15 YEARS
Science in the Service of Humanity

BfR
Bundesinstitut für Risikobewertung

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

Skin sensitisation in consumers

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Outline

1. Introduction

2. Most frequent contact sensitizers in consumers (1)

   - **Nickel** and products leading to sensitization
   - Problems identifying nickel in consumer articles
   - Specific consumer groups at risk
   - Regulation / Ni Directive, REACH, cosmetics, toys, others

3. Most frequent contact sensitizers in consumers (2)

   - **Fragrances** and products leading to sensitization
   - Problems identifying fragrances in consumer articles
   - Specific consumer groups at risk
   - Regulation / cosmetics, toys

Outline ff

4. Most frequent contact sensitizers in consumers (3)
   - **Methylisothiazolinone** and products leading to sensitization
   - Problems identifying MI (MIT) in consumer articles
   - Specific consumer groups at risk

5. Most frequent contact sensitizers in consumers (4)
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Outline ff

6. Contact sensitizers in consumers (5 / 6)

- **Chrome VI / III** and products (leather) leading to sensitization
- **Dyes** / and products (textiles) leading to sensitization

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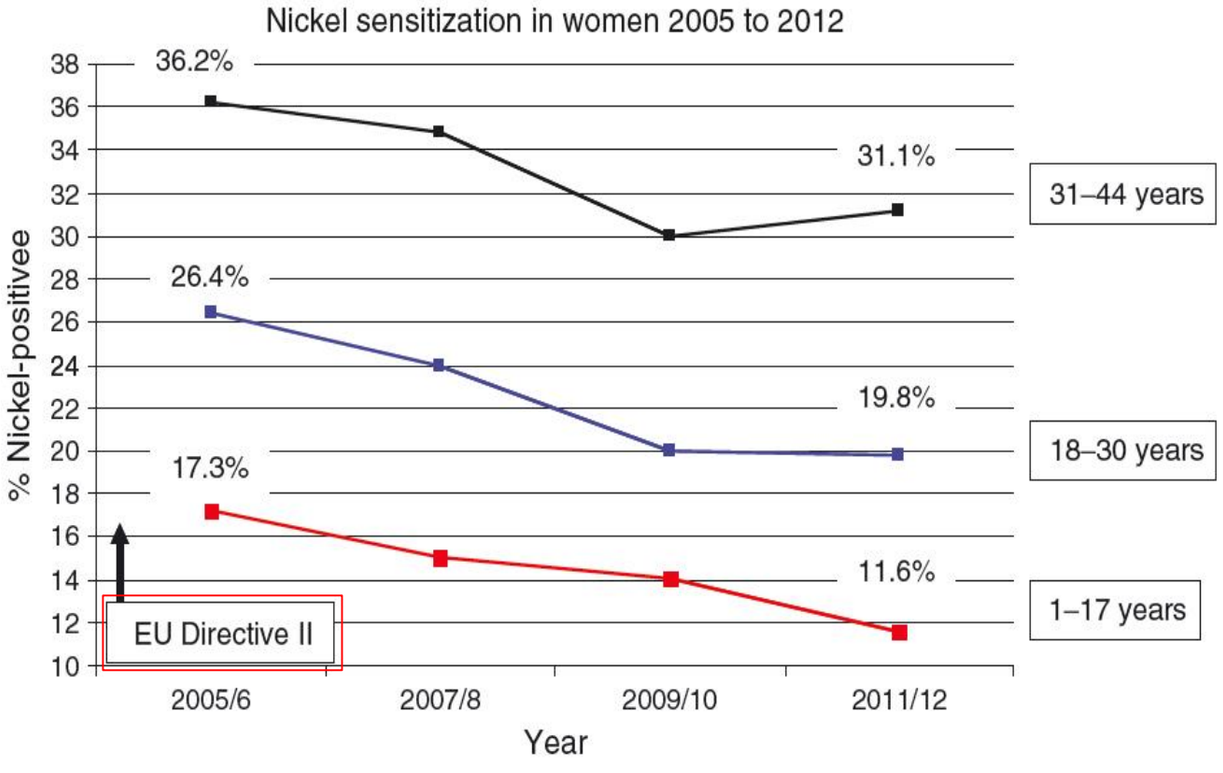
Most frequent contact sensitizers in consumers - **nickel**

Nickel Allergy	Study	Reference
29.56% sensitized to Ni; women younger than 40y old – 36,0%; older 22,8%; women 33%, men 6,1% positive.	N=547, **patients**, 2014-16; Lithuania Vilnius University Hospital. Sensitization to **cobalt** was related to sensitization to Ni. Sensitivity rate to **palladium** and Ni indicates possible cross-reactivity.	2017, Linauskienė K, BioMed Research International, ID 3964045.
14.5% (95%, CI 13.2-15.8) positive patch test Ni.	**General population**, **EU**, 5 countries; 12,377 interviews, 3,119 patch tests; EU baseline series tested: 27.0% at least 1 positive reaction; women>men.	2016, Diepgen TL, Br J Dermatol. 174:319-29.
36,7% positive for Ni, 1992 **25.8%** positive for Ni, 2001	Germany, before and after **regulation**. **Patients**.	2012, Thyssen, Con Derm, Suppl 1, 66:53-70.
17.3-17.7% positive Ni test; **15%-20%** prevalence estimated for Germany; 20% young women.	N≈10,000 per year (2006/2007), **patients.**	2008, IVDK, Germany; Weißbuch Allergie in D, 3.Aufl. 2010, Springer,
26.1% positive Ni tests (5.5 occupationally; **20.5%** non-occupational).	**Patients**. Hospital, Spain.	1993, cited by Basketter, Con Derm 28:15-25.(Romaguera 1988, Con Derm 19:52)

Most frequent contact sensitizers in consumers - **nickel**



IVDK / Germany / N=74854

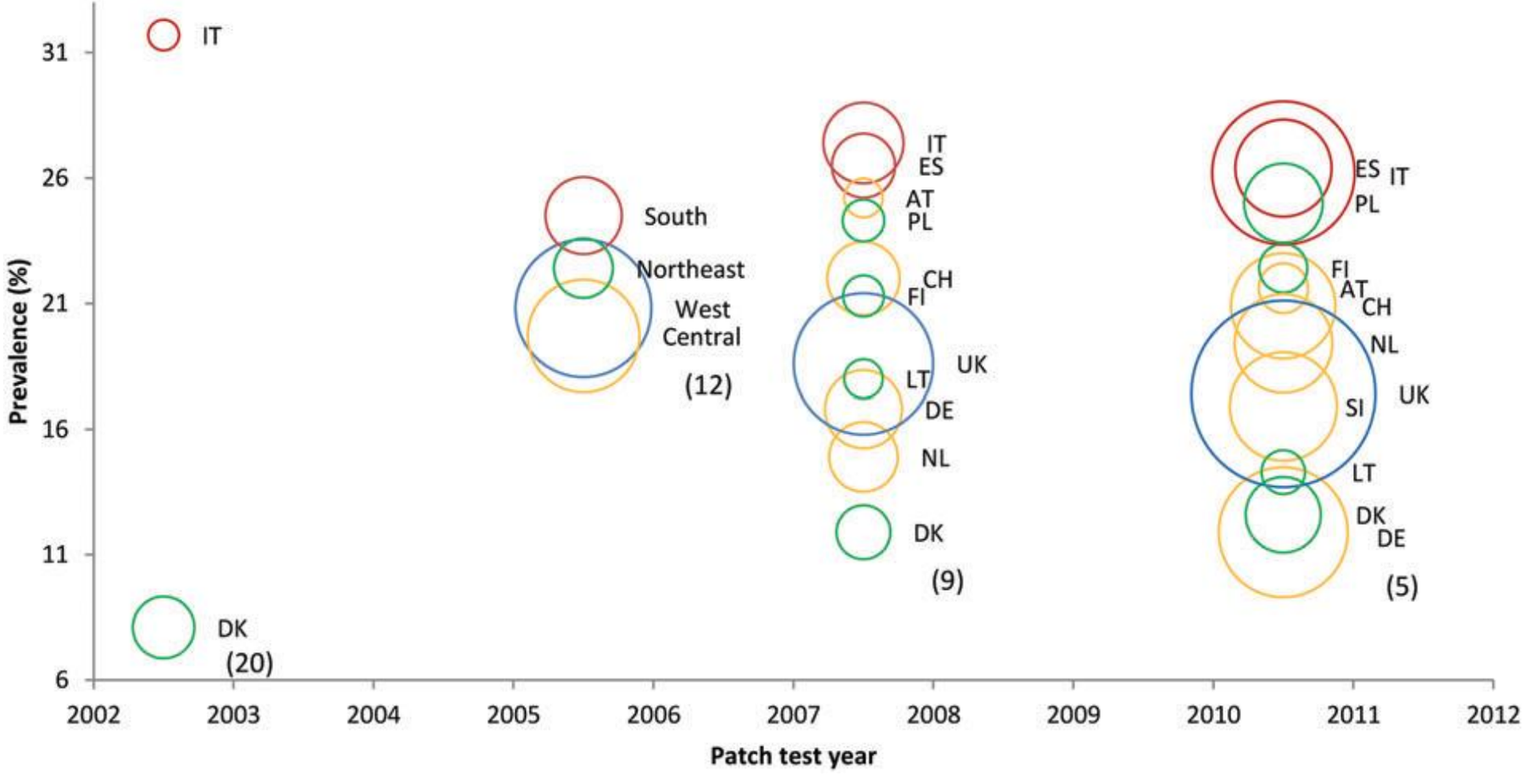
N=56550 women / trend
N=28304 men / no trend

With **>50 million nickel** allergic persons in the EU, there is a tremendous for nickel **regulation** …

Schnuch & Schwitulla, 2013, *ConDerm*, 69.251
Thierse & Luch, 2014, *UMID*, 2.87-95.

Most frequent contact sensitizer in EU - **nickel**

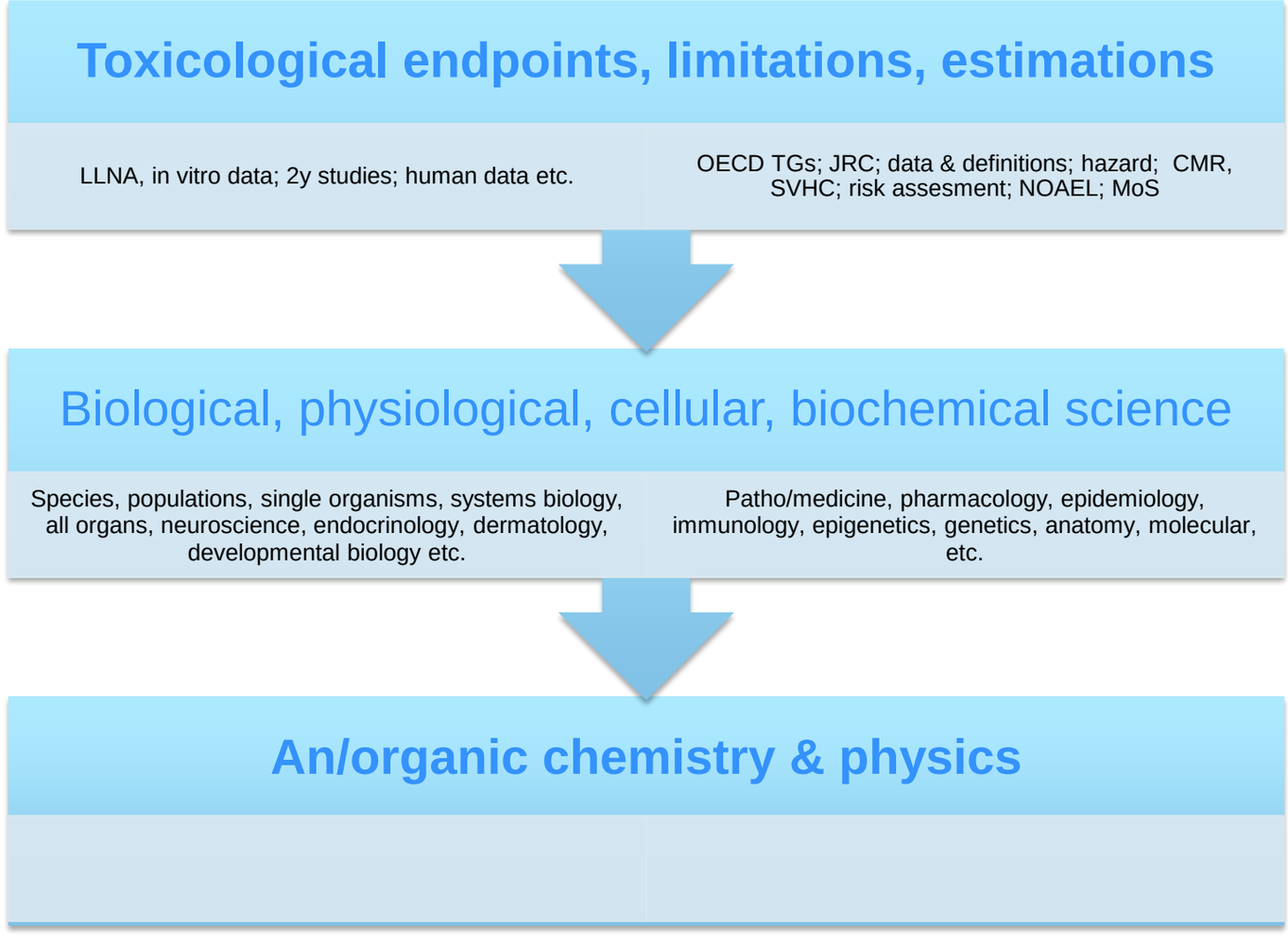
Prevalence of nickel allergy in dermatitis patients by country or region, patch tested in the European Surveillance System on Contact Allergies network (literature study).



Still a problem - shown by prevalences **of 9.8% among Swedish women aged 16–19 years** in 2011–2013 and **14–18% in adults of both sexes in other EU countries in** 2008–2011... **high prevalence (11.6%)** is seen among **girls** in 2012 in **Germany, CH and A**. Ahlström et al., 2017, *ConDerm*, 77.193

Some thoughts in between – concerning **nickel** – (outlier?)

How do we “reach” regulation? Need for quality matched regulation.



But who is **nickel ?** A short “elementary” reminder 1/4.

MW 58,7 - relative density 8,9g/cm^3.

In the periodic table of the **elements transition metal** Ni is related to Palladium (Pd), Platinum (Pt) und Darmstadtium (Ds; Eka-Platin).

natural environment

Earth - surficial shell of compression (geol.)
contains metals like **Ni** – Pd – Pt
at a mass ratio of **1000** – 1 – 1

Earth’s core: 7% Ni Iron-meteorite: up to 9%.

Earth crust: **Ni 3x > Co.**
Mining: Canada, Russia, Scandinavia, Zimbabwe, Australia

Five nickel isotopes in nature: **^{58}Ni (68%)**, ^{60}Ni (26%), ^{61}Ni (1,1% for **NMR**), ^{62}Ni (3,6%), ^{64}Ni (0,9%).

Artificial isotope as tracer: ^{58}Ni, ß$^-$radiation, t ½ = 92y.

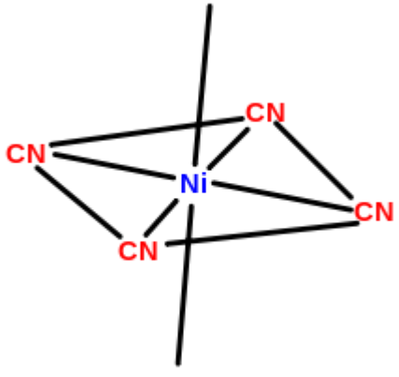
Pentlandite, $(Fe,Ni)_9S_8$
Ni-source: 90%
(iron nickel pyrites)

Ni-source: vulcany

But who is **nickel ?** A short “elementary” reminder 2/4.

Physical / chemical properties (just few)

- Melting point 1453°C; boiling point 2730°C
- **Silver-white**, ferromagnetic substance; passivating metal which can be rolled, welded, forged.
- Heat conducive and can be current-carrying.
- Resistant against water and air (oxidation).



products

Usage: steel industry = non-corrosive nickel is used in many alloys – **59% used in stainless steel** and 13% used in **300 (!) other alloys**; and 11% for galvanization.

Usage: nickel-titanium alloys. NiTi/ Nitinol.

- with temperature dependent **shape memory-effects** !
- applied in **stent-implantation** for vascular dilatation using the body’s temperature

(debate in Lancet – on stent implantation and **human ACD**)

Ref. Holleman & Wiberg, 102. Aufl., 2007. Lehrbuch Anorg. Chemie;
Marquadt, Schäfer, Barth 3.Aufl., Toxikologie, 2013.

But who is **nickel ?** A short “elementary” reminder 3/4.

higher biological species

Plants as Ni-accumulators

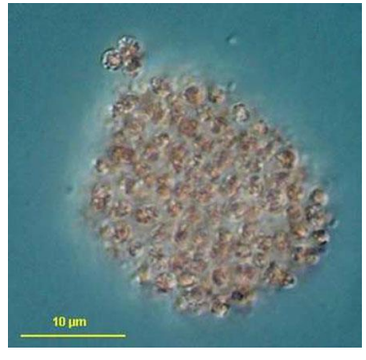
- ***Aplyssum murale***, as a “Ni hyper-accumulator” Ni concentrations **> 1000 µg / g**; **up to 0.1% Ni** in dried leaves.

- Also pines accumulate Ni up to **700-fold** if compared to soil.
- Some foods have higher Ni concentrations as well (s.b.).

Alyssum murale

Methanogenic *archaea bacteria* may tolerate up to **50g/L Ni**.

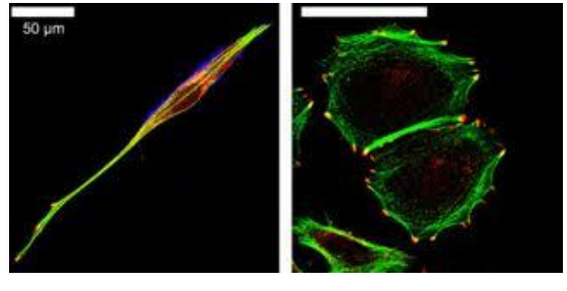
Ni-enzymes	**Function**
Urease	hydrolysis urea
Co-Dehydrogenase	catalysis (H_2 plus CO_2) bacteria
Factor F-430	catalysis (H_2 plus CO_2) methanogenic bacteria
Hydrogenases	catalysis (H_2 to $2H^+ + 2e$)
Superoxiddismutase	catalysis (O°_2 -> $H_2O_2 + O_2$)



Sulfur bacteria

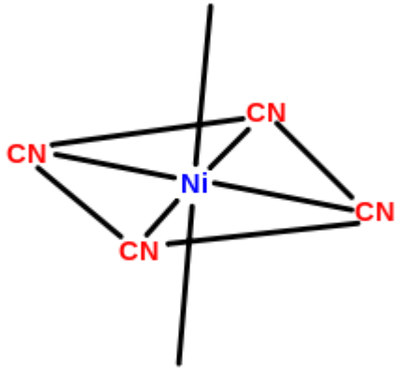
Fungi / invertebrates may have Ni-dependent ureases / hydrogenases.

Human adaptive immune response against **immunodominat Ni-containing** Urease from ***H.pylori*** (**infected cells ->**).



But who is **nickel ?** A short “elementary” reminder 4/4.

1. It’s very specific: a metal element as **non-classical HUMAN contact allergen**
2. In the human body, Ni **between** health & disease:
   a. an **ultra-trace** element / Ni homoeostasis? (A. Hartwig)
   b. between **foreign / self**, need for new immunological concept
   c. <150µM: immunological effect, T cell activation (Weltzien)
   d. >250µM: cell death effect in monocytes (Jakob)
   e. > 1mM binding to TLR4 (Schmidt)
   f. xxxx t**oxicological** effect on DNA repair mechanism; CMR 2.



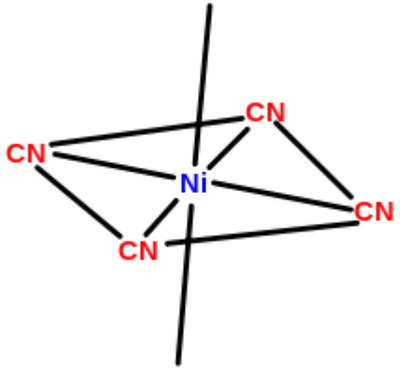
disease

Differential nickel uptake (References: accidents, post mortem; application of isotopes; animals)		
LUNG	**GUT**	**SKIN**
Nickel inhalation – 20-35% reabsorbed	Water soluble Ni, higher rate of uptake. **Food.**	**Hair follicele** **Perspiratory glands**
-> industrial worker	-> skin reaction possible /Ni	-> **ACD**

Nickel in human body		Serum: Zn, Fe, Cu 100 µg/L
0.6-0.75 µg/L **SERUM** / Albumin bd. 3 – 11µg/L Refinery workers 1-28 µg/L (< 1) **WHOLE BLOOD**	**0.1-10 µg/d URIN** 0,1- 8 µg/L 8- 800 µg/L Refinery workers 100- 2500µg/L Ni carbonyl pois.	**260** ±120 **µg/d** **FECES** **0.01- 1.8 µg/g** **HAIR**

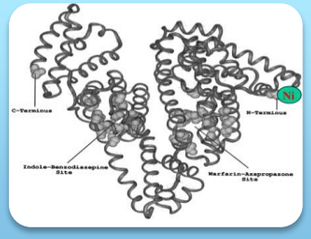
Nickel with molecular/cellular - **immune/**toxic function

complex formation
in
biological system



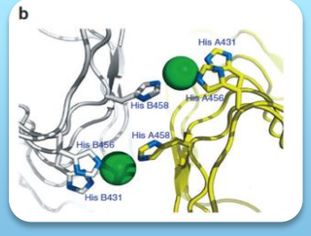
nickel ligands,
binding amino acid,

metallotransporters,
channels,
hapten-like,
neo-epitopes,
ACD



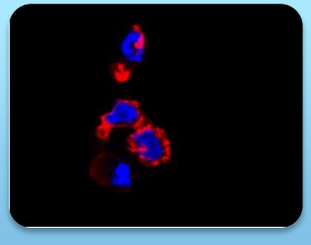
Binding to selfprotein ->ACD

- Skin protein, sweat protein (AOP-1: MIE; Ni binding in skin)
- Albumin-Ni complex -> activate T cells (AOP-4)
- Thierse et al., 2004; HSA function also shown for PPD, Coulter, 2008; for DNBS, Dietz, 2010; Heiss, 2005, Ni binding molecules in B cells)



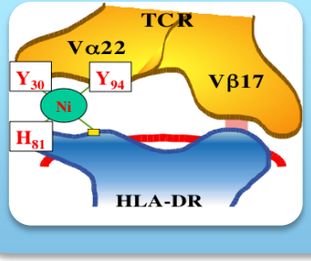
Binding to TLR-4

- Costimulatory signal -> ACD
- Allergen/hapten -> microbial target; role for HIS



Additional nickel effects

- Monocyte cell death(independent of caspase-3; Jakob, 2017)
- ROS (irritant effect; contributes to ACD)
- Toxic effects on higher dose



Direct ligand formation at T cell receptor - MHC

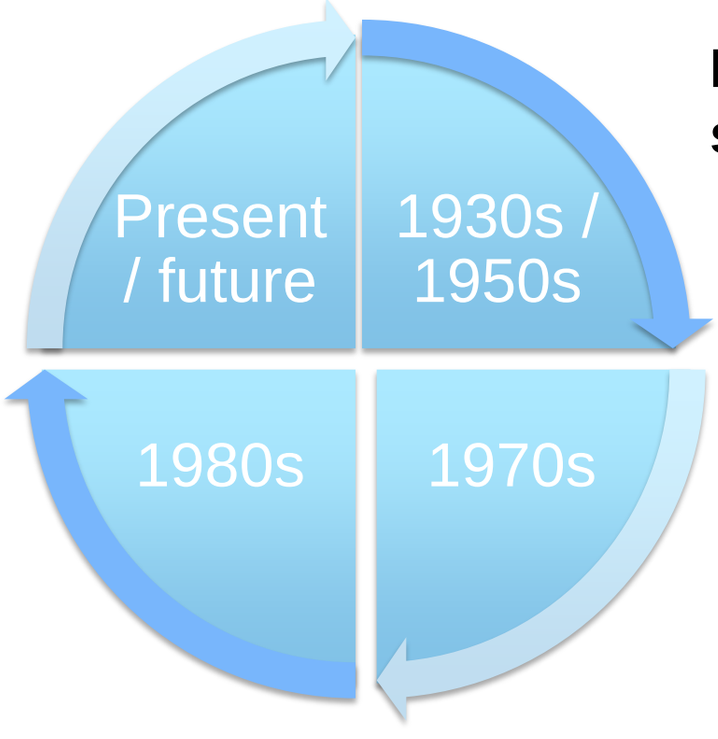
- Direct activation of human T cell clones (Gamerdinger, 2003; Li, 2003)
- One way of polyclonal T cell activation -> ACD

Consumer products have a pivotal role for **Ni** in ACD

"Historically, **nickel** skin contact sites have changed with (women's) fashions".

Body-piercings,
(low cost) **jewelry …**

tattoos,
toys …



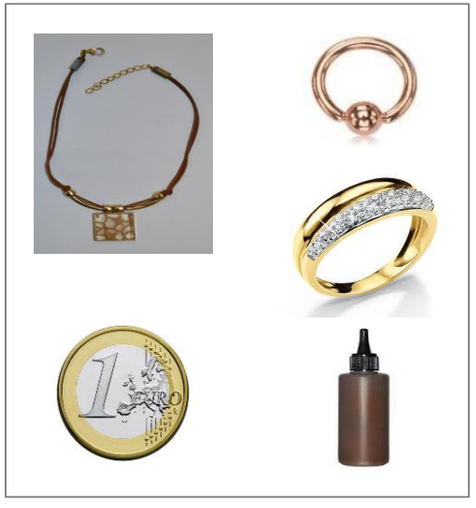
Nickel plated stocking suspender claps.

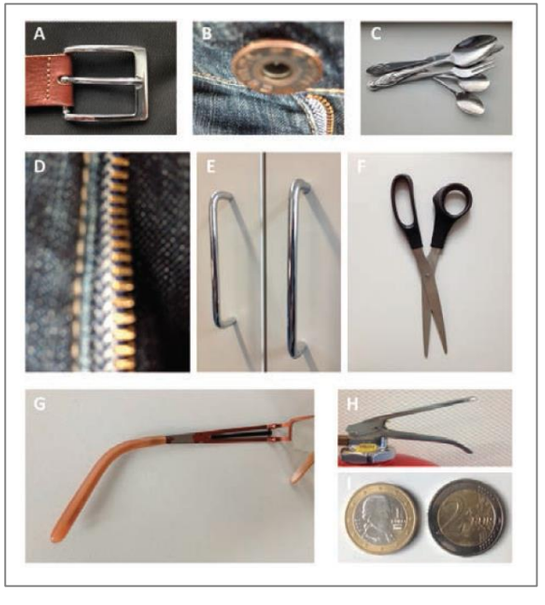
Ear-piercings and jewelry.

Studs, and metal buttons and zippers in blue jeans.

Johansen JD, Frosch PJ, Lepoittevin JP, Contact Dermatitis, 2011,Springer, Berlin.
Wells GC, 1956, The British J of Derm, 68.237-42.

Consumer products have a pivotal role for **Ni** in ACD





Products in traditional nickel exposure

... but amount of nickel migration/release may differ between **utilized and unutilized** products … jewelry … eyeglasses.

… consumer groups at risk (?)

IMPLANTS & PROTHESES

(a) Orthopedic
(b) Dental
(c) Cardiac

(a) Jewelry
(b) Belts
(c) Glasses
(d) Zippers
(e) Rivets
(f) Snaps
(g) Buttons
(h) Accessories
(i) Make-up
(j) Cleaners and detergents
(k) Tools
(l) Keys
(m) Coins
(n) Mobile phones
(o) Computers
(p) Scissors
(q) Watches
(r) Music instruments

Thierse & Luch, 2014, UMID, 2:87-95. Hamann D. et al., 2013, Current Opinion in Allergy and Clinical Immunology, 13(5):525-30.

Identifying sensitizer **Ni** released by consumer products

Method 1

Method	Comment	References
Dimethylglyoxime (**DMG**) spot test 	Rapid analysis. Detection of 10ppm nickel or 0.5mg nickel/cm2/week. High specificity (97,5%) but a **modest sensitivity** (59,3%) – if compared to EN 1811. -> Past exposure studies may have underestimated nickel release from consumer products. (Thyssen, 2010) "… **was the reference test for the Danish nickel regulation** but was replaced with a laboratory test, the European Standard (EN1811), in the EU Nickel Directive."	DIN / EN as pretest (2017) Menne T et al. 1987, Contact Dermatitis, 16:255–259. Thyssen JP et al. 2010, Contact Dermatitis 62:279–288. Herro EM, Jacob SE, 2012, Dermatitis. 23:183–4. **Test principle is not new** Minster JT, 1946, Analyst. 71:424-8. Choman BR, 1962, Stain Technol. 37:325-6. Shore RN, Binnick S, 1977, Arch Dermatol. 113:1734.

Identifying sensitizer **Ni** released by consumer products

Methods 2 and 3

Method	Comment	References
ICP-MS (inductively coupled plasma mass spectrometry), ICP-OES or GF-AAS (Graphite furnace atomic absorption spectrometry)	According DIN EN 1811, DIN EN 16128, analytical method **capable to determine** concentrations of **0.01mg/L Ni**.	DIN EN 1811 (2012-10) DIN EN 16128 (2016-02)
ICP-MS	**Detection limit** Blood **0.3-0.4 µg/L** Urine **0.2-0.3 µg/L**	2017, Saravanabhavan G, Internat J Hyg and Env Health 220.189–200

= >> **Skin related**: usage of **artificial sweat** for product contact.

Limiting the risk to consumers: The EU **Ni** Directive

Table 1. The original European Union Nickel Directive and reference methods

		CEN standard
Part 1	Original requirement (before 2005): Nickel was prohibited in postassemblies which were inserted into pierced ears and other pierced parts of the human body during epithelialization of the wound, unless they were homogenous and the nickel concentration was below 0.05%	EN1810 (Flame Atomic Absorption Spectrometry. Nickel content is expressed as mass of nickel to total mass)
	New requirement (from 2005): Nickel release from all items inserted into pierced parts of the body (not only during epithelialization after piercing) should be less than 0.2 $\mu g/cm^2$/week	EN 1811 [Items under investigation are placed in artificial sweat for 1 week and the concentration of dissolved nickel in the solution is determined by atomic absorption spectrometry (or other methodology) and expressed in $\mu g/cm^2$/week]
Part 2	Nickel may not be used in products intended to come into direct and prolonged contact with the skin such as earrings, necklaces, bracelets, chains, anklets, finger rings, spectacle frames, wrist-watch cases, watch straps, zippers, buttons and mobile phones if nickel release from the parts coming into direct and prolonged contact with the skin is greater than 0.5 $\mu g/cm^2$/week	EN 1811.
Part 3	Nickel is prohibited in products such as those listed under point 2 if these have a coating and if these do not fulfill the requirement under point 2 for a period of at least 2 years of normal use of the product	EN 12 472 (Method for simulation of wear and corrosion for the detection of nickel release from coated items. The item under investigation is exposed to a corrosive atmosphere and then placed in a container together with abrasive chips, water and a wetting agent. The container is rotated to smooth the surface and abrade the coating. Finally, the item is subjected to the EN 1811)

Hamann D. et al., 2013, Current Opinion in Allergy and Clinical Immunology, 13(5):525-30.

Fully harmonized EU **Ni** regulations ?

Regulation concerning REACH
Annex XVII / Restrictions
1907/2006 Entry 27

- (1)(a) Shall not be used – pierced- unless rate of Ni release is less than **0.2µg/cm2/week** (migration limit)
- (b) … in articles coming into direct and prolonged contact with the skin **such as** ... if rate is greater than **0.5µg/cm2/week**
- (c) = (b) but with non-Ni coating, such coating is sufficient to ensure …that rate of Ni release coming in contact … will not exceed 0.5µg/cm2/week for a period of 2 years.
- (2) Articles shall not be placed on market unless they conform ..
- (3) CEN methods shall be used … conformity.

Regulation on cosmetic products
Annex II / Substances prohibited
1223/2009

- e.g. Reference number 455, Nickel monoxide; RN 1093, Nickel.
- Substances classified as CMR substances ... However, such substances may be used in cosmetic products by way of exception where, subsequent to their classification as CMR substances of category 1A or 1B under Part 3 of Annex VI to Regulation (EC) No 1272/2008, all of the following conditions are fulfilled: ... (a) they comply with the food safety requirements; (b) there are no suitable alternative substances available; (d) they have been evaluated and found safe by the **SCCS**
- International Nomenclature of Cosmetic Ingredients (INCI) – labelling cosmetics.
- **However**: Mascara: **5.07-46.6 mg/kg** Ni (Borowska, 2015, J Appl Toxicol 35: 551–572)

Directive on safety of Toys
Annex II /Safety requirements
48/2009

- General part of directive, paragraph 21, CMR and REACH, ... should, however, also be adapted to the particular needs of children, who are a vulnerable group of consumers... Nickel (CMR 2) in stainless steel has proven to be safe, and consequently it is appropriate that it can be used in toys.
- Annex II: ..... following **migration limits**, from toys or components of toys, shall not be exceeded: (a) Nickel - in dry, brittle, powder-like or pliable toy material – **75 mg/kg**; (b) Nickel - in liquid or sticky toy material – **18.8 mg/kg**; (c) Nickel - in scraped-off toy material, **930 mg/kg**.

Fully Harmonized EU **Ni** regulations ?

Role of new guidance document 2017- **drafted by ECHA for EU-COM**

Prolonged skin contact

Method	Comment	References
3x 10 min 1x 30 min As prolonged skin contact.	Additional data on sensitization time points / mechanism in humans seem to be necessary.	So far ECHA, Plus 2 publication Plus unpublished data.

= >> **Starting point, 1994**: Regulation based on clinical symptoms from earrings etc.

= >> **Today, 2017 ff:** New products are added based on assumptions (?)of their role in ACD.

= >> **Discussion**: Are clearer criteria (e.g. clinical data) needed for categorizing sensitizers and sensitizing products, in relation to “prolonged skin contact” ?

EU **Ni** regulations – future perspectives

Integrated approach on harmonized regulations

= >> **Panel**.

= >> Is there any **overestimation** (patch test and products potentially sensitizing humans; Manchester 2016)? Adaptations to new insights?

Most frequent contact sensitizers in consumers - **fragrances**

Fragrance-Mix I / II	Study	Reference
7.8% FM I positive. Trend women 2011-15 **8.0% to 10.4 % FM I** positive. Trend men 2011-15 **4.4% to 7.3 % FM I** positive	N=24 168, **patients**, 1986-2015; Department of Dermatology and Allergy, Copenhagen University Hospital Herlev-Gentofte, Denmark. 2006-10 vs 2011-15 significant changes: >40y women from 9.7% to 12.6% pos. >40y men from 5.2%. to 8.5% pos.	2017, Bennike NH, British Journal of Dermatology, 176:1035-1041.
1.8% FM I positive. 1.9% FM II positive	**General population**, **EU**, 5 countries; 12,377 interviews, 3,119 patch tests.	2016, Diepgen TL, Br J Dermatol. 173:1358-9.
2.6% FM I petrolatum; positive. 1.9% FM II petrolatum; positive.	**General population**, **EU**, 5 countries; 12,377 interviews, 3,119 patch tests; prevalence to fragr. in women about twice those in men.	2015, Diepgen TL, Br J Dermatol. 174:319-29.
8.4% FM I 5.5% FM II	Sensitization prevalence of patients. Hitlist.	2012, Schnuch, All@rgy, 67.847-857.
6.6% FM I positive (2006/7). 4.9% FM II positive (2006). 4.6% FM II positive (2007).	N≈10,000 per year (2006/2007), **patients.**	2008, IVDK, Germany; Weißbuch Allergie in D, 3.Aufl. 2010, Springer,

Fragrance mix I – **FM I** – a short reminder.

Consisting of **seven fragrance** chemicals (amyl cinnamal, cinnamyl alcohol, cinnamal, eugenol, geraniol, hydroxy-citronellal and isoeugenol) and the natural extract Evernia prunastri (oakmoss absolute), FMI has remained unchanged in composition **since 1984,** when the concentration of the individual constituents was reduced from 2% **to 1%,** and the emulsifier **sorbitan sesquioleate (SSO)** was **added** to the mix.

Amyl cinnamal

Cinnamyl alcohol

Cinnamal

Eugenol

Geraniol

Hydroxycitronellal

Isoeugenol

Extract Evernia prunastri

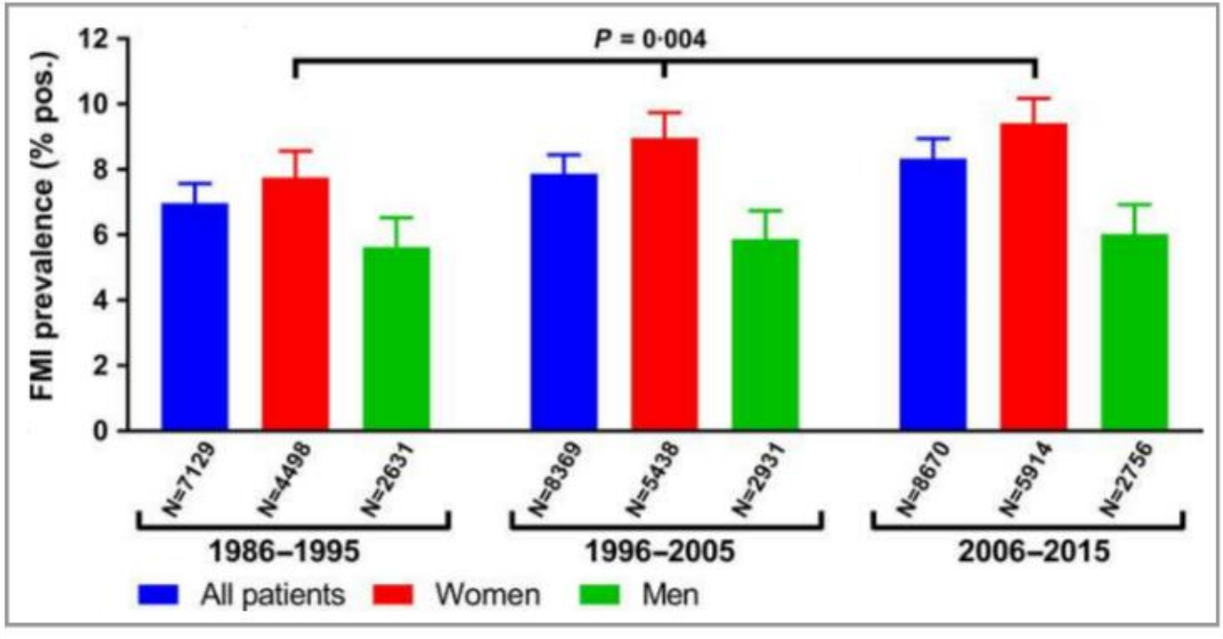
There are more than 5000 different fragrances that are in use today.

FM I => **8**/5000

Critical: Low level of biomonotoring for each substance. Gap of information.

https://www.dermnetnz.org

Most frequent contact sensitizers in consumers - **fragrances**



DK

women / trend
men / no trend

Overall trends in contact allergy to **fragrance mix I** over three decades, stratified by sex, see text for additional details.

Bennike et al. 2017, *Brit J Derm*, 176.1035-41.

Consumer products and **FM I** 1/2

"Contact allergy to fragrances is very common, and a prevalence rate of up to 14% has been reported in studies of clinical populations".

Fragrance	Used/found
Cinnamic alcohol. Odour of hyacinth Ester in natural fragrances such as Balsam of Peru, storax, cinnamon leaves, hyacinth oil and propolis	Fragrance **in perfumes, cosmetics, deodorants, paper, laundry detergent products, toilet soap**, personal hygiene products. Flavouring in **beverages** (cola, bitters, Vermouth), chewing gums, toothpaste and mouthwash.
Cinnamic aldehyde Warm spicy odour with a taste of cinnamon. Constituent of cinnamon oil.	
Eugenol, powerful spicy odour of clove with a pungent taste. Found in oils of clove and cinnamon leaf, also found in roses, carnations, hyacinths and violets.	Fragrance in perfume, cosmetics, colognes, toilet waters, **hair cosmetics, aftershave**, personal hygiene products. Flavouring in toothpaste, mouthwash and food flavourings. Used **in dental** cement and packing agents thus giving the characteristic odour ... Inherent **insecticidal and fungicidal** properties — used to preserve meats and other foods. **Pharmaceutical** creams and lotions for its **antiseptic properties**.
Isoeugenol. Odour of clove weaker than that of eugenol. Constituent of nutmeg oil and ylang ylang oil; isomerization of eugenol.	

Consumer products and **FM I** 2/2

Fragrance	Used/found
Geraniol. Sweet floral odour of rose Constitutes a large portion of rose and palmarose oil, geranium oil, lavender oil, jasmine oil and citronella oil Present in over 250 essential oils	**Most widely used** fragrance in perfumes, colognes, facial make-up and skin care products.
Alpha amyl cinnamic alcohol Intense odour of jasmine. Synthetic essential oil	Found in **perfumes, soaps, cosmetics** and toothpaste
Hydroxycitronellal. Sweet fresh odour of lily of the valley. **Synthetic floral fragrance**	**Found in perfumes, soaps,** cosmetics, eye cream, aftershaves Also used in **insecticides** and antiseptics.
Oak moss absolute. Earthy, woody, masculine odour Essential oil produced by solvent extraction of tree lichen.	Commonly used in **colognes, aftershaves** and scented products for men

Allergenic fragrance chemicals are indeed ubiquitous in our environment, not only in fine fragrances, but also in a wide range of **cosmetic, household**- and **industrial products** and **even topical medicaments**.

Nardelli, 2008, Con Derm 58.134

https://www.dermnetnz.org

Consumer products and fragrances

Lysmeral,
synthetic fragrance used **in** a variety of consumer products like **perfumes**, **after shave lotions**, **COSMETICS** and others, e.g. **cleaning agents**, air care products.

→ **Products in traditional fragrance exposure**

Limonene-containing pollutants.

Group at risk

58 Allergenic fragrances in **plush TOYS**

… children …

… consumer groups at risk …

Linalool- a significant contact sensitizer **after** air exposure.

Moisturizer use**,**
e.g. whole-body moisturizing products (at least **1 fragrance** cross-reactor or botanical ingredient)

Indoor dust with fragrances.

Products for the **hair, face, buccal hygiene, hands, feet, body, shaving** and depilation, **sunscreens, deodorants** as well as **products** specifically intended for **babies.**

Wang, 2017, J Sep Science, 1615-9306,
doi: 10.1002/jssc.201700556.

Identifying sensitizer **fragrances** released by consumer products

Method 1 & 2

Method	Comment	References
HS GC-MS	Sufficient sensitivity (limits of quantification: **0.02-10 mg/kg**) for 58 fragrances, indicating its accuracy and reliability. The average recoveries ranged from 71.3 to 137.4%, and the relative standard deviation (n = 6) varied from 1.1 to 18.0%. … determining the semi-volatile analytes in toys, textiles, and other products. This study is the first to meet the requirement for **simultaneously** determining **66 fragrances**, except for eight natural extracts restricted by the European Toy Safety Directive 2009/48/EC.	Wang Z, J Sep Sci. 2017 Nov 17. doi: 10.1002/jssc.201700556.
GC with ion trap MS/MS	Simultaneous determination of **48 fragrance allergens** in four types of toys (plastic toys, play clays, plush toys, and paper toys) based on GC with ion trap MS/MS. (Limitation for natural products).	Lv Q, J Sep Sci. 2013 Nov;36(21-22):3534-49. doi: 10.1002/jssc.201300586.

Identifying sensitizer **fragrances** released by consumer products

Method 3

Method	Comment	References
UPLC-MS/MS	**Lysmeral** (2-(4-tert-Butylbenzyl)propionalde-hyde), lilial or lily-aldehyde (CAS No 80-54-6) is a synthetic fragrance. Metabolismus study, human biomonitoring, urine samples. We estimated median exposure doses for lysmeral in a group of 40 human volunteers from the general population of approximately 140-220µg per day.	2017, Scherer M, Int J Hyg Environ Health 220:123-129.

=>> DIN / EN Development.

EU **fragrances** regulations

Regulation on cosmetic products / Annex II / Substances labbelled 1223/2009	**EU Directive on safety of Toys Annex II /Safety requirements 48/2009**
26 substances are required to be **labelled in cosmetics**. Most occur also in children's cosmetic.	Toys **shall not** contain the following allergenic fragrances: **n=55.**
	However, the presence of traces shall be **allowed** provided that such presence is **technically unavoidable** under GMP and does **not exceed 100 mg/kg.**
	Allergenic fragrances **shall be listed** on the toy if added to a toy, as such, at concentrations **exceeding 100 mg/kg in** the toy or components thereof (n=11)

EU **fragrances** regulations – future perspectives

Integrated approach on harmonized regulations

= >> **Panel**.

= >> Is there any under-estimation ? Question on availability of pure isolated substances for patch testing? Human data? Limited data on single substance reactivity?

= >> How to address concerns related to fragrances / MIX I in relation to regulation of nickel? Other contact allergens?

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Thank you for your attention !

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