ISSN 1070-3632, Russian Journal of General Chemistry, 2013, Vol. 83, No. 13, pp. 2633–2646. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © I.V. Shugalei, A.V. Garabadzhiu, M.A. Ilyushin, A.M. Sudarikov, 2012, published in Ekologicheskaya Khimiya, 2012, Vol. 21, No. 3, pp. 172–186.

Some Aspects of the Effect of Aluminum and Its Compounds on Living Organisms

I. V. Shugalei, A. V. Garabadzhiu, M. A. Ilyushin, and A. M. Sudarikov

St. Petersburg State Institute of Technology (Technical University), Moskovskii pr. 26, St. Petersburg, 190013 Russia
e-mail: shugalei@mail.ru

Received September 11, 2012

Abstract—The data on toxicity of aluminum compounds to various organisms were collected and summarized. The problems of occupational diseases in workers exposed to aluminum compounds in the production process were considered. The data of experimental researches on animals obtained for different aluminum compounds were summarized.

Keywords: Aluminum, toxicity, health problems, hygienic regulations, accumulation in tissues.

DOI: 10.1134/S1070363213130082

INTRODUCTION

Aluminum is one of the most abundant elements in nature and is ranked third after oxygen and silicon, in combination with which it forms aluminosilicates accounting for more than 82% of the Earth's crust weight. As written by D.I. Mendeleev in his classic textbook "Principles of Chemistry," "aluminum is the most widely distributed metal in nature; it will be sufficient to mention that it enters into the composition of clay to demonstrate the universal distribution of aluminum in the Earth's crust. Aluminum is so named from its being the metal of alums (*alumen*)" [1].

Chemical forms of aluminum in nature are extremely diverse.

There are more than 250 known minerals, the composition of which includes aluminum. Many of them are actively used by people in various fields of activity [2].

Until recently it was believed that aluminum as a very reactive metal could not be found in nature in a free state. However, in 1978 native aluminum was found in the rocks of the Siberian platform in the form of crystal whiskers of only 0.5 mm in length (and several micrometers in thickness [3]). Native aluminum was also found in lunar soil samples delivered to the Earth from the regions of Mare Crisium (the Sea of Crises) and Mare Fecunditatis (the Sea of Fertility) [4].

Soils contain 150–600 mg/kg of aluminum, atmospheric air in cities – approximately 10 μg/m^3 and in rural areas – 0.5 μg/m^3 [5]. Acidification of soils contributes to accumulation of aluminum. Acidification of water bodies results in the transfer of insoluble forms of aluminum into soluble forms, which causes a sharp increase in the concentration of aluminum in the water.

As one of the most abundant elements of the Earth's crust aluminum is contained in almost any natural water. Aluminum enters natural waters both in a natural way as a result of partial dissolution of clays and aluminosilicates and a result of harmful emissions from certain production types (electrical engineering, aviation, chemical, and oil refining industries, machine engineering, construction, optical engineering, and missile and nuclear industries) with atmospheric precipitations or wastewaters [6]. Aluminum sulfate is widely used as a coagulant in water treatment processes in the housing and public utility sector. The presence of significant amounts of aluminum in drinking water results from violations of the technology and insufficient control over these processes. The content of aluminum in water sources varies in a wide range of values from 2.5 to 121 mg/L [7–8]. Sometimes the abovementioned figures can be exceeded hundreds of times. According to research works carried out in the United States, the content of

aluminum in groundwaters can reach 14–290 mg/L and in surface waters – 16–1170 mg/L [9]. In humid climates, where decaying remains of abundant vegetation form a lot of organic acids, aluminum migrates in soils and waters in the form of organo-mineral colloidal compounds [10].

In steppe and desert regions, where there is little living matter and waters are neutral or alkaline, aluminum almost does not migrate. The most active aluminum migration is observed in volcanic regions with highly acidic river and groundwaters, rich in aluminum [11]. In places where acidic waters meet alkaline (sea) waters, for example, in river mouths, aluminum is precipitated, forming bauxite deposits.

Maximum permissible concentrations (MPC) of aluminum in water are well-known and are determined by the category of the water body. For fishery water objects MPC = 0.04 mg/L, whereas for drinking water objects and water objects for municipal and household use MPC is 0.5 mg/L. The recommended content of aluminum in drinking water is 0.2 mg/L [12]. In the United State the threshold limit value for aluminum in drinking water is 0.05 mg/L [8.13].

As the most widespread metal in the Earth's crust aluminum actively influences the vital processes of living organisms of different levels [14–15].

Effects of Aluminum on Plant Life

Aluminum has a harmful effect on plants, starting from the concentration of 1 mg/L of water [16]; therefore, the use of aluminum-containing wastewater for irrigation of agricultural crops is not advisable. Aluminum forms insoluble compounds with phosphates, disturbing phosphate absorption by plant roots [17]. An excess of aluminum in the soil causes deformation of plant organs. The leaves of the majority of plants get twisted and covered with white spots; there is a decrease in the yield of cereal crops growing on acid soils (approximately 40% of all cultivated lands) [18, 19]. In case of acid rains, the toxicity of aluminum increases as it becomes soluble and is washed out of clay [20]. In this situation cells of the root meristem suffer various genome, chromosome, and chromatid aberrations [21, 22]. A biochemical model of aluminum toxicity to plants has been developed. One of the ways of toxic damage is the production of reactive oxygen species. Apart from that, there is a competition between aluminum and iron resulting in inhibition of iron absorption by plant cells [23]. A negative effect of aluminum on assimilation of nitrogen is also identified [24]. Aluminum ions cause root growth inhibition, which has been observed for such extremely important agricultural crops as peas [25] and onions [26]. However, the influence of soil acidity is not so unambiguous. The presence of organic acids in nutrient solutions reduces the toxic effect of aluminum on certain varieties of wheat [27].

Studies of sorghum, which is the fifth most important cereal crop in the world, led to cloning of a previously unknown gene, which is responsible for resistance to soil aluminum [28]. This gene encodes a membrane carrier, which is activated in response to aluminum exposure and ensures the release of citric acid, which effectively binds toxic ions and prevents their penetration into the roots [29], thus paving the way for the creation of aluminum-resistant crops [30–32]. So, at present research works aimed to increase the resistance of rice to aluminum are carried out [33].

Some organisms are known to concentrate aluminum, for example, club moss (Lycopodiaceae), which contain up to 5.3% of aluminum in ash.

Sources for Aluminum Entry into Human Body

At present, aluminum is numbered among vital elements found in trace amounts.

For an adult the daily demand for aluminum is 35–49 mg [34]. One of specific sources for aluminum entry into the human body is the ever increasing use of aluminum in food industry (kitchenware, packaging materials, and food additives) [35–37] and pharmacology [38]. Aluminum is included into the composition of pharmaceuticals with analgesic, absorbent, and antacid effects, as it helps to reduce the acidity of the gastric juice [39]. Aluminum compounds are applied in treatment of gastric ulcers, a number of pancreatic diseases, gastritis, and heartburns [40]. The total content of aluminum in the daily mixed human diet is 80 mg.

Aluminum is included into the composition of animal and plant tissues. The amount of aluminum found in the organs of mammals ranges from 10^{-3} to 10^{-5}% of aluminum calculated for natural moisture material. Aluminum can enter the animal body with drinking water, air, and plant food [41]. The content of aluminum in wheat is 42 mg/kg, in peas – 36 mg/kg, in corn – 16 mg/kg, in potatoes – 4 mg/kg, in turnips – 46 mg/kg, in honey – 4 mg/kg, and in meat and meat products – from 1.6 to 20 mg/kg. Cauliflower, carrots,

and tomatoes are also characterized by a high content of aluminum. Apples contain up to 150 mg/kg of aluminum, and the content of aluminum in tea leaves reaches 850–1400 mg/kg [42]. Aluminum is contained in oatmeal, rice, avocados, artichokes, savoy cabbage, eggplants, Jerusalem artichokes, kiwis, peaches, cabbage, beans, and semolina. Vegetable products contain 50–100 times more aluminum than products of animal origin [43].

Bread is also enriched with aluminum as it is baked in aluminum cookware.

The sources for increased delivery of aluminum into the human body can be also represented by canned food [44, 45], some herbs and processed cheese, antiperspirants, paper towels, and products contacting with aluminum foil.

Necessity of Aluminum for Humans and Warm-Blooded Animals

Aluminum plays an important physiological role in the body as it participates in the formation of phosphate and protein complexes and in the processes of regeneration of bone [46], connective, and epithelial tissues; depending on concentrations, aluminum has an inhibitory or activating effect on digestive enzymes; and it can affect the functions of parathyroid glands [47–48].

A deficiency in aluminum can develop if the human body receives less than 1 μg of aluminum per day; however, there are no data on harmful effects of the lack of this trace element on the human body as it almost never happens. In this connection, there are no data on possible pathogenic effects of aluminum deficiency in the human body. An increase in the number of miscarriages, a reduction in productivity, growth retardation, dystaxia, and weakness in limbs are observed in experimental animals with aluminum deficiency.

Aluminum Content and Distribution in Tissues

At present it is assumed that the total content of aluminum in the blood of an adult lies within a range of 50–140 mg. The content of aluminum in different organs and tissues is as follows: in the blood – 0.024–0.070 mg/mL (mostly in blood serum), in the lungs – 0.59 mg/g, in the tubular bones – 0.5 mg/g, in the teeth – up to 0. 33 mg/g, in the heart – 0.056–0.210 mg/g, in the muscles – 0.015 mg/g, in the brain – up to 0.016 mg/g, in the breast milk – up to 0.01 mg/mL, in the ovaries – 0.4 μg/g, in the testes – 0.4 μg/g, and in the lymph nodes – 0.032 mg/g. The greatest content of aluminum is found in the nails (up to 0.93 mg/g) [49].

Table 1. Characteristics of acute toxicity of some aluminum salts

Substance	Animal species	LD_{50}, mg/kg
Aluminum sulfate	Mice	520
	Rats	410
	Guinea pigs	490
Aluminum chloride	Mice	390
	Rats	315
Aluminum nitrate	Mice	370
	Rats	280

Aluminum is deposited in human bones, liver, lungs, and grey matter of the brain. The content of this element in the lungs and the brain increases with age. Aluminum is excreted from the body with urine, feces, sweat and exhaled air [50].

Evaluation of aluminum content in the human body is made based on the results of blood, urine, and hair analyses. The average content of aluminum in blood plasma is approximately 2 μg/L. The aluminum content in urine lies within a range of 1–20 μg/L, whereas for hair this parameter amounts to 1–20 mg/kg.

An increased content of aluminum in hair is more often observed in men than in women; for children this parameter is higher as compared to adults.

Aluminum Toxicity

Despite its abundance, aluminum falls into the category of toxic elements [51]. The data on acute toxicity of aluminum are given in Table 1.

Target organs for excessive concentrations of aluminum in the body include the central nervous system, kidneys, bones, lungs, bone marrow, ovaries, uterus, and mammary glands.

Biochemical signs of aluminum intoxication are well-expressed and diverse. Aluminum can cause precipitation of proteins and formation of insoluble protein compounds in the form of fibrous substances with no signs of inflammation [52, 53]. The high ability of aluminum to form complex compounds determines its role in reducing the activity of many enzymes and their systems [54–56].

Aluminum toxicity is largely associated with its antagonism to calcium [52] and magnesium [58], phosphorus, zinc, and copper [59], as well as with its ability to affect the functions of the parathyroid glands, to easily form compounds with proteins [52, 53], and to accumulate in the kidneys, bone and nervous tissues [60].

Aluminum inhibits the absorption of calcium, magnesium, iron, B_6 and C vitamins, and some sulfur-containing amino acids [61].

It is found that aluminum compounds display a hemolytic effect. In vitro experiments have demonstrated that there is a reduction in the hemolytic effect in the line of aluminum hydroxide, acetate, and sulfate [62]. Under conditions of experimentally induced anemia, aluminum salts inhibit the recovery of hemoglobin levels to the initial content [63]. Aluminum causes various disturbances of biochemical processes in cells [64]. It is found that aluminum compounds interrupt phosphorylation processes (ATP synthesis) [65]. Aluminum competes with phosphorus, calcium, and iron for absorption; it can cause magnesium and manganese deficiency. Aluminum changes energy exchange in cells, as a result of which cells lose their ability to normal reproduction and start dividing chaotically, generating tumors [66]. It is noted that aluminum can induce apoptosis [67, 68].

A reduced delivery of phosphates into the human body results in an inhibition of carbohydrates transport linked to phosphates. It is necessary to specially mention the effect of aluminum compounds on membrane transport, as aluminum has a significant impact on the state of membrane lipids [69].

Aluminum intoxication results in a significant reduction in the level of ATP, which causes severe disturbances of tissue metabolism. In case of chronic oral exposure to aluminum salts, the disturbances of phosphorus metabolism result in a reduced absorption of glucose from the intestine, which causes hypoglycemia, a reduction in the level of glycogen in the liver, and an increase in the level of lactate in the liver and pyruvate in the liver and muscles [70].

Accumulation of aluminum in the body can cause disturbances in cholinergic transmission of nerve impulses [71]. At concentrations of approximately 100 μmol aluminum ions halve the activity of purified cholinesterase in human blood plasma. It is demonstrated that aluminum ions act as a non-competitive inhibitor of cholinesterase; however, calcium ions eliminate this influence, whereas magnesium ions do not have a similar protective effect [72].

One of the possible mechanisms of aluminum toxic effects on the body can be a disturbance of iron transport, which depends on transferrin [73, 74]. At toxic doses of aluminum a reduction in iron transport can cause an iron deficiency anemia [75].

Intoxication with high doses of aluminum (up to 200 mg per kg) causes an increase in the activity of aldolase in blood plasma, which is accompanied by hyperglycemia. Reduced oxygen consumption in tissues is detected on liver slices of experimental animals. In vitro, soluble aluminum salts increase erythrocyte agglutination. It is probable that various toxic manifestations of aluminum effects are related to active binding of aluminum by proteins. High affinity of aluminum to lactoferrin and transferrin is demonstrated [76].

Aluminum reduces the absorption of phosphorus in the body, which can cause disturbances in calcium and phosphorus metabolism. There are data on mutagenic activities of aluminum [77]. Aluminum causes anemia in children [78], as it inhibits the synthesis of hemoglobin [79, 80], kidney and liver diseases, and colitis. Aluminum intoxication is often accompanied by such signs as muscle twitching and cramping, pains in the stomach and in the whole body, constipations, loss of appetite and weight, changes in the blood composition (lymphocytosis, eosinopenia, and anemia) [81], persistent coughing, disorientation, loss of memory, disturbances in calcium and phosphorus metabolism, reduced synthesis stability and damage of the DNA, and development of fibrotic indurations in soft tissues. Intoxication with aluminum is often accompanied by disturbances in renal functions (nephropathy and increased risk of urolithiasis).

The syndromes that are distinguished in the clinical picture of aluminum intoxication as the most significant are neurological, bone, and hematologic [82].

Nervous System Responses to Aluminum Intoxication

Aluminum is known to be a neurotoxic metal [83]. Aluminum ions slowly but irreversibly accumulate in neurons, which are rather long-living cells [84]. Aluminum can be transported by transferrin; furthermore, specific transferrin receptors found in brain capillaries [85] ensure bound aluminum's

crossing of the blood-brain barrier [86]. Citric and other organic acids do not only enhance aluminum absorption but also contribute to the accumulation of aluminum in tissues [28]. Accumulation of aluminum in the brain tissue results in the development of encephalopathy characterized by severe mental disorders.

Major clinical manifestations of the neurotoxic effect of aluminum include motor activity problems, convulsions, decline or loss of memory, psychopathic reactions, learning difficulties, tendency to depressions, and encephalopathy [87, 88].

Responses of the nervous system to aluminum intoxication are quite diverse. Aluminum is considered to play a significant role in the development of such severe diseases of the nervous system as Alzheimer disease (occurring at mature age; manifesting itself with memory lapses, reality orientation problems, depressions, and progressive dementia) [89], Lou Gehrig's disease (manifesting itself with progressive paralysis of muscles; causing death as a result of cardio-respiratory arrest in a few years' time), and Parkinson's disease (manifesting itself with head, hands, lower jaw, and feet tremor due to muscle hypertension; causing psycho-emotional problems in the form of obtrusiveness, selfishness, and resentfulness) [90, 91].

The association between the consumption of aluminum with drinking water and the development of dementia was detected [28]. Moreover, by using aluminum preparations in experiments on animals it was possible to trigger the development of different pathological changes and clinical symptoms similar to the changes and symptoms of the Alzheimer type dementia [92, 93]. Apparently, aluminum can enhance oxidative and inflammatory reactions, leading to tissue damage, and can contribute to the progress of neurodegenerative changes [94, 95]. If aluminum really does participate in the pathogenesis of Alzheimer disease, it testifies to the fact that the toxic effects of aluminum can manifest themselves decades later.

Some neurological symptoms accompanying aluminum intoxication are given in Table 2.

Children and elderly people are particularly susceptible to the negative effects of aluminum [96]. An excess of aluminum causes hyperexcitability, motor response problems, and headaches in children. Teenagers' hyperactivity, hyperexcitability, aggressive behavior, and memory and learning problems can result from even a minor increase in the concentration of aluminum ions in the body [97].

Table 2. Neurological signs and symptoms of aluminum intoxication

Clinical picture	Symptoms
Acute aluminum intoxication	Retardation Coma Unconsciousness
Chronic early-stage aluminum intoxication	Temporary speech disorders (stammering) Deterioration of skills
Chronic late-stage aluminum intoxication	Permanent speech disorders Full loss of skills Recognition problems Myoclonic seizures Personality change Full dementia Unconsciousness

Aluminum is often found in tissues of some elderly people suffering from loss of memory, absent-minded behavior, or dementia and it can cause degradation of personality [98].

Skeletal System Changes Caused by Aluminum Intoxication

Disorders of the skeletal system are also one of the leading manifestations of aluminum intoxication. On the background of high aluminum concentrations in blood serum incorporation of aluminum into the bone tissue is observed [46].

Histologically, patients with skeletal problems caused by aluminum intoxication suffer from reduced deposition of calcium salts in the osteoid. The intensity of osteomalacia is closely correlated with the content of aluminum in the bone tissue. The places of aluminum depositions in the form of structures 20–100 nm in size are characterized by an almost complete absence of active osteoblasts; furthermore, endoplasmic reticulum cannot be detected in cells lining the bone surface. In case of aluminum intoxication, the bone tissue looks inactive and is characterized by a sharp slowdown of bone tissue remodeling (new growth) processes. Further accumulation of aluminum eventually leads to the development of osteomalacia [61]; organic acids significantly change the biochemical effect of aluminum [27].

The mechanism by which aluminum induces changes in the bone tissue is not fully deciphered.

Table 3. Typical changes in bone tissue related to aluminum intoxication

Clinical picture	Signs
Clinical symptoms	Diffuse bone pain Muscular weakness (especially in the legs) Spontaneous fractures
Laboratory symptoms	Gradual increase in the level of calcium in blood serum, which can accelerate after application of D vitamin. Normal or insignificant increase in parathormone in serum. An increase in the level of aluminum in serum.
Biopsy data	A reduction in the amount of mineralized bone (osteomalacia). An increase in aluminum content in bones (more than 15–20 μg/kg).

However, research works carried out on the bone tissue culture have demonstrated that via the hydroxyl group aluminum forms a metal-citrate complex with citrate and this complex disturbs the growth of calcium phosphate crystals and inhibits mineralization of the osteoid [100].

Aluminum in concentrations of 54–135 μg/L can inhibit the growth of calcium phosphate crystals. Citrate enhances the inhibitory effect of aluminum; the inhibitory activity of the metal-citrate complex, which is deposited on the surface of the crystals, is many times higher.

Insufficient calcification of a large part of the osteoid subsequently leads to softening of the bones and development of deformities and pathologic fractures. Some manifestations of aluminum-induced bone changes are summarized in Table 3.

Aluminum intoxication causes the development of degenerative disc disease, rickets, and other locomotor disorders [101]. According to some data, aluminum can cause or enhance bone neoplasms [102].

Aluminum and Pregnancy

Animal experiments indicate that aluminum crosses the placenta and accumulates in fetal tissues, causing various fetal development disorders, including intrauterine death, fetal malformations, delayed formation of the skeleton, and growth retardation [103]. The possibility of aluminum intoxication in case of oral application greatly depends on bioavailability of the applied preparation and the presence of other substances enhancing the absorption of aluminum in the food [104].

The fetus and the newborn are more susceptible to toxic effects of aluminum as compared to the body of an adult [105].

Aluminum is found in women's breast milk [28, 106], which suggests a possibility of aluminum delivery into the body of breastfed newborns [107]. A strong negative impact of aluminum on the development of preterm infants was identified. A comparison of effects of standard parenteral nutrition solutions and solutions with reduced aluminum content on preterm infants was carried out. After a period of 18 months the infants who received standard solutions had a lower neurological development index than the comparison group infants. Although, for newborns there is little risk of aluminum intoxication by oral application (with the exception of infants suffering from renal failure); nevertheless, application of aluminum-containing parenteral nutrition solutions to newborns should be avoided [108].

In many European countries there are certain restrictions on the use of aluminum-containing antacids in pregnant and lactating women. For example, in Austria, France, Italy, Spain, and Switzerland medication guides for this type of preparations indicate that during pregnancy and lactation they should be applied only when recommended by a doctor or a pharmacist [109].

Aluminum and Immunity

Aluminum is considered an immunotoxic element [110].

Aluminum cumulates and suppresses the function of macrophages, T-lymphocytes, and B-lymphocytes. In this situation, it does not only cause suppression of cellular responses, but also a mitogenic effect on lymphocytes [111]. It is assumed that aluminum can be one of the reasons for senile cellular immunodeficiency [112]. Apart from that, aluminum can cause allergies, which is associated with the suppressive effect of this trace element on the mutagen-mediated immune response [113]. At the same time, aluminum exacerbates a whole range of autoimmune diseases in elderly and senile patients. It is considered that aluminum compounds can penetrate the skin upon contact and have a systemic impact on the immune system without causing the development of contact dermatitis [114].

Experimental Studies of Toxicity of Aluminum and Its Compounds

Identification of a wide range of biochemical changes under the influence of aluminum compounds stimulated experimental studies on their toxicity [115]. Both acute and chronic effects of aluminum compounds were studied. In the course of studies on acute aluminum toxicity soluble aluminum salts were introduced into the stomach of experimental animals [116]. Albino rats were used as experimental animals; aluminum salts were introduced in the amount of 0.25 of LD_{50}. In case of introduction of aluminum salts into the stomach, the median effective lethal dose was 980 mg/kg for $Al_2(SO_4)_3$ and $AlCl_3$ and 204 mg/kg for $Al(NO_3)_3$ [117]. In a state of acute poisoning the animals demonstrated the following symptoms: excitement, respiratory failure, and convulsions; a reduced level of glycogen in the liver, hyperglycemia, and an increased activity of aldolase in blood serum were also observed [118]. When experimental rats were exposed to aluminum compounds, there was an increase in the activity of xanthine oxidase and changes in the antioxidant status of the animals [119].

Experimental chronic poisoning of laboratory animals (albino rats) was simulated by inhalation of aluminum dust (18 000 particles per 1 mL) for 44 h a week during 6 weeks.

Pulmonary fibrosis and more frequent cases of pneumonia were observed in experimental animals subjected to the exposure.

An interstitial pneumonia and clusters of cells filled with aluminum were observed in rabbits inhaling aluminum and aluminum bronze dust for 1–2 h a day during 20–40 days. There is a constant formation of emphysemas in the lungs of laboratory animals inhaling dust. Nodular and diffuse pneumosclerosis, pulmonary vascular sclerosis, liver vascular sclerosis, and an increased content of hemoglobin and erythrocytes were observed in rabbits inhaling aluminum dust (in the amount of 80 mg/m^3 for 20 min a day during 4–7 months) [120]. Under similar experimental conditions (dust inhalation in the amounts of 15, 30, 50, and 100 mg/m^3 for 6 h a day during 12 months) a significant increase in the level of lipids was observed in the blood of rats, guinea pigs, and hamsters [121]. A month after 50–100 mg of aluminum nitride was introduced into the trachea of albino rats the following symptoms were observed: an increase in the content of collagenous proteins in the lungs, appearance of focal nodules in interalveolar septa, sections of emphysema, and bronchitis; 6 months later a weak pneumosclerosis and dystrophy of liver cells were evidenced. Inhalation of an aerosol formed in the process of aluminum welding (in the amount of 120–140 mg/m^3 for 3 h a day during 12 months) by rats resulted in thickening of alveolar septa, appearance of cell-dust foci, and growth of collagen fibers. Fumes formed in the process of electrode burning (~10^9 aluminum particles in 1 m^3 inhaled for 1–2 min a day during 12 months) cause pneumonia. The majority of albino rats and rabbits inhaling Al_2O_3 fumes in concentrations of 0.2 mg/L for 5 h a day during 7 months died of pneumonia, bronchitis, and pulmonary edema. Alumina dust (~33 g/m^3 inhaled for 5 h a day) causes serious damage to the airway epithelium of rats. Exposure to synthetic corundum dust (200 mg/m^3 inhaled for 2 h a day) causes sponginess of epithelium of the laboratory rats' upper respiratory tract after the first three months. After 6 months, nasal epithelial injuries and dystrophic changes of the tracheal cartilage tissue were observed in the experimental animals; after 8 months, erosions of the nasal and tracheal mucosa, necrosis of cartilage rings, and manifestations of diffuse and microfocal sclerosis in the lungs were evidenced [122].

No fibrotic changes were found in the lungs of guinea pigs subjected to intratracheal injection of dust, settling down at bauxite-melting furnaces, with the particle size from ultramicroscopic to 40 μm (containing 6.8% of SiO_2, 50% of corundum, 9% of Fe_2O_3, 4% of TiO_2, and 10–11% of other metal oxides). The experimental animals received 0.5 mL of 5% suspension once a week during one year. After a period of 2–4 months under the same conditions, fumes collected above bauxite-melting furnaces (particle size ranging from several hundredths to 0.5 μm; 32.3% of SiO_2 and 56% of Al_2O_3) caused the formation of dust cell clusters in lung tissues and fibrosis. After 8 months, the fibrosis intensified; after 12 months, the development of pleuropulmonary adhesions, cicatrices, and diffuse pulmonary fibrosis was observed [123]. Out of the three types of dust (bauxite ore, limestone and bauxite mixture, and limestone and soda bauxite sintered materials) the latter turned out to be the most toxic under conditions of intratracheal injection (50 mg). In this case one third of experimental rats died within several h or days after the injection as a result of pulmonary edema; it was observed that the surviving animals and the animals of the other groups had a slowly developing pulmonary

sclerosis. Prolonged inhalation of sintered mixture dust (0.9–91.7 mg/m^3 for 5 h a day during 10 months) causes purulent inflammation of nasal mucosa and a slowly developing pulmonary sclerosis in sections with dust deposits. Inhalation of sintered mixture dust (mixture of bauxites and soda calcined at 1200°C) causes purulent inflammations in nasal and tracheal mucosa and, less frequently, inflammatory changes in the lungs [124].

The dust from casting of aluminum alloys is also toxic. After 7 months of silumina injections (intratracheal injections in the amount of 50 mg) a reduction in the growth rate of rats and a sharp intensification of hippuric acid synthesis are observed. Post-mortem dissection of the animals shows dystrophy of parenchymal organs and a weakly expressed pulmonary sclerosis. An aerosol formed in the production of aluminum and magnesium alloys is also aggressive [125].

The experiments on rats and rabbits demonstrate that subcutaneous injections of aluminum bioinorganic complexes result in the formation of edemas at the injection sites. Inflammatory processes can be associated with an increase in oxidative stress [126] and intensification of production of intracellular oxidants [127]. It is possible to talk about an aluminum-induced oxidative stress; however, some data on antioxidant activity of aluminum are also available.

It is found that introduction of solutions of aluminum salts into the brain of rats and cats results in the development of nodules or tangles in the neurons, which are similar to formations observed in the brain of a person suffering from a severe form of senile dementia, i.e. Alzheimer disease [51, 97]. Experiments on rabbits demonstrate that aluminum neurotoxicity is caused by activation of caspase-32 in the neurons [128]. Some researchers recommend using different chemicals to reduce the content of aluminum in the brain. Such substances include deferoxamine and fluorine compounds [129]. It is shown that the distribution of aluminum in the body changes under the influence of an increased delivery of fluorine ions. In particular, if rats are given fluorine for 540 days, there is a reduction in the content of aluminum in their bones [130].

Recent research works have revealed the effect of aluminum on the reproductive system. In particular, there are data on suppression of spermatogenesis in case of aluminum intoxication in rats [131]. Experiments on rats demonstrate that aluminum crosses the placental barrier and enters the body of infant rats with the mother's milk [132].

Toxicokinetics and Distribution of Aluminum Compounds in the Body

Considerable attention is paid to the issues of kinetics of aluminum absorption and removal. It is found that absorption of aluminum salts from the gastrointestinal tract is insignificant, which can be related to the ability of aluminum to form insoluble compounds with phosphorus in the intestine [133]. The amount of aluminum that is absorbed in the human gastrointestinal tract is 2–4% of the incoming aluminum; furthermore, soluble salts (such as $AlCl_3$) are absorbed best [134].

Prolonged introduction of aluminum salts into the body of dogs resulted in some accumulation of aluminum only in the liver. In healthy people approximately 90% of aluminum, coming from the gastrointestinal tract into blood, is soon excreted by kidneys and, to a lesser extent, in bile. In case of parenteral introduction, aluminum bypasses the intestinal protective barrier and is deposited in various tissues, primarily, in the bones, liver, spleen, and kidneys, as well as in the brain and other parts of the nervous system. In case of intramuscular or intraperitoneal introduction of small amounts of soluble inorganic aluminum salts, the process of aluminum delivery into blood is slow and takes several days. The content of aluminum in the blood of alumina loading workers before work was 42.8 μg % and after work it reached 206.6 μg % (against 5.1 μg % in the control group) [135]. Although, aluminum is mainly excreted through the intestine, it was found that the content of aluminum in the urine of people working with aluminum compounds for a long time reached 0.62 mg % (against the normal rate of 0.2 mg %). In case of formation of poorly soluble colloidal particles of aluminum compounds in blood vessels, they are removed from the blood stream by phagocytosis.

Characteristics of Health Disorders in Aluminum Industry Workers

In parallel with toxicological studies involving the use of laboratory animals hygienic observations were systematized [136].

Inhalation of aluminum dust or fumes by people mainly affects their lungs. The disease is called pulmonary aluminosis or "aluminum lungs" [137]. Aluminum production workers often suffer from

catarrhs of the upper respiratory tract (rhinitis, laryngitis, and pharyngitis). Before, these diseased used to be attributed to silicon impurities. There are descriptions of serious diseases in workers whose activities involve spraying of aluminum paint and production of pyrotechnic aluminum powder with aluminum concentrations of 4–50 mg/m^3 [138]. After a year of such work, loss of weight, severe fatigue, dyspnea, coughing, and dry and moist rales in the lungs are observed; X-ray examination shows significant shadows in the lungs [139].

The growth and severity of diseases in this industry are related to the extremely high dispersion of dust and the additions of small amounts of stearic acid to the powder, which probably reduces the solubility of aluminum particles.

Workers contacting with dust, containing aluminum metal or oxide (for example, in work with corundum), can suffer from bronchopulmonary inflammation problems or irreversible fibrotic changes in the lungs [140].

Workers, involved in alumina production based on the wet alkaline method, have a 5–10 times higher disease rate with regard to catarrhs of the upper respiratory tract even before their period of work reaches 1 year. The most pronounced mucosal changes are observed in calcination plant workers [141].

Workers, involved in alumina production based on the dry method, frequently suffer from catarrhs of the upper respiratory tract as well; cases of pneumosclerosis, perforation of the nasal septum, and neuritis of the auditory nerve are also observed [142]. Workers, involved in alumina loading activities, suffer from gum bleeding [143], voice hoarseness, and mouth and nasal cavity dryness [144]. There are descriptions of severe diseases in people working at bauxite-melting furnaces, in manufacturing of artificial abrasives [145]. In this case, dust and fumes contain 41–62% of Al_2O_3, 30–40% of SiO_2, and minor amounts of other metal oxides. Usually the size of dust and fume particles does not exceed 1 μm.

The diseases in people working at furnace ends and as crane operators (with 3–8 years of working experience) were characterized by a severe course, a fast development of diffuse pulmonary fibrosis, and an occurrence of spontaneous pneumothoraxes, which were often fatal. The examined workers complained about a moist or dry cough and a fast-developing dyspnea; sometimes coarse or minor rales in the lungs were observed [146].

Late development (11–15 years) of pneumoconiosis, rarely complicated with tuberculosis, are characteristic for bauxite mine workers. Alunite dust causes destruction of tooth enamel and dentin [147], parodontosis, and atrophic and degenerative processes in the gingival mucosa [148, 149].

A vascular dystonia, reduced pulmonary ventilation, and a reduced content of erythrocytes and hemoglobin in the blood were observed in workers involved in alunite roasting and reduction [150–153].

Fine aluminum dust causes skin and eye damage. When aluminum particles enter a human eye, focal necrosis, changes in corneal pigmentation, changes in the lens, and clouding of the vitreous body are observed. Skin exposure to aluminum dust can result in the development of acnes, eczemas, and dermatitis. Eczemas and dermatitis occur acutely and chronically; they are accompanied by itching and burning and are sometimes resumed when exposed to other irritating agents [154]. Under the influence of aluminum and duralumin dust the smallest cuts and wounds take a long time to heal. Frequent phlegmons (appearing even after small scratches) and inflammations of lymphatic viae and glands are observed [155].

Cases of eczema and dermatitis are observed in alumina plant workers. Often itching is accompanied by sweating, skin sensitivity problems, and impotence. Objectively, the performance of the disease resembles “nickel itch” [156]. Under the influence of potassium alum solutions the skin gets tough like tanned leather.

The source for an increased delivery of aluminum into the body of workers can be the dust-filled air of paint and varnish, textile, and paper plants [157].

Hygiene Regulations on Aluminum and Its Compounds

Taking into account a high risk of health deterioration among workers exposed to aluminum compounds and the priority hazard of the inhalation way of aluminum compounds delivery into the human body in production conditions, maximum permissible concentrations (MPC) of aluminum compounds in the air of the working area are accepted [158].

The maximum permissible concentrations of aluminum and its alloys are limited to 2 mg/m^3; MPC of aluminum oxide (including an admixture of silicon dioxide) in the form of condensation aerosol – to 2 mg/m^3; MPC of aluminum oxide (electrocorundum) in a mix-

ture with nickel alloy (up to 15% of nickel) – to 4 mg/m^3; MPC of aluminum oxide in the form of disintegration aerosol (alumina, electrocorundum, and monocorundum) – to 6 mg/m^3; MPC of electrocorundum mixed with alloyed steels – to 6 mg/m^3, MPC of aluminum hydroxide – to 6 mg/m^3, and MPC of aluminum nitride and lanthanum aluminate-calcium titanate – to 6 mg/m^3. The maximum permissible concentration of alunite ore dust is 2 mg/m^3 and MPC of the dust of alunite ore concentrate is 4 mg/m^3.

Special Features of Toxicity of Aluminum Organic Compounds

Liquid aluminum tri-alkyls are highly toxic. Toxicological studies demonstrated that acute poisoning of laboratory animals with aluminum trialkyls and aluminum dialkyl chlorides caused irritation of the eyes and the upper respiratory tract, depression of the nervous system, oxygen consumption reduction, and death in the course of exposure. Post-mortem dissection of the animals shows hyperemia of the brain and internal organs, emphysema, and partial pulmonary edema.

It was observed that rats exposed to triisobutylaluminum and diisobutylaluminum chloride in concentrations 0.03–0.17 mg/L and 0.017–0.47 mg/L (aerosol), respectively, for five months suffered from growth retardation and inhibition of the nervous system functions.

Accidents among aluminum tri-alkyl production workers were associated with fires and burns; symptoms resembling a metal fume fever were observed.

The risk factor for the development of aluminum intoxication sharply increases under the influence of citrate, which enhances aluminum absorbability in the intestine [159, 160]. An increased absorbability of aluminum in the intestine is also characteristic for iron-deficiency conditions.

CONCLUSIONS

Therefore, at present it is convincingly shown that aluminum, which is one of the most abundant metals in the Earth's crust, has diverse toxic effects on warm-blooded animals and humans [161]. Intoxication with aluminum compounds causes irreversible damage to the human body and reduction of the human life span. There are extensive experimental data, which make it possible to develop scientifically based principles and methods for hygienic regulation of aluminum compounds in the environment and to create modern principles for organization of production [162].

The extremely wide range of the toxic effects of aluminum on warm-blooded animals and humans requires serious health control with regard to workers exposed to aluminum compounds. In this situation the most important test is the determination of the level of aluminum in blood serum. An increased concentration of aluminum in blood serum exceeding 50–60 μg/L indicates the presence of aluminum intoxication.

In case of suspected aluminum intoxication, it is also necessary to determine the content of this element in urine, hair, bone biopsy samples, and cerebrospinal fluid, to perform encephalography, and study renal and pulmonary functions.

In cases of rehabilitation treatment and as a preventive measure against excessive delivery of aluminum into the body it is possible to use certain pharmaceuticals and biologically active supplements, containing calcium, magnesium, phosphorus, zinc, manganese, iron, and copper, as these preparations act as antagonists to aluminum, slowing its absorption and filling the shortage of vital substances. It is usual to use complexing agents in cases of acute or chronic aluminum intoxication. The symptomatic therapy can include diuretics, cholagogue products, antioxidants, and nootropics, depending on the clinical picture in each individual case.

REFERENCES

1. Mendeleev, D.I., *Osnovy khimii* (Principles of Chemistry), St. Petersburg: Tipografiya M P. Frolovoi, 1903.
2. Venetskii, S.I., *Rasskazy o metallakh* (Stories about Metals), Moscow: Metallurgiya, 1993.
3. Kardanova, O.F. and Filosofova, T.M., *Materialy i sessii kamchatskogo Otdeleniya VMO* (Proc., I Meeting of Kamchatka Branch of Russian Mineralogical Society), Vladivostok, 1992, part II, p. 19.
4. Novgorodova, M.I., Generalov, M.Z., and Glavatskikh, S.F., *Dokl. Akad. Nauk*, 1997, vol. 354, no. 4, p. 524.
5. Sirina, N.V., *Izv. Irkutsk. Gos. Univ.*, 2008, vol. 1, p. 181.
6. Sirina, N.V., *Vestnik irkutskogo universiteta: Spetsial'nyi vypusk: Materialy ezhegod. nauch.-teor. konf. mol. uchenykh* (Irkutsk University Herald: Special Issue: Proc., Annual Scientific and Theoretical Conference of Young Scientists), Irkutsk: Irkut. Gos. Universitet, 2006, p. 31.
7. Tulakina, N.V., *Gigien. Sanitar.*, 1991, no. 11, p. 12.

8. Vasyukovich, L.Ya., *Gigien. Sanitar.*, 1978, no. 5, p. 101.
9. Synzynys, B.I., Abstract of Proceedings, *CLARIENT Final Conference*, Vienna, 2000, p. 19.
10. Hartwell, B.L. and Pember, F.R., *Soil Sci*., 1998, vol. 6, p. 259.
11. Baker, J.P. and Schofield, C.L., *Water, Air, and Soil Pollut*., 1982, vol. 18, p. 289.
12. Drozdov, A., *Trinadtsatyi element* (Thirteenth Element), Moscow: Biblioteka Rusala, 2007.
13. Bdyugina, O.E., *Cand. Sci. (Biol.) Dissertation*, Kazan, 2006.
14. Gromyko, E.P., *Cand. Sci. (Biol.) Dissertation*, 1966.
15. Ryzhikov, I.A. and Sokolov, V.G., *Materialy II nauchno-tekh. konf. "Aktual'nye problemy ekologii Yaroslavskoi oblasti"* (Proc., II Sci. and Tech. Conf. "Topical Environmental Problems in Yaroslavl' Region"), Yaroslavl', 2003, p. 174.
16. Synzynys, B.I., Bulanova, N.V., and Koz'min, G.V., *S.-Kh. Biologiya*, 2002, no. 1, p. 104.
17. Fleming, A.L. and Foy, C.D., *Agron. J*., 1968, vol. 60, p. 172.
18. Dovgalyuk, A.I., Kalinyak, T.B., and Blyum, Ya.B., *Tsitologiya i Genetika,* 2001, vol. 35, no. 1, p. 3.
19. Shirokikh, I.G., *Pochvovedenie*, 2004, no. 8, p. 961.
20. Orlov, A.S., *Khimiya pochv* (Soil Chemistry), Moscow: Nauka, 1992.
21. Bulanova, N.V., Synzynys, B.I., and Koz'min, G.V., *Genetika,* 2001, vol. 31, no. 12, p. 1725.
22. Zonin, S.V., *Cand. Sci. (Biol.) Dissertation*, DSU, 1992.
23. Amosova, N.V., *S.-Kh. Biologiya*, 2005, no. 1, p. 46.
24. Berezovskii, K.K. and Klimashevskii, E.L., *Sibirsk. Vestnik S.-Kh. Nauki*, 1975, no. 4, p. 22.
25. Dedov, V.M., *Effects of Aluminum Ions on Pea Root Growth Rate (Variety and Fertilizer),* Irkutsk, 1974, p. 235.
26. Dovgalyuk, A.I., Kalinyak, T.B., and Blyum, Ya.B., *Tsitologiya i Genetika,* 2001, vol. 1, p. 3.
27. Synzynys, B.I., Nikolaeva, O.I., and Rukhlyada, N.N., *Vest. Ross. Akad. Selskokhoz. Nauk*, 2004, vol. 75, p. 42.
28. Amosova, N.V., *Cand. Sci. (Biol.) Dissertation*, Kaluga, 2005.
29. Kinraide, T.B. and Parker, D.R., *Plant Phisiol*., 1987, vol. 83, p. 546.
30. McLean, F.T. and Gilbert, B.E., *Soil Sci*., 1927, vol. 24, p. 163.
31. Delhaize, E., Ryan, P.R., and Randall, P.J., *Plant Phisiol*., 1993, no. 103, p. 695.
32. Farago, M.E., *Coord. Chem. Revs*., 1981, vol. 36, no. 2, p. 155.
33. Hoveler, R.H. and Cadavid, L.F., *Agr. J*., 1976, vol. 68, no. 4, p. 551.
34. Kortev, A.I., Lyasheva, A.P., and Dontsov, G.I., *Mikroelementy v klinicheskom osveshchenii* (Trace Elements in Clinical View), Sverdlovsk, 1969, p. 114.
35. Reilly, C., *Metally dlya izgotovleniya upakovochnykh materialov: aluminii i olovo* (Metals for Manufacturing of Packaging Materials: Aluminum and Tin), Moscow, 1985, p. 112.
36. Rosival, L., Engst, R., and Sokolai, A., *Postoronnie veshchestva i pishchevye dobavki v produktakh* (Foreign Substances and Food Additives in Food Products), Moscow: Legkaya i Pishchevaya Promyshlennost', 1982.
37. Osmolovskaya, M.S. and Kovalev, N.I., *Voprosy Pitaniya*, 1954, no. 5, p. 48.
38. Belousov, Yu.B. and Gurevich, K.G., *Farmateka,* 2005, no. 12 (107), p. 75.
39. Gupta, P.K., *Adv. Drug. Deliv. Rev*., 1998, no. 32, p. 155.
40. Gallieni, M., Broncaccio, D., and Padovese, P., *Kidney Int*., 1992, vol. 42, p. 1191.
41. Lopez, F.F., Cabrera, C., and Lorenzo, M.L., *Health Stream*., 2002, no. 28, p. 11.
42. Shu, W.S., *Chemosph.,* 2003, vol. 52, no. 9, p. 1475.
43. Greger, J.L., *Food Technol.*, 1985, vol. 39, p. 73.
44. *GOST 28914-91: Konservy i preservy iz ryby i moreproduktov* (State Standard 28914-91: Canned and Preserved Fish and Seafood), Moscow: Izd. Standartov, 1991.
45. Laurie, S.H., *J. Intern. Metab. Dis*., 1983, vol. 6, no. 1, p. 9.
46. Skoblin, A.P. and Belous, A.M., *Mikroelementy v kostnoi tkani* (Trace Elements in Bone Tissue), Moscow: Meditsina, 1968.
47. Ganrot, P.O., *Health Perspect.*, 1986, vol. 65, p. 363.
48. Former, P., Moriniere, Ph., and Sebert, G., *Kidney Int*., 1986, vol. 29, no. 1, p. 114.
49. Uteshev, A.B., Potopovich, G.M., and Musagagieva, G.M., *Zdrav. Turkmenistana*, 1983, no. 7, p. 35.
50. Teagarden, D.L., *Pharm. Sci.,* 1981, no. 70, p. 758.
51. *Public Health Services Agency for Toxic Substances and Disease Registry*, Atlanta, 1998.
52. Trapp, G.A., *Life Sci*., 1983, vol. 33, no. 4, p. 311.
53. Trapp, G.A., *J. Environ. Pathol. Toxicol. Oncol*., 1985, vol. 6, no. 1, p. 15.
54. Bantan, T., Milacic, R., and Mitrovac, B., *Anal. Chem*., 1999, vol. 365, p. 545.
55. Cochran, M., Elliott, D.C., Brennan, P., and Chawtur, V., *Clin. Chim. Acta*, 1990, vol. 194, p. 167.
56. Staurnes, M., Sigholt, T., and Reite, O.B., *Experientia*, 1984, vol. 40, p. 226.
57. Zhao, X.J., Sucoff, E., and Stadelmann, E.J., *Plant Phisiol*iol., 1987, vol. 83, p. 159.
58. Blair, L.M. and Taylor, G.J., *Environmental and Experimental Botany*, 1997, vol. 37, p. 25.

59. Clarkson, E.M. and Sanderson, J., *J. Exp. Bot*., 1971, vol. 22, p. 837.
60. Clarkson, D.T., *Ann. Bot. N. S*., 1965, vol. 29, p. 309.
61. Cannata, A., *Nephrol. Dial. Transplantation*, 1996, vol. 11, no. 3, p. 6973.
62. Mahieu, S., *Toxicol. Lett*., 2000, vol. 111, no. 3, p. 235.
63. Albero, K., Glass, J., and Sella, M., *Kidney Int*., 1990, vol. 37, p. 677.
64. Exley, C. and Birchall, J.D., *J. Theoret. Biol*., 1992, vol. 159, p. 83.
65. Johnson, G.V.W., Cogkill, K.W., and Jope, R.S., *Neurobiol. Aging*, 1990, vol. 11, p. 209.
66. Ronneberg, A., *Occup. Environ. Med*., 1995, vol. 52, p. 255.
67. Ohyashiki, T., Satoh, E., Okada, M., Takadera, T., and Sahara, M., *Toxicology,* 2002, vol. 176, p. 195.
68. Savory, J., Herman, M., and Ghribi, O., *J. Inorg. Biochem*., 2003, vol. 97, p. 151.
69. Vierstra, R. and Haug, A., *Biochem. Biophys. Res. Commun*., 1978, vol. 84, no. 1, p. 138.
70. Greger, J., *Ann. Rev. Nutr*., 1993, vol. 13, p. 43.
71. Cherroret, G., Desor, D., and Leht, P.R., *Bull. Environ. Contam. Toxicol*., 1994, vol. 52, p. 487.
72. Shivani, M., Shah, P.S., and Bala, L.S., *Acta Pharmacol. Sin*., 2001, no. 1, p. 37.
73. Han, J.M., *Toxicology,* 2000, vol. 142, no. 2, p. 97.
74. Baranovskaya, A.T., *Cand. Sci. (Biol.) Dissertation*, Omsk, 2009.
75. Touam, M., Martinez, F., Locour, B., Bourdon, R., Zingraff, J., DiGiulio, S., and Drueke, T., *Clin. Nephrol*., 1983, vol. 19, p. 295.
76. Moshtaghie, A.A. and Skillen, A.W., *Biochem Soc. Trans*., 1986, vol. 14, p. 916.
77. Synzynys, B.I., Kharlamova, O.T., and Bulanova N.T., *Toxicology Lett*., 2003, vol. 144, p. 126.
78. Stancheva, E., *Gematologiya i Transfuziologiya*, 2003, no. 3, p. 36.
79. Albero, K., Glass, J., and Sella, M., *Kidney Int*., 1990, vol. 37, p. 677.
80. Mahieu, S., *Toxicol. Lett*., 2000, vol. 111, no. 3, p. 235.
81. Ershov, Yu.A. and Pletneva, T.V., *Mekhanizmy toksicheskogo deistviya neorganicheskikh soedinenii na eritropoez* (Mechanisms of Toxic Action of Inorganic Compounds on Erythropoiesis), Moscow: Meditsina, 1989.
82. Flaten, T., Alfrey, A., and Birchall, J., *J. Toxicol. Environ. Health*., 1996, vol. 48, p. 527.
83. Yokel, R., *Neurotoxicology,* 2000, vol. 21, no. 5, p. 813.
84. Levesqye, L., *Brain Res*., 2000, vol. 877, no. 2, p. 191.
85. Peerson, G. and Skoog, I., *Intern. J. of Geriatric Psychiatry*, 1996, vol. 11, p. 15.
86. Deloncle, R., Guillard, O., Clanet, F., Courtois, P., and Piriou, A., *Biol. Elem. Res*., 1990, vol. 25, p. 39.
87. Gerunova, L.K., Zhabin, N.P., Baranovskaya, A.T., and Bdyukhina, O.E., *Materialy mezhdunarod. nauchno-prakt. konf*. (Proc., International Scientific and Practical Conference), Moscow, 2006, p. 541.
88. Tuneva, E.O., *Cand. Sci. (Biol.) Dissertation*, Moscow, 2005.
89. Flaten, T., *Brain Res. Bull*., 2001, vol. 55, no. 2, p. 187.
90. Exley, C., *Biorg. Chem*., 1999, vol. 76, p. 133.
91. Campbell, A., *Nephrol. Dial. Transplant*., 2002, vol. 17, no. 2, p. 17.
92. Kurbanov, A.Ch., Avgonov, Z.T., Soliev, F.G., and Odinaev, Sh.F., *Materialy III nauchno-prakt. konf. sanatoriya Vulgrad* (Proc., III Sci. and Pract. Conf. at Vulgrad Sanatorium), 2006, p. 227.
93. Candy, J.M., Oakley, A.E., Klinowski, J., Carpenter, T.A., Perry, R.H., Atack, J.R., Perry, E.K., Blessed, G., Fairbairn, A., and Edwardson, J.A., *Lancet,* 1986, vol. 1, p. 354.
94. Bondy, S.C., Ali, S.F., and Guo-Ross, S., *Mol. Chem. Neuropathol*., 1998, vol. 34, p. 219.
95. Campbell, A. and Bondy, S.C., *Cell Mol. Biol*., 2000, vol. 46, p. 721.
96. Gibert-Barnes, E., Barness, L., and Wolff, J., *Arch. Pediatr. Adolese Med*., 1998, vol. 152, p. 511.
97. Privalova, L.I., Malykh, O.L., Katsnel'son, B.A., et al., *Sbornik nauchnykh trudov FNTs im. F.F. Erismana* (Collection of Scientific Works, F. F. Erisman Federal Research Center for Hygiene), Moscow, 2001, no. 1, p. 488.
98. Sviridov, N.K., *Laboratornoe Delo*, 1966, no. 12, p. 699.
99. Slanina, P., Falkeborn, Y., Freeh, W., and Cedergren, A., *Food Chem. Toxicol*., 1984, vol. 22, p. 391.
100. Robinson, R.F., *J. Toxicol. Clin. Toxicol*., 2002, no. 5, p. 604.
101. Roslyi, O.F. and Domnin, S.G., *Sbornik nauchnykh trudov: voprosy gigieny truda, professional'noi patologii i promyshlennoi toksikologii* (Collection of Scientific Works: Problems of Labor Hygiene, Occupational Pathology, and Industrial Toxicology), Yekaterinburg, 1996, p. 18.
102. Vanghan, J., *The Physiology of Bone*, Oxford, Charedon, 1975.
103. Domingo, J., Gomez, M., and Colomina, M., *Contrib. Sci*., 2000, vol. 1, no. 4, p. 479.
104. Yumoto, S., *Meth. Phys. Res. B*, 2000, no. 2, p. 925.
105. Plotko, E.P., Gurvich, V.B., Selyankina, K.P., Borzuyanova, E.A., and Ryzhov, V.V., *Sbornik nauchnykh trudov FNTs im. F.F. Erismana* (Collection of Scientific Works, F. F. Erisman Federal Research Center for Hygiene), Voronezh, 2002, no. 6, p. 308.

106. Broussard, C. and Riechter, J., *Drug Saf*., 1998, vol. 1, no. 4, p. 325.
107. Bennet, R., Persaud, T., and Moore, K., *Anat. Anz*., 1975, vol. 138, p. 365.
108. Lewis, J.H. and Weingold, A.B., *Amer. J. Gastroent*., 1985, vol. 80, no. 11, p. 912.
109. Synzynys, B.I., Sharetskii, A.N., and Kharlamova, O.V., *Gigien. Sanitar.*, 2004, no. 4, p. 70.
110. Golub, M.S., Takeuchi, P.T., Gershvin, M.E., Yoshida, S.H., *Immunofarmacology and Immunotoxicology*, 1993, vol. 15, no. 5, p. 605.
111. Tsidil'kovskaya, E.S., *Cand. Sci. (Biol.) Dissertation*, Moscow, 2005.
112. Karaulov, A.V., *Allergiya, Astma i Klinicheskaya Immunologiya*, 2000, no. 1, p. 24.
113. Litovskaya, A.V. and Egorova, I.V., *Meditsina Truda i Prom. Ekologiya*, 2000, no. 2, p. 8.
114. Berlyne, G., Ben-Ari, J., and Knopf, E., *Lancet,* 1972, vol. 1, p. 564.
115. Farina, M., *Toxicol. Lett*., 2002, vol. 132, no. 2, p. 131.
116. Cochran, M., Goddard, G., and Ludwigson, N., *Toxicol. Lett*., 1990, vol. 51, p. 287.
117. Batra, K., Taneja, O.P., and Khemali, L.D., *Bull. Environ. Contam. Toxicol*., 1994, vol. 52, p. 662.
118. Moumen, R., Ait-Oukhatar, N., Bureau, F., Fleury, C., Bougie, D., Arhan, P., Neuville, D., and Viader, F., *J. Trace Elem. Med. Biol*., 2001, vol. 15, p. 89.
119. Chmienicka, J., Nasiadek, M., and Lewandowska-Zyndul, E., *Biol. Trace Elem. Res.,* 1994, vol. 40, p. 127.
120. Farina, M., *Toxicol. Lett*., 2002, vol. 132, no. 2, p. 131.
121. Velichkovskii, B.T., *Meditsina Truda i Prom. Ekologiya*, 1998, no. 10, p. 28.
122. Milishnikova, V.V., *Doctoral (Med.) Dissertation*, Moscow, 1990.
123. Tislenko, L.N., *Cand. Sci. (Biol.) Dissertation*, Krasnoyarsk, 1992.
124. Sterekhova, N.P., Khalevina, S.N., and Likhacheva, E.I., *Toksiko-pylevye bronkhity* (Toxic-Dust Bronchites), Sverdlovsk: Izd. Ural. Universiteta, 1989.
125. Kaneko, N., Yasui, H., Takada, J., Suzuki, K., and Sakurai, H., *J. Inorg. Biochem*., 2004, vol. 98, p. 2022.
126. Johnson, V.J., Tsunoda, M., Murray, T.F., and Sharma, R.P., *Environ. Toxicol. Pharmacol.*, 2005, vol. 19, p. 221.
127. Ghribi, O., Herman, M., and Savory, J., *Neurosci. Lett*., 2002, vol. 324, p. 217.
128. Aswathnarayana, U., *Proc. Int. Symp. Geochem. Health (Royal Society),* 1985, p. 271.
129. Ahn, H.W., Fulton, B., Moxon, D., and Jeffery, E.H., *J. Toxicol. Environ. Health*, 1995, vol. 44, p. 337.
130. Rashidi, I.M.D., *Toxicoll. Lett*., 2003, no. 1, p. 110.
131. Friberg, L., *Handbook on the Toxicology of Metals*, Elsevier, 1979.
132. Zigel', Kh. and Zigel', A., *Nekotorye voprosy toksichnosti ionov metallov* (Some Aspects of Metal Ions Toxicity), Moscow: Mir, 1993.
133. Kaehny, W., Hegg, A., and Alfrey, A., *N Engl. J. Med*., 1977, vol. 296, p. 1389.
134. Sjogren, B., Knutsson, A., Bergstrom, H., and Fellenius, E., *Central European Journal of Occupational and Environmental Medicine*, 2002, vol. 8, no. 1, p. 49.
135. Kondrik, E.K., *Gigien. Sanitar.*, 1993, no. 8, p. 25.
136. Clonfero, E., Mastrangelo, F., and Cortese, M., *Med. d. Lavoro*, 1981, no. 4, p. 301.
137. Domnin, S.G., Lemyasev, M.F., Lipatov, G.Ya., and Shcherbakov, S.V., *Promyshlennye aerozoli i profilaktika zabolevaemosti rabotayushchikh v tsvetnoi metallurgii* (Industrial Aerosols and Preventive Health Care for Nonferrous Metallurgy Workers), Sverdlovsk: Izd. Ural. Universiteta, 1990.
138. Alekseeva, O.G., *Immunologiya professional'nykh khronicheskikh bronkholegochnykh zabolevanii* (Immunology of Occupational Chronic Bronchopulmonary Diseases), Moscow: Meditsina, 1987.
139. Tret'yakova, M.A., *Aktual'nye voprosy profpatologii i vnutrennei meditsiny* (Topical Issues of Occupational Diseases and Internal Medicine), 1994, p. 117.
140. Roslyi, O.F., Gerasimenko, T.N., Tartakovskaya, L.Ya., and Zhovtyak, E.P., *Meditsina Truda i Prom. Ekologiya*, 2000, no. 3, p. 13.
141. Golomidov, N.F., *Cand. Sci. (Biol.) Dissertation*, Dnepropetrovsk, 1975.
142. Shugalei, I.V., Dubyago, N.P., Iloyushina, T.M., Sudarikov, A.M., and Kamyshanskii, D.V., *Materialy mezhdunarod. konf. VIII Vishnyakovskie chteniya: "Sotsial'no-ekonomicheskie kontseptsii vuzovskoi nauki regiona"* (Proc., VIII Vishnyakov's Readings Int. Conf. "Social and Economic Concepts of University Science in the Region), St. Petersburg, 2005, vol. 1, p. 201.
143. Nordberg, G., *Environ. Health*, 1978, vol. 25, p. 3.
144. Panaiotti, Z.F. and Kravtsov, I.M., *Sb. nauchnykh trudov: voprosy gigieny i professional'noi patologii v metallurgii* (Collection of Scientific Works: Issues of Hygiene and Occupational Diseases in Metallurgy), Moscow, 1989, p. 30.
145. Roslyi, O.F., Likhacheva, E.I., Zhovtyak, E.P., and Plotko, E.G., Abstracts of Papers, *Mezhdunarod. konf. "Sotsial'naya otvetstvennost' rabotodatelya za zdorov'e rabotnikov"* (Int. Conf. "Employer's Social Responsibility for Employees' Health"), Moscow, 2003, p. 82.
146. Barannik, N.G., *Cand. Sci. (Biol.) Dissertation*, Kiev, 1978.

147. Trunova, O.A., *Meditsina Truda i Prom. Ekologiya*, 1999, no. 2, p. 22.

148. Narzullaeva, B.B., *Cand. Sci. (Biol.) Dissertation*, Dushanbe, 2003.

149. Larsson, K., Klund, A., and Arns, R., *Scand. J. Work. Environ. Health*, 1989, vol. 15, no. 4, p. 296.

150. Kurbanov, A.Ch., *Cand. Sci. (Biol.) Dissertation*, Dushanbe, 2007.

151. Mukhamedzhanov, R.Sh., *Cand. Sci. (Biol.) Dissertation*, Tomsk, 2004.

152. Khasanova, G.E. and Oranskii, I.E., *Fundamental'nye Issledovaniya*, 2011, no. 10, p. 166.

153. Soliev, F.G., *Cand. Sci. (Med.) Dissertation*, Dushanbe, 1997.

154. Tret'yakova, M.A., *Sb. nauchnykh trudov "Aktual'nye voprosy profpatologii i vnutrennei meditsiny"* (Collection of Scientific Works "Topical Issues of Occupational Diseases and Internal Medicine"), Irkutsk, 1994, p. 113.

155. Alekseeva, O.G. and Dueva, L.A., *Allergiya k promyshlennym khimicheskim soedineniyam* (Allergy to Industrial Chemicals), Moscow: Meditsina, 1978.

156. Khaidarova, Kh.Kh., *Cand. Sci. (Biol.) Dissertation*, Dushanbe, 2004.

157. Bandman, A.L., *Vrednye khimicheskie veshchestva: neorganicheskie soedineniya elementov 1–4 Grup* (Harmful Chemicals: Inorganic Compounds of Elements of 1–4 Groups), Leningrad: Khimiya, 1988.

158. Coburn, J., Mishel, M., and Goodman, W., *Am. J. Kidney Dis*., 1991, vol. 17, no. 6, p. 708.

159. Weberg, B.A*., Eur. J. Clin. Invest*., 1986, vol. 16, p. 428.

160. Nicolini, M., Zatta, P.F., and Corain, B., *Cortina Int.,* 1991.

161. Tracey, J.A., *J. Clin. Toxicol*., 2001, vol. 39, no. 3, p. 240.