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ENTEROSORPTION IN THE TREATMENT OF HEAVY METAL POISONING

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Abstract. Heavy metals (HM) and their compounds are classified among most toxic substances to human health. As environmental pollutants, they can enter the human body with air, water and foodstuff. Some of them are ubiquitous in earth's crust and thus may be naturally present in the environment at levels dangerous to living organisms, but more often they pollute the environment as a result of anthropogenic activities and accidents. Although cases of acute HM poisoning are rare, the chronic exposure of the population living in the areas of intensive industrial or agricultural activities and the occupational exposure of the personnel to heavy metals pose a serious health hazard affecting a large number of people worldwide. At present, only a few medical agents are available for the treatment of acute poisoning with some heavy metals and none have been designed for the treatment of people chronically exposed to HM. In this paper, the potential use of enterosorbents as a cost-effective and efficient means of reducing the health hazards of chronic exposure to HM including radioactive contaminants is discussed.

Keywords: heavy metal, enterosorbent, radioactivity, chronic exposure.

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List of abbreviations and notations:

HM	Heavy metals
WHO	World Health Organisation
UNEP	United Nations Environment Programme
IARC	International Agency for Research on Cancer
ATC	Anatomical therapeutic chemical
BAL	British anti-Lewisite
DMPS	2,3-Dimercapto-1-propanesulfonic acid
DMSA	Dimercapto-succinic acid
NAC	*N*-acetylcysteine
DFO	De(s)feroxamine mesylate
EDTA	Ethylenediaminetetra-acetic acid
DVB	Divinylbenzene
MDR	Medical devices regulations
FDA	Food and Drug Administration
GRAS	Generally recognised as safe
GIT	Gastrointestinal tract
NPPs	Nuclear power plants
ACs	Activated carbons
BAA	Biologically active additives

Introduction

Although the definition of heavy metals (HM) seems to be self-explanatory implying chemical elements with metallic properties and high density, in practice the meaning of the term HM depends on the context in which it is used. In the broadest sense, any element which may be considered as a human health hazard and/or a pollutant with a significant potential negative impact on the environment is often deemed a "heavy metal". Such metalloids as arsenic also belong to this category of HM or heavy elements. [1]. Radioactive contamination, which mostly comprises radioactive isotopes of HM, can also be referred to this category of environmental pollutants. However, it has been estimated that the total combined toxicity of HM released in the environment due to anthropogenic activity by far exceeds the combined total toxicity of all radioactive and organic wastes generated by humans [2]. The toxicity of HM depends on their chemical state and oxidation number; for some elements such as mercury, the most toxic form is the organic methylmercury compound, whereas for others, such as arsenic, the inorganic compounds of As(III) are the most dangerous. For chromium, its compounds in the highest

oxidation state, Cr(VI) are much more harmful than Cr(III) compounds [3]. The biggest problem with HM pollution is that they are chemically indestructible, and once they are released in the environment, they remain there forever. The scale of HM impact on health and environment has been continuously upgraded in the late XX^{th} – XXI^{st} centuries due to the new data obtained with regard to their biogeochemistry, accumulation in the food chain, routes to the human body and mechanisms of their harmful effects. Reflecting on this new information, national and international legislation bodies have been tightening their regulations regarding the environmental quality standards and revising the priority lists of the most hazardous substances adding new items and standards [4-6]. It has been recognized that the best way to reduce the anthropogenic emissions of HM is to phase out or reduce their use in industry and agriculture. A successful example of such an approach is banning the use of leaded petrol in most countries. It resulted in the dramatic reduction of lead emissions by the turn of the century, particularly in urban areas where transport remains the main source of pollution. Nevertheless, lead pollution was not completely solved as there are many other sources of lead exposure.

The goal of this paper is to assess the current state of the art in the treatment of acute and chronic heavy metal poisoning.

Background

The World Health Organisation (WHO) lists four HM – Pb, Hg, As and Cd and their compounds among top 10 chemicals of major public health concern [7]. Of these four heavy metals, Hg has the most stringent guidelines for its permitted levels in water. The extremely high toxicity of Hg led to the adoption of the legally binding global treaty tackling the problem of Hg contamination, the Minamata Convention on Mercury, to date signed by 128 signatories and ratified by 105 countries and the EU [8]. The Minamata Convention has introduced a radical approach to the Hg contamination aiming at a complete phase-out of its use in a number of applications and switch to alternative Hg-free technologies and phase down its use in the processes where it cannot be replaced yet. Despite these dramatic measures, the global anthropogenic Hg emissions have been increasing and according to the latest United Nations Environment Programme (UNEP) report, they have risen by 20% between 2010 and 2015 [9]. Whilst 10% of these emissions is attributed to natural processes, and 30% to new anthropogenic emissions, mainly in rapidly developing countries of East and South-East Asia, up to 60% are due to the recycling of previous anthropogenic emissions, which may be historically attributed mainly to the industrialised countries, including in Europe.

The health effects caused by chronic exposure to HM depend on the intake amount and the route into the body. Some HM and/or their compounds such as As, Cd, Ni, Cr(VI) belong to Group 1 human carcinogens according to the International Agency for Research on Cancer (IARC), meaning that there is sufficient or strong evidence of their carcinogenicity in humans, others, such as Hg, are potent neurotoxins (Table 1).

Table 1

WHO guidelines for maximum allowed level of the four most hazardous heavy metals in water *(μg/L)* and air *(μg/m^3)* and their impact on human health [10-13].

HM	*Drinking water*	*Air (annual average)*	*Health effects of chronic exposure*
Pb	10	0.5	Nervous system, IQ (in children), haematological effects (anaemia), neurological disturbances (headache, irritability, lethargy, convulsions, muscle weakness, ataxia, tremors and paralysis).
Hg	1	1	Neurotoxin, kidney toxicity. Neurological and behavioural disorders: tremors, insomnia, memory loss, neuromuscular effects, headaches and cognitive and motor dysfunction.
Cd	3	5×10^{-3}	Renal tubular dysfunction, which results in increased excretion of low molecular weight proteins in the urine. Irreversible chronic kidney disease. Softening of the bones and osteoporosis; chronic obstructive airway disease. Proven carcinogen - can cause lung cancer.
As	10 (subject to further revision)	No safe level* [14]	Skin lesions, peripheral neuropathy, gastrointestinal symptoms, conjunctivitis, diabetes, renal system effects, enlarged liver, bone marrow depression, destruction of erythrocytes, high blood pressure and cardiovascular disease. Proven carcinogen - can cause cancers of the skin, bladder and lungs.

**For As, as a proven carcinogen, there is no safe threshold limit.*

In the case of As, the maximum allowed level in water has been decreased 5-fold, from 50 to 10 μg/L, in the light of new data on its health impact.

Heavy metal poisoning and treatment

The current medical guidelines concerning HM poisoning and treatment practically do not consider chronic exposure. The suggested treatment is relevant to acute cases of poisoning and acute HM poisoning is classified as a rare or orphan disease [15]. According to the U.S. National Institutes of Health definition, a rare disease affects less than 1 in 200,000 people [16], whereas in the EU the definition of a rare disease is a life-threatening or chronically debilitating condition affecting fewer than 1 in 2,000 people [17]. The word "rare" is somewhat misleading. A real number of people affected could be quite significant. For example, in the U.S. in 2016 more than 10,000 patients were reported suffering from acute HM poisoning [18]. These diseases are called "orphan" because pharmaceutical companies are not interested in developing drugs for their treatment as it usually incurs financial losses. The drugs currently recommended for the treatment of acute HM poisoning are mostly generic chelatinG agents as shown in Table 2 [19]. The drug description, their ATC (anatomical therapeutic chemical) codes and chemical structures are given in Table 3. The ATC classification system is recommended by WHO for drug monitoring and research.

Chelating agents are usually bidentate or multidentate ligands containing -SH, $-NH_2$ or >C=O groups [48]. With regard to chronic poisoning with HM, there are only a few metals for which therapeutic treatment has been developed. These include Cu (Wilson's disease) and Fe (haemochromatosis), both are genetic diseases causing excessive load of copper and iron, respectively. Many chelating drugs are sparsely soluble in water and have to be administered by a parenteral route which normally requires a professional supervision by a qualified nurse or a medical doctor. Succimer, penicillamine and Unithiol are soluble in water and their use as oral adsorbents to reduce the level of Pb and As in human patients has been reported [49]. However, in a later study it was proven that intravenous administration of chelators is more efficient and should be the first treatment choice [50]. The likelihood of side-effects of chelating therapy via any route remains an issue. Adverse effects such as nausea/vomiting, fever, hypertension, tachycardia, headache, diarrhoea and more serious complications such as renal failure have been reported [51]. The use of chelating agents for the treatment of a chronic HM exposure has not been fully accepted by conventional medicine. However, not having an efficient treatment for the population chronically exposed to HM, mainly through drinking water, does not eliminate this problem and its negative health effects, particularly in developing countries [1,52,53].

Table 2

Acute heavy metal poisoning and their treatment [adapted from 19].

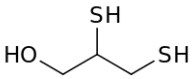
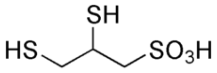
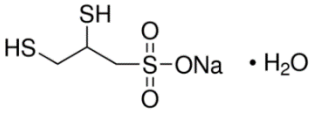
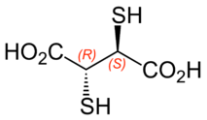
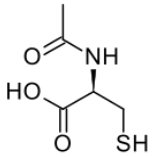
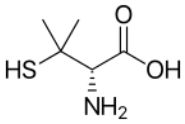
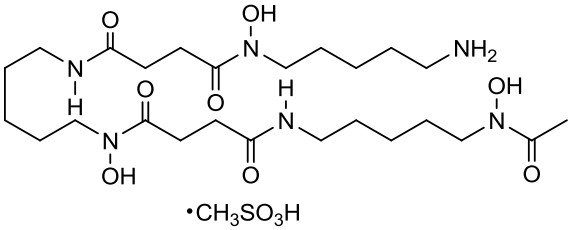
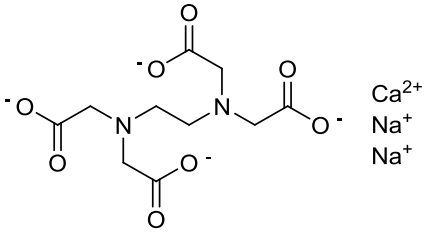
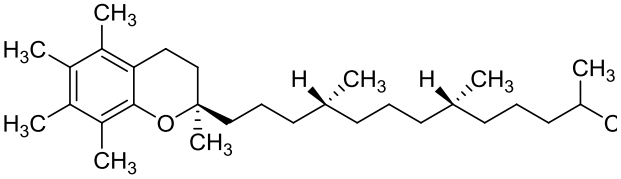
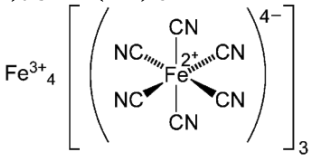
HM	*Treatment*	*References*
As*	BAL** (acute, symptomatic); Succimer; DMPS (Europe)	[20-22]
Bi	No accepted chelation regimen. DMPS (experimental)	[23]
Cd	No accepted chelation regimen. NAC (experimental), Salinomycin (experimental)	[24-26]
Cr	No proven antidote. NAC** (experimental)	[25,27,28]
Co	NAC; $CaNa_2EDTA$	[25,28]
Cu	BAL; D-Penicillamine; Succimer	[29,30]
Fe	Deferoxamine	[31,32]
Pb	BAL; $CaNa_2EDTA$; Succimer	[21,33-35]
Mn	No accepted chelation regimen, chelators (experimental)	[36]
Hg	BAL; Succimer; DMPS (Europe)	[21,22]
Ni	No accepted chelation regimen, sodium diethyldithiocarbamate (experimental)	[37]
Se*	No accepted chelation regimen	[38]
Ag	Selenium, vitamin E, DMSA (experimental)	[39]
Tl, Cs	Multi-dose AC; Prussian blue	[40-45]
Zn	No accepted chelation regimen	[46]

**As and Se are heavy elements rather than metals but traditionally considered together with HM.*

***The explanation of the acronyms is given in Table 3.*

Table 3

Names and chemical structure of the drugs recommended for the treatment of acute HM poisoning.

Drug	*Acronym and other names*	*ATC Code* [47]*	*Chemical formula*
British anti-Lewisite	BAL	V03AB09	
2,3-Dimercapto-1-propanesulfonic acid	DMPS, Dimerval	V03AB43	
2,3-Dimercapto-1-propanesulfonic acid, sodium salt	Unithiol	V03AB43	
Succimer	Chemet, Dimercapto-succinic acid, DMSA	V09CA02	
N-acetylcysteine	NAC, Acetylcysteine	R05CB01	
D-penicillamine	3,3′-Dithiobis-D-valine	M01CC01	
De(s)feroxamine mesylate	DFO, Desferal	V03AC01	
Ethylenediaminetetra-acetic acid, calcium disodium salt	EDTA, $CaNa_2$ salt	V03AB03	
Vitamin E	Tocopherol	A11HA03	
Prussian blue	Radiogardase®	V03AB31	$Fe_4[Fe(CN)_6]_3$, $Fe_7(CN)_{18}\ xH_2O$, where x= 14–16 

Enterosorption

The use of oral adsorbents could be an alternative, cost-effective and efficient approach to reducing the impact of chronic exposure to heavy metals. In modern literature, different terminology is used to define insoluble materials that are administered orally and act as adsorbents in the gastrointestinal tract (GIT), where they bind exogenous and/or endogenous toxins. In English literature the terms "oral" or "intestinal" adsorbents are used. The word "enterosorbents" is more common in the literature published in the former Soviet Union countries [54,55], although the term "enterosorption" probably first appeared in a paper written in English [56] describing the adsorption of substances by a material passing through the GIT [57]. These materials are neither metabolised nor adsorbed inside the body and are excreted unchanged removing from the organism harmful substances. Among enterosorbents, activated carbon (AC), or charcoal, has been known for millennia [58].

A number of materials of natural or synthetic origin have been approved for use as enterosorbents (Table 4). To date, enterosorbents have been mainly used for the treatment of acute conditions such as exogenous poisoning, diarrhoea and bacterial infections. The mechanism of their therapeutic action is complex, and its analysis is beyond the scope of this review. It has been described in detail elsewhere [61,67,71,72]. The number of cases related to the use of enterosorbents for heavy metal removal from the human body or in animal experiments is significantly lower than the number of publications concerning their other medical applications or the use of such materials in environmental decontamination from HM. Here are highlighted the key factors contributing to the HM binding capacity of enterosorbents:

(i) ionised or ionisable polar functional groups capable of binding HM ions (cations and anions) by ion exchange;
(ii) functional groups capable of complex formation with HM ions;
(iii) molecular adsorption of HM containing species (neutral molecules, protein-bound HM);
(iv) functional groups with high affinity to specific HM

The surface complex formation is similar to the action of chelating agents described above.

In terms of their pharmaceutical classification, enterosorbents could be defined as medicinal drugs or medical devices. If medicinal products – they are regulated under the EC Community code on medicinal products for human use (and amendments) [73]. If they are classified as medical devices – they are regulated by the EU Medical Devices Regulations (MDR) [74] and respective UK regulations [75]. Many products including a number of enterosorbents, have been transferred from being regulated under the medicines legislation to being regulated under the MDR, which allows their faster approval for use in therapeutic treatment. According to the Rule 21, of the MDR (EU) 2017/745, enterosorbents are classified as class IIb medical devices, because their "…*principal intended action is typically fulfilled by physical means (including mechanical action, physical barrier, replacement of, or support to, organs or body functions)*" [76]. However, by consensus of EU Member States active charcoal / carbon solutions for treatment of acute poisoning are considered to be medicinal products.

Table 4

Main types of enterosorbents.

Generic name	*Examples*	*References*
Natural polymers	Polysaccharides: microcrystalline cellulose, chitosan (alkaline deacetylated chitin), pectins, alginates. Lignin (hydrolysed lignin Polyphepan, Lignosorb).	[59-62]
Synthetic polymers	Cholestyramine (or colestyramine) resin comprising styrene-divinylbenzene (DVB) copolymer with quaternary nitrogen groups; hydrophobic styrene-DVB resins (polystyrene cross-linked with DVB); polyvinylpyrrolidone (Enterosorb, Enterodesum, Povidon).	[63-65]
Inorganic sorbents	Silica (Silix, "white clay", "white carbon", Polisorb, colloidal silica), clays, bentonite, diosmectite (Smecta®), montmorillonite, kaolinite, zeolites, aluminium hydroxide (Antacid).	[66-69]
Organosilicates	Polymethylsiloxane (hydrated, Enterosgel®, or polymethylsilicic acid polyhydrate).	[57,70]
Activated carbons (ACs)	Various ACs from synthetic and natural precursors; granular, fibrous and tablets.	[55,58,61,67]

In post-USSR countries (Russia, Ukraine, *etc*.) enterosorbents are medicinal products and 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 or 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 strict rules applied to the assessment of medical devices or medicinal products, which often creates uncertainties with regard to their efficiency in protecting human health.

According to their chemical structure, enterosorbents originated from natural polymers or inorganic minerals, have a large number of functional groups of types (i) and (ii). For example, polysaccharides have -OH and -O- and -COOH groups, chitosan also has -NH_2 groups, lignin has phenolic groups, whereas inorganic enterosorbents based on silica and silicates contain M-OH groups, M being Si, Al or Mg. In natural minerals, H is partly replaced by Na or Ca. Thus, inorganic enterosorbents, which are different types of zeolites and clays, have ion exchange groups, mainly with cation exchange properties. It has been shown that they are capable of binding a number of HM, some of them even in anionic form [72,73-77], but these results have been obtained in model systems not always resembling GIT environment. Encouraging results confirming the ability of natural minerals to remove lead from the organism of small animals and prevent accumulation of cadmium in pigs have been reported for zeolites [78,79]. The correction of mineral balance in 53 children receiving zeolite-based enterosorbent for one month has been reported [80]. Its regular administration reduced the content of Cr, As and Ni and increased the content of Mg and Ca in the tissues, bringing it closer to the mineral content in healthy children tissues. Oral administration of clinoptilolite led to a significant increase of urinary excretion of Al, Sb, As, Bi, Cd, Pb, Hg, Ni and Sn in two groups of healthy male volunteers (each consisting of 11 individuals, aged 35-71 years, group 1 administered for 7 days and group 2 for 30 days) compared to the placebo control group [81]. A negative impact on electrolyte profiles was absent. The mechanism of increased urinary excretion of HM upon enterosorption is not clear and may not be a result of a direct adsorption of HM by clinoptilolite. Vermiculite as an enterosorbent significantly reduced the concentration of radiocaesium-137 in rats after two and three weeks of administration, showing the most significant effect compared to another inorganic enterosorbent, palygorskite. It has been suggested that in addition to direct binding of Cs-137, enterosorbents may exhibit a beneficial effect by removing radiotoxins produced *via* lipid peroxidation activated by incorporated radioactivity [82]. The use of bentonite, a montmorillonite clay, proved beneficial in reducing the level of lead, cadmium and nickel in the blood of cows (n= 10 animals) by 36 to 46% against the control group (n= 10) after 60 days, with the daily administration dose of 50 g per experimental animal [83].

However, it should be noted that recently the use of one of the most popular enterosorbents, Smecta®, has been discouraged and even forbidden for children under 2 years of age because the natural mineral diosmectite, which is the basis of Smecta®, contains natural traces of HM and in particular lead, which may be released inside the body [84]. It raises concerns about the safety of other enterosorbents obtained from natural minerals which might also have Pb and other HM as their natural impurities [85] and require additional purification prior to their possible oral administration [86]. It has been argued that despite the possible presence of heavy metal traces as natural impurities in mineral enterosorbents, due to their strong affinity with the mineral matrix, HM retention prevails and prevents them from being released into the body. However, this issue remains controversial and requires further investigation.

Synthetic silicon-based sorbents, such as silica and organosilicon polymers, are not contaminated with HM due to the conditions of their synthesis which allow controlling the impurities. Among these materials, highly dispersed silica produced under different trade names and Enterosgel® have been most often used as enterosorbents (Table 4). Highly dispersed silica has a large specific surface area (up to 400 m^2/g) [87,88]. Its core structure comprises tetrahedral -Si-O-Si-O- units (Figure1).

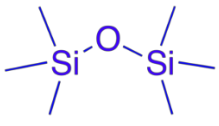


Figure 1. **The core structural unit of silica.**

In the surface layer, the silicon atoms contain terminal -OH groups in the silica, and -OH and $-CH_3$ groups in the hydrated polymethylsiloxane (Enterosgel®). The surface hydroxyl groups are capable of binding HM ions, which was confirmed mostly in *in vitro* experiments and in animal studies. The use of silica and Enterosgel reduced the level of lead, cadmium and some other heavy metals in the blood and tissues of animals, normalised their biochemical metabolism and had a protective action of the internal organs, such as liver and kidneys, against HM [70,89-91]. Silica (Aerosil®) added to the diet of cows at a dose of 40 mg/kg body weight (n= 10) for three months reduced by more than 50% ($p< 0.05$) zinc, cadmium and lead content in the milk of animals against the control group and it also outperformed the group which received the chelating agent EDTA at a dose of 2% by weight of the diet dry matter [92]. However, Enterosgel® has not been widely used for HM removal as its adsorption capacity for ionic and low molecular weight substances is low in comparison with most other enterosorbents.

Enterosorbents based on natural biopolymers such as alginates and pectins, have also been reported as being able to bind HM *in vitro* [93]. Oral administration of a purified citrus pectin (molecular weight 15,700) in a small group of children (n= 7, aged 5 to 12 years) with blood Pb levels >20 μg/dL, who received 15 g/day of citrus pectin for 2 to 4 weeks led to a drop in blood Pb levels by an average of 161%, and urinary lead excretion increased by an average of 132%. The authors noted that there were no safety concerns with using this procedure and this preparation was on the official register of GRAS (generally regarded as safe) substances under the U.S. Code of Federal Regulation 21CFR184.1588 [94]. The same commercially produced pectin preparation, used in a pilot trial on eight healthy volunteers, 39 to 52 years of age, statistically significantly increased urinary excretion of As, Pb and Cd within 1-6 days of its administration of 15-20 g per day, divided into three or four 5 g doses. A 150% increase in cadmium excretion and a 560% increase in lead excretion on day 6 were reported [95]. The authors explained this effect by chelating properties of pectin attributed to the presence of rhamnogalacturonan II in its composition and the mobilization of metals from body stores. Essential minerals such as Ca, Zn, and Mg were not noted to increase in the urinary analysis. In a series of case reports, five patients with different illnesses took purified citrus pectin alone or in combination with alginate for up to eight months. The patients showed a 74% average decrease in toxic heavy metals after treatment [96]. However, in another study, which used rhamnogalacturonan-II dimer, a pectic polysaccharide, as the enterosorbent administered for 6-9 weeks, failed to increase urinary or faecal excretion of Pb in rats exposed to chronic oral lead administration [97]. Importantly, pectin enterosorption did not affect the level of essential elements such as Mg and Ca, which could be related to the different affinity between the chelator and metal ions [93,95]. Nevertheless, no mechanism was proposed to explain the enhanced urinary excretion and the analysis of faeces which were likely to contain most of the excreted HM [81,95]. In [98], 20 patients with chronic pancreatitis living in a HM contaminated area were administered citrus pectin, at 10 g daily dose for 10 days. The content of Pb and Cd determined in their saliva was significantly reduced compared to the control group of patients (n= 20) who did not receive pectin, in which the HM content did not change. The authors also mentioned that pectin enterosorption reduced the level of essential microelements in saliva, but no data were presented. Several pectin-based preparations have been approved for use as food supplements in post-USSR countries to remove HM from the population living in contaminated areas and workers exposed to HM as an occupational hazard [99].

Chitosan and calcium alginate enterosorption were reported to significantly reduce the content of HM in tissues and internal organs of cattle, in particular Pb in bones, Zn and Pb in muscles, Zn, Cu and Pb in liver and Cd in kidneys. Enterosorption also had a positive effect on the immune system of the animals. Both enterosorbents were administered to 3-4 months old calves in the dose of 100 mg/kg weight, both experimental and control groups had 20 animals each [100]. In another work, lead acetate was administered to rats for three weeks, followed by three weeks of enterosorption using different materials (calcium alginate, calcium pectate, AC and lignin) at the daily dose of 0.5 g/kg body weight. Of the enterosorbents tested, calcium pectate and calcium alginate showed similar results and were more efficient in accelerating removal of Pb with faeces and reducing its content in kidneys and femur but, surprisingly, increased its content in the liver and heart [101]. This controversial result suggests a complex mechanism of lead – enterosorbent interaction and requires a cautious approach to the use of

these materials and conducting more comprehensive studies.

A comparative study of cotton lignin-based and citrus pectin-based enterosorbents in the treatment of rats exposed to a mixture of the salts of Cu(II), Mn(VII), Cr(VI) and Mo(VI) for four weeks followed by oral administration of sorbents for three weeks showed positive dynamics in the cell structure of internal organs, in particular, morphological normalisation of liver and kidneys [102]. The authors attributed better results obtained with the pectin sorbent to a larger content of chelating groups in the pectin structure compared with the lignin structure and thus more efficient binding and removal of HM. It has been suggested that the HM binding capacity of pectins is dependent on the availability of free carboxylic groups in H-form rather than esterified groups which have much weaker binding properties. This assumption is based on the ion-exchange mechanism of HM adsorption, however there is also evidence of surface complexation which involves OH-groups [103]. It should be noted that comparing adsorption efficiency of pectin-based sorbents is difficult because their properties depend on the technology of extraction and chemical modification of pectins which varies widely between different manufacturers.

Although HM enter the human body mainly with contaminated food and water, *via* the gastrointestinal route, they are then distributed through the blood to other tissues and organs [104]. The use of pectin-based enterosorbents for the prophylactic treatment of the population living in the HM-polluted environment and the personnel exposed to HM as an occupational hazard was suggested in [105,106], although probably the use of pectins for preventing lead accumulation in the human body was first suggested in 1953 [107]. It was shown that the prophylactic use of pectin-based enterosorbents was efficient in preventing lead or mercury accumulation in the organism of workers engaged with manufacturing lead batteries and mercury recycling [108]. Several pectin-containing compositions comprising a combination of sugar beet pectin and apple pectin with vitamin additives have been approved by the Ministry of Health of Ukraine for the prophylactic use as dietary supplements or biologically active additives (as they are known in post-USSR countries) which protect the general population and personnel against accumulation of heavy metals [109]. A comprehensive study of the effect of the prophylactic use of pectin-based enterosorbents was carried out in [110]. The pectin prophylactic treatment of 272 children, 4-6 years old, for 28 days resulted in decreasing the lead content in the blood accompanied by its enhanced renal elimination and normalisation of aminolevulinic acid (ALA) activity measured by the reduction of creatinine in the urine. 91% of the examined children showed improvement in psychophysiological testing. The authors hypothesised that the enhanced renal elimination of lead is also caused by the pectin prophylaxis which facilitated the release of incorporated lead from tissue depots although they gave no data explaining this mechanism. The pectin enterosorbent was administered in small quantities, four dragées daily, and the results were not compared with a control group. A positive protective effect of the pectin prophylaxis on children against heavy metals Pb, As, Cu, Cr and Cd was also reported in [111]. At present, the use of pectins of different origin for eliminating HM or preventing their accumulation in the human body has been recommended by ministries of health in Russia, Ukraine and some other post-USSR countries [109,112].

Encouraging results were reported in [113]. In this study, 64 healthy pregnant women (in II and III trimesters) received 3 g of apple-beetroot pectin, 4 tablets, daily for 20 days, 30 min before meal. By the end of the treatment period, a statistically significant ($p<0.05$) reduction in the blood level of Cd (40%) and Pb (26%) was registered. It should be noted that pectin administration also led to a significant reduction of the blood level of organochlorine pesticides suggesting that this type of enterosorbent offers protection against a broad range of xenobiotics of different classes.

It should be noted that the pectin-based formulations have been approved for use as dietary supplements rather than medical adsorbents in these countries. This decision is in line with the U.S. FDA approval of pectins as GRAS substances [114]. Pectin containing supplements have been designed in a variety of forms, such as dragées, tablets, marmalades, drinks and jellies [115]. Taking into account that the pectin content in natural products is low, in the range of 0.4-2.0%, the use of dragées or tablets enriched with pectins is preferable for the prophylaxis of HM accumulation. In these formulations, pectin is contained in powders extracted from the natural products, which also have natural fibres and a wide range of vitamins thus, in addition, improving digestion and strengthening the immune protection of the

organism. Although insufficient data are available regarding the optimal daily pectin intake for the prophylaxis of HM accumulation, usually the dose of up to 2 g per administration is suggested. The dose and the daily frequency of intake depends on the age of the person, and importantly, it is recommended for adults and children from 2-3 years of age.

AC is the earliest enterosorbent known to humankind and used to treat poisoning of different origins. [116,117]. Its main use in medicine remains the treatment of acute poisoning. A single- or multi-dose AC enterosorption has been recognized as the only efficient treatment of acute poisoning [118]. Undoubtedly, AC has the ability to adsorb heavy metal species from aqueous solutions, mainly by the mechanism of complex formation and ion exchange between its surface functional groups such as phenolic and carboxylic groups and metal ions or *via* molecular adsorption of uncharged metal compounds [119,120]. The ability to adsorb metal ions is enhanced if the AC is oxidized, due to the introduction of a larger number of acidic groups on its surface compared to the unoxidized precursor AC [121]. The greatest advantage of AC is its large specific surface area, which makes it the most powerful physical adsorbent among all materials. However, it has been seldom used as an enterosorbent for chronic poisoning treatment partly because of its poor palatability and appearance (black colour) and partly because its main advantage of high adsorption capacity could turn into a disadvantage by depleting the organism of other medicines and nutrients, and thus requiring precautions regarding the time of its administration and the dietary requirements. In general, AC administration is not considered effective in treating metal poisoning [116,118,122]. The exception seems to be acute thallium poisoning, in which use of AC enterosorption proved to be efficient if administered early [123]. The reason of this efficiency is probably related to the presence of thallium in a nonionic form and adsorption occurs *via* a molecular mechanism rather than ion exchange or complexation.

Radionuclides – a special case of heavy metal poisoning

Following accidents at Chornobyl, Ukraine (26 April 1986) and Fukushima Daiichi, Japan (11 March 2011) nuclear power plants (NPPs) which affected large cohorts of population in the surrounding areas, exposure to radionuclide contamination and both acute and chronic intake by humans has become a major issue. The majority of counter-measures are focused on preventing personnel and civil population from direct contact with and reducing the exposure to radioactive materials and/or ionizing radiation. They include using personal protection equipment, disposing of contaminated materials, washing skin and hair and sealing protected areas from radioactivity penetration and, if necessary, evacuation of the population from the contaminated territories. These measures effectively protect the human bodies against external radiation and significantly reduce risk of internal contamination. They do not, however, reduce harmful effects of radioactivity, which has already been incorporated in the body due to an earlier exposure or radionuclides which could enter the body through the food chain. There are no means to neutralize internal radioactivity, which has to be eliminated from the body to terminate its destructive action. In this sense, incorporated radioactivity is similar to poisoning with non-radioactive heavy metals.

After the Chornobyl disaster 135,000 people were evacuated and an estimated number of 800,000 “liquidators” took part in clean-up activities at the site and within the 30-km Exclusion Zone. These cohorts and a large number of people living in nearby areas have been continuously exposed to low-level radiation, which resulted in accumulation of elevated levels of internal radioactivity caused by incorporated radionuclides. Before the erection of Sarcophagus, or Shelter in November 1986, military personnel and specialists were exposed to higher doses of radioactivity and the risk of internal contamination with radionuclides was significant, as confirmed by the analysis of blood, urine and faeces [124]. Although radionuclides can be extremely toxic as chemicals, and plutonium and polonium in particular exhibit high chemical toxicity, this feature is unlikely to make significant contribution to detrimental health effects of radioactive substances, because their chemical concentration in the body is expected to be very low. Nevertheless, incorporation of radionuclides in human body may have long lasting health effects caused by ionising radiation. The only medical concept which can be exploited at present to prevent negative health effects of low-level radioactivity is to accelerate removal of radionuclides from the body. Use of laxatives for accelerated excretion of radionuclides from the gastrointestinal tract may be recommended only immediately after the contamination event [125].

Certain drugs, such as penicillamine or dimercaprol (British antilewisite) may bind

radionuclides converting them into a less soluble and less bioabsorbable state and thus reducing their biological half-life [125-127]. Although this approach has a chemical rationale, it can hardly be recommended for a regular treatment of patients. These drugs are rather toxic and can be used only in small doses and for a few days. They have not been tested on most radionuclides.

Enterosorption using AC proved its efficiency in the prophylactic protection of personnel against internal accumulation of radionuclides (Table 5). Two groups of military personnel, 25-50 y.o. males, worked for 10-18 days during April-July 1986 as "liquidators" in the Chornobyl zone. One group (57 persons) was administered the dose of 5-7 g of AC, 3 times a day, 1-1.5 hours before meal, and the control group (30 persons) did not receive the enterosorbent [124]. The prophylactic enterosorption with AC resulted in a significant reduction of radioactivity in the blood of personnel in comparison with the control group (Table 5).

A similar, but less pronounced effect of enterosorption on the level of radionuclides in the blood and urine was registered in the personnel who received the same AC treatment as described above, but started 2-3 days after their exit from the zone. After two weeks of treatment the total radioactivity in their blood and urine was statistically significantly lower than in the control group which did not receive the treatment. The greatest reduction of radioactivity was due to the removal of La-140 and I-131, whereas the difference in the levels of Cs-134 and Cs-137 between the two groups was insignificant [125]. The effect of enterosorption on radionuclide removal from the human organism was enhanced using simultaneously medical preparations which stimulated bile or gastric juice secretion. The positive effect of enterosorption on removing incorporated radionuclides was also reported using other AC adsorbents and Enterosgel®. These results seemingly contradict the low efficiency of some enterosorbents in binding and removing non-radioactive heavy metals; however, the cause of this controversy is the extremely low mass concentration of radioisotopes in the human body in comparison with the concentration of non-radioactive HM that could accumulate in the organism. For example, the specific activity of Cs-137 is 87 Ci/g [128], which corresponds to its concentration of ca. 3×10^{-10} g/L (in Table 5). At such a low mass concentration of the target radionuclide, even an adsorbent with a small number of functional groups with chelating properties is sufficient to bind it.

Chitosan-, pectin- and alginate-based chelators and enterosorbents have been shown to possess radionuclide binding properties, as well. A commercial chitosan lactate, 90% deacetylated, or chitosan oligosaccharide, 40% deacetylated, were orally administered to rats immediately after the intravenous injection or oral intake of Co-60 dichloride with the activity of 7 to 13.2 kBq/animal. Two doses of ca. 300 mg/kg of body weight were administered within 48 h. In the animals treated with chitosan chelators, the accumulation of Co-60 in internal organs and skeleton was significantly lower (by 56-62%) than in the control group, whereas the effect of chitosan lactate was less significant [129]. Calcium alginate is recommended for decorporation of radiostrontium and other calcium salts have also been effective in its binding. [130].

There are numerous reports about the efficiency of pectin containing enterosorbents in radionuclide decorporation. After Chornobyl NPP accident different pectin-based formulations were proven effective in decorporation of radionuclides in animal studies and from the human organism, in particular removing radiostrontium and radiocaesium, which are the main radioactive contaminants [131,132].

Table 5

Prophylactic use of activated carbon SCN as an oral adsorbent [adapted from 125].

Radionuclide	*Radioactivity in blood, Ci/L×10^{8}*		*(1)/(2)*
	Without sorbent (1) (n= 30)	*With sorbent (2) (n= 57)*	
I-131	5.16±0.41	0.71±0.07	7.3
Ru-103, -106	2.86±0.15	0.66±0.08	4.7
La-140	51.8±4.7	3.01±0.38	17.2
Cs-134, -137	2.34±0.19	1.19±0.80	2.1
Zr-95	2.15±0.34	0.82±0.08	2.6
Nb-95	3.32±0.32	1.68±0.11	2.0
Ce-141, -144	5.69±0.67	2.32±0.25	2.5
Average total	67.7±21.1	7.98±2.38	8.4

Most of these data were published in the context of the Chornobyl NPP accident, which released large amounts of a range of radionuclides in the environment and affected several million people, many of whom continue living in the contaminated territories [133]. The environmental and health consequences of the Fukushima Daiichi NPP accident are mainly associated with the release of Cs-134 and Cs-137 and short-living I-131 (half-life 8 days) [134]. In comparison with the Chornobyl NPP accident, the external and internal radiation exposure levels of humans living in the contaminated area are low and the potential health risks are also considered to be low [135]. With regard to radiocaesium, the adsorbents of choice since 1987, after the accident in Goiânia, Brazil, have been the Prussian blue capsules or Radiogardase® (Table 3), approved by FDA [136]. The use of combined enterosorbent formulations comprising different combinations of AC, a modified palygorskite clay, commercial alginates, alginate from the seaweed *Laminaria* and citrus, apple or beetroot pectin proved to be efficient in adsorbing a range of heavy metals and radionuclides in the experiments *in vitro* [137]. To increase the adsorption efficiency towards Cs, palygorskite was modified by impregnation with copper ferrocyanide. All preparations were proven safe in animal trials. In the follow-up trials on volunteers who lived in the territories contaminated by Chornobyl NPP fallout and were exposed to low level radiation, the preparation "Ultrasorb" comprising 40% by weight of oxidised AC charged with cations of K, Mg and Zn and 60% by weight of modified palygorskite, showed the best results. In the experimental group (n= 5), which received 7-8 g of Ultrasorb three times a day for 14 days, the overall internal body radioactivity reduced by 14% on the 7th day and by 20% on the 14th day, whereas in the control group (n= 5) which did not receive the enterosorbent, there was no statistically significant reduction of radioactivity [137].

A new impetus to research on the development and use of enterosorbents in human protection against radioactivity exposure has originated from a "dirty bomb" threat [138]. A dirty bomb, or a radiological dispersal device is a potential radiological weapon that can disperse radioactive substances using conventional explosives. Its alleged purpose is to contaminate large inhabited areas with radioactivity making them hazardous to human health. Although to date no such terrorist activities have been reported, one could argue that the Chornobyl NPP accident was an inadvertently made dirty bomb at a very large scale in terms of its consequences and impact on the environment and health.

Several decorporation strategies after a nuclear accident, intentional or not, have been considered [139]. It has been suggested that the decorporation measures should be taken as soon as possible once the radiological threat has been confirmed. An early treatment would also have a profound psychological effect on general public because of their fear of radioactivity – an "invisible enemy". It means that enterosorbents should be stockpiled in advance to enable an immediate action.

Conclusions

Enterosorption is a safe and efficient method of reducing internal body load with harmful heavy metals and radionuclides eliminating them by adsorption. As an auxiliary method to medical treatment, it reduces the negative impact of heavy metals on health. It is an important tool for protecting population chronically exposed to the intake of heavy metals or radioactivity due to industrial activities or in the aftermath of technogenic or natural accidents.

The prophylactic use of enterosorption is efficient in preventing heavy metal and radioactivity accumulation in the organism and could be recommended for first responders and personnel exposed to occupational hazards.

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Short biography of the author

Professor Sergey Mikhalovsky is a Physical Chemist, with main research interests in surface chemistry and chemistry of materials. His research track record spans over 40 years in academia in the UK, USA, France, Ukraine and Kazakhstan. He graduated from Shevchenko National University of Kyiv with MSc in Chemistry and defended his PhD (Chemical Kinetics and Catalysis) at the National Academy of Sciences of Ukraine. From 1994 Sergey worked at the University of Brighton, UK, where he was Professor of Materials Chemistry and led the research group in the area of biomaterials and biomedical devices. In 2018 Professor Mikhalovsky has founded an R&D company ANAMAD Ltd, which is focused on advanced nanostructured materials design and consultancy. His international collaborations include academic and industrial partners from Europe, USA, China, Kazakhstan, Central and South-East Asia.

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