«General pharmaceutical chemistry »

METHODS FOR THE DETERMINATION OF HEAVY METAL AND ARSENIC IMPURITIES IN MEDICINAL PRODUCTS

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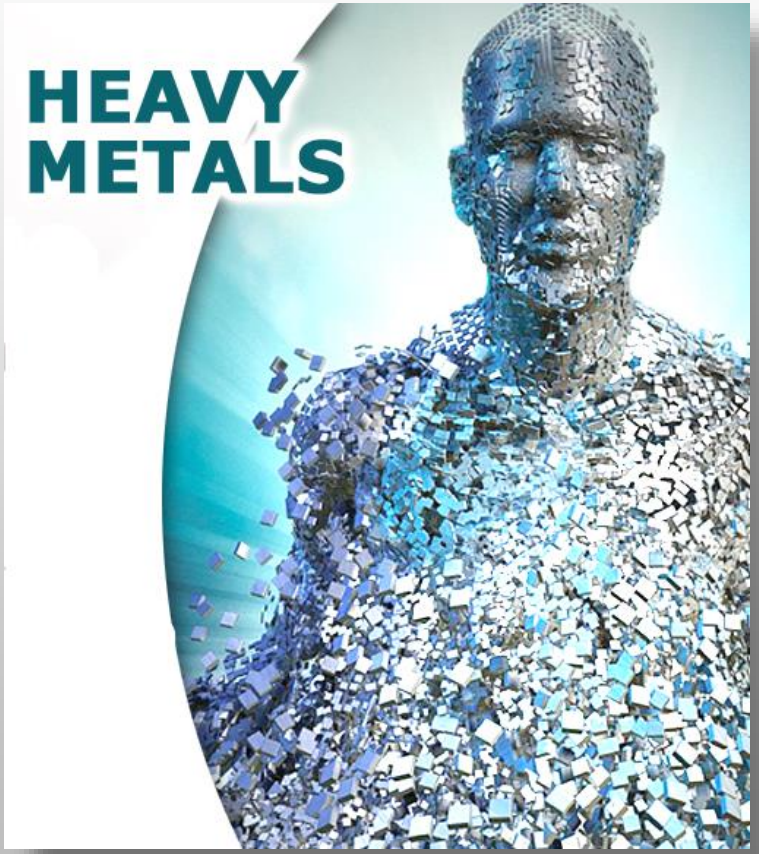
The definition of heavy metals

The concept of a “heavy metal” is not clearly scientifically defined.
The State Pharmacopoeia of the Russian Federation lists the following heavy metals:

- ✓ lead, Pb
- ✓ mercury, Hg
- ✓ bismuth, Bi
- ✓ antimony, Sb
- ✓ tin, Sn
- ✓ cadmium, Cd
- ✓ silver, Ag
- ✓ copper, Cu
- ✓ molybdenum, Mo
- ✓ vanadium, V
- ✓ ruthenium, Ru
- ✓ platinum, Pt
- ✓ palladium, Pd

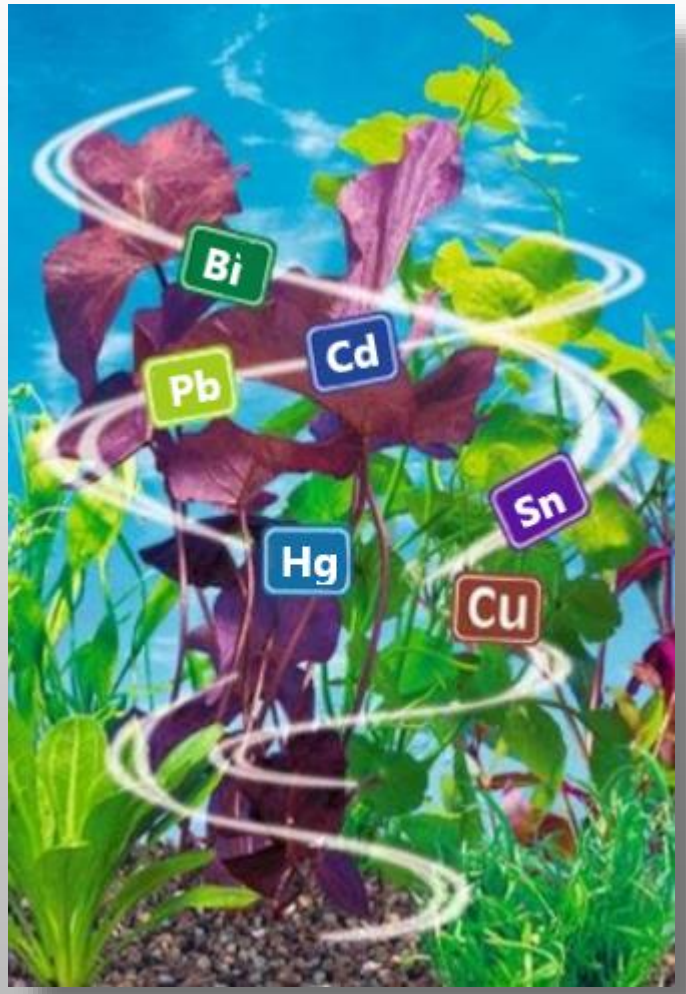
The origin of heavy metals in nature

- Heavy metals are largely found in nature as minerals and ores.
- They get into the environment as a result of being extracted, from erosion or from volcanic activity.
- Heavy metals are used in a number of technical applications and processes and can get into the environment or into products unintentionally.



Heavy metals in medical plants

- Intake of heavy metals occurs in the growth process of plants by absorption from water, from the ground and by aerosols from the ambient air.
- Contamination can also occur from the spillage of pesticides or sewage sludge containing heavy metal.



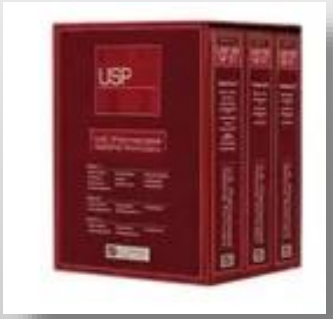
Heavy metals in finished products and raw materials

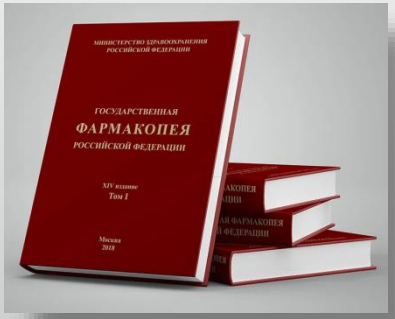
In the manufacturing of pharmaceutical products, catalysts containing heavy metals are often involved in the synthesis.

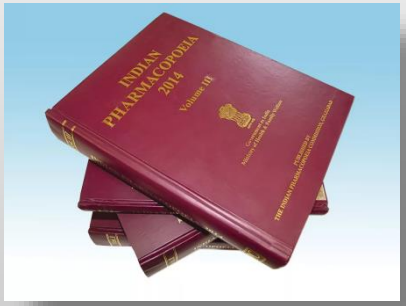
Heavy metals can also transfer into the process by abrasion or by leaching (e.g. Fe, Ti, Cu, Cr and so on.) If they are not removed efficiently, then the tainted products could get into the market.

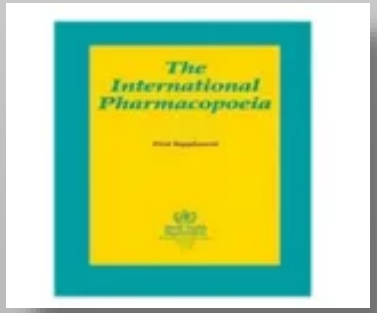
Legal regulations

For many years, it has been known that certain heavy metals exhibit toxic effects even at low concentrations. As a result, limit values for the protection of the patients have been defined in the legislation and in the various pharmacopoeias (e.g. SPRF., Ph. Eur., USP, JP, BP).



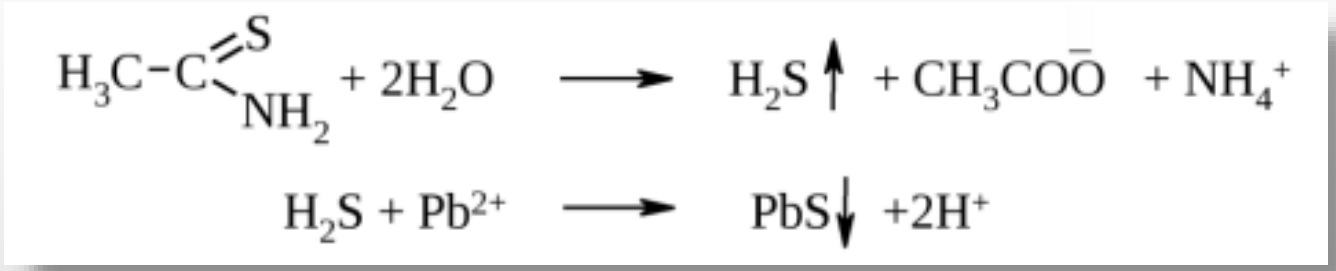




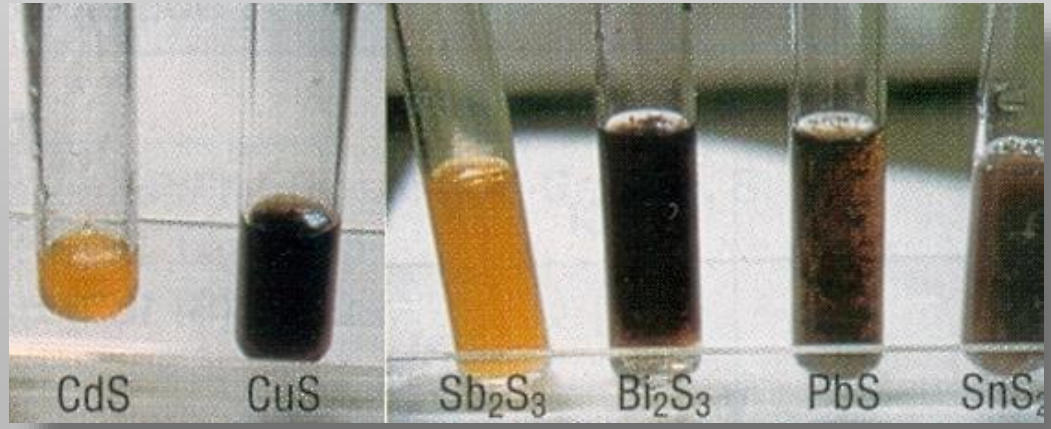


Detection methods

Method 1



Method 2



Detection methods

Test is considered accurate if the reference solution has a slight brownish colour compared to blank solution.

Detection methods

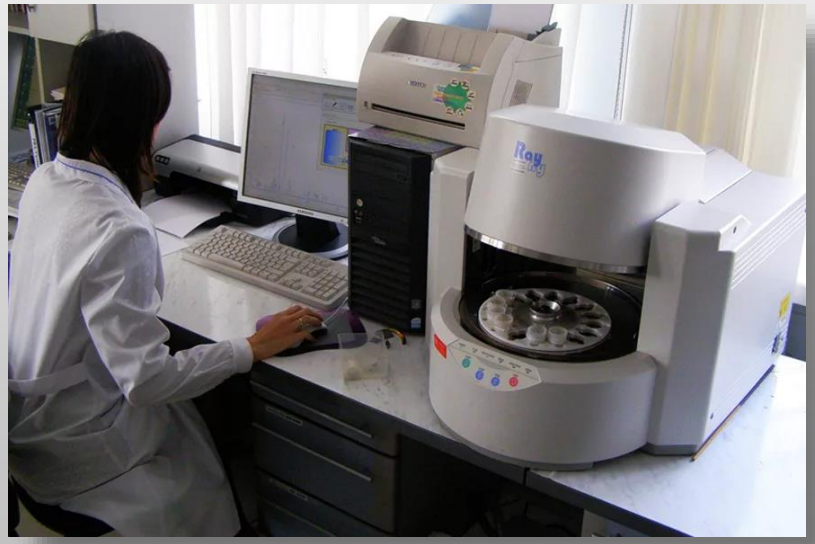
- These limit tests still form the majority of testing for heavy metals in the current national and international Pharmacopoeias. Thereby, it is possible however to make only a semi-quantitative statement about the total contents of heavy metals in the sample.
- Determination of heavy metal content in pharmaceutical products is possible **for substances that form a clear, colourless solution and do not affect the interaction between metal ions with sulphide-ions** due to complex-forming properties.
- In all other cases, determination is performed using sulphate ash or other mineralization technique of the test pharmaceutical product.

Detection methods

Maximum permissible content of heavy metals, testing method and conditions for preparation of the test sample must be indicated in the general monograph.

The following methods can be used for quantitative determination:

- atomic absorption spectrometry;
- atomic emission spectrometry with inductively coupled plasma;
- inductively coupled plasma mass spectrometry.



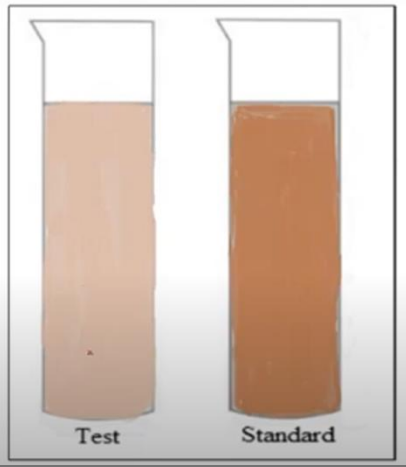
Determination of heavy metals in pharmaceutical solutions

Test solution. 10 ml of a test solution prepared according to the general monograph.
Reference (Standart) solution. Add 8 ml of water to 2 ml of lead ion reference solution (5 µg/ml).
Blank solution. 10 ml of water.

Method 1. To the obtained solutions add 2 ml of acetate buffer solution pH 3.5, stir, add 1 ml of thioacetamide reagent, stir and compare colouring of solutions after 2 minutes.

Method 2. To the obtained solutions add 1 ml of diluted 30% acetic acid, 2 drops of 2% sodium sulphide solution, stir and compare colouring of solutions after 1 minute.
Slight opalescence of test solutions from precipitated sulphur is acceptable.

If the **brown color** produced in **sample** solution is **less intense** than that of standard solution, then the sample **passes** the limit test for heavy metals.



Arsenic

33
As
Arsenic
74.921

Arsenic (Latin Arsenicum, chemical symbol — As) — chemical element of the 15th group of the fourth period of the periodic system; has the atomic number 33.

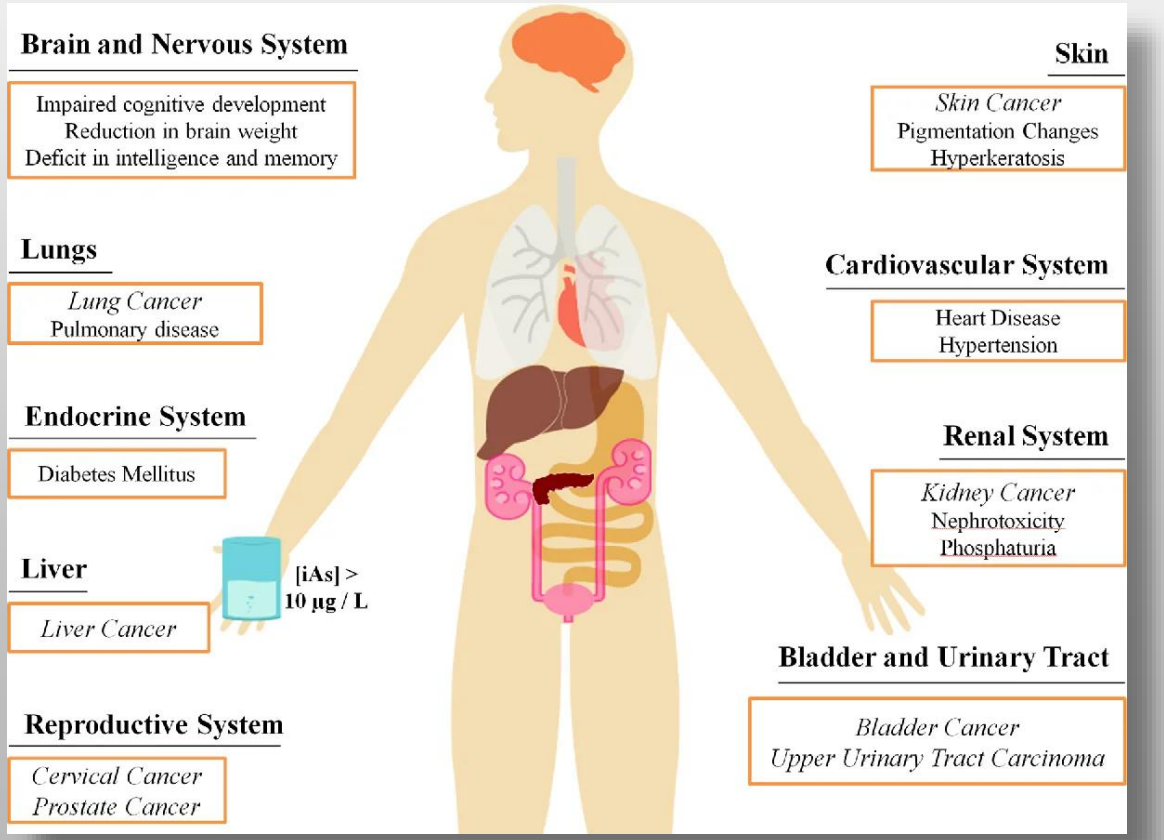
The simple substance is a brittle steel-colored semi-metal with a greenish tinge (in a gray allotropic modification).

Poison and carcinogen. The lethal dose of arsenic for humans is 50-170 mg.

Arsenic

Arsenic can get into medicines

- from the material of equipment used in the manufacture of drugs,
- together with raw materials, solvents, most often with sulfuric acid, used in most pharmaceutical industries.



Methods for detecting arsenic impurities

- [x] Bugo and Thiele
- [x] Gutzeit
- [ ] Bettendorf
- [ ] Marsh

Gutzeit method

1. Reduction of arsenic compounds to arsin AsH_3.

$$2H_3AsO_3 + 6Zn + 12HCl \longrightarrow 2AsH_3 + 6\,ZnCl_2 + 6\,H_2O$$

2. The interaction of arsin with a solution of silver nitrate, which is soaked with filter paper.

$$AsH_3 + 6AgNO_3 \longrightarrow Ag_6[As(NO_3)_3] + 3\,HNO_3$$

3. Under the influence of moisture, the complex is destroyed with the release of metallic silver, which forms a dark spot on the filter paper.

$$Ag_6[As(NO_3)_3] + 3\,H_2O \longrightarrow H_3AsO_3 + 6\,Ag + 3\,HNO_3$$

Disadvantages of the Gutzeit method

- Arsenic can be determined by the Gutzeit reaction if it is known that there are no antimony or phosphorus impurities in the samples under study. Since under these conditions of reduction of arsenic compounds by zinc, SbH_3 and PH_3 can be formed from these impurities, which will mask the main reaction to arsenic.
- It is impossible to open an impurity of arsenic in the presence of mercury or silver salts, since they are also restored and mask the discovery of arsenic.
- Oxidizing agents, compounds forming chlorine, bromine, iodine, hydrogen sulfide, and sulfur dioxide in an acidic environment, which have high volatility and can react with $AgNO_3$ solution, interfere with the reaction.

Modified version of the Gutzeit reaction

1. Reduction of arsenic compounds to arsin AsH_3.

$$2H_3AsO_3 + 6Zn + 12HCl \longrightarrow 2AsH_3 + 6\,ZnCl_2 + 6\,H_2O$$

2. Filter paper soaked with an alcoholic solution of sulema (mercury dichloride) $HgCl_2$ as an AsH_3 fixative

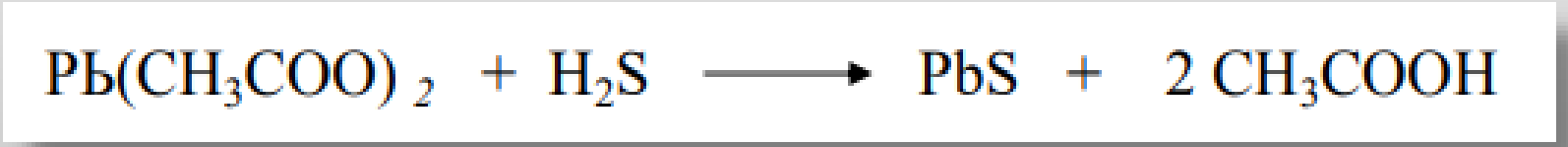
$$AsH_3 + 5\,HgCl_2 \longrightarrow As(HgCl)_3 * Hg_2Cl_2 + 3\,HCl + Cl_2$$

3. Decomposes to form arsenic and mercury chloride (I):

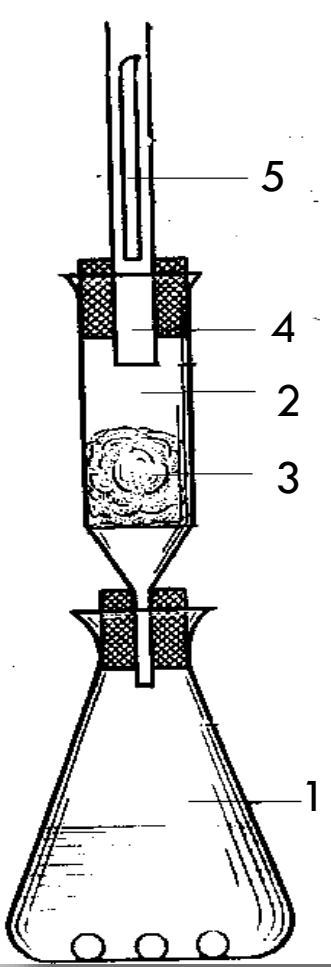
$$2\,As(HgCl)_3 * Hg_2Cl_2 \longrightarrow 2As + 5\,Hg_2Cl_2$$

Capturing the hydrogen sulphide released

A cotton swab soaked with lead acetate is placed in the test tube where the reaction takes place. It captures hydrogen sulfide H2S, which is formed if there are sulfur compounds in the test sample.



The device for the determination of arsenic by Gutzeit method



1. flask;
2. glass tube;
3. cotton swab soaked in lead acetate;
4. glass tube;
5. a strip of paper soaked in a solution of mercury dichloride.

The Bugo and Thiele method

Under the action of sodium hypophosphite in an acidic medium, when heated, arsenic compounds are reduced by phosphoric acid to elemental arsenic. Depending on the concentration of arsenic, a brown precipitate or dark brown staining of the liquid is observed.

$$NaH_2PO_2 + HCl \longrightarrow NaCl + H_3PO_2$$

$$3\ H_3PO_2 + 2\ H_3AsO_3 \longrightarrow 2\ As + 3\ H_3PO_3 + 3\ H_2O$$

$$As_2O_3 + 3H_3PO_2 \longrightarrow 2As\downarrow + H_3PO_3$$

$$As_2O_5 + 5H_3PO_2 \longrightarrow 2As\downarrow + 5H_3PO_3$$

Options for testing

Method A (without using a standard solution) - by browning the solution or the formation of a brown precipitate;

Method B - by comparing the intensity of the resulting color with the color of the reference solution.

The disadvantage of the method

The Bugo and Thiele method, although less sensitive than the Gutzeit method.

The advantage of the method

It can be used for testing for arsenic in the presence of antimony compounds, phosphorus, lead, sulfides that are not reduced by phosphoric acid.

Thank you for attention!