, subjects with mango dermatitis may display positive patch-test reactions to poison ivy urushiols, and vice versa¹⁷⁶. In a similar manner, subjects sensitive to cashew shell oil extract may display sensitivity to poison ivy¹⁸¹. Cross-sensitization could be a consequence of an identical chemical sensitizer being present in different plants, or due to similarity in chemical structures of sensitizers in different plants¹⁹¹. In this case, the use of pure chemicals with different plant origin for patch-testing helps define immune response specificities¹⁹². Another caveat of these studies is that one cannot exclude the possibility that “cross-reactivity” is actually due to sensitization from encounters to both plants, of which only one encounter is remembered by subjects. An example is the development of mango dermatitis in American teenagers, with a known sensitivity to poison ivy but no history of mango sensitivity, who developed a mango contact dermatitis from picking mangos in Israel¹¹. Furthermore, observations using experimental animals where history of antigen encounter can be controlled with more certainty argue for significant cross reactivity between compounds with similar chain lengths (1-3 carbons)¹⁸⁸. Given that major phenolic compounds in poison ivy/oak, cashew nuts and mango differ by three carbons in side chains (15 for poison ivy/oak and cashew nuts; 17 for mango), it can be concluded that data obtained with experimental animals support immunological cross-reactivity of these compounds.

Urushiol variations can be found in plants outside of Anacardiaceae family^{165,174}, including Ginkgo^{193,194}, Philodendron¹⁶⁵ and Grevillea¹⁹⁵: these plants can promote skin sensitization. While some studies have shown cross-reactivity between these plants and Toxicodendron plants^{194,195}, patch-testing results of patients with contact history to only Toxicodendron or only Philodendron did not support such cross reactivity, even though the most prominent phenolic compound in Philodendron extracts was

heptadecadienyl resorcinol with 17 carbons side chain¹⁶⁵ (Table 3). An apparent reason for this discrepancy, however, may be explained by use of different *Philodendron* extracts for patch-testing. *Philodendron*-sensitive subjects did not seem to react to an extract that contained exclusively heptadecadienyl resorcinol but reacted to a mixture that contained heptadecadienyl resorcinol plus other three alk(en)yl resorcinols with longer side chains (21, 23 and 25 carbons). Thus, although less abundant (25%, 15% and 10% for 21, 23 and 25 carbons long side chains, respectively, compared to 50% for the 17 carbons long side chain) these longer side chain containing alk(en)yl resorcinols appear to be more immunogenic. This is in agreement with the impact of side chain length on immunogenicity of alk(en)yl catechols¹⁸⁸. Given that cross-reactivity is limited to compounds of similar side chain length¹⁸⁸, this can explain the absence of cross-reactivity between *Philodendron* and *Toxicodendron*.

Developmental (oral) tolerance and cross-tolerance. Evidence to suggest possible oral tolerogenic effects of urushiols has been reported for two centuries. The best-known examples are anecdotal reports of Native Americans displaying lower sensitivity to poison ivy because they had the habit of chewing poison ivy leaves. Actual references of some of these reports are no longer available, but indirectly referenced in more recent papers; a list of original references that considered the effects of oral poison ivy consumption and their sources are provided in Table 4. Despite the widely held belief of lower poison ivy sensitization in Native Americans, more recent studies using objective measurements of sensitization rates have not supported these impressions. A study of patch-testing rates to poison ivy between Native Americans and Caucasians found rates to be indistinguishable¹⁹⁶. Possible reasons for this finding were not discussed and could include: 1) oral consumption of poison ivy did not start early in childhood; 2) the habit of oral consumption was abandoned by the tribes examined; 3) tribal differences in consuming poison ivy; and 4) relying on erroneous self-reporting in the past.

Table 4. Historic references to oral consumption of poison ivy by American natives.

Historic reference author	Historic reference publication year	Reference where quoted
Dakin	1829	^{54,197}
Lindley	1908	¹⁹⁸
Lain	1913	¹⁹⁶
Alderson	1921, 1925	¹⁹⁹

Other suggestions of possible oral tolerance derive from studies using oral application of antigenic urushiol preparations to induce hyposensitization in individuals sensitized to poison ivy. One of the earliest studies reported successful hyposensitization, although objective measures of sensitization were not stated²⁰⁰. A number of subsequent studies have demonstrated measurable effects of hyposensitization with oral administration of antigen, but patients went through a phase characterized by symptom eruption induced by the oral preparation^{197,199,201}. Because of these side effects and because of difficulties in quality control of botanical preparations (and consequent reproducibility issues) the interest in pursuing hyposensitization studies has waned. It is of interest that the possibility of applying the same regimen as prevention in individuals before the sensitization to poison ivy developed has not been prominently discussed in the literature. Although hyposensitization does not represent a form of developmental tolerance (because sensitization preceded tolerance induction attempts), these studies contribute to the notion that oral exposure to urushiols can lead to tolerance.

Evidence suggesting tolerance to sensitizing effects of Anacardiaceae has been observed in populations that regularly consume Anacardiaceae fruits during early childhood. For example, reduced rates of sensitization to mango in Hawaii²⁰², South America¹⁷⁸ and the Caribbean²⁰³ have been attributed to tolerance developed by early contacts with mango in these populations. Mango is noted to be very popular amongst children in these locations and it is consumed in a specific way by sucking the juice through a hole followed by eating the remaining pulp¹⁷⁸.

A number of epidemiological observations supporting cross-tolerance between distinct Anacardiaceae species have been reported. Examples include adult subjects with patch-test-proven poison ivy or poison oak reactivity developing hyposensitization after working in the cashew nut processing facility²⁰⁴, or after oral consumption of cashew nut oil²⁰⁵. Also, early consumption of mango was proposed to be responsible for reduced rates of poison ivy sensitization in Japanese, Chinese, Filipinos and Hawaiians born in their respective countries, relative to the same populations born in the US¹⁹⁸. These observations suggest that cross-tolerance may exist between cashew nut or mango phenolic compounds and poison ivy urushiol, but more data are needed to establish this association.

Conclusions. Review of available evidence from human subject data suggests that oral exposure to various urushiol-containing plants or foods in certain populations may lead to immunological tolerance, thus preventing or reducing development of urushiol sensitization. The strength of evidence is based on both direct and indirect observational data. The best direct evidence for oral tolerogenic effect has been shown by oral application of poison ivy antigenic preparations. However, these studies have only shown a possible hyposensitization effect and it is still unclear if early (before skin contact sensitization occurs) or continued oral exposure to these preparations in sensitized individuals would lead to

complete tolerance. Moreover, using these preparations clinically for preventing poison ivy sensitization may not be feasible due to side effects and other quality control issues. There are multiple indirect observations from defined geographic areas in which consumption of Anacardiaceae (as extracts or fresh fruit), such as mango, early in life appears to protect against development of skin sensitization to mango later in life. Prospective studies of mango and other Anacardiaceae (as extracts or fresh fruit), ideally in diverse geographic populations, are still needed to establish a more causal association between oral exposure and reduced sensitization. Furthermore, in light of antigenic similarities between urushiols, such as of alk(en)yl catechols (present in poison ivy) and alk(en)yl resorcinols (present in mango), some evidence of immunological cross-tolerance between Anacardiaceae fruits and poison ivy has been observed with early consumption of mango providing protection against development of sensitization to poison ivy in certain populations. However, additional controlled studies in wider populations and to various Anacardiaceae are needed to confirm these observations.

SESQUITERPENE LACTONES

Sources and chemical composition. SLs are the main allergens in the plants of Compositae (also known as Asteraceae) family²⁰⁶. Compositae family plants are widely used as food, spices, valued medicinal plants, cosmetic ingredients as well as indoor or outdoor landscape plants^{207,208}. Compositae family has thus become a very important allergenic plant family for research purposes²⁰⁷. Plants other than Compositae, such as magnolia (Magnoliaceae), bay leaf (Lauraceae) and liverworts (Jubulaceae), may also harbor SLs²⁰⁹. These and some of the plants belonging to the Compositae family and their respective SLs are listed in Table 5.

Table 5. Sesquiterpene lactones (SLs) in select Compositae and non-Compositae plants.

Plant name	Plant family	Representative individual SLs	SL type ^c	Reference	α,β -unsaturated cyclopentenone/ cyclohexenone ^d	α -methylene- γ -lactones ^d	Epoxide/ peroxide bridge ^e
German chamomile ^{a,b} (<i>Matricaria recutita</i>)	Compositae	Matricarin	Guaianolides	210	Yes	No	No
		Achillin			Yes	No	No
		Acetoxyachillin			Yes	No	No
		Leucodin			Yes	No	No
Roman chamomile (<i>Chamaemelum nobile</i>)	Compositae	Nobilin	Germacranolides	207	No	Yes	No
Yarrow ^{a,b} (<i>Achillea millefolium</i>)	Compositae	α -peroxyachifolid	Guaianolides	207	No	Yes	Yes
Cushion bush (<i>Lucophyta brownii</i>)	Compositae	Calocephalin	Guaianolides	208	No	Yes	Yes
		Leucophytalin A	Guaianolides		No	Yes	No
		Pseudoivalin	Guaianolides		No	Yes	No

		Pseudoivalin acetate	Guaianolides		No	Yes	No
		Tomentosin	Other		No	Yes	No
		4 α -hydroxy-5 α H, 10 α H-1,11(13)-guaidien-8 β , 12-olide	Guaianolides		No	Yes	No
		4 α -hydroxy-1 α 2 α -epoxy-5 α H, 10 α H-1,11(13)-guaidien-8 β , 12-olide	Guaianolides		No	Yes	Yes
Arnica ^a (<i>Arnica montana</i>)	Compositae	Xanthalongin	Other	207	No	Yes	No
		Helenalin	Pseudoguaianolides		Yes	Yes	No
Elecampane (<i>Inula helenium</i>)	Compositae	Alantolactone	Eudesmanolides	207	No	Yes	No
		isoalantolactone			No	Yes	No

Sticky elecampane (<i>Inula viscosa</i>)	Compositae	2-desacetoxy-xanthinin	Other	207	No	Yes	No
		Inuviscolide	Guaianolides		No	Yes	No
Costus (<i>Saussurea lappa</i>)	Compositae	Dehydrocostus lactone	Guaianolides	207	No	Yes	No
		Costunolide	Germacranolides		No	Yes	No
Feverfew ^b (<i>Tanacetum parthenium</i>)	Compositae	Parthenolide	Germacranolides	207	No	Yes	Yes
Dandelion ^b (<i>Taraxacum officinale</i>)	Compositae	Glucopyranoside of taraxinic acid	Germacranolides	211	No	Yes	No
Lettuce ^b (<i>Lactuca sativa</i> L)	Compositae	Lactucopicrin	Guaianolides	211	Yes	Yes	No
		Lactucin			Yes	Yes	No
Chrysanthemum ^{a,b} (<i>Dendrathera cultivars</i>)	Compositae	Arteglasin A	Guaianolides	206,212,213	No	Yes	Yes
		Pyrethrosin	Germacranolides		No	Yes	Yes
		Alantolactone	Eudesmanolides		No	Yes	No

Tansy ^b (<i>Tanacetum Vulgare</i> <i>L</i>)	Compositae	Arbusculin A	Eudesmanolides	211	No	Yes	No
		Tanacetin	Eudesmanolides		No	Yes	No
		Parthenolide	Germacranolides		No	Yes	Yes
Rag weeds ^b (<i>Ambrosia spp.</i>)	Compositae	Artemisifolin	Germacranolides	211	No	Yes	No
		Isabelin			No	Yes	No
Sunflower (<i>Helianthus annuus</i>)	Compositae	Argophyllin	Germacranolides	214	No	Yes	Yes
Mugwort (<i>Artemisia</i> <i>Vulgaris</i>) ^a	Compositae	Artemisinin	Other	206,215,216	No	No	Yes
		Yomogin	Eudesmanolides		Yes	Yes	No
		Arteglasin A	Guaianolides		No	Yes	Yes
Stinkwort ^b (<i>Inula graveolans</i>)	Compositae	2 α -hydroxy-2R-xanthalongin	Other	217	No	Yes	No
		4-epi- isoinuviscolide	Guaianolides		No	Yes	No
		8-epi-helenalin	Pseudoguaianolides		Yes	Yes	No
		bigelovin	Pseudoguaianolides		Yes	Yes	No
Dogweed ^b (<i>Cassinia</i>)	Compositae	Eupatolide	Germacranolides	218	No	Yes	No

<i>aculeate</i>)		Epitulipinolide			No	Yes	No
Capeweed ^b (<i>Arctotheca</i> <i>calendula</i>)	Compositae	Dehydro- brachylaenolide	Eudesmanolides	219	Yes	Yes	No
		Isosantonin			Yes	Yes	No
		4,5-Dihydro- α - santonin			Yes	Yes	No
		Tuberiferin			Yes	Yes	No
Wormwood ^b (<i>Artemisia</i> <i>absinthium</i>)	Compositae	Anabsin	Guaianolides	220	No	No	No
		Absinthin	Guaianolides		No	No	No
		Anabsinthin	Guaianolides		No	No	No
		3'-hydroxy- anabsinthin	Guaianolides		No	No	No
		Ketopelenolide b	Germacranolides		No	No	No
Marigold ^{a,b} (<i>Tagetes</i> <i>patula</i>)	Compositae	Unknown	N/A	207	N/A	N/A	N/A
Magnolia (<i>Magnolia</i>	Magnoliaceae	Parthenolide	Germacranolides	211	No	Yes	Yes

<i>grandiflora</i>)							
Liverwort (<i>Frullania</i>)	Jubulaceae	Frullanolide 1	Eudesmanolides	²²¹	No	Yes	No
Bayleaf (<i>Laurus nobilis</i>)	Lauraceae	Dehydrocostus lactone	Guaianolides	²²²	No	Yes	No
		Costunolide	Germacranolides		No	Yes	No

^aGrows in India ²²³

^bGrows in Australia ^{224,225}

^cRefer to Fig. 3 for SL type structures

^dThese functional groups are potential immunochemical requisites of causing ACD ²²⁶⁻²²⁸.

^eThis functional group is related to biological activities such as antitumor and antimalarial properties ^{215,229}.

Chemically, SLs are fifteen carbon compounds formed by condensation of three isoprene units, followed by cyclization and oxidative transformation to make a *cis* or *trans*-fused lactone²¹⁵. The γ -lactone ring, usually with an α -methyl group, is a significant characteristic of SLs. The number of distinct SL structures identified is growing rapidly- from more than 1600 reported in the year 2000²³⁰ to more than 6000 reported in 2017²³¹. The composition of sesquiterpene lactones from each of these plants differs, but all the components are very similar in structure. SLs belong to more than 40 structural types of which four are the most widespread, which are eudesmanolides, germacranolides, guaianolides and pseudoguaianolides²³¹ (Fig. 3). One plant species usually produces one type of sesquiterpene lactones

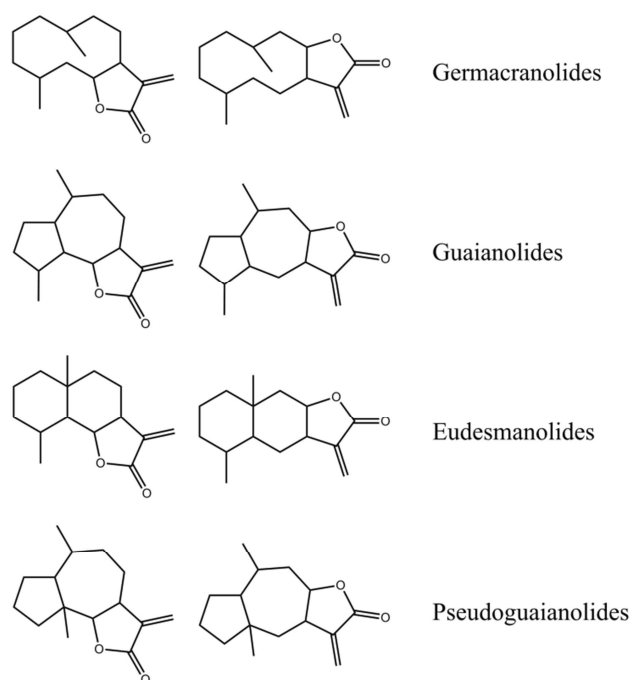


Figure 3. General chemical structures of the four most widespread classes of sesquiterpene lactones. Lactones can be formed in different orientations depending on the position of the hydroxyl group for intramolecular esterification. Two typical examples are given on the left and right side for each class.

²¹⁵, although some exceptions have been noted

²³²⁻²³⁸.

Contact dermatitis induction. The frequency of sensitization with SLs ranges from 0.7 to 1.9% in

Europe and North America^{239,240}. Occupational exposure appears to be the primary source of sensitization for Compositae in general²³⁹, although tea consumption may be an important sensitization source for some plants, e.g. German Chamomile^{207,241}. In addition to the classical form of ACD, Compositae cause a form of airborne photodermatitis that carries different names in distinct geographic locations, mostly with warm climate²⁴². Ragweed dermatitis is described in some areas of the US²⁴³, bush dermatitis in Australia^{224,244}, and parthenium dermatitis in India^{211,245-247}.

As mentioned earlier, SLs are main allergens for Compositae plants, although other allergens have been reported, such as bisabolol (sesquiterpene alcohol) from German chamomile (*Chamomilla recutita*) and Roman chamomile (*Chamomilla nobile*), butenylbithiophene and α -terthienyl (thiopene) from French marigold (*Tagetes patula*), herniarin (coumarin) from German chamomile, β -caryophyllene (terpene) from Achillea, Artemisia, Helichrysum and Eupatorium as well as flavonoids from German chamomile^{207,248,249}. Sensitivity to SLs is tested using a mixture of three SLs in equimolar concentrations: alantolactone (eudesmanolide class), costunolide (germacranolide class) and dehydrocostus lactone (guaianolide class), with a total concentration of 0.1% in petrolatum²⁵⁰ (Fig. 4). This SL mix is included in European standard series. When testing with individual constituents of SL mix, costunolide (germacranolide class) is the most prevalent sensitizer and elicits positive reactions in 90% of SL-sensitized subjects, while dehydrocostus lactone (guaianolide class) and alantolactone (eudesmanolide class) respectively elicit 66% and 42% of positive reactions²³⁰. However, the SL mix confirms sensitivity to Compositae in less than 50% of cases. Better sensitivity is achieved by the use of five Compositae plant extracts²⁵¹⁻²⁵³ but the use of plant extracts for patch-testing is impractical from a standardized manufacturing protocol point of view. Hence, attempts have been made to expand the list of SLs used in standard testing by adding parthenolide²⁵⁴ or three other structurally dissimilar SLs²⁵⁵. It appears that immunological specificities for parthenolide largely overlaps with specificities for the standard SLs mix²⁵⁴, while the contributions of the three structurally dissimilar SLs remains

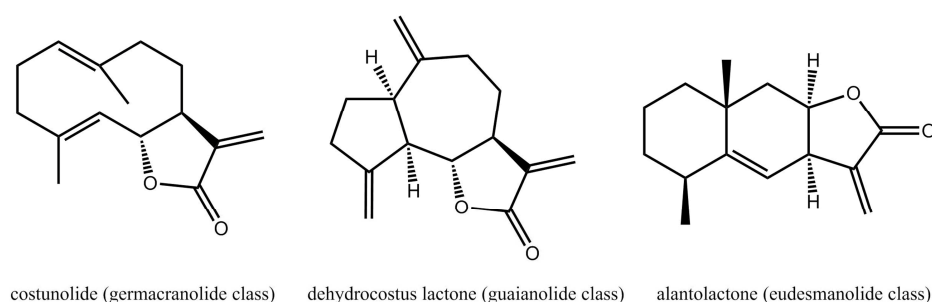


Figure 4. Chemical structures (cis and trans forms included) of individual sesquiterpene lactones used for patch-test.

unclear.

Immunological cross-sensitivity. There is reported evidence that people are more likely to experience allergic reactions to chamomile if they are allergic to related plants such as chrysanthemum, feverfew, yarrow or tansy²⁵⁶⁻²⁵⁹. This “co-morbidity” could be due to coexisting separate immune responses, or to cross-reactive responses to chemically related (or in some cases identical) compounds. Distinguishing between these possibilities is difficult given the rising number of identified SLs^{230,231} and the fact that plants frequently harbor more than a single SL (Table 5). Some cases of “co-morbidity” can be explained by the presence of the same SL in different plants, even those not belonging to the Compositae family. For example, feverfew, chrysanthemum, tansy, ragweed, and magnolia share parthenolide²⁶⁰ (germacranolide class). Also, clinical cross-reactivity between non-Compositae plants that harbor SLs (magnolia, bay leaf and liverwort) and Compositae species has been noted^{209,221,261}. Sensitization to sunflower is frequently observed among individuals sensitized to chrysanthemum²¹⁴, which can be explained by presence of distinct germacranolides (Table 5). Cross-reactivity was also suggested by a study where high prevalence of positive patch-tests to feverfew (95%), tansy (89%) and chamomile (78%) extracts were found in patients sensitized with chrysanthemum²⁵⁹, even though no common SL is known for these four plants (Table 5). Finally, patients from Tenerife have been observed to be sensitized and have immediate hypersensitivity reactions to extracts of *Matricaria Chamomile*, even though this plant does not grow on the island²⁶². This observation suggests that these individuals may have developed this sensitization from previous exposure to another Compositae plant, *Artemisia vulgaris*, that is typically found on the island. While *Artemisia* and German Chamomile do not share an identical SL, they both produce guaianolides (Table 5). Thus, despite demonstrating immune effector

responses reflective of immediate rather than delayed type hypersensitivity, the study findings support possible immune cross-reactivity between distinct Compositae plants.

While co-sensitization to different classes of SLs has been described^{208,226}, cross-reactivity between distinct classes of SLs remains to be confirmed. In fact, it has been argued that even SL subtypes (e.g. guaian-8,12-olides vs. guaian-6,12-olides) may be sufficiently structurally divergent to preclude cross-reactivity²⁶³. Skin sensitization experiments in guinea pigs have suggested that cross-reactivity is dependent largely on configuration (*cis* or *trans*) of α -methylene group in the γ -butyrolactone ring²²⁷ and is limited to compounds with similar number of carbon atoms²²⁸. Patch-testing in SL-sensitive patients also confirmed the importance of α -methylene group for sensitization^{206,213}. It should be noted that reactivity to different plants can sometimes be explained by reactivity to non-SL common compounds. This is evidenced by positive patch-test reactions to the Compositae plant extracts in the absence of reactivity to SL mix²⁶⁴. Cross-reactivity in this case was likely caused by terpene or other terpenoid allergens present in Compositae mix while in a few patients exhibiting cross-sensitization to Compositae and Narcissus extracts cross-reactivity was likely due to other chemicals²⁶⁴.

Developmental (oral) tolerance and cross-tolerance. In a study of sensitization frequencies to 25 allergens of the European standard series, which comprised patch-test results from 26,210 patients from 10 centers across 8 European countries from 1996-2000²⁶⁵, the prevalence of positive reactions to SLs in Portugal was significantly lower than in other countries (0.1% versus 0.7-1.9%; Table 6). This relatively low prevalence rate does not appear to be an anomaly of testing, as an independent study conducted in neighboring Spain (that was not part of the eight country study) also revealed a rate (0.49%) lower than in the rest of the Europe²⁶⁶. Possible explanations for these lower rates are either

paucity of antigen (and hence absence of exposure to plants from the Compositae family) or some form of tolerance induction. Absence of exposure to sensitizer(s) as a hypothesis appears unlikely. It is well

Table 6. Percentage of positive reactions to sesquiterpene lactone mix 0.1% (shown in Fig. 4) by centers in Europe 1996–2000 ²⁶⁵.

Centers	Patients (n)	Positive reactions (%)
Oulu, Finland	2542	1.2
Malmo, Sweden	3301	0.9
Odense, Denmark	2372	1.9
Copenhagen, Denmark	4180	1.4
Amersham, UK	3067	0.9
Leuven, Belgium	3286	0.7
Amsterdam, the Netherlands	2915	1.1
Dortmund, Germany	1956	0.8
Erlangen, Germany	2041	1.7
Almada (Lisbon), Portugal	550	0.1

known that *Achillea* plants are relatively abundant in Portugal and that these plants contain guaianolides ²⁶⁷. Furthermore, ACD caused by *Frullania* is relatively common in Portugal ²⁶⁸. Although it is a member of the Jubulaceae family, and not Compositae, *Frullania* contains SLs ^{221,226}. Thus, absent or reduced exposure to Compositae antigens in Portugal appears to be an unlikely explanation. With regards to the tolerance induction, there is no direct evidence to support this hypothesis. However, it is interesting to

note that because of growing concerns for botulism Portugal's food and economic safety body (ASAE) warned its citizens in 2013 against the use of chamomile tea in young children for treatment of toothaches or baby colic ²⁶⁹. The need for this public warning implies that the use of chamomile tea by small children in Portugal was relatively frequent. By association, therefore, this early chamomile introduction in young children may have contributed to tolerance induction and lower prevalence of allergies to SL in Portugal. This hypothesis, however, remains to be tested prospectively.

In another study inspired by previous reports of lower prevalence of allergies to SL in Singapore than in Europe, Mak *et al.* compared SL mix patch-testing results from hospitals in Singapore and London ³³. They reported that the sensitization rate to SL mix 0.1% in petrolatum differed significantly between the two centers, with 1.37% of patients positive in the London cohort and only 0.34% positive in the Singaporean cohort. Combined with the fact that Compositae skin allergies (ACD) are also rarely seen in other Asian countries such as Japan ²⁷⁰, where chrysanthemum is commonly used as food ingredient ²⁷¹, the study authors postulated that the consumption of chrysanthemum tea induced oral tolerance to SLs in Singapore leading to reduced SL sensitization rates ³³.

The concept of tolerance induction is also supported by unusually high rates of sensitization to SLs when plants are introduced in a new geographic area. Feverfew (*Parthenium hysterophorus*) is a Compositae member that was accidentally introduced to India in 1956 in cereal and grass seed shipments from USA ²⁴⁵. Over the course of 35 years the plant has spread almost all over the subcontinent except some minor pockets ²⁷². With the appearance of this plant came a true epidemic of Parthenium dermatitis ²⁴⁶, with sensitization rates to SLs as high as 23.3% ²⁷³. Given that the SL standard patch test was developed only in 1990 ²⁵⁰, it is impossible to know what the sensitization rates were before feverfew was

introduced to India, and what was the resulting change in prevalence. Nevertheless, these rates are more than two-fold higher than the rates of skin sensitization to nickel in India. This is in contrast to other parts of the world where allergies to nickel are much more prevalent than ACD to SLs^{240,265}. In direct comparison to SL sensitization rates in other parts of the world (0.7-1.9%), sensitization in India is about 10-20-fold higher. Interestingly, the same feverfew species has been introduced to Australia at roughly the same time and in a similar manner as in India²⁷⁴. Due to its invasive character, feverfew also spread quickly over the continent²⁷⁵. However, the rates of SL sensitization in Australia are no different than to those in Europe and US^{276,277}. What could then explain this difference in parthenolide sensitization between Australian and Indian populations? One possible explanation is tolerance induction in the Australian population. A potential source of tolerance in the Australian population is exposure to calocephalin from cushion bush^{224,244}, through cross reactivity of calocephalin with parthenolide. A survey of major Compositae species in Australia and India (see Table 5), and their main SLs, found a preponderance of germacranolide-producing plants in Australia while India harbors mostly guaianolide producers. Thus, prior exposure of Australians to germacranolides may have induced tolerance to parthenolide (another germacranolide). The difference in exposure to germacranolides can be also inferred from different rates of cross-reactivity of Compositae-sensitive patients to chrysanthemum in India versus Australia. In Australia 69.2% (9/13) patients reacted to chrysanthemum, while in India this rate ranged between 22.8% (13/57)²⁷⁸ and 41.7% (25/60)²⁷⁹. Relatively low rates of reactivity to chrysanthemum in India (indicative of reactivity to germacranolide artemisinin-A) compared to high sensitization rates to another germacranolide (parthenolide) suggest lower overall exposure to germacranolides in India, albeit confirmatory studies with larger numbers of subjects are needed. While there are no indications that Australians become exposed to Compositae via the oral route, consumption of chrysanthemum flowers and leaves as food is common in Japan²⁷¹ and in China²⁸⁰ and may explain the low rates of Parthenium sensitization in these countries, despite evidence that the plant

grows invasively in Japan and China as well²⁷⁵. Taken together, these observations suggest alternate paths of tolerance induced by prior exposures in Australia and Japan, but not India.

Conclusions. Review of human data from studies of certain geographic areas suggests that oral consumption of Compositae (chamomile tea; chrysanthemum flowers, leaves, and tea) starting in early life may be a source of antigenic exposure leading to immunological tolerance, thus leading to reduced rates of sensitization to SLs. However, direct evidence is not available, and additional controlled studies are needed to confirm that SLs can induce developmental tolerance.

OVERALL CONCLUSIONS AND FUTURE DIRECTIONS

Early exposure to antigenic substances through the oral route may lead to oral tolerance and prevention of subsequent sensitization to these substances. Given this concept and examples of allergic skin sensitizers that can be encountered from both oral and dermal exposures, it is important to understand whether oral consumption of skin sensitizing chemicals may impact the sensitization and/or reactivity potential of these sensitizers when exposed via the skin. Finding ways or strategies to minimize the prevalence of skin sensitization would be beneficial to public health because sensitization and clinical reactivity to skin sensitizers appears to be increasing and becoming a more pronounced health care burden^{6,281}. Recent therapeutic strategies have shown that oral peanut immunotherapy may effectively desensitize a large percentage of peanut allergic patients to high dose peanut oral challenge and achieve sustained tolerance in some of these patients²⁸²⁻²⁸⁴. While the case of peanut immunotherapy did not achieve sustained tolerance in all patients and focused on an allergy mainly of the oral route, involving

immediate IgE-mediated hypersensitivity, these data support the concept of oral antigenic intervention as an immunological approach to prevent allergic sensitization and reactivity possibly from other exposure routes, as well. As such, the effects of early consumption of foods containing nickel, alk(en)yl phenolic compounds (e.g. mango), and SLs, for example, could lead to reduced sensitization rates to nickel, poison ivy, and Compositae plants, respectively, in Western countries.

We chose to study data on three distinct skin sensitizers that are prevalent causes of contact dermatitis and differ chemically and in distribution. Nickel is a heavy metal ubiquitously present in food, air, and water, and consequently may be regularly ingested by humans. Nickel may also be released into the oral cavity from orthodontic appliances. While no prospective study data are available, there is a correlation between exposure to nickel and rates of nickel sensitization in defined populations that may be used to evaluate the potential of oral nickel exposure to induce tolerance. Urushiols and SLs, on the other hand, are chemically more complex compounds present in plants and, therefore, not continuously ingested by humans. However, some retrospective data are available in which exposure to or consumption of certain plants containing urushiols and SLs may occur in certain geographic areas. Studying sensitization differences in these geographical areas can help to assess questions such as whether consumption of certain sensitizer-associated compounds early in life may protect against development of sensitization by closely related chemicals (e.g. alkenyl resorcinol in mango protecting against poison ivy dermatitis, or SLs in chrysanthemum or chamomile tea protecting against Parthenium dermatitis). Table 7 summarizes our review of data suggestive of developmental (oral) tolerance from human studies involving the three distinct skin sensitizers. There is little evidence of a direct or prospective association between oral consumption of skin sensitizer compounds and tolerance to skin sensitization based on controlled studies, such as double-blinded clinical studies, where carefully controlled quantities of food or other

oral substances with known chemical content are introduced at predefined developmental stages of human development, to provide definitive support for tolerance. More studies of this magnitude are clearly needed. However, our review of the literature on mostly retrospective human clinical and

Table 7. Summary of reviewed data suggesting developmental (oral) tolerance to nickel (Ni), urushiols, and sesquiterpene lactone (SLs).

Chemical compound	Data supporting developmental (oral) tolerance	Possibility of cross-tolerization	Reference
Ni	Correlation of Ni levels in urine of general population and Ni sensitization rates in different countries	No	Fig. 1; Table 1
	Effects of wearing dental braces on Ni sensitization rates	No	Table 2
	Correlation of Ni levels in drinking water on Ni sensitization rates in adjacent regions of Russia and Norway	No	92,110
Urushiols	Hyposensitization using oral preparations of urushiols	No	197,199,201
	Correlation of sensitization rates to mango in the US vs. Hawaii, South America, and the Caribbean	No	178,202,203
	Hyposensitization to poison ivy following exposure to cashew nuts or oils	Yes	204,205
	Correlation of sensitization rates to poison ivy in Japanese, Chinese, Filipinos, or Hawaiians born in the US or in their respective countries where mango is consumed early in life	Yes	198

SLs	Correlation of reduced sensitization rates to SLs with early life consumption of chamomile or chrysanthemum	Yes/No	33,265
	High rates of Parthenium dermatitis in India where exposure to germacranolide SL-producing plants is lower	Yes	273,276,277 and Table 5

epidemiological studies finds credible evidence of clinical observations that suggest potential cross-tolerance between early oral exposure to substances related to important skin sensitizers and reduced sensitization rates or reactivity to these skin sensitizers. While we observed a potentially novel finding of an inverse correlation between the mean nickel levels in urine and the nickel sensitization rates in general population (Table 1), we found too many confounding variables to link the high urinary nickel levels with oral nickel exposure alone. More compelling evidence of an oral exposure effect is described for poison ivy and SLs. This conclusion is based primarily on geographic differences in sensitization rates to skin sensitizers and presence of other related chemicals that may be orally consumed and unique to those respective geographic areas. Noted examples include hyposensitization to poison ivy following exposure to cashew nuts or oils; correlation of sensitization rates to poison ivy in Japanese, Chinese, Filipinos, or Hawaiians born in the US or in their respective countries where mango is consumed early in life; correlation of reduced sensitization rates to SLs with early life consumption of chamomile or chrysanthemum; and high rates of parthenium dermatitis in India where exposure to germacranolide SLs producing plants is lower. It should be noted that experimental animal studies also support the same conclusion²⁸⁵⁻²⁸⁷.

While there are over 4000 different skin sensitizers, we found compelling evidence for only three chemicals that support the possibility of oral developmental tolerance. This highlights the degree to

which developmental tolerance to skin sensitizers is understudied. Therefore, examination of additional chemicals for evidence of oral developmental tolerance would be beneficial. It would be important to investigate the degree of cross reactivities between different chemicals, as this information could lead to identification of foods or other oral substances that could promote tolerance induction (e.g. use of mango rather than poison ivy itself) and prevent sensitization.

Another important avenue of further study is the quantitative aspect of tolerance induction to examine whether developmental tolerance can be induced without causing harm. There are no reports on nickel toxicity in countries with higher levels of nickel in urine, and consumption of mango or cashews early in life in South America, Hawaii, East Asia, and the Caribbean is not associated with adverse effects. The greatest impact of introducing germacranolide SLs (e.g. chrysanthemum, chamomile) early in life would be in areas with high incidence of Parthenium dermatitis (e.g. India). However, beneficial effects in some western countries should not be discounted, judging from the lower rates of sensitization to SLs in Portugal and East Asia.

Is there a broader impact of developmental tolerance beyond the three groups of antigens considered in this review? What could be the relationship between diet and allergies to certain cosmetic ingredients? As mentioned earlier, compounds used as fragrances in the cosmetics industry are present as flavors in various foods, most frequently in fruits, vegetables, and spices²⁸⁻³⁰. An important question in that respect is whether humans already consume tolerance-promoting produce early in life, in which case the rates of sensitization seen are already reduced. However, a recent report from the Centers for Disease Control and Prevention suggests that only 10% of adult Americans consume recommended amounts of fruits and vegetables²⁸⁸. Although children were not included in this study, consumption of

fruits and especially vegetables by children is also below recommended levels²⁸⁹. Therefore, future studies could explore the potential to further impact public health by promoting greater intake of tolerance-promoting produce and assessing the sensitization rates for decreases over time. Examples of some foods with potential impact on public health through the process of developmental tolerance induction are listed in Table 8. Obvious examples of possible future studies come from the topics reviewed in this manuscript: Controlled early life introduction of nickel, alk(en)yl phenolic compounds of mango, and germacranolides of chamomile or chrysanthemum and their impact on sensitization rates to nickel, poison ivy and SLs, respectively (Fig. 5). Further, association studies for other ingredients might be considered. For example, effects of early consumption of jasmine tea on sensitization rates to fragrance ingredient farnesol, or early citrus fruit consumption on sensitization rates to citronellol or limonene. These are only few examples of possible studies that can be derived from Table 8.

Table 8. Examples of potential impact of developmental tolerance induction by early consumption of certain foods on public health.

Food category	Food	Contact sensitizer	Health condition affected
Fruits	Nuts	Nickel	Sensitization to nickel
	Mango	Alk(en)yl phenolic compounds	Poison ivy/oak dermatitis
	Cashew	Alk(en)yl phenolic compounds	Poison ivy/oak dermatitis
	Citrus fruits	Cinnamates, limonene, citral, citronellol, geraniol	Fragrance allergies
Teas/oils	Chamomile	Germacranolide SLs	Parthenium dermatitis

	Chrysanthemum	Germacranolide SLs	Parthenium dermatitis
	Lavander	Linalool	Fragrance allergies
	Jasmine	Farnesol, benzyl alcohol	Fragrance allergies
	Rose	Farnesol, linalool, citronellol, geraniol	Fragrance allergies
Spices	Cinnamon spice	Cinnamic aldehyde, eugenol	Fragrance allergies
	Vanilla	Vanillin, anisyl alcohol	Fragrance allergies
	Dill	Eugenol, isoeugenol	Fragrance allergies
	Allspice	Eugenol	Fragrance allergies
	Nutmeg and mace	Eugenol, isoeugenol	Fragrance allergies
	Anise	Eugenol, cinnamates, anisyl alcohol	Fragrance allergies
	Bay leaves	Eugenol, cinnamates	Fragrance allergies
	Basil	Eugenol, isoeugenol, cinnamates, linalool, citronellol	Fragrance allergies
	Curry	Eugenol, cinnamates, vanillin	Fragrance allergies
Vegetables	Tomato	Eugenol, cinnamates	Fragrance allergies
	Soybeans	Nickel	Sensitization to nickel
	Coco	Nickel	Sensitization to nickel
	Asparagus	Vanillin	Fragrance allergies
	Pickles	Eugenol, cinnamates, vanillin	Fragrance allergies
	Cloves	Eugenol, isoeugenol, vanillin	Fragrance allergies

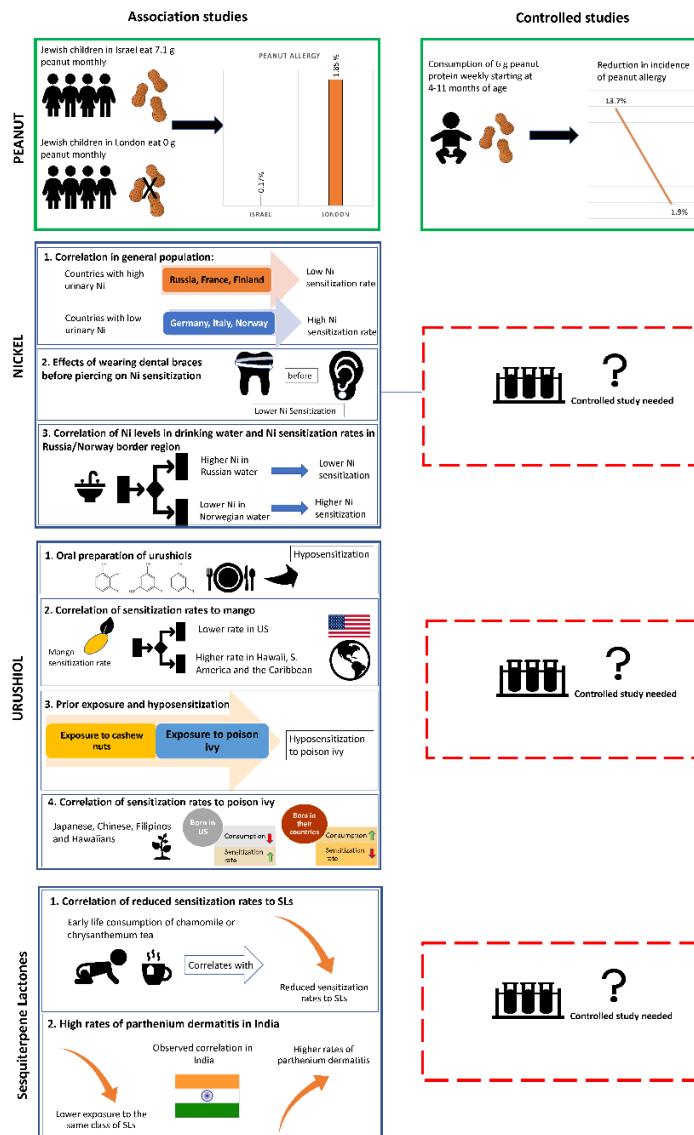


Fig. 5. Summary of the most important points of this review. A change in recommendations with regards to the peanut allergy based on the association and controlled studies of allergen-specific oral tolerance induction is depicted in the top green outlined boxes (taken from references 79,80). The existing association studies for nickel, urushiols and SLs (as referenced in Table 7) is depicted in blue outlined boxes, as well as an indication that controlled studies are needed for all three sensitizers are depicted in blue “clouds”. The red dashed outlined boxes are indicating the gap in knowledge and the need for controlled studies for all three sensitizers.

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REFERENCES

1. Karlberg AT, Bergstrom MA, Borje A, Luthman K, Nilsson JL. Allergic contact dermatitis--formation, structural requirements, and reactivity of skin sensitizers. *Chem Res Toxicol*. 2008;21(1):53-69.
2. Vocanson M, Hennino A, Rozieres A, Poyet G, Nicolas JF. Effector and regulatory mechanisms in allergic contact dermatitis. *Allergy*. 2009;64(12):1699-1714.
3. Vukmanovic S, Sadrieh N. Skin sensitizers in cosmetics and beyond: potential multiple mechanisms of action and importance of T-cell assays for in vitro screening. *Crit Rev Toxicol*. 2017;47(5):415-432.
4. de Groot AC. *Patch Testing: Test Concentrations and Vehicles for 4350 Chemicals*. de Groot; 2008.
5. de Groot AC. New Contact Allergens: 2008 to 2015. *Dermatitis*. 2015;26(5):199-215.
6. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55(3):490-500.
7. Kulberg A, Schliemann S, Elsner P. Contact dermatitis as a systemic disease. *Clin Dermatol*. 2014;32(3):414-419.
8. Fabbro SK, Zirwas MJ. Systemic contact dermatitis to foods: nickel, BOP, and more. *Curr Allergy Asthma Rep*. 2014;14(10):463.
9. Gladman AC. Toxicodendron dermatitis: Poison ivy, oak, and Sumac. *Wilderness & Environmental Medicine*. 2006;17(2):120-128.
10. Calvert ML, Robertson I, Samaratunga H. Mango dermatitis: allergic contact dermatitis to *Mangifera indica*. *Australas J Dermatol*. 1996;37(1):59-60.
11. Hershko K, Weinberg I, Ingber A. Exploring the mango-poison ivy connection: the riddle of discriminative plant dermatitis. *Contact Dermatitis*. 2005;52(1):3-5.
12. Diogenes MJ, de Moraes SM, Carvalho FF. Contact dermatitis among cashew nut workers. *Contact Dermatitis*. 1996;35(2):114-115.
13. Bruynzeel DP. Bulb dermatitis. Dermatological problems in the flower bulb industries. *Contact Dermatitis*. 1997;37(2):70-77.
14. Cronin E. Dermatitis of the hands in caterers. *Contact Dermatitis*. 1987;17(5):265-269.
15. Wu PA, James WD. Lavender. *Dermatitis*. 2011;22(6):344-347.
16. Heratizadeh A, Geier J, Molin S, Werfel T. Contact sensitization in patients with suspected textile allergy. Data of the Information Network of Departments of Dermatology (IVDK) 2007-2014. *Contact Dermatitis*. 2017.
17. Rose RF, Lyons P, Horne H, Mark Wilkinson S. A review of the materials and allergens in protective gloves. *Contact Dermatitis*. 2009;61(3):129-137.
18. Hatch KL, Maibach HI. Textile fiber dermatitis. *Contact Dermatitis*. 1985;12(1):1-11.
19. CBSNews. Are American Airlines' Uniforms Making Employees Sick? 2017; <https://www.cbsnews.com/news/american-airlines-uniforms-employees-sick/>. Accessed November 24, 2017.
20. Thyssen JP, Menne T. Metal allergy--a review on exposures, penetration, genetics, prevalence, and clinical implications. *Chem Res Toxicol*. 2010;23(2):309-318.
21. Freeman S. Shoe dermatitis. *Contact Dermatitis*. 1997;36(5):247-251.

22. Uter W, Johansen JD, Borje A, et al. Categorization of fragrance contact allergens for prioritization of preventive measures: clinical and experimental data and consideration of structure-activity relationships. *Contact Dermatitis*. 2013;69(4):196-230.
23. Admani S, Jacob SE. Allergic contact dermatitis in children: review of the past decade. *Curr Allergy Asthma Rep*. 2014;14(4):421.
24. Uter W, Yazar K, Kratz EM, Mildau G, Liden C. Coupled exposure to ingredients of cosmetic products: II. Preservatives. *Contact Dermatitis*. 2014;70(4):219-226.
25. Goossens A. Contact-allergic reactions to cosmetics. *J Allergy (Cairo)*. 2011;2011:467071.
26. Uter W, Spiewak R, Cooper SM, et al. Contact allergy to ingredients of topical medications: results of the European Surveillance System on Contact Allergies (ESSCA), 2009-2012. *Pharmacoepidemiol Drug Saf*. 2016;25(11):1305-1312.
27. Pennington JA, Jones JW. Molybdenum, nickel, cobalt, vanadium, and strontium in total diets. *J Am Diet Assoc*. 1987;87(12):1644-1650.
28. Isaac-Renton M, Li MK, Parsons LM. Cinnamon Spice and Everything Not Nice: Many Features of Intraoral Allergy to Cinnamic Aldehyde. *Dermatitis*. 2015;26(3):116-121.
29. Scheman A, Rakowski EM, Chou V, Chhatriwala A, Ross J, Jacob SE. Balsam of Peru: past and future. *Dermatitis*. 2013;24(4):153-160.
30. Scheman A, Scheman N, Rakowski EM. European Directive fragrances in natural products. *Dermatitis*. 2014;25(2):51-55.
31. Lesage-Meessen L, Bou M, Sigoillot JC, Faulds CB, Lomascolo A. Essential oils and distilled straws of lavender and lavandin: a review of current use and potential application in white biotechnology. *Appl Microbiol Biotechnol*. 2015;99(8):3375-3385.
32. Avonto C, Rua D, Lasonkar PB, Chittiboyina AG, Khan IA. Identification of a compound isolated from German chamomile (*Matricaria chamomilla*) with dermal sensitization potential. *Toxicol Appl Pharmacol*. 2017;318:16-22.
33. Mak RK, White IR, White JM, McFadden JP, Goon AJ. Lower incidence of sesquiterpene lactone sensitivity in a population in Asia versus a population in Europe: an effect of chrysanthemum tea? *Contact Dermatitis*. 2007;57(3):163-164.
34. Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. *Pharmacological Reviews*. 2001;53(3):357-379.
35. Weiner HL, da Cunha AP, Quintana F, Wu H. Oral tolerance. *Immunol Rev*. 2011;241(1):241-259.
36. Vaz N, Faria AM, Verdolin BA, Carvalho CR. Immaturity, ageing and oral tolerance. *Scand J Immunol*. 1997;46(3):225-229.
37. Elkon KB. Immunologic tolerance and apoptosis. In: Rich RR, Fleisher, T.A., Shearer, W.T., Kotzin, B.L., Schroeder, H.W.Jr., ed. *Clinical immunology: principles and practice*. 2nd ed.: Mosby-Year Book; 2001.
38. Allam JP, Novak N. Immunological mechanisms of sublingual immunotherapy. *Curr Opin Allergy Clin Immunol*. 2014;14(6):564-569.
39. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy*. 2011;66(6):740-752.
40. Allam JP, Novak N. Local immunological mechanisms of sublingual immunotherapy. *Curr Opin Allergy Clin Immunol*. 2011;11(6):571-578.
41. Sindher S, Fleischer DM, Spergel JM. Advances in the Treatment of Food Allergy: Sublingual and Epicutaneous Immunotherapy. *Immunol Allergy Clin North Am*. 2016;36(1):39-54.
42. McGowan EC, Wood RA. Sublingual (SLIT) versus oral immunotherapy (OIT) for food allergy. *Curr Allergy Asthma Rep*. 2014;14(12):486.
43. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol*. 2012;129(5):1187-1197.

44. White JM, Goon AT, Jowsey IR, et al. Oral tolerance to contact allergens: a common occurrence? A review. *Contact Dermatitis*. 2007;56(5):247-254.
45. Chase MW. Inhibition of Experimental Drug Allergy by Prior Feeding of the Sensitizing Agent. *Proceedings of the Society for Experimental Biology and Medicine*. 1946;61(3):257-259.
46. Vela Ramirez JE, Sharpe LA, Peppas NA. Current state and challenges in developing oral vaccines. *Adv Drug Deliv Rev*. 2017.
47. Vashishtha VM, Kamath S. A Brief History of Vaccines Against Polio. *Indian Pediatr*. 2016;53 Suppl 1:S20-S27.
48. Kaplan DH, Igyarto BZ, Gaspari AA. Early immune events in the induction of allergic contact dermatitis. *Nat Rev Immunol*. 2012;12(2):114-124.
49. Martin SF. Allergic contact dermatitis: xenoinflammation of the skin. *Curr Opin Immunol*. 2012;24(6):720-729.
50. Martin SF. New concepts in cutaneous allergy. *Contact Dermatitis*. 2015;72(1):2-10.
51. Cooling L. Blood Groups in Infection and Host Susceptibility. *Clin Microbiol Rev*. 2015;28(3):801-870.
52. Garratty G. Blood groups and disease: a historical perspective. *Transfus Med Rev*. 2000;14(4):291-301.
53. Concha C, Canas R, Macuer J, et al. Disease Prevention: An Opportunity to Expand Edible Plant-Based Vaccines? *Vaccines (Basel)*. 2017;5(2).
54. Spiewak R. Immunotherapy of allergic contact dermatitis. *Immunotherapy*. 2011;3(8):979-996.
55. Marchant A, Goldman M. T cell-mediated immune responses in human newborns: ready to learn? *Clin Exp Immunol*. 2005;141(1):10-18.
56. Adkins B, Leclerc C, Marshall-Clarke S. Neonatal adaptive immunity comes of age. *Nat Rev Immunol*. 2004;4(7):553-564.
57. PrabhuDas M, Adkins B, Gans H, et al. Challenges in infant immunity: implications for responses to infection and vaccines. *Nat Immunol*. 2011;12(3):189-194.
58. Siegrist CA, Aspinall R. B-cell responses to vaccination at the extremes of age. *Nat Rev Immunol*. 2009;9(3):185-194.
59. Tatari-Calderone Z, Luban NL, Vukmanovic S. Genetics of transfusion recipient alloimmunization: can clues from susceptibility to autoimmunity pave the way? *Transfus Med Hemother*. 2014;41(6):436-445.
60. Kan B, Razzaghi HR, Lavoie PM. An Immunological Perspective on Neonatal Sepsis. *Trends Mol Med*. 2016;22(4):290-302.
61. West LJ. Defining critical windows in the development of the human immune system. *Hum Exp Toxicol*. 2002;21(9-10):499-505.
62. Dowling DJ, Levy O. Ontogeny of early life immunity. *Trends Immunol*. 2014;35(7):299-310.
63. Maddux AB, Douglas IS. Is the developmentally immature immune response in paediatric sepsis a recapitulation of immune tolerance? *Immunology*. 2015;145(1):1-10.
64. de Brito CA, Goldoni AL, Sato MN. Immune adjuvants in early life: targeting the innate immune system to overcome impaired adaptive response. *Immunotherapy*. 2009;1(5):883-895.
65. Waldmann H. Mechanisms of immunological tolerance. *Clin Biochem*. 2016;49(4-5):324-328.
66. Miller J. Self-nonself discrimination by T lymphocytes. *C R Biol*. 2004;327(5):399-408.
67. Mackay IR. Autoimmunity since the 1957 clonal selection theory: a little acorn to a large oak. *Immunol Cell Biol*. 2008;86(1):67-71.
68. Lechler RI, Garden OA, Turka LA. The complementary roles of deletion and regulation in transplantation tolerance. *Nat Rev Immunol*. 2003;3(2):147-158.
69. Nutsch KM, Hsieh CS. T cell tolerance and immunity to commensal bacteria. *Curr Opin Immunol*. 2012;24(4):385-391.

70. Scharschmidt TC. Establishing Tolerance to Commensal Skin Bacteria: Timing Is Everything. *Dermatol Clin*. 2017;35(1):1-9.
71. Torow N, Hornef MW. The Neonatal Window of Opportunity: Setting the Stage for Life-Long Host-Microbial Interaction and Immune Homeostasis. *J Immunol*. 2017;198(2):557-563.
72. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A*. 2010;107(26):11971-11975.
73. Burnet FM, Fenner F. *The production of antibodies*. Melbourne: Macmillan; 1949.
74. Billingham RE, Brent L, Medawar PB. Actively Acquired Tolerance of Foreign Cells. *Nature*. 1953;172(4379):603-606.
75. Billingham RE, Brent L, Medawar PB. Quantitative Studies on Tissue Transplantation Immunity .3. Actively Acquired Tolerance. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences*. 1956;239(666):357-412.
76. Coutinho A. The Le Douarin phenomenon: a shift in the paradigm of developmental self-tolerance. *Int J Dev Biol*. 2005;49(2-3):131-136.
77. Sakaguchi S. Regulatory T Cells: History and Perspective. In: Kassiotis G, Liston A, eds. *Regulatory T Cells: Methods and Protocols*. Totowa, NJ: Humana Press; 2011:3-17.
78. Strobel S. Neonatal oral tolerance. *Ann N Y Acad Sci*. 1996;778:88-102.
79. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008;122(5):984-991.
80. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803-813.
81. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol*. 2017;139(1):29-44.
82. Colowick AB, Bohn RL, Avorn J, Ewenstein BM. Immune tolerance induction in hemophilia patients with inhibitors: costly can be cheaper. *Blood*. 2000;96(5):1698-1702.
83. Pan H, Gazarian A, Dubernard JM, Belot A, Michallet MC, Michallet M. Transplant Tolerance Induction in Newborn Infants: Mechanisms, Advantages, and Potential Strategies. *Front Immunol*. 2016;7:116.
84. Krishnamurthy B, Selck C, Chee J, Jhala G, Kay TW. Analysis of antigen specific T cells in diabetes - Lessons from pre-clinical studies and early clinical trials. *J Autoimmun*. 2016;71:35-43.
85. Silverstein AM, Rose NR. On the mystique of the immunological self. *Immunol Rev*. 1997;159:197-206; discussion 207-118.
86. Siegrist CA. Neonatal and early life vaccinology. *Vaccine*. 2001;19(25-26):3331-3346.
87. Marchant A, Newport M. Prevention of infectious diseases by neonatal and early infantile immunization: prospects for the new millennium. *Curr Opin Infect Dis*. 2000;13(3):241-246.
88. Lu LK, Warshaw EM, Dunnick CA. Prevention of nickel allergy: the case for regulation? *Dermatol Clin*. 2009;27(2):155-161, vi-vii.
89. Bocca B, Forte G. The epidemiology of contact allergy to metals in the general population: Prevalence and new evidences. *Open Chem Biomed Methods J*. 2009;2:26-34.
90. Pizzutelli S. Systemic nickel hypersensitivity and diet: myth or reality? *Eur Ann Allergy Clin Immunol*. 2011;43(1):5-18.
91. Smith-Sivertsen T, Lund E, Thomassen Y, Norseth T. Human nickel exposure in an area polluted by nickel refining: the Sor-Varanger study. *Arch Environ Health*. 1997;52(6):464-471.
92. Smith-Sivertsen T, Tchachtchine V, Lund E, Bykov V, Thomassen Y, Norseth T. Urinary nickel excretion in populations living in the proximity of two russian nickel refineries: a Norwegian-Russian population-based study. *Environ Health Perspect*. 1998;106(8):503-511.

93. Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from Northern Norway. *Contact Dermatitis*. 2007;56(1):10-15.
94. Dotterud LK. The prevalence of allergic contact sensitization in a general population in Tromsø, Norway. *Int J Circumpolar Health*. 2007;66(4):328-334.
95. Roggi C, Merlo E, Minoia C. Nickel food exposure. *Annali di Igiene: Medicina Preventiva e di comunità*. 1996;9:221-227.
96. Turconi G, Minoia C, Ronchi A, Roggi C. Dietary exposure estimates of twenty-one trace elements from a Total Diet Study carried out in Pavia, Northern Italy. *Br J Nutr*. 2009;101(8):1200-1208.
97. Ohashi F, Fukui Y, Takada S, Moriguchi J, Ezaki T, Ikeda M. Reference values for cobalt, copper, manganese, and nickel in urine among women of the general population in Japan. *International Archives of Occupational and Environmental Health*. 2006;80(2):117-126.
98. Minoia C, Sabbioni E, Apostoli P, et al. Trace element reference values in tissues from inhabitants of the European community. I. A study of 46 elements in urine, blood and serum of Italian subjects. *Sci Total Environ*. 1990;95:89-105.
99. Diepgen TL, Ofenloch RF, Bruze M, et al. Prevalence of contact allergy in the general population in different European regions. *Br J Dermatol*. 2016;174(2):319-329.
100. Seifert M, Anke M. Alimentary nickel intake of adults in Germany. *Trace Elements and Electrolytes*. 1999;16(1):17-21.
101. Anke M, Groppel B, Krause U, Arnhold W, Langer M. Trace element intake (zinc, manganese, copper, molybdenum, iodine and nickel) of humans in Thuringia and Brandenburg of the Fed. Rep. of Germany. *J Trace Elem Electrolytes Health Dis*. 1991;5(2):69-74.
102. Angerer J, Lehnert G. Occupational chronic exposure to metals. II. Nickel exposure of stainless steel welders--biological monitoring. *Int Arch Occup Environ Health*. 1990;62(1):7-10.
103. Biego GH, Joyeux M, Hartemann P, Debry G. Daily intake of essential minerals and metallic micropollutants from foods in France. *Sci Total Environ*. 1998;217(1-2):27-36.
104. Flyvholm MA, Nielsen GD, Andersen A. Nickel content of food and estimation of dietary intake. *Z Lebensm Unters Forsch*. 1984;179(6):427-431.
105. De Brouwere K, Buekers J, Cornelis C, Schlekot CE, Oller AR. Assessment of indirect human exposure to environmental sources of nickel: oral exposure and risk characterization for systemic effects. *Sci Total Environ*. 2012;419:25-36.
106. Larsen EH, Andersen NL, Møller A, Petersen A, Mortensen GK, Petersen J. Monitoring the content and intake of trace elements from food in Denmark. *Food Additives & Contaminants*. 2002;19(1):33-46.
107. Kristiansen J, Christensen JM, Iversen BS, Sabbioni E. Toxic trace element reference levels in blood and urine: influence of gender and lifestyle factors. *Sci Total Environ*. 1997;204(2):147-160.
108. Nielsen NH, Menne T. Allergic Contact Sensitization in an Unselected Danish Population. *Acta Derm Venereol*. 1992;72:456-460.
109. Thyssen JP, Linneberg A, Menne T, Johansen JD. The epidemiology of contact allergy in the general population--prevalence and main findings. *Contact Dermatitis*. 2007;57(5):287-299.
110. Smith-Sivertsen T, Tchachtchine V, Lund E. Environmental nickel pollution: does it protect against nickel allergy? *J Am Acad Dermatol*. 2002;46(3):460-462.
111. Myron DR, Zimmerman TJ, Shuler TR, Klevay LM, Lee DE, Nielsen FH. Intake of nickel and vanadium by humans. A survey of selected diets. *Am J Clin Nutr*. 1978;31(3):527-531.
112. Sunderman FW, Jr., Hopfer SM, Crisostomo MC, Stoeppeler M. Rapid analysis of nickel in urine by electrothermal atomic absorption spectrophotometry. *Ann Clin Lab Sci*. 1986;16(3):219-230.

113. Sunderman FW, Jr. A review of the metabolism and toxicology of nickel. *Ann Clin Lab Sci*. 1977;7(5):377-398.
114. Prystowsky SD, Allen AM, Smith RW, Nonomura JH, Odom RB, Akers WA. Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. Relationships between age, sex, history of exposure, and reactivity to standard patch tests and use tests in a general population. *Arch Dermatol*. 1979;115(8):959-962.
115. Varo P, Koivistoinen P. Mineral element composition of Finish foods. XII. General discussion and nutritional evaluation. *Acta Agric Scand Suppl*. 1980;22:165-171.
116. Kiilunen M, Jarvisalo J, Makitie O, Aitio A. Analysis, storage stability and reference values for urinary chromium and nickel. *Int Arch Occup Environ Health*. 1987;59(1):43-50.
117. Peltonen L. Nickel sensitivity in the general population. *Contact Dermatitis*. 1979;5(1):27-32.
118. Arnich N, Sirot V, Riviere G, et al. Dietary exposure to trace elements and health risk assessment in the 2nd French Total Diet Study. *Food Chem Toxicol*. 2012;50(7):2432-2449.
119. Leblanc JC, Guerin T, Noel L, Calamassi-Tran G, Volatier JL, Verger P. Dietary exposure estimates of 18 elements from the 1st French Total Diet Study. *Food Addit Contam*. 2005;22(7):624-641.
120. Noel L, Leblanc JC, Guerin T. Determination of several elements in duplicate meals from catering establishments using closed vessel microwave digestion with inductively coupled plasma mass spectrometry detection: estimation of daily dietary intake. *Food Addit Contam*. 2003;20(1):44-56.
121. Nisse C, Tagne-Fotso R, Howsam M, et al. Blood and urinary levels of metals and metalloids in the general adult population of Northern France: The IMEPOGE study, 2008-2010. *Int J Hyg Environ Health*. 2017;220(2 Pt B):341-363.
122. Hildebrand HF, Veron C, Martin P. Nickel, chromium, cobalt dental alloys and allergic reactions: an overview. *Biomaterials*. 1989;10(8):545-548.
123. Rietschel RL, Fowler JF, Warshaw EM, et al. Detection of nickel sensitivity has increased in North American patch-test patients. *Dermatitis*. 2008;19(1):16-19.
124. Nielsen NH, Menne T. Nickel sensitization and ear piercing in an unselected Danish population. Glostrup Allergy Study. *Contact Dermatitis*. 1993;29(1):16-21.
125. Ehrlich A, Kucenic M, Belsito DV. Role of body piercing in the induction of metal allergies. *Am J Contact Dermat*. 2001;12(3):151-155.
126. Bruckner AL, Weston WL, Morelli JG. Does sensitization to contact allergens begin in infancy? *Pediatrics*. 2000;105(1):e3.
127. Rigatelli G, Cardaioli P, Giordan M, et al. Nickel allergy in interatrial shunt device-based closure patients. *Congenit Heart Dis*. 2007;2(6):416-420.
128. Thyssen JP, Jakobsen SS, Engkilde K, Johansen JD, Soballe K, Menne T. The association between metal allergy, total hip arthroplasty, and revision. *Acta Orthop*. 2009;80(6):646-652.
129. Shah M, Lewis FM, Gawkrödger DJ. Nickel as an occupational allergen. A survey of 368 nickel-sensitive subjects. *Arch Dermatol*. 1998;134(10):1231-1236.
130. Kiec-Swierczynska M. Occupational allergic contact dermatitis in Lodz: 1990-1994. *Occup Med (Lond)*. 1996;46(3):205-208.
131. Schmidt M, Raghavan B, Muller V, et al. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. *Nat Immunol*. 2010;11(9):814-819.
132. Lu L, Vollmer J, Moulon C, Weltzien HU, Marrack P, Kappler J. Components of the ligand for a Ni⁺⁺ reactive human T cell clone. *J Exp Med*. 2003;197(5):567-574.
133. Thierse HJ, Moulon C, Allespach Y, et al. Metal-protein complex-mediated transport and delivery of Ni²⁺ to TCR/MHC contact sites in nickel-specific human T cell activation. *J Immunol*. 2004;172(3):1926-1934.

134. Olivarius FD, Menne T. Skin Reactivity to Metallic Cobalt in Patients with a Positive Patch Test to Cobalt Chloride. *Contact Dermatitis*. 1992;27(4):241-243.
135. Gawkrödger DJ, Vestey JP, Wong WK, Buxton PK. Contact clinic survey of nickel-sensitive subjects. *Contact Dermatitis*. 1986;14(3):165-169.
136. Kranke B, Aberer W. Multiple sensitivities to metals. *Contact Dermatitis*. 1996;34(3):225.
137. Walton S. Patch testing with copper sulphate. *Contact Dermatitis*. 1983;9(4):337.
138. Walton S. Investigation into patch testing with copper sulphate. *Contact Dermatitis*. 1983;9(1):89-90.
139. Wohrl S, Hemmer W, Focke M, Gotz M, Jarisch R. Copper allergy revisited. *J Am Acad Dermatol*. 2001;45(6):863-870.
140. 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.
141. Faurschou A, Menne T, Johansen JD, Thyssen JP. Metal allergen of the 21st century--a review on exposure, epidemiology and clinical manifestations of palladium allergy. *Contact Dermatitis*. 2011;64(4):185-195.
142. Rachmawati D, Bontkes HJ, Verstege MI, 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):331-338.
143. 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):3308-3315.
144. Pistor 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):92-95.
145. Gawkrödger DJ, Cook SW, Fell GS, Hunter JAA. Nickel Dermatitis - the Reaction to Oral Nickel Challenge. *British Journal of Dermatology*. 1986;115(1):33-38.
146. Wilhelm M, Eberwein G, Holzer J, et al. Influence of industrial sources on children's health--hot spot studies in North Rhine Westphalia, Germany. *Int J Hyg Environ Health*. 2007;210(5):591-599.
147. Mann E, Ranft U, Eberwein G, et al. Does airborne nickel exposure induce nickel sensitization? *Contact Dermatitis*. 2010;62(6):355-362.
148. Kasper-Sonnenberg M, Sugiri D, Wurzler S, et al. Prevalence of nickel sensitization and urinary nickel content of children are increased by nickel in ambient air. *Environ Res*. 2011;111(2):266-273.
149. Christiansen ES, Andersen KE, Bindselev-Jensen C, et al. Low patch test reactivity to nickel in unselected adolescents tested repeatedly with nickel in infancy. *Pediatric Allergy and Immunology*. 2016;27(6):636-639.
150. Park HY, Shearer TR. In vitro release of nickel and chromium from simulated orthodontic appliances. *Am J Orthod*. 1983;84(2):156-159.
151. Barrett RD, Bishara SE, Quinn JK. Biodegradation of orthodontic appliances. Part I. Biodegradation of nickel and chromium in vitro. *Am J Orthod Dentofacial Orthop*. 1993;103(1):8-14.
152. Kerosuo H, Moe G, Kleven E. In vitro release of nickel and chromium from different types of simulated orthodontic appliances. *Angle Orthod*. 1995;65(2):111-116.
153. Grossman Z, Paul WE. Dynamic tuning of lymphocytes: physiological basis, mechanisms, and function. *Annu Rev Immunol*. 2015;33:677-713.
154. Weissler KA, Caton AJ. The role of T-cell receptor recognition of peptide:MHC complexes in the formation and activity of Foxp3(+) regulatory T cells. *Immunol Rev*. 2014;259(1):11-22.

155. Cempel M, Nikel G. Nickel: A review of its sources and environmental toxicology. *Polish Journal of Environmental Studies*. 2006;15(3):375-382.
156. Van Hoogstraten IM, Boos C, Boden D, Von Blomberg ME, Scheper RJ, Kraal G. Oral induction of tolerance to nickel sensitization in mice. *J Invest Dermatol*. 1993;101(1):26-31.
157. Todd DJ, Burrows D. Nickel Allergy in Relationship to Previous Oral and Cutaneous Nickel Contact. *Ulster Medical Journal*. 1989;58(2):168-171.
158. Kerosuo H, Kullaa A, Kerosuo E, Kanerva L, HenstenPettersen A. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. *American Journal of Orthodontics and Dentofacial Orthopedics*. 1996;109(2):148-154.
159. Mortz CG, Lauritsen JM, Bindselev-Jensen C, Andersen KE. Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). *Acta Dermato-Venereologica*. 2002;82(5):359-364.
160. Van Hoogstraten IMW, Andersen KE, Vonblomberg BME, et al. Reduced Frequency of Nickel Allergy Upon Oral Nickel Contact at an Early Age. *Clinical and Experimental Immunology*. 1991;85(3):441-445.
161. Fors R, Stenberg B, Stenlund H, Persson M. Nickel allergy in relation to piercing and orthodontic appliances--a population study. *Contact Dermatitis*. 2012;67(6):342-350.
162. WebTM SAot. Acid Plant Database. 2016; <http://www.sulphuric-acid.com/sulphuric-acid-on-the-web/Acid%20Plants/Kola%20MMC%20-%20Pechenganickel.htm>. Accessed July 10, 2019.
163. Crawford GH, McGovern TW. Poison ivy. *N Engl J Med*. 2002;347(21):1723-1724; author reply 1723-1724.
164. Goldstein N. The ubiquitous urushiols Contact dermatitis from mango, poison ivy, and other "poison" plants. 1968. *Hawaii Med J*. 2004;63(8):231-235.
165. Knight TE, Boll P, Epstein WL, Prasad AK. Resorcinols and catechols: a clinical study of cross-sensitivity. *Am J Contact Dermat*. 1996;7(3):138-145.
166. Baer H. Chemistry and immunochemistry of poisonous Anacardiaceae. *Clin Dermatol*. 1986;4(2):152-159.
167. Symes WF, Dawson CR. Poison Ivy Urushiol. *Journal of the American Chemical Society*. 1954;76(11):2959-2963.
168. Tadjimukhamedov FK, Huang G, Ouyang Z, Cooks RG. Rapid detection of urushiol allergens of Toxicodendron genus using leaf spray mass spectrometry. *Analyst*. 2012;137(5):1082-1084.
169. Ma XM, Lu R, Miyakoshi T. Recent advances in research on lacquer allergy. *Allergol Int*. 2012;61(1):45-50.
170. Corbett MD, Billets S. Characterization of poison oak urushiol. *J Pharm Sci*. 1975;64(10):1715-1718.
171. Gross M, Baer H, Fales HM. Urushiols of Poisonous Anacardiaceae. *Phytochemistry*. 1975;14(10):2263-2266.
172. Knodler M, Reisenhauer K, Schieber A, Carle R. Quantitative determination of allergenic 5-alk(en)ylresorcinols in mango (*Mangifera indica* L.) peel, pulp, and fruit products by high-performance liquid chromatography. *J Agric Food Chem*. 2009;57(9):3639-3644.
173. Tyman JH, Kiong LS. Long chain phenols: Part XI. Composition of natural cashew nutshell liquid (*Anacardium occidentale*) from various sources. *Lipids*. 1978;13(8):525-532.
174. Kozubek A, Tyman JH. Resorcinolic Lipids, the Natural Non-isoprenoid Phenolic Amphiphiles and Their Biological Activity. *Chem Rev*. 1999;99(1):1-26.
175. Schulze-Kaysers N, Feuereisen MM, Schieber A. Phenolic compounds in edible species of the Anacardiaceae family - a review. *Rsc Advances*. 2015;5(89):73301-73314.

176. Oka K, Saito F, Yasuhara T, Sugimoto A. A study of cross-reactions between mango contact allergens and urushiol. *Contact Dermatitis*. 2004;51(5-6):292-296.
177. Guin J, Baer H, Beaman J. Toxic Anacardiaceae. In: *Dermatologic Botany*. Informa Healthcare; 1999.
178. Hurtado I. Poisonous Anacardiaceae of South America. *Clin Dermatol*. 1986;4(2):183-190.
179. Sareen R, Shah A. Hypersensitivity manifestations to the fruit mango. *Asia Pac Allergy*. 2011;1(1):43-49.
180. McGovern TW. Botanical briefs: The cashew tree--*Anacardium occidentale* L. *Cutis*. 2001;68(5):321-322.
181. Marks JG, Jr., DeMelfi T, McCarthy MA, et al. Dermatitis from cashew nuts. *J Am Acad Dermatol*. 1984;10(4):627-631.
182. Rosen T, Fordice DB. Cashew nut dermatitis. *South Med J*. 1994;87(4):543-546.
183. Thoo CH, Freeman S. Hypersensitivity reaction to the ingestion of mango flesh. *Australas J Dermatol*. 2008;49(2):116-119.
184. Wiwanitkit V. Mango dermatitis. *Indian J Dermatol*. 2008;53(3):158.
185. Kim AS, Christiansen SC. Mango: pulp fiction? *Contact Dermatitis*. 2015;73(2):123-124.
186. Itokawa H, Totsuka N, Nakahara K, Takeya K, Lepoittevin J-P, Asakawa Y. Antitumor Principles from *Ginkgo biloba* L. *CHEMICAL & PHARMACEUTICAL BULLETIN*. 1987;35(7):3016-3020.
187. Cirigottis KA, Cleaver L, Corrie JET, et al. Chemical Studies of Proteaceae .7. Examination of Woods of 17 Species for Resorcinol Derivatives. *Australian Journal of Chemistry*. 1974;27(2):234-255.
188. Baer H, Watkins RC, Kurtz AP, Byck JS, Dawson CR. Delayed contact sensitivity to catechols. 3. The relationship of side-chain length to sensitizing potency of catechols chemically related to the active principles of poison ivy. *J Immunol*. 1967;99(2):370-375.
189. Keil H, Wasserman D, Dawson CR. The Relation of Hypersensitiveness to Poison Ivy and to Cashew Nut Shell Liquid. *Science*. 1945;102(2646):279-280.
190. Keil H, Wasserman D, Dawson CR. Mango dermatitis and its relationship to poison ivy hypersensitivity. *Ann Allergy*. 1946;4:268-281.
191. Lepoittevin JP, Benezra C. Allergic contact dermatitis caused by naturally occurring quinones. *Pharm Weekbl Sci*. 1991;13(3):119-122.
192. Kligman AM. Poison ivy (*Rhus*) dermatitis; an experimental study. *AMA Arch Derm*. 1958;77(2):149-180.
193. Nakamura T. Ginkgo tree dermatitis. *Contact Dermatitis*. 1985;12(5):281-282.
194. Becker LE, Skipworth GB. Ginkgo- tree dermatitis, stomatitis, and proctitis. *JAMA*. 1975;231(11):1162-1163.
195. Menz J, Rossi ER, Taylor WC, Wall L. Contact dermatitis from *Grevillea* 'Robyn Gordon'. *Contact Dermatitis*. 1986;15(3):126-131.
196. Deibert O, Menger EF, Wigglesworth AM. Studies in specific hypersensitiveness - Relative susceptibility of the American Indian race and the white race to poison ivy. *Journal of Immunology*. 1923;8(4):287-289.
197. Kligman AM. Hyposensitization against *Rhus* dermatitis. *AMA Arch Derm*. 1958;78(1):47-72.
198. Epstein E, Claiborne ER. Racial and Environmental Factors in Susceptibility to *Rhus*. *Archives of Dermatology*. 1957;75(2):197-201.
199. Goldman L. Oral prophylaxis for poison ivy dermatitis in children. *American Journal of Diseases of Children*. 1942;64(2):241-247.
200. Schamberg JF. Desensitization of persons against ivy poison. *Journal of the American Medical Association*. 1919;73:1213-1213.

201. Epstein WL, Byers VS, Frankart W. Induction of antigen specific hyposensitization to poison oak in sensitized adults. *Arch Dermatol*. 1982;118(9):630-633.
202. Geroso AM, Elpern DJ. Some observations on mango and mokihana dermatitis from Hawaii. *Contact Dermatitis*. 1992;26(5):346-347.
203. Lampe KF. Dermatitis-producing Anacardiaceae of the Caribbean area. *Clin Dermatol*. 1986;4(2):171-182.
204. Reginella RF, Fairfield JC, Marks JG, Jr. Hyposensitization to poison ivy after working in a cashew nut shell oil processing factory. *Contact Dermatitis*. 1989;20(4):274-279.
205. Kligman AM. Cashew nut shell oil for hyposensitization against rhus dermatitis. *AMA Arch Derm*. 1958;78(3):359-363.
206. Mitchell JC, Dupuis G. Allergic contact dermatitis from sesquiterpenoids of the Compositae family of plants. *Br J Dermatol*. 1971;84(2):139-150.
207. Paulsen E. Contact sensitization from Compositae-containing herbal remedies and cosmetics. *Contact Dermatitis*. 2002;47(4):189-198.
208. Paulsen E, Hyldgaard MG, Andersen KE, Andersen F, Christensen LP. Allergenic sesquiterpene lactones from cushion bush (*Leucophyta brownii* Cass.): new and old sensitizers in a shrub-turned-a-pot plant. *Contact Dermatitis*. 2017;76(5):280-286.
209. Paulsen E. Compositae dermatitis: a survey. *Contact Dermatitis*. 1992;26(2):76-86.
210. Tschiggerl C, Bucar F. Guaianolides and volatile compounds in chamomile tea. *Plant Foods Hum Nutr*. 2012;67(2):129-135.
211. Lakshmi C, Srinivas C. Parthenium the terminator: An update. *Indian Dermatol Online J*. 2012;3(2):89-100.
212. Hausen BM, Schulz KH, Jarchow O, Klaska KH, Schmalle H. A first allergenic sesquiterpene lactone from *Chrysanthemum indicum* L.: arteglin-A. *Naturwissenschaften*. 1975;62(12):585-586.
213. Bleumink E, Mitchell JC, Geismann TA, Towers GH. Contact hypersensitivity to sesquiterpene lactones in *Chrysanthemum* dermatitis. *Contact Dermatitis*. 1976;2(2):81-88.
214. Paulsen E, El-Houri RB, Andersen KE, Christensen LP. Sunflower seeds as eliciting agents of Compositae dermatitis. *Contact Dermatitis*. 2015;72(3):172-177.
215. Ivanescu B, Miron A, Corciova A. Sesquiterpene Lactones from *Artemisia* Genus: Biological Activities and Methods of Analysis. *J Anal Methods Chem*. 2015;2015:247685.
216. Lee KH, Matsueda S, Geissman TA. Sesquiterpene Lactones of *Artemisia* - New Guaianolides from Fall Growth of *a-Douglasiana*. *Phytochemistry*. 1971;10(2):405-&.
217. Abou-Douh AM. New eudesmane derivatives and other sesquiterpenes from the epigeal parts of *Dittrichia graveolens*. *Chem Pharm Bull (Tokyo)*. 2008;56(11):1535-1545.
218. Zdero C, Bohlmann F, King RM. Eudesmane Derivatives and Other Constituents from *Apalochlamys-Spectabilis* and *Cassinia* Species. *Phytochemistry*. 1990;29(10):3201-3206.
219. Tschirritzis F, Jakupovic J, Bohlmann F. Sesquiterpene Lactones and Farnesol Derivatives from *Arctotis* and *Arctotheca* Species. *Phytochemistry*. 1990;29(1):195-203.
220. Aberham A, Cicek SS, Schneider P, Stuppner H. Analysis of Sesquiterpene Lactones, Lignans, and Flavonoids in Wormwood (*Artemisia absinthium* L.) Using High-Performance Liquid Chromatography (HPLC)-Mass Spectrometry, Reversed Phase HPLC, and HPLC-Solid Phase Extraction-Nuclear Magnetic Resonance. *Journal of Agricultural and Food Chemistry*. 2010;58(20):10817-10823.
221. Foussereau J, Muller JC, Benezra C. Contact allergy to *Frullania* and *Laurus Nobilis*: cross-sensitization and chemical structure of the allergens. *Contact Dermatitis*. 1975;1(4):223-230.
222. Matsuda H, Shimoda H, Ninomiya K, Yoshikawa M. Inhibitory mechanism of costunolide, a sesquiterpene lactone isolated from *Laurus nobilis*, on blood-ethanol elevation in rats:

- Involvement of inhibition of gastric emptying and increase in gastric juice secretion. *Alcohol and Alcoholism*. 2002;37(2):121-127.
223. Mukherjee SK. Some members of Compositae in India and their commercial exploitation for health care. *Proc Botanical Health Care*. 2010:107-112.
 224. Burry JN, Kuchel R, Reid JG, Kirk J. Australian bush dermatitis: compositae dermatitis in South Australia. *Med J Aust*. 1973;1(3):110-116.
 225. Burry JN, Kloot PM. The spread of Composite (Compositae) weeds in Australia. *Contact Dermatitis*. 1982;8(6):410-413.
 226. Mitchell JC, Fritig B, Singh B, Towers GH. Allergic contact dermatitis from Frullania and Compositae. The role of sesquiterpene lactones. *J Invest Dermatol*. 1970;54(3):233-239.
 227. Schaeffer M, Talaga P, Stampf JL, Benezra C. Cross-reaction in allergic contact dermatitis from alpha-methylene-gamma-butyrolactones: importance of the cis or trans ring junction. *Contact Dermatitis*. 1990;22(1):32-36.
 228. Schlewer G, Stampf JL, Benezra C. Synthesis of alpha-methylene-gamma-butyrolactones: a structure-activity relationship study of their allergenic power. *J Med Chem*. 1980;23(9):1031-1038.
 229. Chadwick M, Trewin H, Gawthrop F, Wagstaff C. Sesquiterpenoids lactones: benefits to plants and people. *Int J Mol Sci*. 2013;14(6):12780-12805.
 230. Paulsen E, Andersen KE. Screening for Compositae sensitization with pure allergens: implications of molecular structure, strength of reaction, and time of testing. *Contact Dermatitis*. 2011;64(2):96-103.
 231. Adekenov SM. Sesquiterpene lactones with unusual structure. Their biogenesis and biological activity. *Fitoterapia*. 2017;121:16-30.
 232. Herz W, De Vivar AR, Lakshmikantham MV. Constituents of Iva species. IV. Structure of pseudoivalin, a new guaianolide. *J Org Chem*. 1965;30(1):118-122.
 233. Dendougui H, Benayache S, Benayache F, Connolly JD. Sesquiterpene lactones from Pulicaria crispa. *Fitoterapia*. 2000;71(4):373-378.
 234. Rustaiyan A, Faramarzi S. Sesquiterpene Lactones from Serratula-Latifolia. *Phytochemistry*. 1988;27(2):479-481.
 235. Rustaiyan A, Habibi Z, Saberi M, Jakupovic J. A nor-Guaianolide and a Glaucolide-Like Eudesmanolide from Pulicaria-Undulata. *Phytochemistry*. 1991;30(7):2405-2406.
 236. Alyahya MA, Elsayed AM, Mossa JS, et al. Potential Cancer Chemopreventive and Cyto-Toxic Agents from Pulicaria-Crispa. *Journal of Natural Products*. 1988;51(3):621-624.
 237. Alyahya MA, Khafagy S, Shihata A, Kozlowski JF, Antoun MD, Cassady JM. Phytochemical and Biological Screening of Saudi Medicinal-Plants .6. Isolation of 2-Alpha-Hydroxy-Alantolactone the Antileukemic Principle of Francoeuria-Crispa. *Journal of Natural Products*. 1984;47(6):1013-1017.
 238. Bohlmann F, Knoll KH, Elemetry NA. New Seco-Sesquiterpene Lactone from Pulicaria-Crispa .214. Naturally Occurring Terpene Derivatives. *Phytochemistry*. 1979;18(7):1231-1233.
 239. Jovanovic M, Poljacki M. [Compositae dermatitis]. *Med Pregl*. 2003;56(1-2):43-49.
 240. Warshaw EM, Maibach HI, Taylor JS, et al. North American contact dermatitis group patch test results: 2011-2012. *Dermatitis*. 2015;26(1):49-59.
 241. Lundh K, Hindsen M, Gruvberger B, Moller H, Svensson A, Bruze M. Contact allergy to herbal teas derived from Asteraceae plants. *Contact Dermatitis*. 2006;54(4):196-201.
 242. Rozas-Munoz E, Lepoittevin JP, Pujol RM, Gimenez-Arnau A. Allergic contact dermatitis to plants: understanding the chemistry will help our diagnostic approach. *Actas Dermosifiliogr*. 2012;103(6):456-477.

243. Epstein S. Role of dermal sensitivity in ragweed contact dermatitis. *Arch Dermatol.* 1960;82:48-55.
244. Burry JN, Reid JG, Kirk J. Australian bush dermatitis. *Contact Dermatitis.* 1975;1(4):263-264.
245. Mitchell JC, Calnan CD. Scourge of India: Parthenium dermatitis. *Int J Dermatol.* 1978;17(4):303-304.
246. Sharma VK, Verma P. Parthenium dermatitis in India: Past, present and future. *Indian Journal of Dermatology Venereology & Leprology.* 2012;78(5):560-568.
247. Handa S, De D, Mahajan R. Airborne contact dermatitis - current perspectives in etiopathogenesis and management. *Indian Journal of Dermatology.* 2011;56(6):700-706.
248. Hausen BM, Helmke B. Butenylbithiophene, alpha-terthienyl and hydroxytremetone as contact allergens in cultivars of marigold (*Tagetes* sp.). *Contact Dermatitis.* 1995;33(1):33-37.
249. Paulsen E, Otkjaer A, Andersen KE. The coumarin herniarin as a sensitizer in German chamomile [*Chamomilla recutita* (L.) Rauschert, Compositae]. *Contact Dermatitis.* 2010;62(6):338-342.
250. Ducombs G, Benezra C, Talaga P, et al. Patch testing with the "sesquiterpene lactone mix": a marker for contact allergy to Compositae and other sesquiterpene-lactone-containing plants. A multicentre study of the EECDRG. *Contact Dermatitis.* 1990;22(5):249-252.
251. Green C, Ferguson J. Sesquiterpene lactone mix is not an adequate screen for Compositae allergy. *Contact Dermatitis.* 1994;31(3):151-153.
252. Goulden V, Wilkinson SM. Patch testing for Compositae allergy. *Br J Dermatol.* 1998;138(6):1018-1021.
253. Hausen BM. A 6-year experience with compositae mix. *Am J Contact Dermat.* 1996;7(2):94-99.
254. Paulsen E, Andersen KE. Patch testing with constituents of Compositae mixes. *Contact Dermatitis.* 2012;66(5):241-246.
255. Jacob M, Brinkmann J, Schmidt TJ. Sesquiterpene lactone mix as a diagnostic tool for Asteraceae allergic contact dermatitis: chemical explanation for its poor performance and Sesquiterpene lactone mix II as a proposed improvement. *Contact Dermatitis.* 2012;66(5):233-240.
256. van Ketel WG. Allergy to *Matricaria chamomilla*. *Contact Dermatitis.* 1987;16(1):50-51.
257. Pereira F, Santos R, Pereira A. Contact dermatitis from chamomile tea. *Contact Dermatitis.* 1997;36(6):307.
258. Rodriguez-Serna M, Sanchez-Motilla JM, Ramon R, Aliaga A. Allergic and systemic contact dermatitis from *Matricaria chamomilla* tea. *Contact Dermatitis.* 1998;39(4):192-193.
259. Paulsen E, Andersen KE, Hausen BM. Sensitization and cross-reaction patterns in Danish Compositae-allergic patients. *Contact Dermatitis.* 2001;45(4):197-204.
260. Lamminpaa A, Estlander T, Jolanki R, Kanerva L. Occupational allergic contact dermatitis caused by decorative plants. *Contact Dermatitis.* 1996;34(5):330-335.
261. Decorres LF. Contact-Dermatitis from *Frullania*, Compositae and Other Plants. *Contact Dermatitis.* 1984;11(2):74-79.
262. de la Torre Morin F, Sanchez Machin I, Garcia Robaina JC, Fernandez-Caldas E, Sanchez Trivino M. Clinical cross-reactivity between *Artemisia vulgaris* and *Matricaria chamomilla* (chamomile). *J Investig Allergol Clin Immunol.* 2001;11(2):118-122.
263. Paulsen E, Christensen LP, Hindsen M, Andersen KE. Contact sensitization to calocephalin, a sesquiterpene lactone of the guaianolide type from cushion bush (*Leucophyta brownii*, Compositae). *Contact Dermatitis.* 2013;69(5):303-310.
264. Paulsen E, Andersen KE. Colophonium and Compositae mix as markers of fragrance allergy: cross-reactivity between fragrance terpenes, colophonium and compositae plant extracts. *Contact Dermatitis.* 2005;53(5):285-291.
265. Bruynzeel DP, Diepgen TL, Andersen KE, et al. Monitoring the European standard series in 10 centres 1996-2000. *Contact Dermatitis.* 2005;53(3):146-149.

266. Cabanillas M, Fernandez-Redondo V, Toribio J. Allergic contact dermatitis to plants in a Spanish dermatology department: a 7-year review. *Contact Dermatitis*. 2006;55(2):84-91.
267. Mohammadhosseini M, Sarker SD, Akbarzadeh A. Chemical composition of the essential oils and extracts of *Achillea* species and their biological activities: A review. *J Ethnopharmacol*. 2017;199:257-315.
268. Goncalo S. Contact sensitivity to lichens and compositae in Frullania dermatitis. *Contact Dermatitis*. 1987;16(2):84-86.
269. Saraiva M, Campos Cunha I, Costa Bonito C, et al. O primeiro caso de botulismo infantil em Portugal. *Riscos e Alimentos*. 2013;6:33-34.
270. Sugai T, Takahashi Y, Okuno F. Chrysanthemum dermatitis in Japan. *Contact Dermatitis*. 1980;6(2):155.
271. Hashimoto Y, Kawada A, Aragane Y, Tezuka T. Occupational contact dermatitis from chrysanthemum in a mortician. *Contact Dermatitis*. 2003;49(2):106-107.
272. Pasricha JS, India, Department of S, Technology, All-India Institute of Medical S. *Contact dermatitis in India*. [New Delhi]: J.S. Pasricha; 1988.
273. Sharma VK. Patch testing with the European standard series and Compositae extracts in patients with airborne contact dermatitis. *Contact Dermatitis*. 2001;44(1):49-50.
274. McFadyen RE. Parthenium weed and human health in Queensland. *Aust Fam Physician*. 1995;24(8):1455-1459.
275. Bajwa AA, Chauhan BS, Farooq M, Shabbir A, Adkins SW. What do we really know about alien plant invasion? A review of the invasion mechanism of one of the world's worst weeds. *Planta*. 2016;244(1):39-57.
276. Greig JE, Carson CF, Stuckey MS, Riley TV. Prevalence of delayed hypersensitivity to the European standard series in a self-selected population. *Australas J Dermatol*. 2000;41(2):86-89.
277. Toholka R, Wang YS, Tate B, et al. The first Australian Baseline Series: Recommendations for patch testing in suspected contact dermatitis. *Australas J Dermatol*. 2015;56(2):107-115.
278. Nandakishore T, Pasricha JS. Pattern of cross-sensitivity between 4 Compositae plants, *Parthenium hysterophorus*, *Xanthium strumarium*, *Helianthus annuus* and *Chrysanthemum coronarium*, in Indian patients. *Contact Dermatitis*. 1994;30(3):162-167.
279. Sharma SC, Kaur S. Airborne contact dermatitis from Compositae plants in northern India. *Contact Dermatitis*. 1989;21(1):1-5.
280. Qian J. Eight Summer Chinese Drinks. 2015; <http://www.smartbeijing.com/articles/wellbeing/the-list-8-chinese-summer-drinks-2015-08-11>, 2017.
281. Peiser M, Tralau T, Heidler J, et al. Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects. Current knowledge assembled at an international workshop at BfR, Germany. *Cell Mol Life Sci*. 2012;69(5):763-781.
282. Wasserman RL, Hague AR, Pence DM, et al. Real-World Experience with Peanut Oral Immunotherapy: Lessons Learned From 270 Patients. *J Allergy Clin Immunol Pract*. 2019;7(2):418-426 e414.
283. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133(2):468-475.
284. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol*. 2011;127(3):654-660.
285. Ashour HM. Immune tolerance elicited via unique ocular and oral routes. *Curr Mol Med*. 2015;15(1):78-81.

- 286. Draeger H, Wu X, Roelofs-Haarhuis K, Gleichmann E. Nickel allergy versus nickel tolerance: can oral uptake of nickel protect from sensitization? *J Environ Monit.* 2004;6(12):146N-150N.
- 287. Watson ES, Murphy JC, ElSohly MA. Immunologic studies of poisonous Anacardiaceae: oral desensitization to poison ivy and oak urushiols in guinea pigs. *J Invest Dermatol.* 1983;80(3):149-155.
- 288. Lee-Kwan SH, Moore LV, Blanck HM, Harris DM, Galuska D. Disparities in State-Specific Adult Fruit and Vegetable Consumption — United States, 2015. *MMWR Morb Mortal Wkly Rep* 2017;66:1241-1247.
- 289. Centers for Disease Control and Prevention. Progress on Children Eating more Fruit, Not Vegetables. 2014; Vital Signs:<https://www.cdc.gov/vitalsigns/fruit-vegetables/index.html>, 2019.

Highlights

- Many skin sensitizers are consumed orally through foods or other sources
- Specific antigen tolerance can be induced through early oral exposure to antigen
- Developmental tolerance to nickel, urushiol and sesquiterpene lactones was explored
- Associations are established between early exposure and reduced sensitization rates
- Controlled studies with specific sensitizer early life exposure are needed

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: