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Enterosorption in the treatment of heavy metal poisoning

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ADSORBENTS FOR REMOVAL OF HEAVY METALS.
CHARACTERISATION, PERSONAL CARE AND WATER TREATMENT
2ND NANOMED WORKSHOP

Some definitions

- Heavy metals – there is no exact definition in the medical context.
- Heavy metals that have no known benefits for human physiology:

Pb, Cd, Hg

Heavy metals that are essential for human physiology:

Zn, Co, Mn, Cu, Se, Cr, Mo, Fe, As (?)

Heavy metals that are used in medical treatment:

Bi, Au, Ba, Ag, Li, Al, Ga – some of them are hardly ‘heavy’…

Radioactive isotopes

Po, Cs, Sr, I, Ra, etc.

<u>Heavy metals are not always heavy and not always metals…</u>

HM poisoning – rare diseases

- In reality, there are few well documented cases of poisoning with HMs
- Mercury, lead, iron and arsenic are most well known
- Mostly related to the occupational causes (industrial exposure)
- Neurotoxic effects, oxidative stress, chemical deactivation of enzymes and other proteins, possible IQ effects, renal toxicity, possibly cancer, heart and liver damage
- Wilson’s disease is a genetic disorder characterised by excess Cu
- Haemochromatosis – excessive iron (genetic disorder)

Why is Hg dangerous?

Neurotoxin – ‘Mad Hatter’

Kidneys

Gastrointestinal tract

IQ

Cancer?



Sir John Tenniel, illustration to *Alice's Adventures in Wonderland* by Lewis Carroll

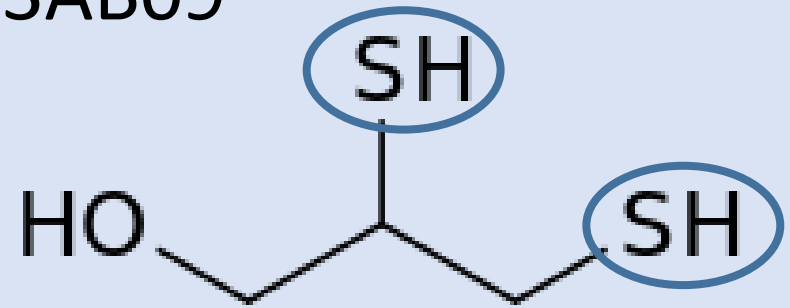
Current treatment methods

- Stage 1 – Emergency – removing the source of poisoning; rarely chelating agent except for lead encephalopathy.
- Stage 2 - Use of various chelating agents that cause the toxic element to bind with the drug and be excreted in the urine.
- Treatment should also be symptomatic and supportive.
- Pumping of the stomach (gastric lavage) will remove some ingested metals.
- Occupational exposure to heavy metals requires prevention through the use of masks and protective clothing.
- Kidney failure may require hemodialysis and/or other special treatment.
- There is no proven effective therapy for the treatment of cadmium poisoning

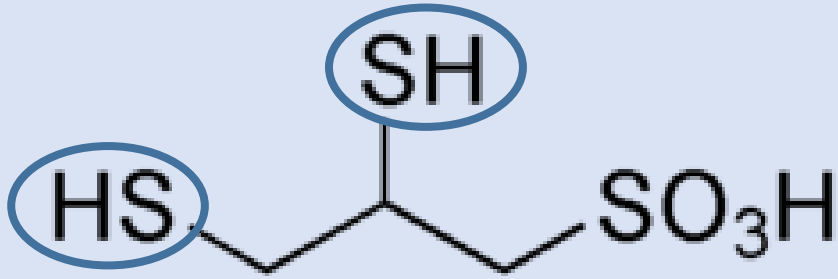
Table. Most Commonly Encountered Metals and Their Treatment

Metal	Treatment
As	BAL (acute, symptomatic); Succimer; DMPS (Europe)
Bi	No accepted chelation regimen
Cd	No accepted chelation regimen
Cr	NAC (*N*-acetylcysteine, experimental)
Co	NAC; $CaNa_2EDTA$
Cu	BAL; D-Penicillamine; Succimer
Fe	Deferoxamine
Pb	BAL; $CaNa_2EDTA$; Succimer
Mn	No accepted chelation regimen
Hg	BAL; Succimer; DMPS (Europe)
Ni	No accepted chelation regimen
Se	No accepted chelation regimen
Ag	Selenium, vitamin E (experimental)
Tl	Multi-dose AC; Prussian blue
Zn	No accepted chelation regimen

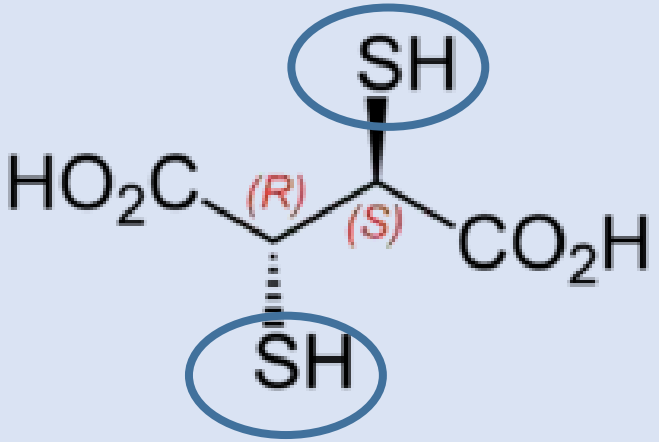
BAL – British Anti-Lewisite, Dimercaprol, ATC code V03AB09



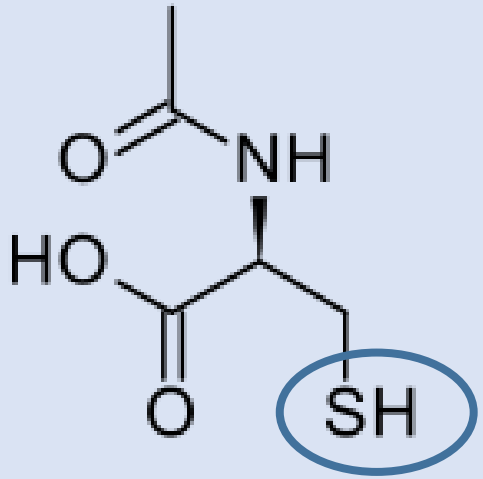
2,3-Dimercapto-1-propanesulfonic acid (DMPS, Dimerval) and its sodium salt (Unithiol), V03AB43



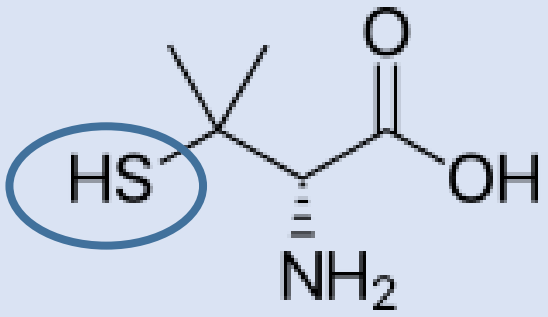
Succimer, Chemet, Dimercaptosuccinic acid, V09CA02



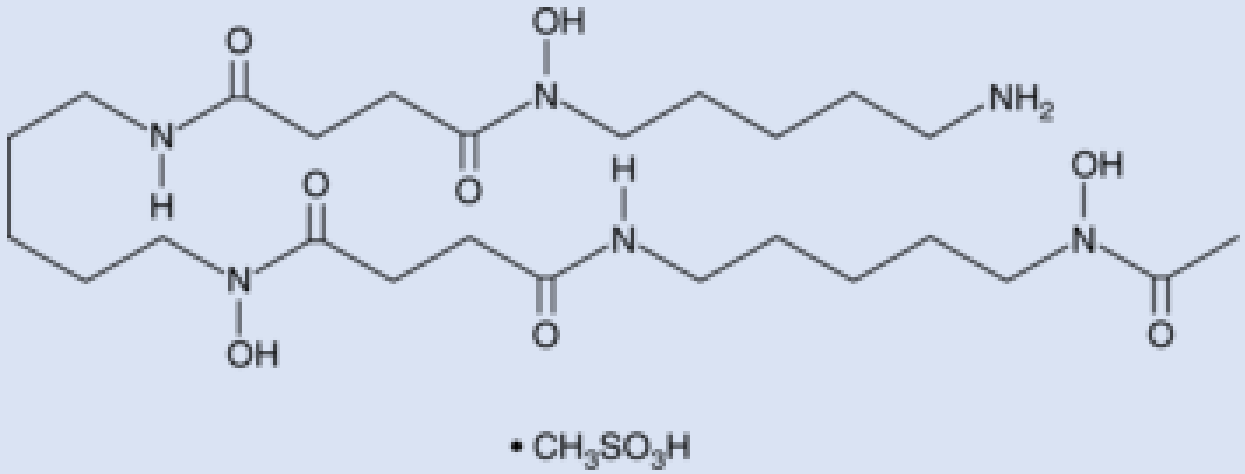
N-acetylcysteine, R05CB01



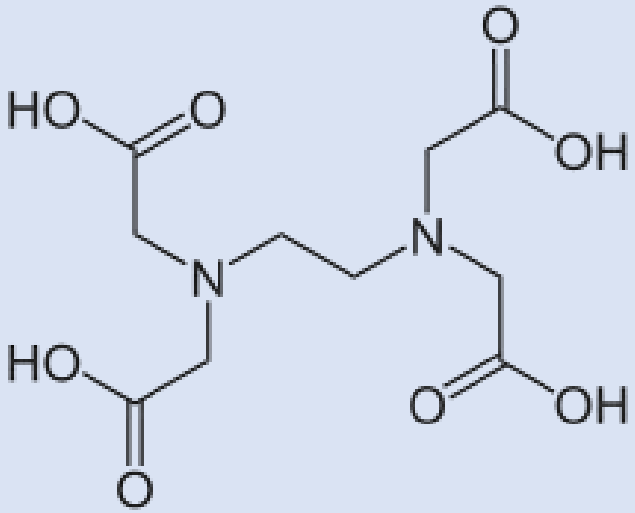
D-penicillamine
M01CC01



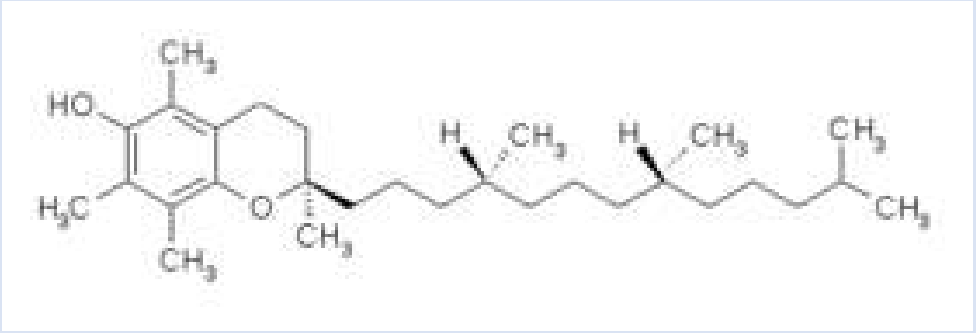
De(s)feroxamine (DFOA), Desferal
V03AC01



EDTA, $CaNa_2$ salt, V03AB03



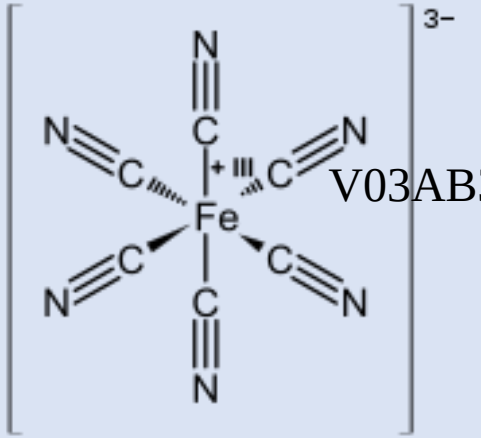
Vitamin E



Prussian blue is $Fe_7(CN)_{18} \cdot xH_2O$, where x = 14–16

V03AB31

$$4Fe^{3+} + 3[Fe^{II}(CN)_6]^{4-} \rightarrow Fe^{III}[Fe^{III}Fe^{II}(CN)_6]_3$$



V03AB31





The Wave, by Hokusai

Adverse effects

- Nausea/Vomiting
- Fever
- Hypertension
- Tachycardia
- Headache
- Renal failure
- Diarrhoea
- And many more…

ATC code

V03AB – antidotes

V03AC Iron chelating agents

M01C – specific antirheumatic agents

M01CC - Penicillamine and similar agents

V09 - Diagnostic Radiopharmaceuticals
V09I - Tumour Detection
V09IA - Technetium (^{99m}Tc) compounds

R05CB Mucolytics

A few words on terminology and definitions - sorbents

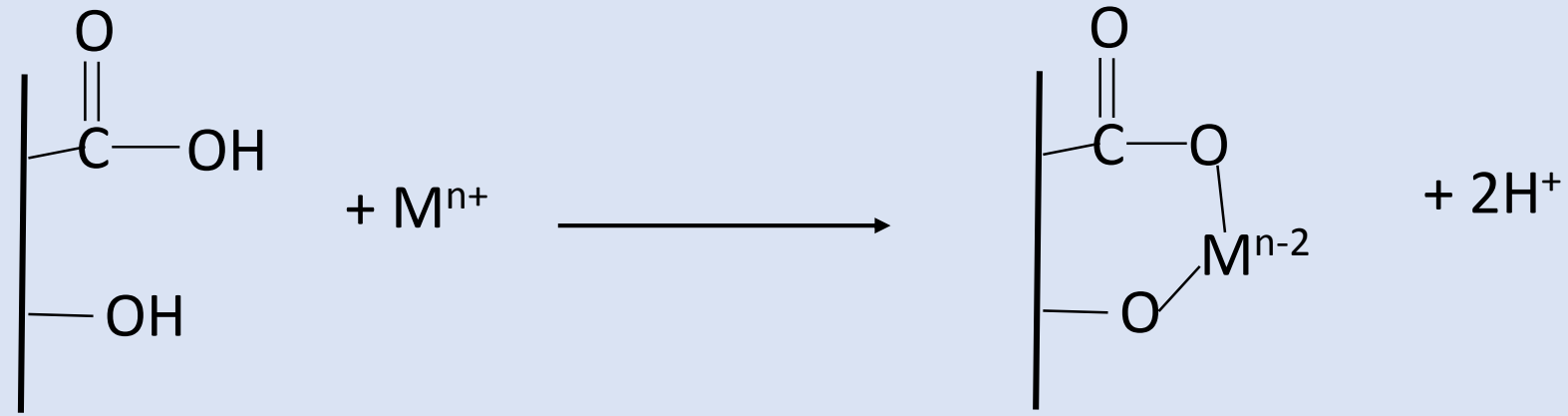
- Enterosorption - **Definition**: Adsorption of substances from the gastrointestinal tract onto an orally administered sorbent such as activated charcoal. This technique is used to eliminate toxic and some biologically active substances and serves to modify the lipid and amino acid spectrum of the intestinal contents (from *www.reference.MD*)
- Alternative terminology: Oral (ad)sorption and intestinal (ad)sorption and (ad)sorbents
- Entero – means related to intestines
- Very popular in the former USSR, where the word Enterosorption is most commonly used.

Main types of enterosorbents

- Polysaccharides (dextran, microcrystalline cellulose, chitosan, pectins),
- Synthetic polymers (cholestyramine or colestyramine resin, piperidol homo- and copolymers – IKhANT hydrogel; styrene-DVB resins XAD)
- Natural polymers - Lignin – natural high MW insoluble plant polymer composed of methoxylated derivatives of benzene (phenylpropanoid alcohols, particularly coniferyl, sinapyl and coumaryl alcohols)
- Inorganic sorbents: silica, clays, bentonite, diosmectite, montmorillonite, kaolinite
- Organosilicates (polymethylsiloxane)
- Activated carbons (from natural and synthetic precursors)

Activated carbon

- Can adsorb heavy metals, mostly cations
- Oxidised AC has larger density of ion-exchange functional groups of acidic nature (carboxylic, phenolic, etc.)
- $Fe^{3+} >> M^{2+} >> M^{+}$ (low Cs^{+} adsorption)
- Possible complex and surface chelate formation



Unexpected side-effects

- Red-ox processes: N-AC + M^{+} → N-AC…M^{0} (Pd, Ag, Au, Pt)
  Zero-valent metals may be more toxic than their salts

Catalytic reactions: may convert less toxic substances into more toxic substances

Urea + water → ammonium + bicarbonate

Toxicity of ammonium, or ammonia >> urea

Creatinine → methylguanidine

Creatinine toxicity << methylguanidine

Combined AC enterosorbents

- Oxidised AC with H^+ ions partially substituted by K^+ , Mg^{2+}, and palygorskite (clay) modified with Prussian blue – for radionuclides including Cs^+ and other heavy metals removal;

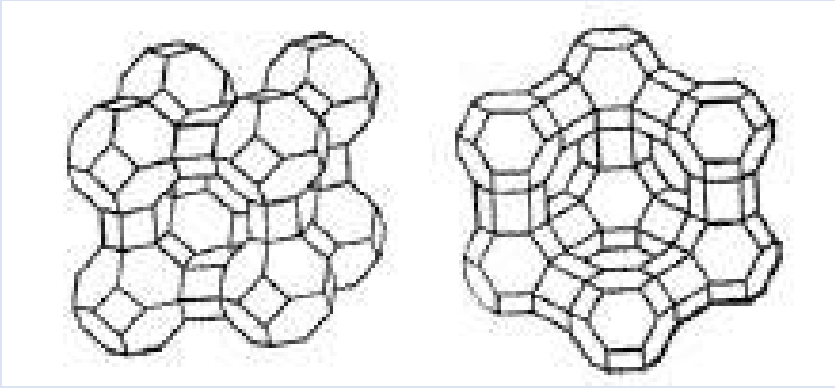
AC with cellulose is recommended for heavy metal removal.

Shungite – natural mineral, 98% carbon, with traces of fullerenes. Its healing properties are unclear.

Two main flaws of AC: black colour and poor organoleptic quality.

Inorganic enterosorbents

- Aluminosilicates and clays
- Geophagia or geophagy – known from times bygone.
- Zeolites



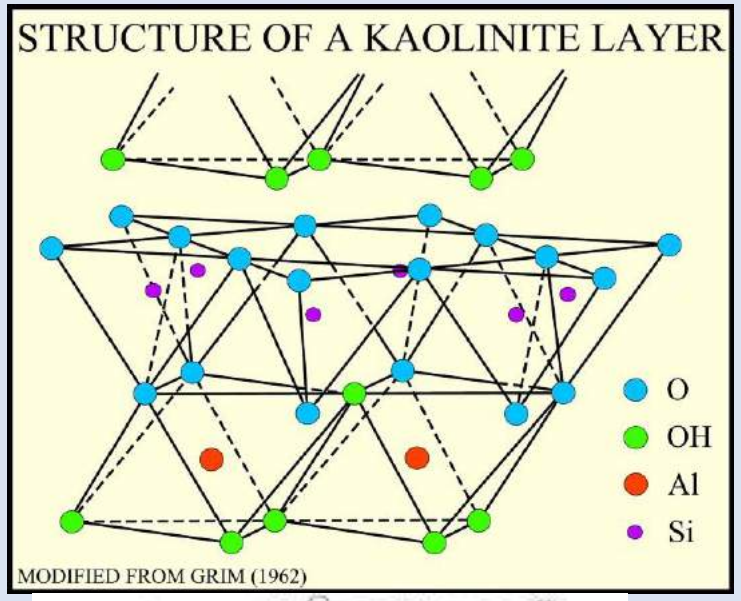
A **B**

A – synthetic zeolite $Na_{12}(Al_{12}Si_{12}O_{48})\cdot 27H_2O$, channel diameter 0.42 nm
B – natural zeolite faujasite $Na_{12}Ca_{12}Mg_{12}Al_{59}Si_{133}O_{384}\cdot 235H_2O$, 0.74 nm
Zeolites have cation-exchange properties

Clays

- Kaolin, or *bolus alba*

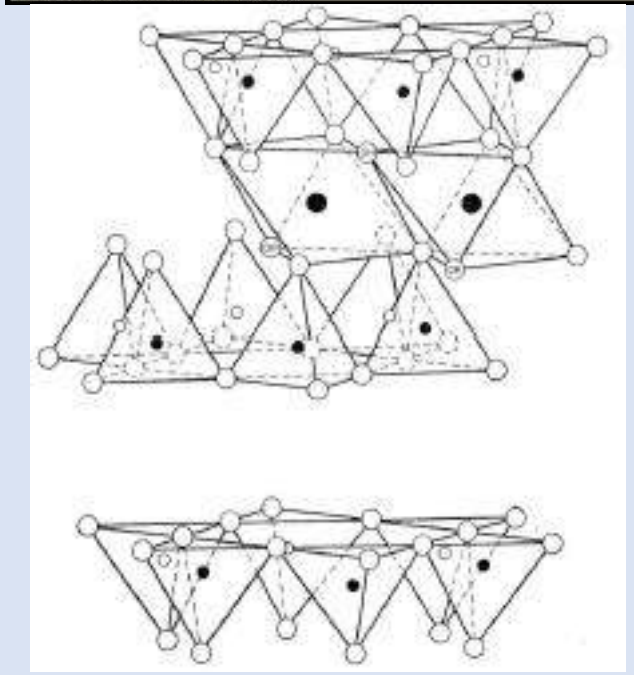
Reported to remove radionuclides



- Smecta®, Ipsen Group, France
- Produced since 1970, and in 2000 opened its production in China.

Diosmectite is a natural aluminomagnesium silicate clay with a lamellar, non-fibrous crystalline structure. Belongs to montmorillonite type of clays.

Mainly used for diarrhoea treatment. Has cation-Exchange properties



Clays

- Attapulgite, or palygorskite, Upjohn, USA

Mixture of magnesium and aluminium silicates and pectin. Needle-like clay mineral. Has been replaced as not very efficient in diarrhoea treatment (FDA).

Silica and organosilicon sorbents

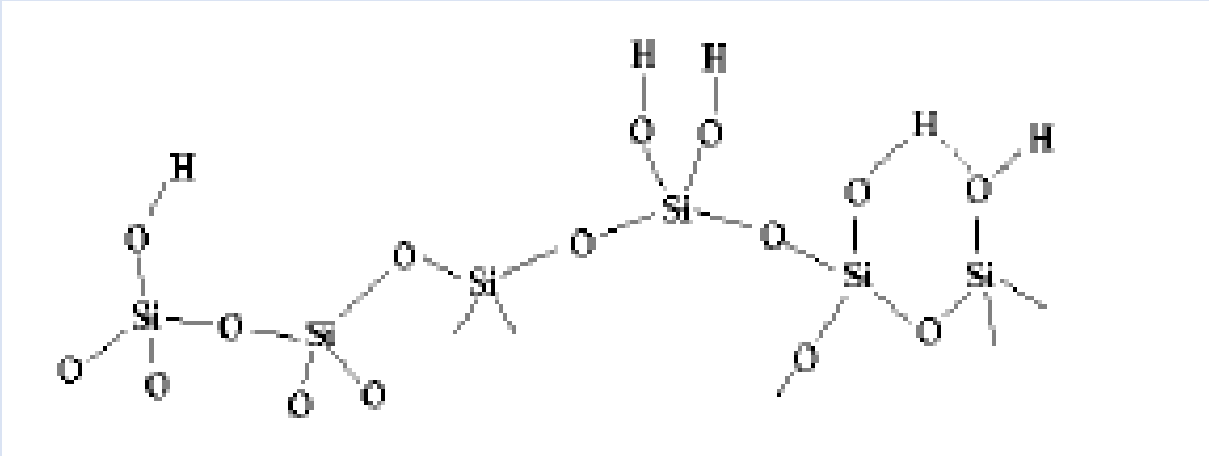
- Silicon dioxide, Aerosil®, highly disperse silica

$$SiCl_4 + 2\,H_2O = SiO_2 + 4\,HCl$$

Surface area 150-300 m^2/g, amorphous.

Surface chemical structure:

Negatively charged surface, low porosity and low adsorption of small solutes.



Enterosgel® - polymethysiloxane polyhydrate, gel

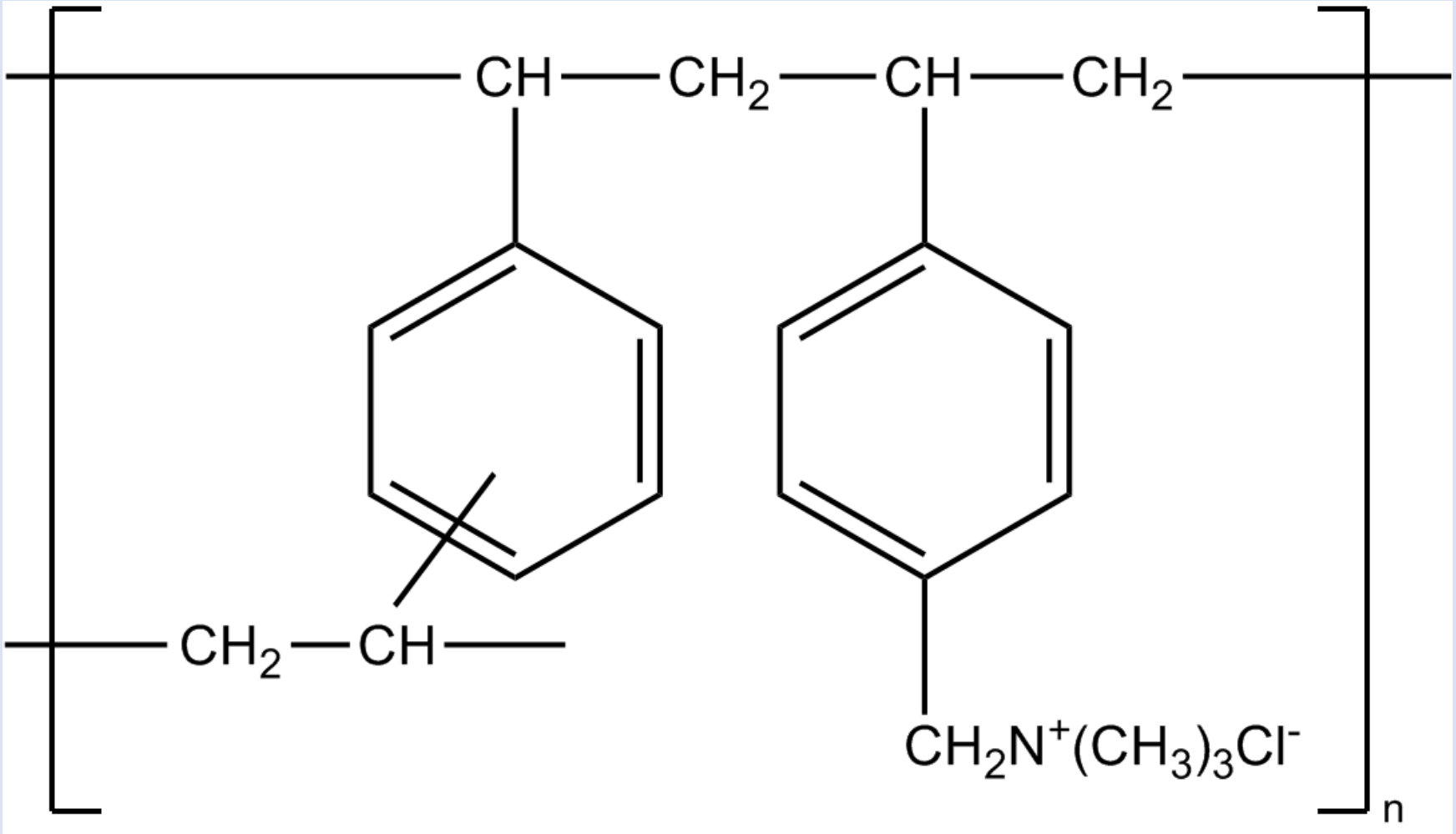
- Surface area 150-200 m2/g; pore volume 2.7 – 3.0 cm^3/g, pore size > 100 nm
- Not effective in binding ions

Biopolymer sorbents

- Cellulose and microcrystalline cellulose – hydroxylic groups, bind heavy metals and radionuclides
- Lignin, polyphepan – hydroxylic, carboxylic and phenolic groups, bind heavy metals
- Pectins – bind heavy metals and radionuclides
- Alginates – bind heavy metals and radionuclides
- Chitin and chitosan – hydroxylic and amino groups, bind heavy metals and radionuclides

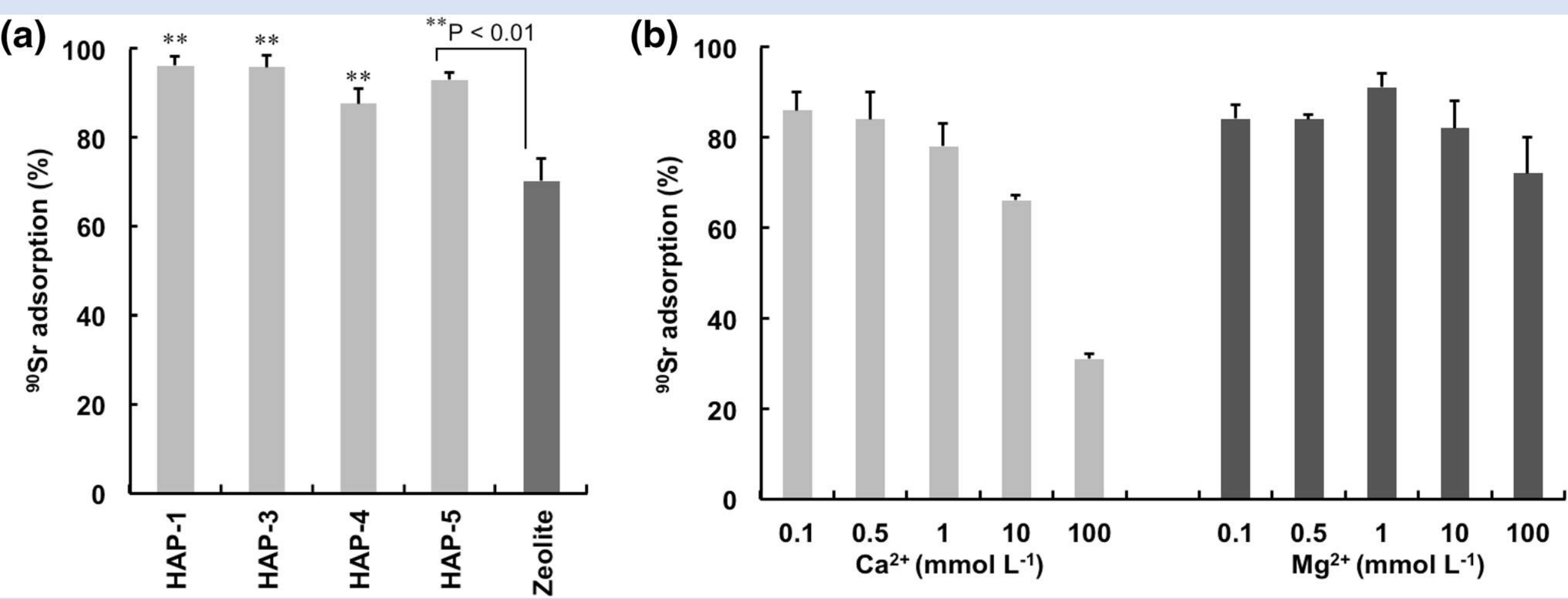
- Alginates and pectins have hydroxylic and carboxylic cation exchange groups which make them efficient heavy metal ions binders
- Low surface area but large number of ion exchange groups

Cholestyramine – styrene-divinylbenzene copolymer with quaternary nitrogen side groups: Questran or Questran Light, Cholybar, Olestyr. Anion exchanger



Sorption of Sr^{2+}

- No known enterosorbent has shown significant selectivity towards Sr^{2+} in the presence of Ca^{2+}.
- However, a number of materials have been reported as having selectivity towards Sr in industrial solutions and wastes.
- Recently it has been reported that hydroxyapatite (J Radioanal Nucl Chem, 2015, DOI 10.1007/s10967-015-4228-9) has adsorbed 90% of Sr ions in the presence of up to 1 mmol/L Ca ions.



Adsorption of Sr-90 onto HAP and zeolite column.

a Adsorption efficiency from competing ion free solution.

b Effect of competing Ca and Mg ions analyzed by HAP-5 column.

The average amount of Ca ions in natural water is (0.375–0.5 mmol/L)

Enterosorbents –are they drugs or devices?

- If medicinal products – they are regulated under the Human Medicines Regulations 2012 (SI 2012/1916) [1]
- If medical devices – they are regulated by a set of European directives [2] and UK laws– the Medical Devices Regulations 2002 (and amendments) [3].

[1] http://ec.europa.eu/health/documents/eudralex/vol-1/

http://www.legislation.gov.uk/

[2] http://ec.europa.eu/health/medical-devices/regulatory-framework/legislation/index_en.htm

[3] the Medical Devices Regulations 2002 Statutory Instrument 2002 No 618, the Medical Devices Regulations 2002 SI 1697, the Medical Devices (amendment) Regulations 2003 and the Medical Devices (amendment) Regulations 2008 SI 2936.

Many products transferred from being regulated under the medicines legislation to being regulated under the MDR.

- Article 1.2 of Directive 93/42/EEC (as amended) [2] defines a medical device as: ‘any … material or other article, whether used alone or in combination, … intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
- - diagnosis, prevention, monitoring, treatment or alleviation of disease,
- … and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means’

Guidance on legislation “Borderlines between medical devices and medicinal products”, MHRA, June 2013

In the case of a medical device, the principal intended action is typically fulfilled by physical means (including mechanical action, physical barrier, replacement of, or support to, organs or body functions).

Active coal / carbon solutions for treatment of acute poisoning

By consensus of EU Member States such products are considered to be medicinal products.

Rule 21, Med Dev REGULATION (EU) 2017/745

- Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body are classified as:

— class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;

— class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body;

— class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx, and achieve their intended purpose on those cavities; and

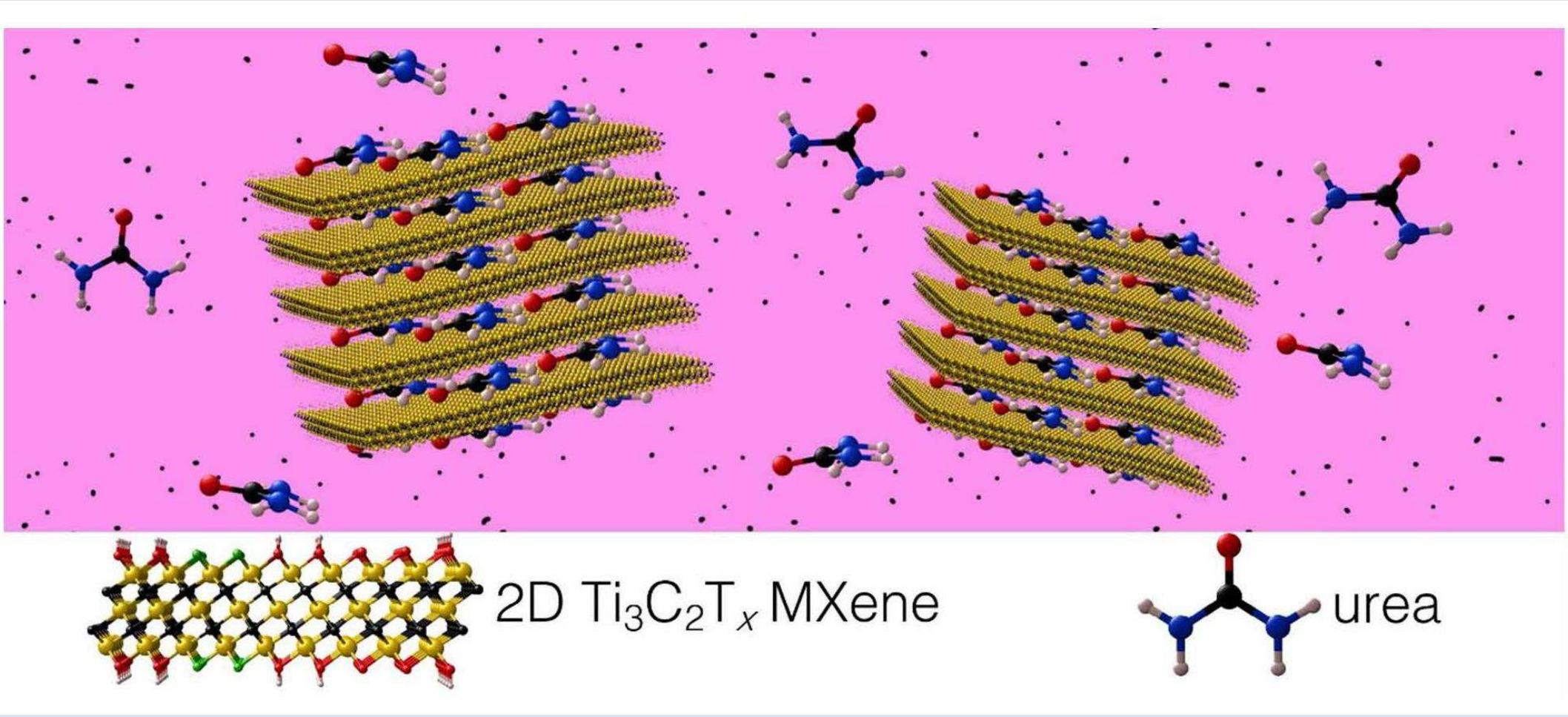
— **class IIb in all other cases**.

Post-USSR countries (Russia, Ukraine, etc.)

- Enterosorbents are medicinal products
- There is no borderline between medicinal products and medical devices
- To bypass this restriction, in Russia enterosorbents may be registered as Biologically Active Additives (BAD in Russian)
- In Ukraine they are called Food additives, Food supplements, Dietary supplements (pectin, cellulose, alginates, bentonite, aluminium silicate)
- Unfortunately, food additives, or BAAs fall in the same category as homeopathic products, which often means that the assessment of their therapeutic action has not been done according to the rules applied to medical devices or medicinal products.

Some conclusions

- Acute heavy metal poisonings are rare events and often there is insufficient information available about the real therapeutic benefits of using different antidotes
- Enterosorbents have potentially a number of advantages over antidotal chelating agents or other medicines, such as fewer side-effects and lower toxicity, which makes them attractive for the treatment of chronically exposed population
- Further improvement of the efficiency of enterosorbents could be achieved by their surface modification with chelating functional groups
- Efficient selective sorption of Sr and Cs ions remains a problem, which may be solved by optimising the porous structure, surface charges and interatomic distances in the enterosorbent structure using hydrothermal methods of synthesis, or novel materials with finely tunable surface properties such as MXenes.



From: **MXene Sorbents for Removal of Urea from Dialysate - a Step Towards the Wearable Artificial Kidney, ACS Nano, 2018**

Acknowledgments

- Project NanoMed, Horizon 2020 RISE programme
- Prof K Laszlo for the invitation