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Review

AEROGENIC POLLUTANTS AS RISK FACTORS CAUSING DEVELOPMENT OF CARDIO-METABOLIC PATHOLOGY (REVIEW)

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Ambient air pollution causes approximately 3.3 million untimely deaths annually (2.1 deaths due to ischemic heart disease and 1.1 million deaths due to stroke). Mortality caused by ambient air pollution is higher than mortality due to such traditional risk factors as smoking, obesity, and elevated dextrose contents in blood. Relative risk of mortality amounts to 1.26 (95 % CI 1.08–1.47) in cities with the highest air pollution against those where air pollution is the lowest. Occupational exposure to various chemical air pollutants can cause more than 1 million untimely deaths all over the world but its contribution to prevalence of cardiovascular diseases has not been determined sufficiently. Aerogenic pollutants are quite variable in their chemical structure and include both particulate matter (PM for short) and gaseous matter. The American Heart Association and the European Society of Cardiology consider $PM_{2.5}$ to be a risk factor causing cardiovascular diseases. This analytical review presents data on effects produced by aerogenic pollutants on development of cardio-metabolic pathology and population mortality due to vascular and metabolic diseases (arterial hypertension, atherosclerosis and ischemic heart disease, heart rhythm disturbances, and type 2 diabetes mellitus). There are also data on mechanisms of pathogenetic influence exerted by aerogenic pollutants on development of such diseases including generation of anti-inflammatory and oxidative mediators and their release into blood flow; developing imbalance in the autonomic nervous system with prevailing activity of the sympathetic nervous system and disrupted heart rate variability; direct introduction of aerogenic pollutants from the lungs into blood flow with developing direct toxic effects. We have also analyzed literature data on protective effects produced by reduction in ambient air pollution on prevalence of cardiovascular pathology.

Key words: *aerogenic pollutants, airborne particulate matter, persistent organic pollutants, cardiovascular pathology.*

Cardiovascular pathology remains a leading cause of mortality among employable population all over the world since 17 million untimely deaths result from it annually; 3.3 million out of them are associated with ambient air pollution with technogenic chemicals [1, 2]. Effects produced by ambient air pollution occupy the 6th rank place among mortality factors being ahead of such traditional risk factors as smoking (2.48 million), obesity (2.85 million), and elevated glucose contents in blood (2.84 million) [3]. Only arterial hypertension (AH) is more significant as a risk factor of cardiovascular mortality than ambient air pollution [2]. According to E. Braunwald, relative risk of mortality amounts to 1.26 (95 % CI 1.08–1.47) in the most polluted cities against the least polluted ones [4]. Occupational exposure to various chemical air pollutants can cause more than 1 million untimely deaths all over the world but its contribution to cardiovascular mortality hasn't been well-determined yet [5].

Ambient air pollutants are quite heterogeneous in their chemical structure and include both particulate matter (PM for short) and

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gaseous matter (volatile organic compounds, ozone, nitrogen oxide, carbon monoxide, sulfur dioxide, etc.). PM in their turn can have various sizes and are usually divided into three basic groups: coarse particles (PM_{10}, diameter is from 2.5 to 10 μm), fine particles ($PM_{2.5}$, diameter is less than 2.5 μm), and ultrafine particles (diameter is less than 0.1 μm); besides, particulate matter are divided into primary and secondary ones. Primary particulate matter are emitted into the atmosphere directly from a polluting source (dust, metals, soot, salt particles, and plants spores) whereas secondary ones are created from aerosol pollutants through nucleation and gaseous fraction transforming into solid one [4]. Chemical structure of PM varies depending on a polluting source and can include complex organic molecules (formaldehyde, acrolein, benzene, xylene, butadiene, and polycyclic aromatic hydrocarbons), carbon, metals, sulfates, and nitrates [1, 4–7]. The American Heart Association and the European Society of Cardiology determine $PM_{2.5}$ as a risk factor that can cause cardiovascular diseases [8]. Several research works confirmed that exposure to $PM_{2.5}$ created elevated risks of cardiovascular mortality and non-fatal cardiovascular events [3, 9–11]. However, no chemical components or $PM_{2.5}$ sources have been detected to possess any unique toxic effects or peculiarities related to pathogenesis of cardiovascular disorders [3]. It was shown in some research works that frequency of cardiovascular mortality grew by 1 % per each 10 μg/m^3 of growing $PM_{2.5}$ concentration in ambient air under short-term exposure [9]. According to meta-analysis data obtained by G. Cesaroni with colleagues, long-term exposure to $PM_{2.5}$ per each 10 μg/m^3 of its contents in ambient air resulted in a 6 % growth in mortality due to all reasons (95 % CI 4–8 %) and to an 11 % growth in cardiovascular mortality (95 % CI 5–16 %) [12]. R. Chen with colleagues showed in their study that there was no "safe" bottom limit in a curve showing "dose – effect" dependence for influence exerted by air pollution with $PM_{2.5}$ on cardiovascular prevalence and mortality [13].

H. Mustafic with colleagues showed in their meta-analysis that short-term exposure to aerogenic pollutants ($PM_{2.5}$, nitrogen, carbon, and sulfur oxides) was associated with a 1–5 % growth in risks of myocardial infarction during the next day [14]. Sub-analysis of acute coronary events in eleven cohorts included into ESCAPE project (more than 100 thousand participants) revealed a statistically significant association between their development and exposure to $PM_{2.5}$ even in concentration that was lower than permitted in the European Union (risk went up by 12 % per each 10 μg/m^3 of growing PM_{10} concentration and by 13 % per each 5 μg/m^3 of growing $PM_{2.5}$ concentration) [12]. 6.2 million strokes were analyzed in 28 countries and this allowed establishing rather small (approximately 1 %) but statistically significant increase in frequency of strokes and mortality due to them per each 10 μg/m^3 of growing $PM_{2.5}$ concentration [15]. At the same time, according to Woman's Health Initiative and ESCAPE surveys, a risk of stroke grew by 17.5 and 19 % in the USA and Europe accordingly per each 5 μg/m^3 of growing $PM_{2.5}$ concentration in ambient air [16, 17]. According to P. Zhang and others, combined exposure to PM_{10} and nitrogen oxide during 12 years was associated with elevated mortality due to cerebrovascular diseases in China and Korea [18, 19]. Results obtained in The Women's Health Initiative study revealed that long-term aerogenic exposure to $PM_{2.5}$ resulted in a 35 % growth in risks of stroke [17]. Short-term increase in concentrations of gaseous pollutants and $PM_{2.5}$ in ambient air was associated with a growing risk of admission to hospital due to heart failure and related mortality. Each 10 μg/m^3 of growing $PM_{2.5}$ concentration led to 1–1.5 % growth in a number of admissions to hospitals due to heart failure [4, 20]. A national cohort study performed in England revealed high frequency of heart failure cases associated with long-term exposure to elevated PM and nitrogen oxide concentrations in ambient air [17–22]; attributive risks of

mortality due to progressing heart failure associated with exposure to aerogenic pollutants could reach 30 % [4, 23].

Pathogenetic mechanisms of cardiovascular pathology associated with exposure to aerogenic pollutants. Multiple studies that have been performed over the last two decades have revealed basic pathogenetic mechanisms of cardiovascular pathology development under exposure to aerogenic pollutants. When aerogenic pollutants penetrate the airways, they start interacting with the mucosa in the upper and lower airways. Coarse and fine particles ($PM_{2.5}$ and PM_{10}) are distributed in the airways in a different way; and since they have different chemical structure, they produce different biologic effects [24]. A primary affecting factor here is PM and other chemicals depositing in airways tissues; it activates three basic mechanisms [25]:

– pro-inflammatory and oxidant mediators are generated and released into blood flow;

– imbalance develops in the autonomic nervous system with prevailing activity of the sympathetic nervous system and disrupted heart rate variability (HRV);

– pollutants penetrate blood flow directly from the lung tissue and this produces direct toxic effects.

Generation of pro-inflammatory and oxidative mediators. Introduction of PM and other chemical components, especially those with redox potential, induces a cascade of oxidative stress reactions and inflammation in lung tissues [9, 22]. Free radicals can both occur in the lung tissue directly due to impacts exerted by some substances, metals, for example, and due to activation of the immune system cells as a result of contacts with PM. Stimulation of redox mechanism with free radicals formation (superoxide and hydroxyl) results in elevated activity of polymorphonuclear leukocytes and production of pro-inflammatory cytokines (interleukin 1β, interleukin-6, interleukin-8, tumor necrosis factor alpha) and chemokines to achieve sequestration of PM that penetrated the lung tissues. It should be noted that the smaller is a diameter of particles that have penetrated the lung tissues, the more apparent oxidative stress is induced by them. Several cohort studies revealed there was a relation between exposure to PM (both in occupational groups and population in general) with elevated contents of protein, lipid, and DNA oxidation products in blood and urine. People with already elevated contents of oxidative stress and inflammation products are more susceptible to effects produced by aerogenic pollutants [23, 26, 27]. Besides, PM contacts with the airways mucosa lead to damage to the surfactant system and induce mechanisms of inborn immunity thus creating a focus of chronic low level non-infectious inflammation in the lung tissues. A key hypothesis regarding this mechanism is that the process is deadaptation in its essence and occurring pro-inflammatory and oxidative reactions are not limited to the lung tissues but also result in excessive release of inflammation mediators in peripheral blood flow; thus, a systemic inflammatory reaction develops together with vascular oxidative stress and inflammation as well as endothelial dysfunction [4]. As redox and pro-inflammatory processes develop and generalize, blood cells (polymorphonuclear leukocytes, T-lymphocytes, macrophages, and thrombocytes) become activated; the same goes for a whole cascade of mediators that affect the cardiovascular system including adipocytokines (resistin and adiponectin) and acute-phase proteins (C-reactive protein, fibrinogen, and coagulation factors). These mediators and proteins are activated from adipocytes and hepatocytes accordingly. The aforementioned mechanism induces several basic chronic pathologic processes including atherosclerosis, endothelial dysfunction, cardiac hypertrophy, vasoconstriction, and pro-coagulant changes, and metabolic disorders [28]. However, this mechanism can potentially cause acute exacerbations such as disrupted stability of atherosclerotic plaque with developing acute ischemic syndromes [25].

Developing imbalance in the autonomic nervous system. Several nerve receptors (no-

ciceptive and adrenergic ones) in the lung tissue are activated by PM and other chemicals that penetrate the airways due to breathing; this creates pathological autonomic reflex arcs. This mechanism induces both dysfunction of the central nervous system (activated vegetative centers) and peripheral disorders that become apparent through sympathetic impacts prevailing over parasympathetic ones (changes in heart rate, blood pressure, lower heart rate variability, and disrupted cardiac repolarization) [29]. Activation of the autonomic nervous system and synthesis of vasoactive mediators stimulate so called "neurogenic inflammation" with activated T-lymphocytes, adhesion molecules, pro-inflammatory cytokines, and free radicals [23]. These data indicate there is a close connection between the first and the second mechanism of pathologic influence by aerogenic pollutants and they produce complex effects on the cardiovascular system. Acute reactions induced by this mechanism include predominantly heart rhythm disturbances; chronic ones are arterial hypertension (AH), cardiac and artery hypertrophy, and metabolic disorders [25].

Introduction of pollutants from the lung tissue into blood flow. A few studies have revealed that fine particulate matter as well as soluble chemicals can penetrate blood flow and produce direct adverse effects on vessel walls and blood cells (thrombocytes in particular) and disrupt vasomotor regulation. However, since there are scarce scientific data on the matter, an insight into this mechanism is still considered to be rather vague and contradictory [25, 30].

In scientific literature, the aforementioned mechanisms predominantly explain most typical pathological processes in the cardiovascular system associated with exposure to aerogenic pollutants (AH, atherogenesis, heart rhythm disturbances, resistance to insulin, metabolic syndrome, and type 2 diabetes mellitus). Next we are going to pay closer attention to statistical, pathophysiological and clinical aspects regarding these disorders in relation with exposure to aerogenic pollutants.

Most common diseases, syndromes, and pathological processes that develop under exposure to aerogenic pollutants. ***Arterial hypertension.*** A lot of studies concentrate on examining correlation between AH and exposure to aerogenic pollutants. According to Global Burden of Disease Study, elevated blood pressure causes approximately 10.4 million deaths and 208.1 million disability-adjusted life years (DALY) worldwide [2]. An increase by 20 mm Hg in systolic blood pressure (SBP) or by 10 mm Hg in diastolic blood pressure (DBP) in people aged 40–69 is associated with more than 2-time growth in a risk of death due to cardiovascular events [31]. Even a slight decrease in blood pressure leads to significantly improved forecasts; a decrease by 2 mm Hg in SBP results in 5 % drop in mortality due to stroke; 4 % drop, due to ischemic heart diseases (IHD); 3 % drop in overall mortality [32]. Keeping in mind statistical data on cardiovascular prevalence and mortality, we can assume that even slight influence on AH risk factors can significantly improve forecasts for an overall population. A substantial database has been accumulated by now on impacts exerted by ambient air pollution on AH development or induction [8, 10, 11, 33–36]. Research works concentrated on describing influence by aerogenic pollutants on blood pressure, development of persistent AH, and a rise in appealability for emergency aid. According to E. Braunwald, blood pressure grows by 1–4 mm Hg per each 10 $\mu g/m^3$ of growing $PM_{2.5}$ concentration in ambient air under short-term exposure. Blood pressure can grow by 8–9 mm Hg during 2–5 days after exposure to elevated $PM_{2.5}$ concentrations [4, 35]. R. Liang with colleagues performed meta-analysis of 25 studies to show that blood pressure increased by 1.4 / 0.9 mm Hg per each 10 $\mu g/m^3$ of growing $PM_{2.5}$ concentration in ambient air [37]. P. Giorgini and colleagues examined 2,078 patients with AH and revealed that average $PM_{2.5}$ concentration in ambient air equal to 12.6 ± 8.2 $\mu g/m^3$ during several previous days was associated with statistically significant rise in blood pressure, by 2.1–3.5 /

1.7–1.8 mm Hg per each standard deviation towards growth in $PM_{2.5}$ concentration. This effect was detected in spite of all research participants constantly being treated with up-to-date hypotensive therapy and ambient air quality was quite optimal if taken in remote prospects [38]. R.D. Brook and others assessed impacts exerted by ambient air pollution on blood pressure of 65 people living in Beijing where $PM_{2.5}$ concentration varied within 9.0–552 μg/m^3. Exposure to high $PM_{2.5}$ concentrations during 1–7 previous days resulted in growth in SBP varying from 2 (95 % CI 0.3–3.7) to 2.7 (95 % CI 0.6–4.8) mm Hg per each standard deviation in $PM_{2.5}$ concentration (67.2 μg/m^3) [39]. Long-term exposure (during the whole previous year) resulted in more apparent hypertensive effects, growth by 7.3 / 9.5 mm Hg [36]. It was established in several research works that "acute" exposure to PM with a wide range of diameters ($PM_{0.1-10}$) and concentrations in ambient air led to rapid rise in blood pressure from 2 to 10 mm Hg and it remained high for several hours [35]. Long-term exposure to $PM_{2.5}$ (during several years) is associated with persistent AH occurrence. An increase in $PM_{2.5}$ concentration in ambient air by 10 μg/m^3 was associated with 13 % of AH prevalence (HR 1.13 (95 % CI 1.05–1.22)) among a cohort made up of 35,303 adult people living on a relatively ecologically clean territory in Canada [40]. Increased appealability for emergency aid due to exacerbated AH was detected during periods when there was growth in ambient air pollution both in countries with high pollution (China) and with lower one (Canada) [41]. Long-term exposure to $PM_{2.5}$ was proven to be associated with an increase in AH-related mortality [42].

Endothelial dysfunction and vasoconstriction. Several studies revealed that exposure to aerogenic pollutants resulted in vasoconstriction and endothelial dysfunction [25, 29]. In particular, S.D. Adar with colleagues established in Multi-Ethnic Study of Atherosclerosis (MESA) performed on a cohort made up of 4,607 patients that exposure to $PM_{2.5}$ influenced reduction of retinal artery lumen. This effects were also observed under both short-term (during a day) and long-term (2 years, on average) exposure [43]. A similar effect was revealed in a study accomplished in Belgium (84 patients) that concentrated on influence exerted by PM_{10} on retinal artery lumen under short-term exposure [44].

Endothelial dysfunction induced by affecting factors (aerogenic pollutants in particular) is among the most significant mechanisms of cardiovascular pathology. A slight increase in $PM_{2.5}$ concentration in ambient air results in authentic decrease in flow-dependent vasodilatation as it was shown in large cohort studies performed in the USA [45, 46]. An increase in average annual $PM_{2.5}$ concentration in ambient air by 3 μg/m^3 can be compared to effects produced on endothelial function by smoking (a decrease by 0.3 %) or additional 5 years of age [46].

Heart rhythm disturbances. According to literature data, exposure to aerogenic pollutants correlates with electrical instability of the cardiac muscle, changes in heart rate, and lower heart rate variability (HRV) [47–50]. High levels of systemic inflammation and oxidative stress markers were established to predispose to more apparent heart rhythm disturbances under exposure to aerogenic pollutants [49]. However, ventricular arrhythmia and atrial fibrillation induced by exposure to pollutants in most cases were detected in people who already suffered from heart diseases [51]. Moreover, studies that involved controlled inhalation exposure to pollutants didn't reveal any developing arrhythmia in healthy participants under acute exposure [52].

Changes in HRV were among first biological effects detected under exposure to aerogenic pollutants [25]. Meta-analysis of 29 epidemiologic studies performed on 18,667 patients revealed that an increase in $PM_{2.5}$ concentration in ambient air by 10 μg/m^3 led to statistically significant decrease in both time and frequency HRV parameters and imbalance in the autonomic nervous system towards prevailing sympathetic activity [53]. A decrease

in HRV is a well-known factor that creates risks of cardiovascular death. Several studies revealed disrupted repolarization in ECG under exposure to PM. These data indicate there are certain changes in ion channels of cardiomyocytes and this can induce heart rhythm disturbances in predisposed people, right up to fatal ventricular arrhythmia [54, 55]. Neurogenic effects produced by exposure to aerogenic pollutants on developing imbalance in the autonomic nervous system were confirmed in a study accomplished by C.M. Barbosa in Brazil. When sugar cane was being burnt, PM concentrations grew in ambient air and this resulted in elevated blood pressure in healthy workers due to growing activity of peripheral sympathetic nerves established with microneurography [56].

Atherosclerosis. Long-term exposure to aerogenic pollutants makes for atherosclerosis development [25]. Several research works have concentrated on this effect by pollutants over the last two decades. According to E.H. Wilker long-term exposure to fine-disperse PM in high concentrations is associated with growing carotid intima-media thickness (CIMT), by 1.1 % annually per each 0.26 μg/m^3 of growing PM concentration in ambient air [57]. The most significant results were obtained in MESA survey. A series of ultrasound examinations were performed on 5,362 people living in 6 cities in the USA where ambient air pollution was high; they revealed that CIMT grew by 5 μm (95 % CI 2.6–7.4) annually per each 2.5 μg/m^3 of growing $PM_{2.5}$ concentration. At the same time, a fall in aerogenic exposure to $PM_{2.5}$ by 1 μg/m^3 resulted in negative CIMT progression (–2.8 μm annually (95 % CI from –1.6 to –3.9)) [58]. First data on influence exerted by ambient air pollution on atherosclerosis progression were obtained by N. Kunzli in a study performed among people in Los Angeles in 2005. Overall, 798 people were examined; they were older than 40 and didn't have either cardiovascular pathology or diabetes in their case history. It was established that carotid intima-media thickness grew by 5.9 % (95 % CI 1.0–10.9) per each 10 μg/m^3 of growing $PM_{2.5}$ concentration in ambient air (within 5.2–26.9 μg/m^3 range) [59]. M. Bauer with colleagues revealed in their study accomplished in 2010 in Germany that a growth in $PM_{2.5}$ concentration in ambient air by 4.2 μg/m^3, and PM_{10} by 6.7 μg/m^3, was associated with an increase in CIMT by 4.3 % (95 % CI 1.9–6.7 %) and 1.7 % (-0.7–4.1 %) accordingly [60]. According to C. Tonne and others, CIMT grows by 5 % (95 % CI 1.9–8.3 %) per each 5.2 μg/m^3 of growing PM_{10} concentration [2].

Insulin resistance, type 2 diabetes mellitus, metabolic syndrome. Over the last two decades a lot of data have been accumulated on impacts exerted by aerogenic pollutants on developing diseases and conditions related to insulin resistance (metabolic syndrome, type 2 diabetes mellitus (DM2), and non-alcoholic fatty liver disease) [61, 62]. These effects produced by aerogenic pollutants have been detected both in regions where ambient air pollution is relatively low and in those where it is considerably high [63, 64]. Insulin resistance is a key pathogenetic mechanism responsible for these disorders. As it was shown by R.D. Brook, when 25 healthy adults were exposed to elevated $PM_{2.5}$ concentrations during 5 days (south-eastern Michigan), it led to a decrease in sensitivity to insulin according to data by Homeostasis Model Assessment of Insulin Resistance Values (HOMA-IR) [65]. The research established that heart rate variability disorders correlated with growing insulin resistance. E.H. Wilker revealed growing insulin resistance and deteriorating control over DM2 in a study conducted in Germany [57]. Long-term exposure to $PM_{2.5}$ leads to elevated risks of manifest DM2 occurrence simultaneously with growing risks of AH development [61]. H. Chen with colleagues examined 62,012 people living in Canada in their research and showed that DM2 risk grew by 11 % per each 10 μg/m^3 of long-term growing $PM_{2.5}$ concentration in ambient air [63]. F. Liang and others observed 88,397 people in China with 6,439

new DN2 cases detected among them; the authors revealed that exposure to $PM_{2.5}$ increased DM2 risks by 15.7 % (95 % CI 6.42–25.70) per each 10 μg/m^3 [66]. A study by Lao X.Q. also established an increase in DM2 risks under long-term exposure to $PM_{2.5}$. As opposed to the first quartile of $PM_{2.5}$ concentration in ambient air, HR amounted to 1.28 (95 % CI 1.18–1.39), 1.27 (95 % CI 1.17–1.38), and 1.16 (95 % CI 1.07–1.26) for the second, third, and forth quartiles accordingly [67]. Meta-analysis by I.C. Eze and a review by X. Rao confirmed that DM2 risks grew by 8–13 % per each 10 μg/m^3 of growing $PM_{2.5}$ concentration in ambient air [68, 69]. Oxidative stress and chronic metaflammation play a leading role in pathogenesis of metabolic disorders and DM2 associated with exposure to aerogenic pollutants due to activation of proinflammatory cytokines and inborn immunity cells in visceral fat depots [61]. This mechanism is quite similar to pathogenesis associated with diabetogenic effects produced by some foods where inflammation plays a leading role in DM2 pathogenesis [70]. Exposure to aerogenic pollutants is associated with elevated levels of tumor necrosis factor, interleukin-6, resistin, and leptin in blood. There is also a growth in concentrations of prothrombotic adipokines (plasminogen activator inhibitor-1) and circulating adhesion molecules (ICAM-1, E-selectin). The latter make for leukocytes adhesion to endothelium of post-capillary venules [71]. Imbalance in the autonomic nervous system towards increasing activity of the parasympathetic section also makes a significant contribution to developing insulin resistance. Some lung receptors such as transient receptor potential ankyrin 1 (TRPA1) can be stimulated by aerogenic pollutants and the sympathetic section in the autonomic nervous system through central mechanisms [72]. Endothelial dysfunction often precedes insulin resistance and is associated with disrupted peripheral glucose utilization [73]. Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs) determine a pathogenetic mechanism responsible for a relation between exposure to aerogenic pollutants and obesity / DM2 [74, 75]. Redox reaction products (palmitoyl-arachidonoyl phosphocholine, hyaluronic acid fragments) activate TLR4 and also make for release of chemokines ligand (CCL-2) that activates monocytes [76]. Overall, there are 4 basic mechanisms of immune activation that lead to developing insulin resistance / DM2:

– direct inflammatory / oxidative stress that stimulates alveolar macrophages to synthesize interleukin-1, tumor necrosis factor alpha, interleukin-6, and chemokines (CCL-2 and CCL-5) which determine cellular response in the bone marrow and spleen [77];

– macrophages capturing inhaled pollutants and presenting them to T-lymphocytes in secondary lymphoid organs [78];

– some pollutants (organic compounds, metals) directly penetrating the blood flow with developing vascular inflammation and insulin resistance [79];

– central inflammation mechanisms being involved through reflex arcs connecting receptors in the lung tissue with the brain [73].

Cardio-metabolic effects produced by persistent organic pollutants. Cardio-metabolic effects produced by persistent organic pollutants (POPs) have been described in scientific literature in much lesser volumes than effects by PM. Such compounds are represented by a lot of toxicants such as polychlorinated biphenyls, dioxins, aromatic compounds, and halogen-substituted aromatic hydrocarbons. Biologic effects produced by such compounds on the cardiovascular system are predominantly examined in cross-sectional population and prospect studies that provide an opportunity to trace remote effects produced by low doses of organic toxicants [34]. As a rule, pathogenetic mechanisms of effects by POPs regarding metabolic disorders have few specific features and are just typical pathological processes. Thus, dioxins and polychlorinated biphenyls affect aryl hydrocarbon receptor (AHR). When this receptor is activated, this leads to growing activity

of cytochrome P450 CYP1A1 and formation of reactive oxygen species together with developing low level inflammation [80]. Simultaneously apoptosis is disrupted and changes occur in the cellular lifecycle, there is also lipid oxidation and accelerated atherosclerotic processes in vascular walls [81]. Some substances influence peroxisome proliferator-activated receptors (PPAR) that disrupt adipocytes differentiation, lipid metabolism, reduce sensitivity to insulin and hence increase risks of DM2 development [82].

There are data in scientific literature on effects produced by POPs on risk factors causing cardiovascular diseases (AH, obesity, and DM2) and ultimate events (myocardial infarction, stroke, or diseases of peripheral arteries). There was an incident in Yucheng that involved mass exposure to polychlorinated biphenyls and polychlorinated dibenzofurans; as a result, a risk of AH development grew by more than 3 times over the next 24 years among women with chloracne manifestations in comparison with patients without this pathology [83]. A.V. Sergeev performed a study among people living on a territory polluted with POPs and revealed that AH risks was by 19 % higher for them (95 % CI 9–31 %) in comparison with the reference group [84]. NHANES cross-sectional study revealed that relative AH risk amounted to 1.8 (95 % CI 1.2–2.7) in the highest quartile as per environmental pollution with polychlorinated biphenyls [85]. It was established in the same study performed with 524 people participating in it that concentrations of dioxin and polychlorinated dibenzofurans in blood correlated with risks of developing AH in women, relative risks being equal to 5–6 for the highest quartile against the lowest one [86]. A cross-sectional study that involved 758 participants (Anniston, the USA) who lived on a territory polluted with polychlorinated biphenyls revealed that relative risk of developing AH amounted to 4.1 (95 % CI 1.3–14) for the upper tertile in comparison with the lower one [34].

Effects produced by POPs are associated with developing metabolic syndrome (MS). At present there are only results of cross sectional studies that focused on influence by POPs on MS occurrence. A national study was performed in Japan and as a result it was established that contents of dioxins and polychlorinated biphenyls in blood of more than 1,300 people correlated with developing MS (*OR* 3.2–4.8 when the upper and the lower quartiles were compared). Elevated POPs concentration in blood was associated with greater frequency of all components in metabolic syndrome [87]. NHANES survey revealed that pesticides concentration in plasma correlated authentically with developing MS (*OR* 5.3, 95 % CI 2.5–11, when the upper and the lower quartiles were compared). Besides, elevated pesticides contents in blood (the upper quartile against the lower one) were associated with *OR* = 2.4 for the waist circumference; 7.1, for triglycerides; 2.3, for low density lipoproteins; 5.6, for glucose; 1.8, for AH [88]. S.K. Park with colleagues (Korea) compared 50 patients with MS with a reference group and revealed a correlation between MS and concentrations of pesticides, beta-hexachlorocyclohexane and heptachlor epoxide in blood plasma (*OR* 4.4–6.0 for the upper and lower quartiles) [89]. Insulin resistance under exposure to POPs was examined as a key pathogenetic mechanism of developing MS in NHANES survey in 749 patients without DM2. 19 various POPs were examined; the most apparent association with HOMA-IR index showing insulin resistance was revealed for pesticides (*OR* = 3.8 for the upper quartile) and this dependence was maximum among people with large waist circumference [90]. PIVUS survey focused on examining an association between POPs and fat mass using DXA. Low-chlorinated polychlorinated biphenyls turned out to correlate positively with fat mass whereas high-chlorinated ones had an inverse correlation with the parameter [91]. This difference in influence exerted by POPs chlorination can be due to pharmacokinetic properties and the fact that low-chlorinated compounds have a shorter semiejection period. A peak in using such POPs was in 70ties last century. M.S. Wolff with colleagues noted that a correlation be-

tween POPs and overweight was always negative under short-term exposure to toxicants due to their depositing in fat tissue. However, it became positive after 2 or 3 semiejection periods in case there was no further POPs introduction [92]. NHANES survey revealed a direct correlation between dioxin concentrations in blood and body mass index (BMI) both in men and women [93]. A population study (13,000 participants) accomplished in Japan allowed establishing positive dependence between concentration of polychlorinated biphenyls in blood and BMI [87]. CARDIA survey yielded similar results during 25 years of observation [94]. Several studies revealed elevated DM2 risks under long-term exposure to POPs. O. Vasiliu with colleagues established in their study (more than 1,300 participants, Michigan) that odds ratio for developing DM2 amounted to 2.0–3.0 for women and 1.7 for men depending on concentration of polybrominated biphenyls in blood (the upper quartile compared with the lower one) [95]. It was established in CARDIA survey that elevated concentrations of trans-nonachlodane pesticide and some polychlorinated biphenyls in blood were predictors of developing DM2. The authors noted that the effect occurred even if a rise in concentration of trans-nona-chlodane in blood was relatively low (*OR* = 5.3 for the second quartile against the first one) [94].

Long-term exposure to POPs can lead to developing atherosclerotic processes. PIVUS cross-sectional study established that polychlorinated biphenyls influenced formation of atherosclerotic plaques even after statistical adjustment per 10 well-known risk factors, lipids included. A similar effect was revealed for phthalate metabolites [96]. A study by IARC that involved 21,863 workers revealed that long-term exposure to dioxins at a workplace was associated with developing IHD (*RR* 1.6, 95 % CI 1.2–2.2). Relative risk of stroke amounted to 1.5 (95 % CI 0.8–2.8) in the same cohort [97]. A.V. Sergeev and I. Shcherbatykh examined a population living on a territory polluted with POPs (New York) and revealed that relative risks of myocardial infarction grew by 20 % (95 % CI 3–39 %); stroke, by 10 % (95 % CI 1.0–1.2) [84, 98]. NHANES survey established that relative risk of myocardial infarction under exposure to bisphenol A amounted to 1.2 (95 % CI 1.1–1.4) per one standard deviation in bisphenol A concentration in urine [99].

Effects produced by prevention activities aimed at reducing influence by ambient air pollution on the cardiovascular system. Randomized studies showed there was a direct protective effect produced by a decrease in pollutants concentrations in ambient air. Use of filtration devices and face masks that are able to filter PM results in decreasing blood pressure, microvascular function improvement, and lower levels of inflammatory biomarkers in adults exposed to $PM_{2.5}$ [100–102]. Results obtained by C.A. Pope with colleagues revealed that in 1970–2000 average life expectancy in the USA grew by 0.61 year per each 10 $\mu g/m^3$ of declining $PM_{2.5}$ concentration in ambient air (demographic, socioeconomic, and behavioral factors taken into account) [103]. According to M. Morishita, declining $PM_{2.5}$ concentration in ambient air in 1970–1990ties resulted in overall mortality going down by 27 %, and cardiovascular mortality, by 31 %, per each 10 $\mu g/m^3$ [104].

Activities aimed at reducing ambient air pollution may be implemented over decades; however, even a short-term decrease in pollutants concentration in ambient air (as it was shown during the Olympics in Beijing) leads to a rapid fall in levels of inflammation markers, oxidative stress, and thrombosis [105]. According to data provided by the US Environmental Protection Agency, activities aimed at ambient air purification prevented more than 160,000 deaths and 130,00 myocardial infarctions in 2010. It is pointed out that activities aimed at reducing concentrations of pollutants are likely to have more apparent effects in countries where quality of ambient air is rather poor [23].

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