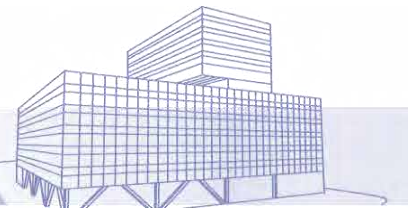




""You only notice it once you realize it"  
*Health effects of exposure to 'medical devices'*

Albert Feilzer

Spring Symposium  
Sections Pharmaceutical Toxicology & Risk Assessment  
"Extractables and Leachables: a concern for our health?"



Disclaimer: I have no conflict of interest!



# Medical-Dental-Material Interaction

- 1982 Dentist
- 1983 -1999 own clinic
- Many patients suffering from Hepatitis C, HIV & AIDS
- 1982- now (part-time → full-time) ACTA
  - Researcher Material Sciences
  - Director of ACTA's Dental Hospital
  - 1999 Full Professor
  - Dean (2009-2019)
  - Full Professor (chair department Restorative and Reconstructive Oral Care)
- 2000-2006 endowed professorship Standardization Rotterdam School of Management
- December 2024, retired



# Topics to be addressed today

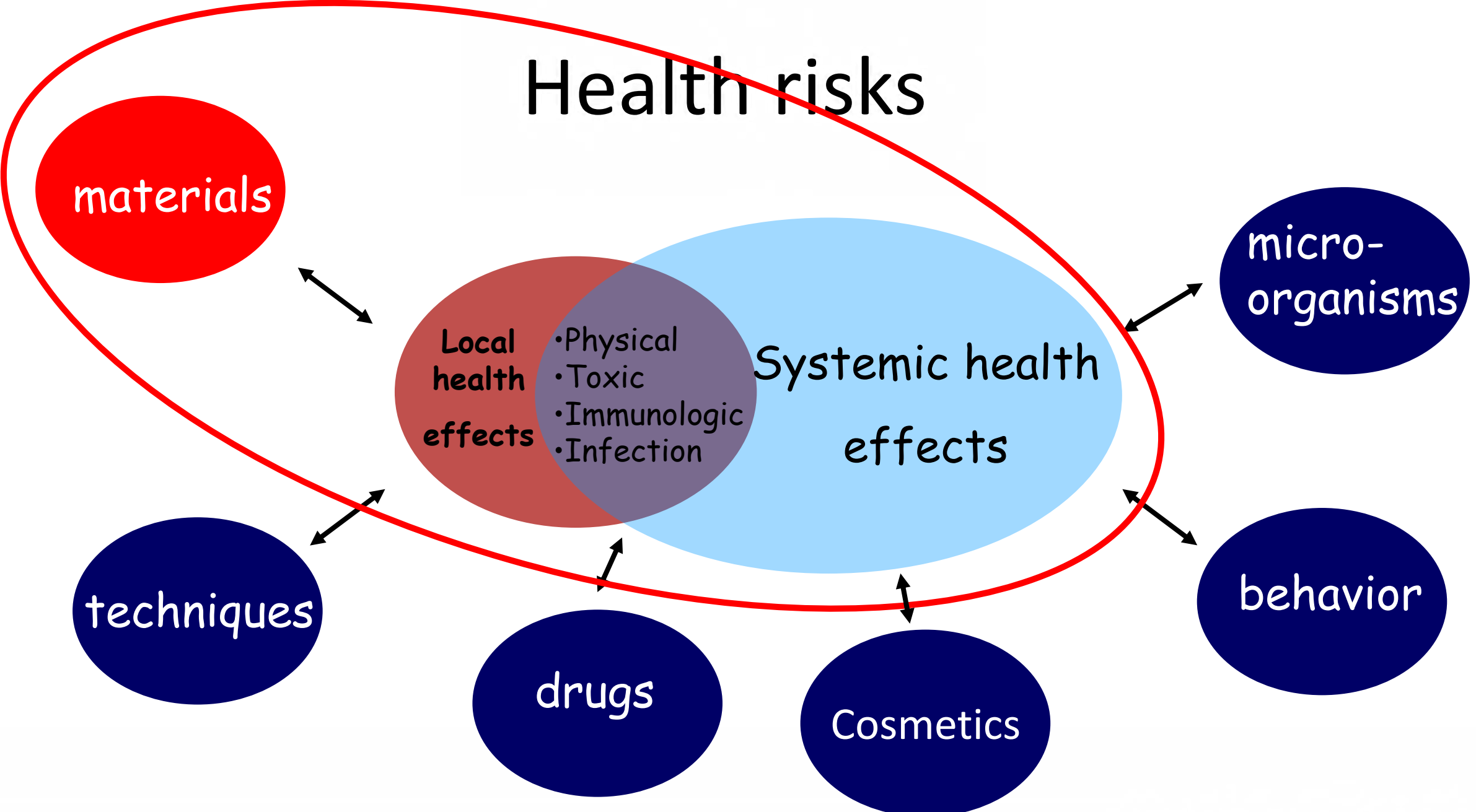
1. Legislation to ensure safety of medical devices
2. Some background on safety of (oral) medical devices

# Exposure to foreign materials

- Medical devices
- Pharmaceuticals
- Cosmetics



# Health risks



# Adverse Event of Medical Devices

*An unexpected event that occurs during or result from 'patient use' of a medical device*

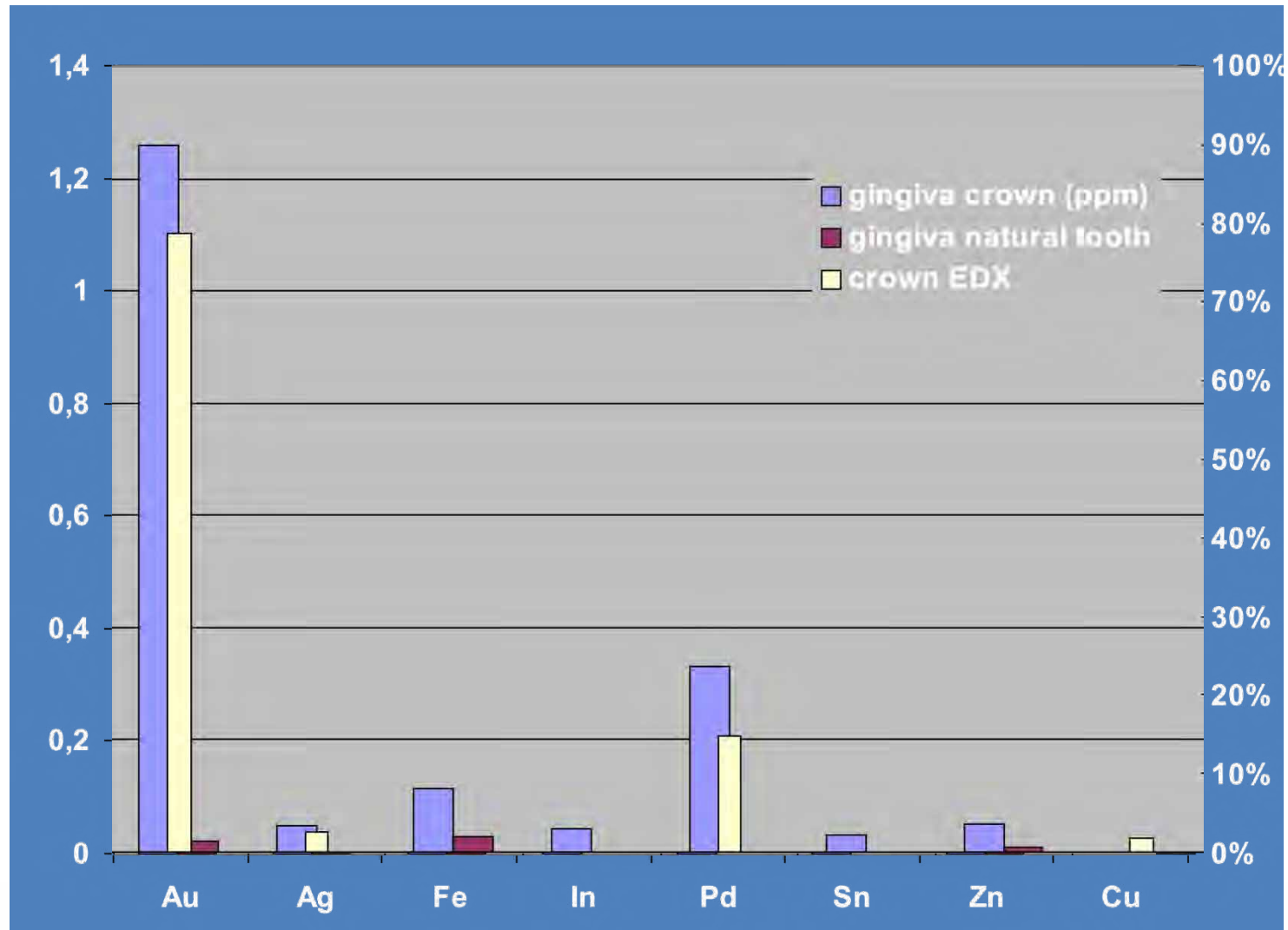
# The mouth is a battleground where biological, chemical, and physical forces interact constantly

- **Mechanical Stress:** Chewing, grinding, and biting exert significant pressure on teeth and soft tissues.
- **Chemical Exposure:** The mouth encounters acidic and enzymatic substances from food, beverages, and saliva
- **Microbial Activity:** It hosts a diverse microbiome
- **Temperature Variations:** Hot and cold foods create rapid temperature shifts that can stress dental materials and tissues.
- **Saliva's Role:** Saliva helps neutralize acids and protect teeth, but it also contains enzymes that break down food and attack tooth restorations and immunological proteins, such as immunoglobulins that are supposed to keep the microbiome healthy.



# Uptake of orally applied metals in the body





# Skin- versus oral mucosa-barrier

## Permeability of Human Skin and Oral Mucosa to Ovalbumin

Region	Kp
Skin	25.5 ± 3.2
Palate	186.3 ± 27.4
Buccal mucosa	177.9 ± 8.7
Lateral border of the tongue	301.4 ± 33.1
Floor of the mouth	426.2 ± 53.3

*Note:* Kp values ( $\times 10^{-7} \pm \text{SEM cm/min}$ )  
(n = 58).

From Lesch, Squier, and Williams, unpublished data.

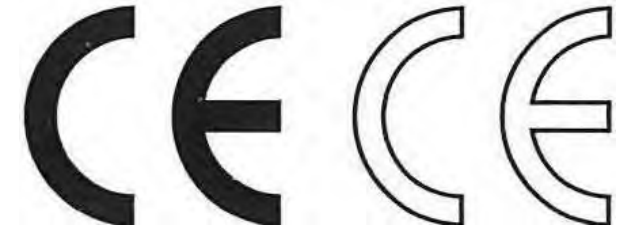
# Regulations

- US → Food and Drug Administration (FDA)
- Europe → Medical Device Directive (MDD) replaced by Medical Device Regulation (MDR)
- Asia → China, Japan, and India have their own frameworks



# CE-marking

- A **CE mark** (Conformité Européenne) is a certification that indicates a product complies with European Union (EU) safety, health, and environmental protection requirements.
- It is mandatory for many products, including **medical devices and cosmetics** when they are placed on the EU market.
- Obtaining the CE mark guarantees access to the entire European market.



# From MDD to MDR

**Directive:** A directive sets out a goal that all EU countries must achieve, but each country can decide how to implement it through national laws.

**Regulation:** A regulation is immediately binding across all member states without the need for separate national laws. It applies uniformly, ensuring consistency.

# Why a change from MDD to MDR?

## PIP Breast Implants

2013: Jean-Claude Mas was sent to prison for four years.

2021: French court found the notified body 'TUV Rheinland' negligent and partially liable for damages.



## *Essure birth control device (Bayer)*

August 2020, Bayer agreed to pay \$1.6 billion to settle tens of thousands of these claims.

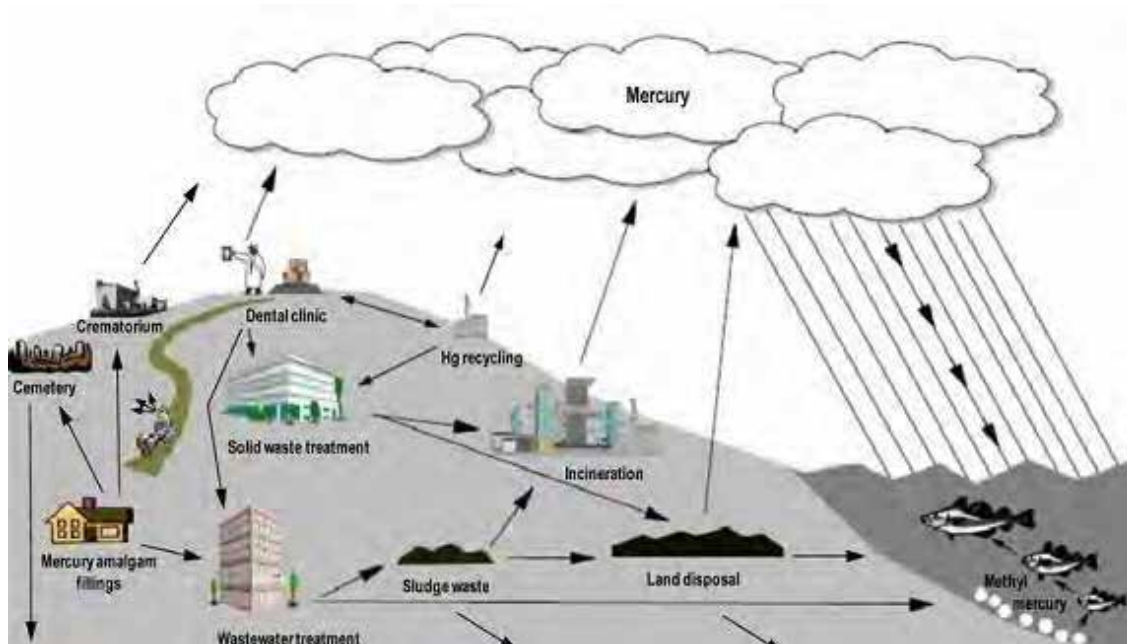


# European Medical Device Regulation (MDR) (Regulation (EU) 2017/745)

- Is a unified framework that applies across all EU member states.
- Stricter conformity assessments: The EU requires *CE marking* and *notified body* reviews, especially for high-risk devices.
- Enhanced post-market surveillance: The MDR mandates clinical evaluations and vigilance reporting.
- Greater transparency: The EUDAMED database provides public access to device information.

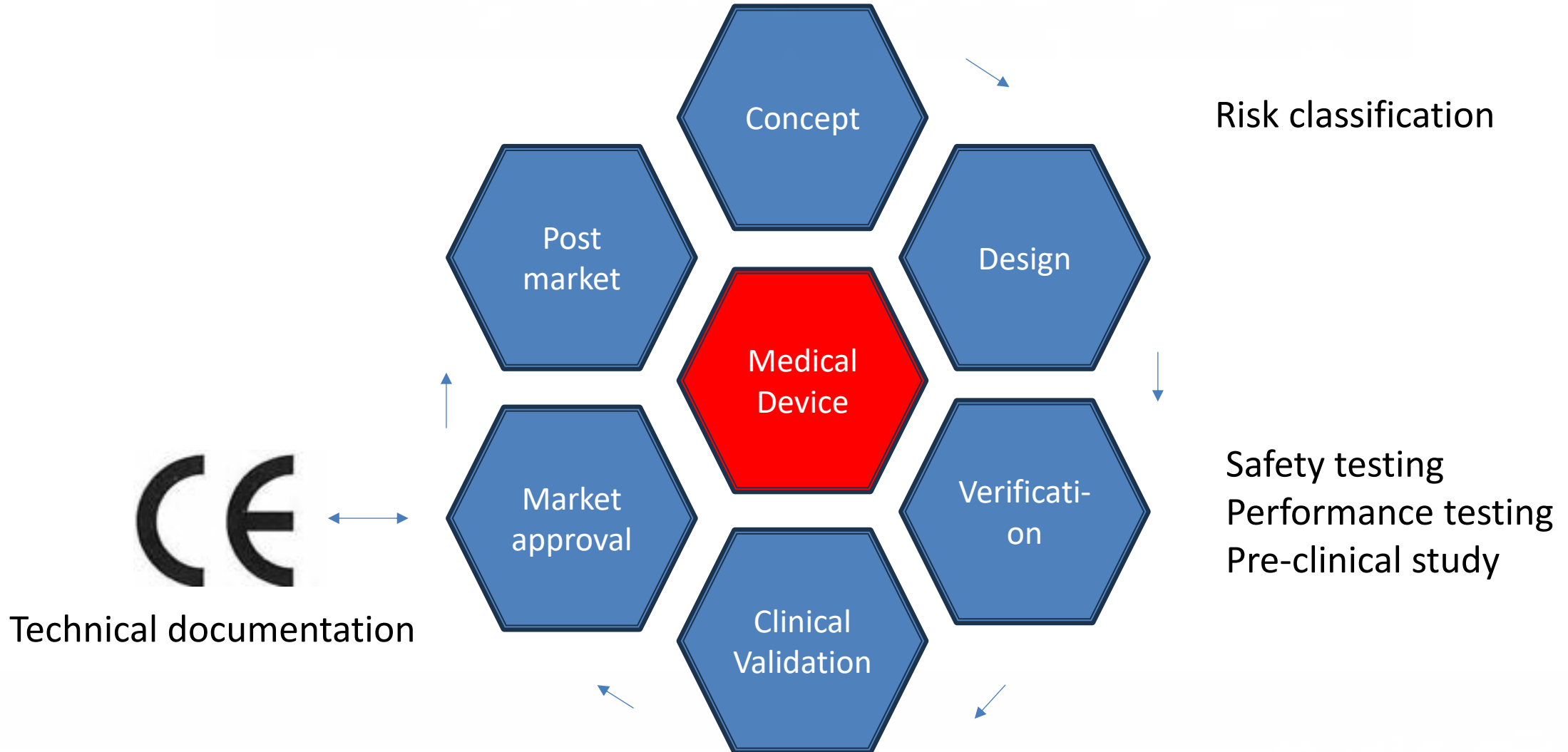
# Adverse events of orally applied medical devices, do they exist?

*Dental Amalgam* (A mercury-tin-silver  
compound)



The European Commission  
Bans Use of Dental Amalgam  
from 2025!

# Medical Device Regulation



# Notified Body

- A **Notified Body** plays a crucial role in the **CE marking** process by assessing whether certain products comply with European regulations before they can be placed on the market. These bodies are independent organizations designated by an EU country to conduct **conformity assessments** when required by legislation

# Notified body

- The number of Notified Bodies designated for MDR compliance assessment has significantly decreased due to stricter regulations! In the European Union, the number of Notified Bodies has dropped from approximately 1.000 to fewer than 100.
- This is due to the extensive and stringent requirements set by the Medical Device Regulation (MDR) for manufacturers and certification bodies.

# Key Functions of a Notified Body in CE Marking

- **Product Evaluation:** They verify whether a product meets the relevant EU standards and regulations.
- **Testing & Certification:** Depending on the directive, they may conduct product testing, factory production control certification, or type examination.
- **Issuing Certificates:** If a product meets the requirements, the Notified Body provides an **EC-type examination certificate**, confirming compliance.
- **Monitoring Compliance:** They ensure that manufacturers maintain conformity throughout production.
- **Providing Identification Numbers:** Products assessed by a Notified Body receive an identification number, which is displayed alongside the CE marking.

# Costs

- The costs for MDR compliance assessment have significantly increased. According to recent studies, manufacturers are facing higher expenses for clinical evaluations, post-market surveillance (PMS), and certification. The variability among Notified Bodies makes financial planning even more challenging.
- Additionally, by the end of a five-year certification cycle, the costs for maintenance and re-certification are expected to rise by 50% for medical device manufacturers and 70% for in-vitro diagnostics manufacturers. This puts substantial financial pressure on companies and could impact innovation in the sector.

# With as consequences:

High costs and long waiting times have resulted in:

1. many low-turnover medical devices have not been recertified
2. many manufacturers have switched from medical devices to cosmetics.
3. some materials necessary for treatment are no available anymore



# Cosmetics: EU Nickel Directive

- The Nickel Directive is part of the European Union directive on Cosmetics and regulating the use of nickel in jewelry and other products that come into contact with the skin
  - 0.2  $\mu\text{g}/\text{cm}^2/\text{week}$  for post assemblies which are inserted into pierced ears and other pierced parts of the human body;
  - 0.5  $\mu\text{g}/\text{cm}^2/\text{week}$  for other products intended to come into direct and prolonged contact with the skin.
- *European cosmetics are nearly nickel free!*

# Nickel in medical devices

Are applied in a range of (implantable) medical devices, ranging from orthopedic applications such as joint replacements to (heart-)stents used in angioplasty.

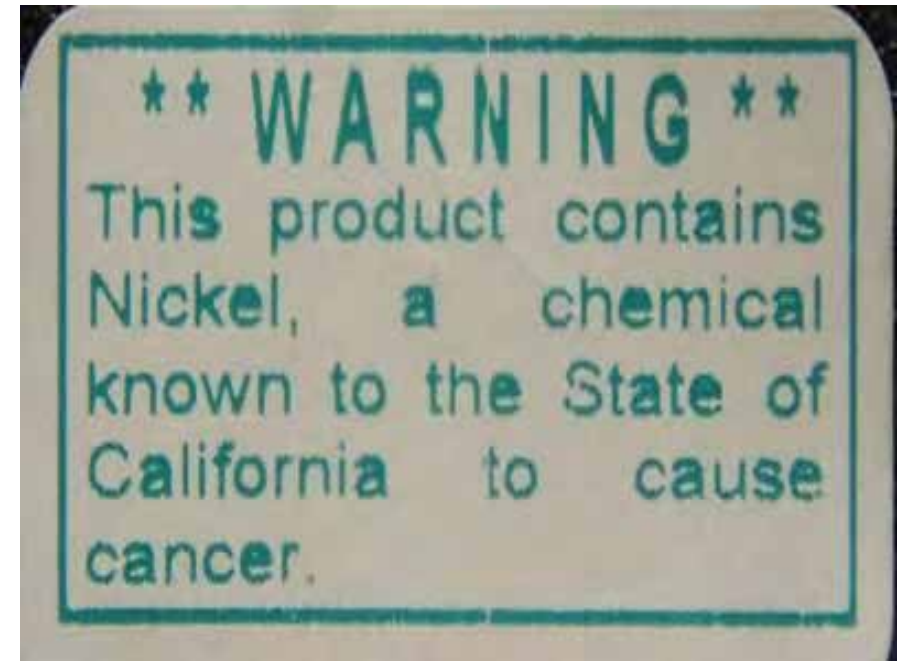
- Surgical steel (type 316 L)
- 10-14% Nickel

# Surgical steel: Stainless steel 316L

- Iron
- Carbon 0.03% max
- Nickel 10 – 14%
- Chromium 16 – 18%
- Manganese 2% max
- Molybdenum 2 – 3%
- Phosphorus 0.045% max
- Silica 1% max
- Sulfur 0.03% max



# Nickel in orthodontics



# Nickel in 'Dental Medical Devices'



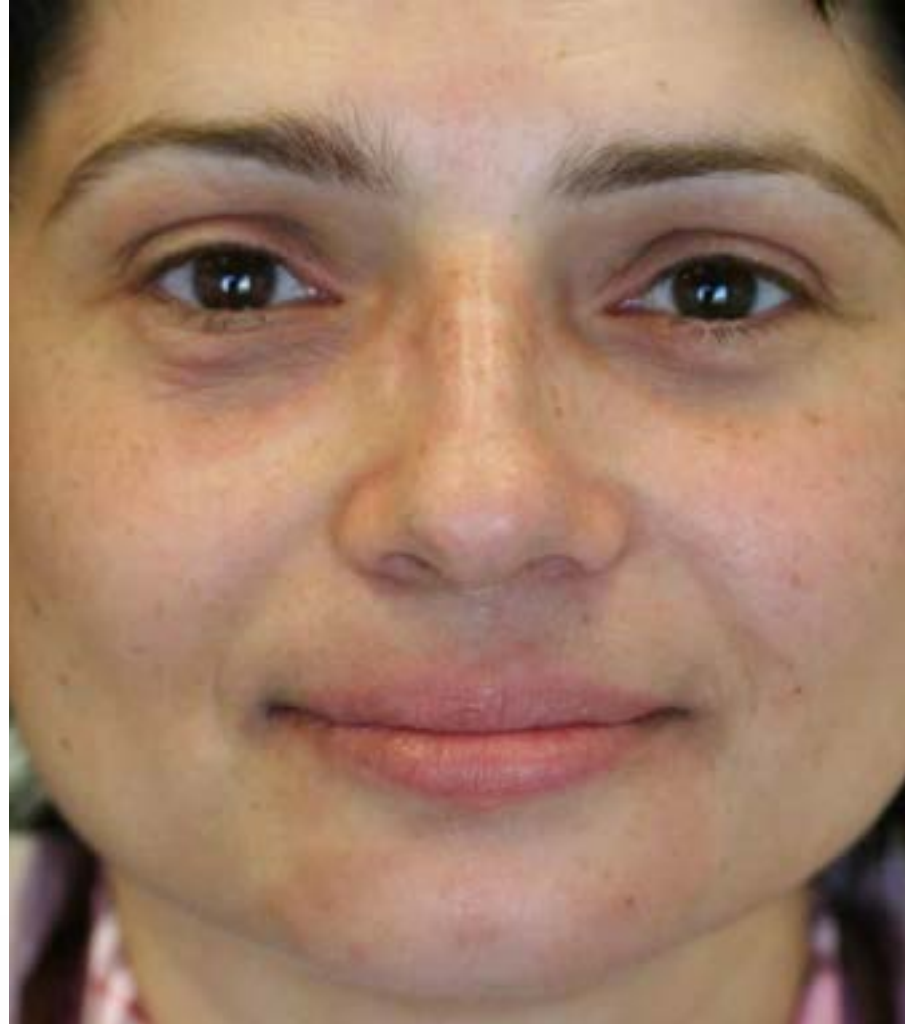
Feilzer AJ, Laeijendecker R, Kleverlaan CJ, van Schendel P, Muris J. Facial eczema because of orthodontic fixed retainer wires. Contact Dermatitis. 2008 Aug;59(2):118-20.

# Nickel release from orthodontic retention wires-the action of mechanical loading and pH



Milheiro A, Kleverlaan C, Muris J, Feilzer A, Pallav P.. Dent Mater. 2012 May;28(5):548-53

# 2 weeks after removal



# Medical device vs. cosmetic device

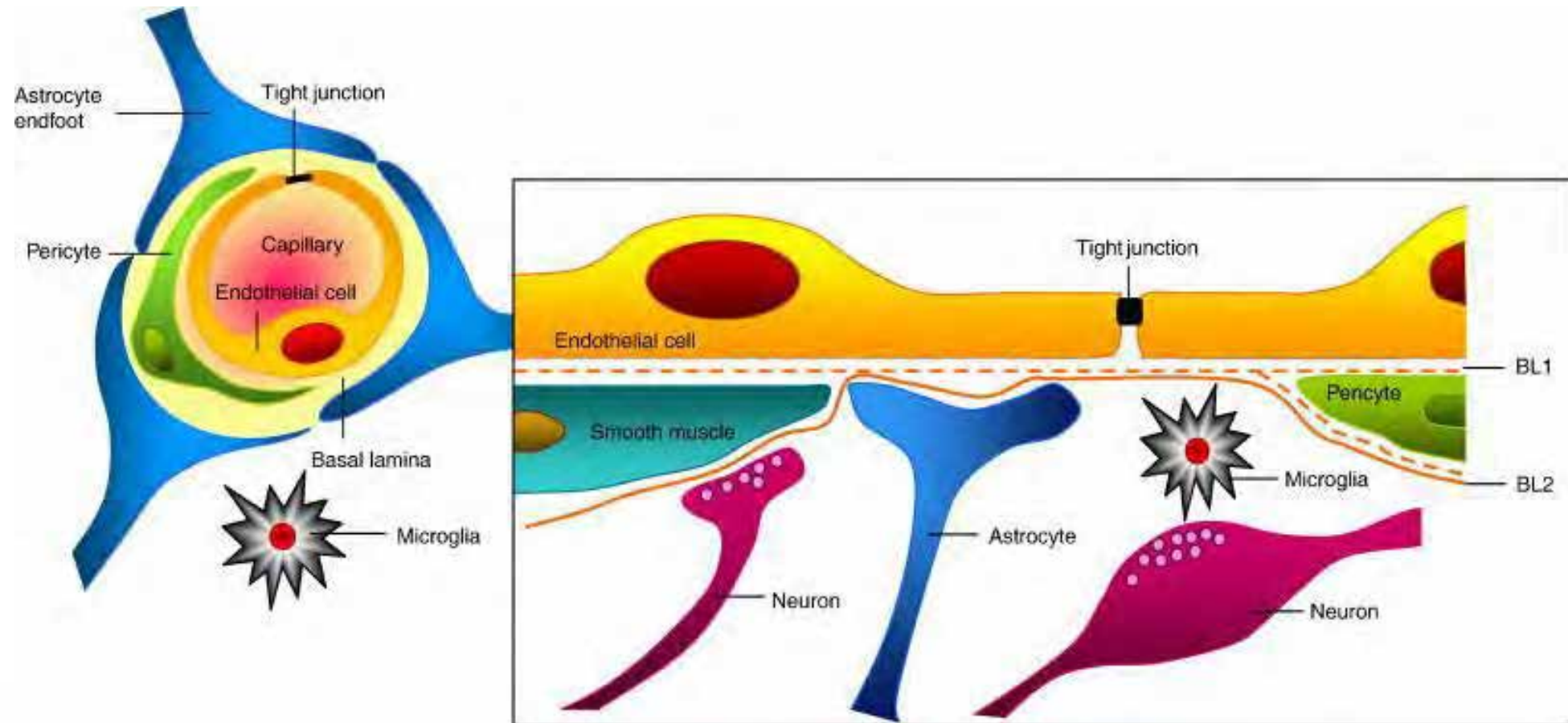
Medical Device, unsafe?



Cosmetic, safer?

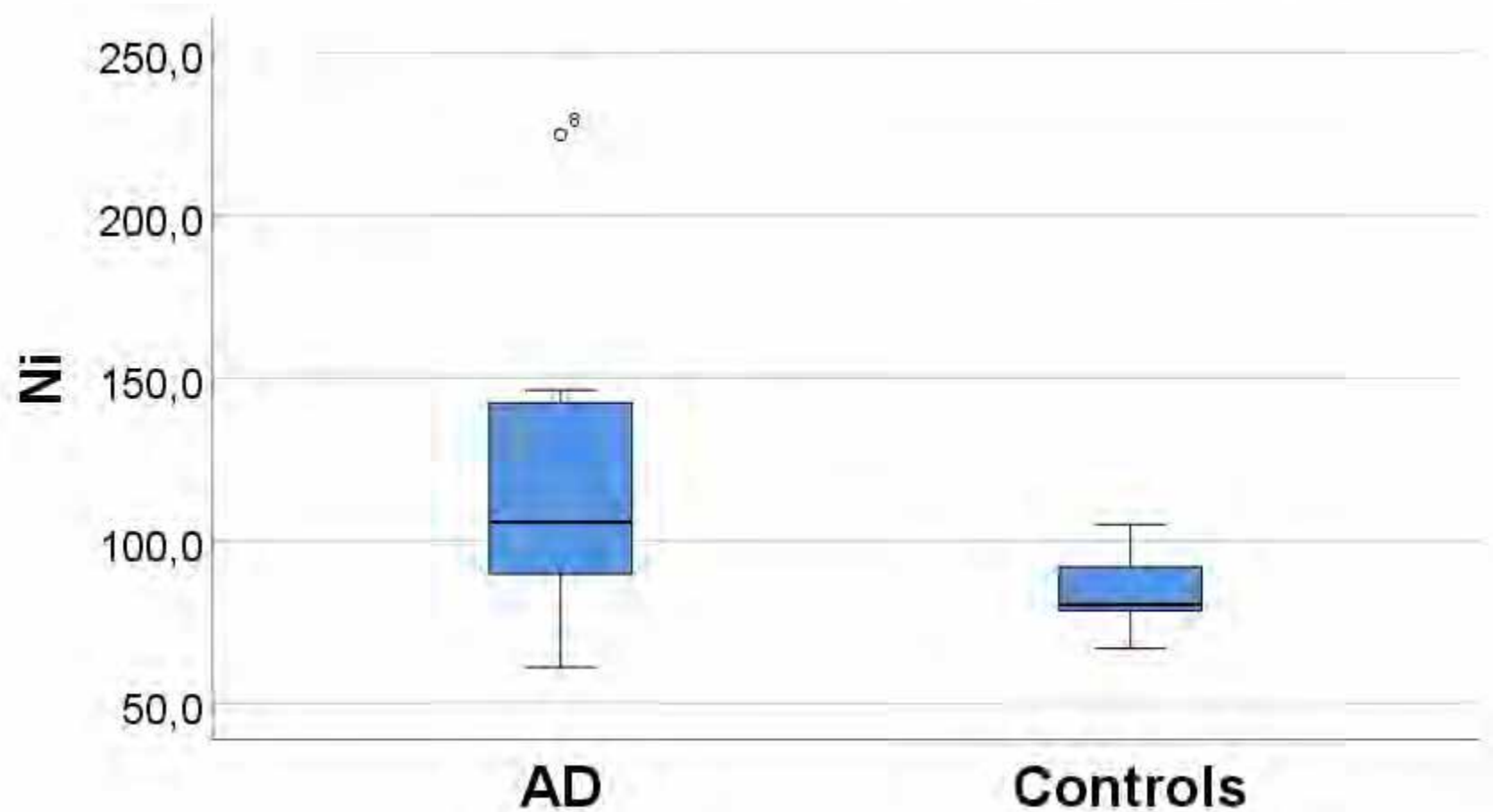


# Metals in the brain?



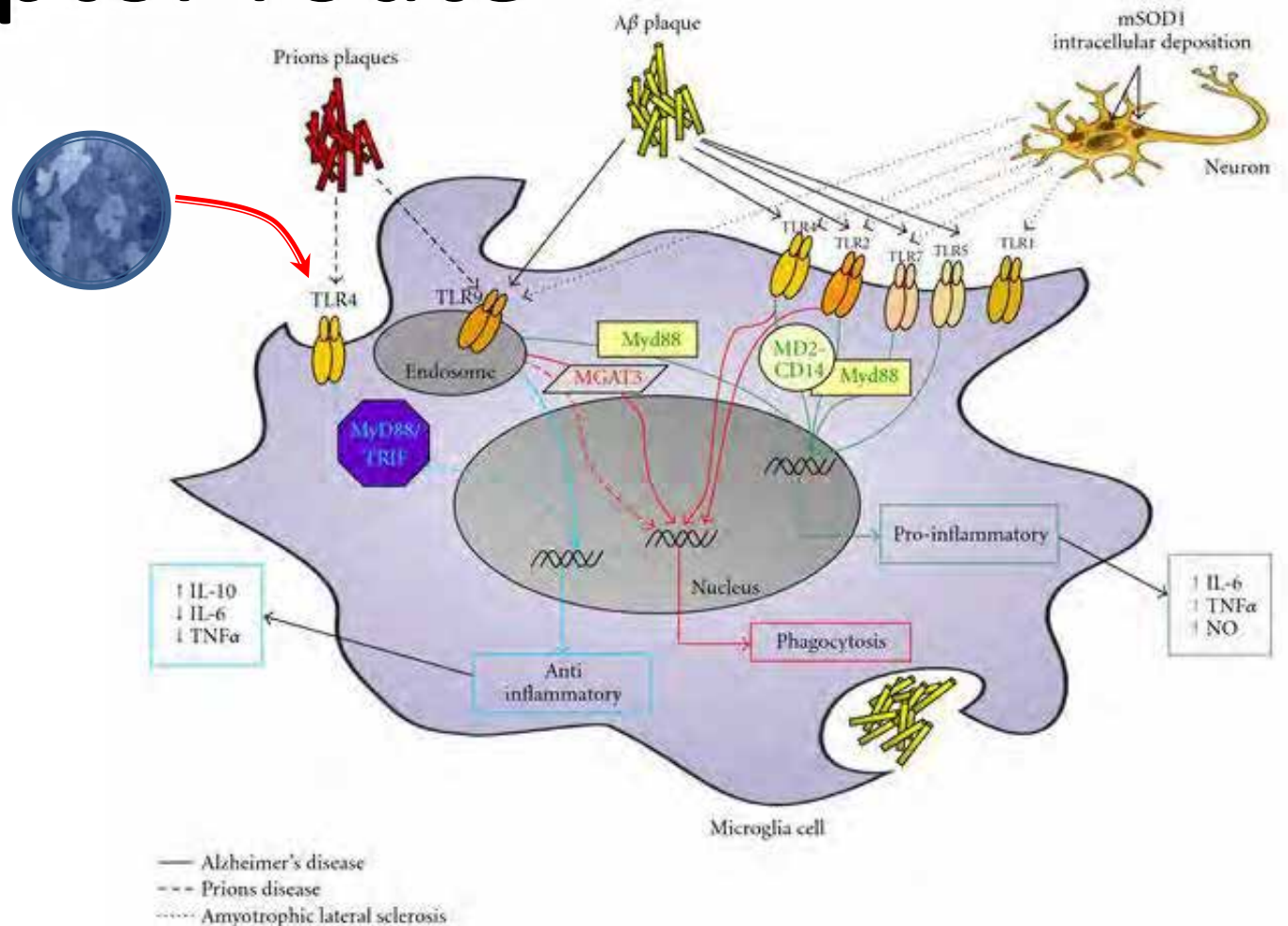
# Pilot study: Metals in the Cerebrospinal Fluid (CSF) of 10 AD patients and 5 healthy controls ( $\mu\text{g}/\text{kg}$ )

Calcium  
Magnesium  
Nickel  
Radium  
Iridium (5x)  
Strontium (14x)  
Titanium (2x)  
Zinc (13x)



# Toll-like receptor route

- Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system.
- Members of the TLR family were detected on glia, neurons and on neural progenitor cells in which they regulate cell-fate decision.



Trudler et al., TMediators Inflamm. 2010;2010:497987

# Toll-like receptor route

- Neuroinflammation and microglial dysfunction are key contributors to the development of Alzheimer's disease (AD).

(Momtazmanesh et al. Toll-like receptors in Alzheimer's disease. J Neuroimmunol. 2020 Nov 15;348:577362.)

- Next to nickel, cobalt and palladium are potent human dendritic cell stimulators

(Rachmawati D, et al.: Transition metal sensing by Toll-like receptor-4: Contact Dermatitis. 2013 Jun;68(6):331-8.)

# Systemic effects of oral exposure to nickel



# Case



Pockets (14 & 24);

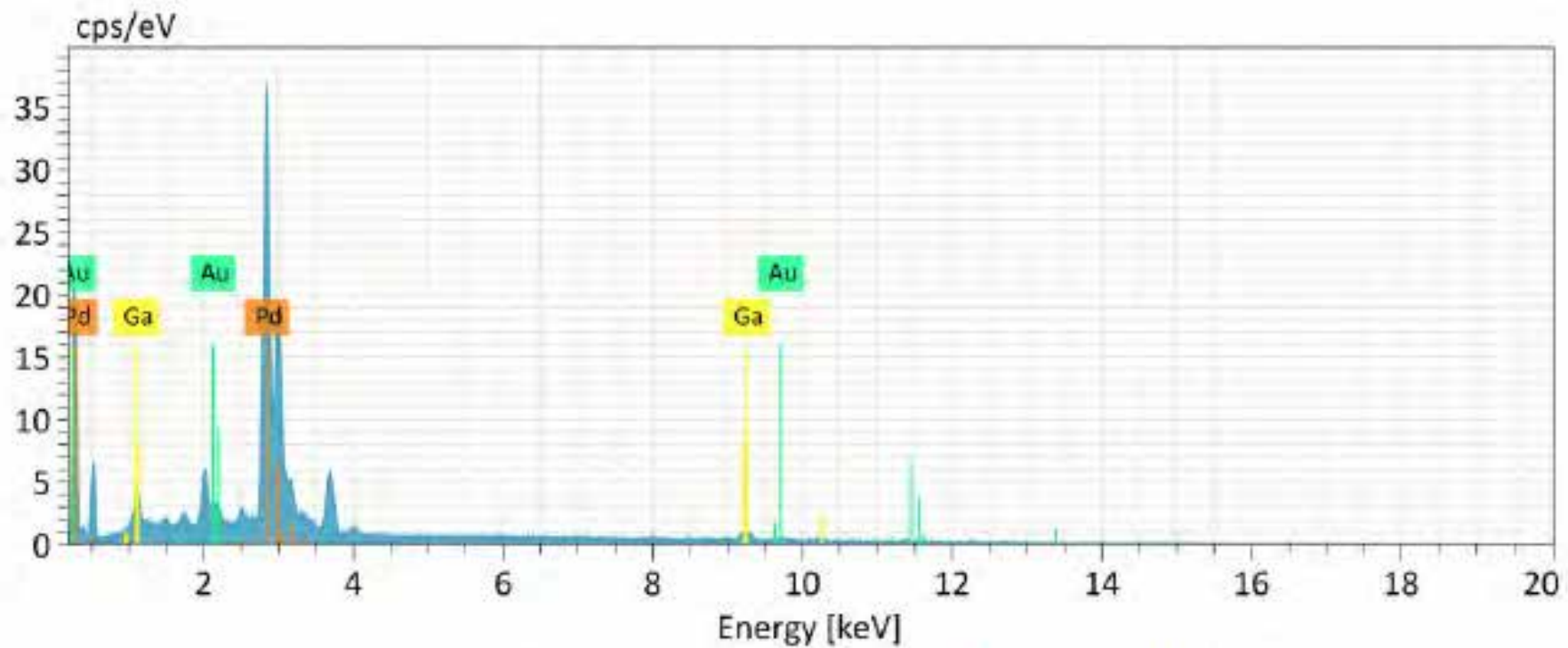
Restorations: crowns, composite, amalgam

Tung and oral mucosa: lingua geografica, amalgamtattoo's



# Micro Analysis for metals





Name	Date	Time	HV [kV]	Real [s]	Live [s]	Dead [%]	Pulses	Input [kcps]	Output [kcps]
Nap-van de Pol 46 1.spx	14/12/2022	11:22:54	20.0	55.9	29.5	47	1091760	34.2	18.1

Nap-van de Pol 46 1.spx

Element	At. No.	Netto	Mass [%]	Mass Norm. [%]	Atom [%]	abs. error [%] (1 sigma)	rel. error [%] (1 sigma)
Palladium	46	312665	51.17	90.28	88.76	1.66	3.24
Gallium	31	5852	3.55	6.27	9.41	0.15	4.25
Gold	79	1646	1.95	3.44	1.83	0.18	9.19
		<b>Sum</b>	<b>56.68</b>	<b>100.00</b>	<b>100.00</b>		

# 'All that glitters is not always gold'

## Energy Dispersive X-ray (EDX) analysis



The nickel-aluminum bronze showed high corrosion rate caused by an inability to create a protective surface layer.

Ardlin et al. 2009

#	Au	Pd	Ag	Al	Cu	Zn	Mn	Fe	Co	Ni
46	45%	8%	35%		12%					
36				15%	47%	1%	5%	6%	9%	17%

# EDX-analysis

	Au	Pt	Cu	Zn	In	Ag	Pd	Ga	Fe	Mn	Cr	Mo	Ni	Co
11	85	11	2	2										
14									2	1	20	9	68	
16									2	1	20	9	68	
24	2		13			2	72	10						
26	6		19			3	55	16						
34	68	5	9	1	1	12	2							
Frameprothese onderkaak										1	30	5		64

# First visit

- An anamnestic suspicion of sensitization to nickel and to palladium.
- Referred for patch testing

# Patchtest

- Flare-up reaction of their hands
- Nikkel++
- Pd+
- → Crown removal

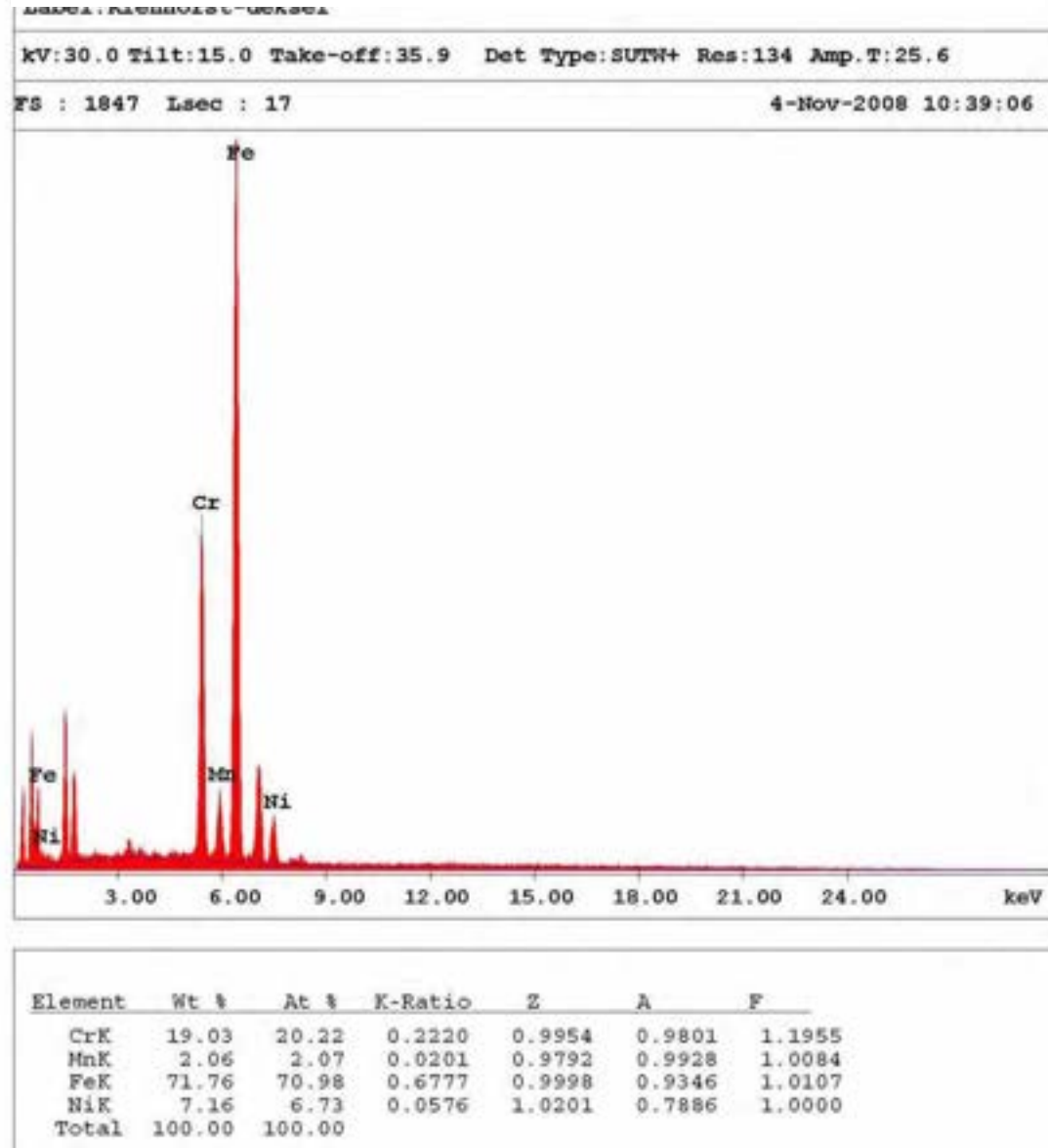
# Treatment

- All crowns replaced, at once, for temporary crowns

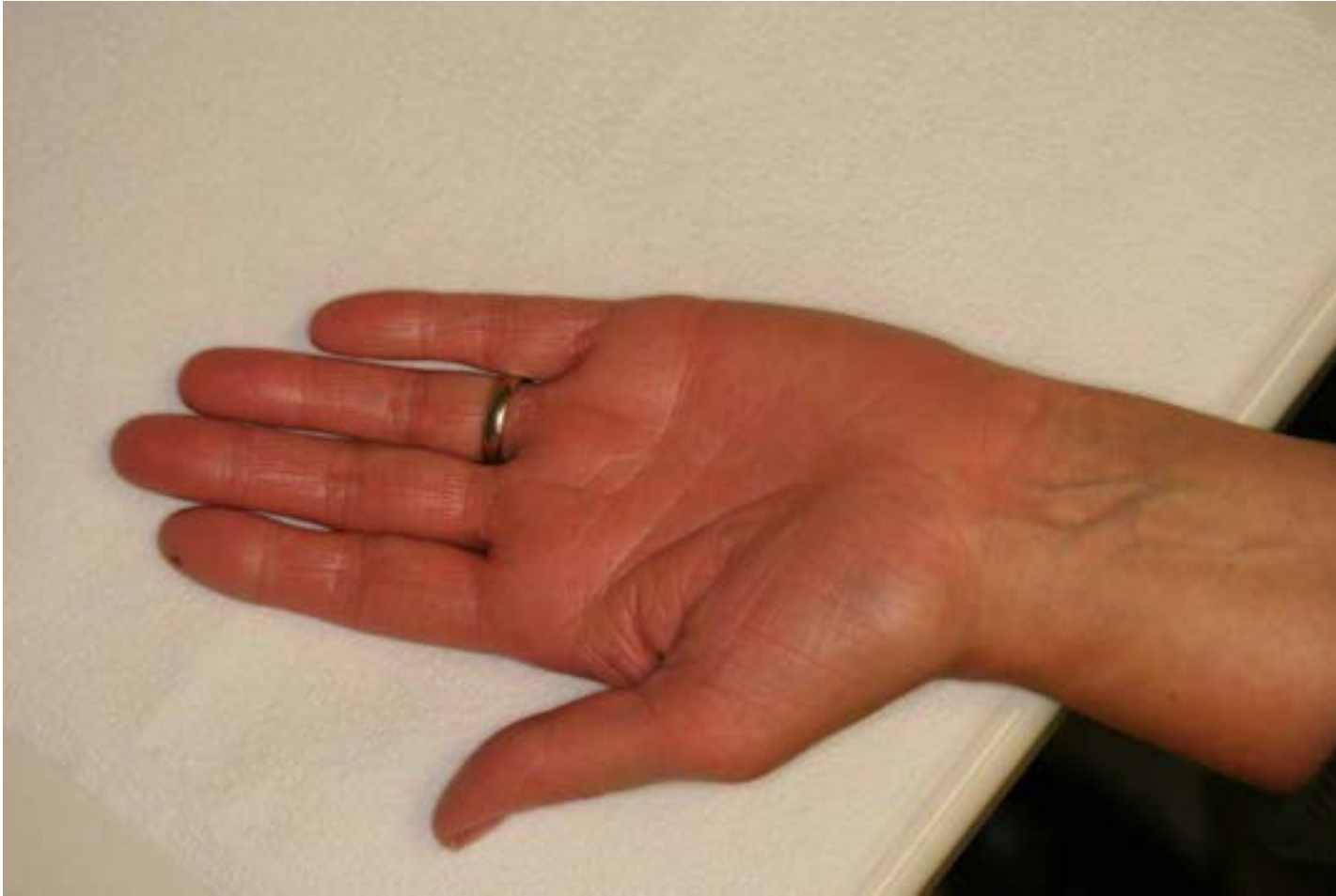
## Result

- Huge flare-up reaction → Cortisone in hospital
- Slow improvement but no total healing

# Stainless steel-pan / Sauerkraut



# After one year



# Beautiful nails but now dental cripple!

Acrylates as a significant cause of allergic contact dermatitis: new sources of exposure.

Kucharczyk *et al.* Postepy Dermatol Alergol. 2021

- In the past allergy to acrylates was mainly of occupational origin and dental technicians were the most often affected professional group.
- Since the long-lasting manicure has become popular, this problem concerns both manicurists and their customers.

# Contact Dermatitis from acrylic/gel nails



# Acrylate allergy / HEMA



# Bisphenol-A Ban?



In April 2023, the European Food Safety Authority (EFSA) published a re-evaluation of BPA's safety, significantly reducing the *tolerable daily intake (TDI)* set in its previous assessment in 2015.



BPA has been banned in plastic bottles and packaging containing food for babies and children under three years since September 2018.

It is used in the synthesis of monomers common to dental resins, such as Bis-GMA, Bis-EMA, Bis-DMA, and BADGE

# The message!

