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Research article

SCIENTIFIC AND METHODOLOGICAL GROUNDS FOR ITERATIVE PREDICTION OF RISK AND HARM TO HUMAN HEALTH UNDER CHEMICAL ENVIRONMENTAL EXPOSURES: FROM PROTEIN TARGETS TO SYSTEMIC METABOLIC DISORDERS

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Increasing the predictive potential of early diagnostics and correction of negative outcomes is becoming especially relevant for preventing and reducing personalized and population health risks, including those caused by environmental exposures. The purpose of the study was to develop scientific and methodological grounds for iterative numerical prediction of risk and harm to human health under chemical environmental exposures. The study design was based on the consistent implementation of an algorithm for system analysis of the development of negative effects under a chemical environmental exposure, from protein targets to systemic metabolic disorders. The in-depth examination covered more than 1 million people living under real long-term combined inhalation exposure at doses up to 5–10 RfC. About 350 digital multifactor models, including about 5.5 thousand parameters, were evaluated.

Structural bioinformation matrices were constructed to identify the sequence of response events at the molecular-cellular level. These events are initiated by the transformation of the protein-peptide profile of human blood plasma, which determine the metabolome. The study clarifies the elements of involvement of 20 target proteins in the pathogenesis of metabolic disorders associated with hypertension, dyslipidemia, obesity, hepatosis, and cognitive dysfunction associated with chemical combined exposure. The criteria for the safe content of 10 contaminants were substantiated, taking into account their combinations in human biological media. Predictive assessments of pathogenetic pathways were confirmed by the facts of their implementation at the cellular-tissue, organ and body level as metabolic disorders and existing diseases of the cardiovascular, nervous systems, lipoprotein metabolism, etc., proven to be associated with effects produced by airborne pollutants, including combined ones.

The study expands the existing methodological approaches to assessing combined effects of chemicals taking into account parameterized cause-effect relations of biomarkers of exposure and effects and quantitative assessment of additional cases of risk occurrence. Assessment of the developed digital models revealed that combined chemical exposures were predominantly synergic and emergent (up to 70 % cases). We developed conceptual grounds and architecture of iterative risk prediction and the development of risk-associated diseases, including real harm to health upon elevated expression of protein targets. Thus, the digitized version of the forecast (digital platform), as a multi-level cascade model, is a tool for scientific analysis of a hygienic situation with the parameterization of expected negative outcomes. It determines methods for their correction and prevention, which increases the reliability of hygienic assessments and the validity of management decisions.

Keywords: *health risk, caused harm, environmental factors, target proteins, negative effect, cascade model, cause-effect relations, forecast, digital platform.*

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Key priorities in the state development policy of the Russian Federation include preservation of the population size, health promotion and provision of better welfare for the country population (The RF President Order issued on May 07, 2024 No. 309 On National Development Goals of the Russian Federation for the period up to 2036)[1].

Persisting serious challenges highlighted in the Strategy for Scientific and Technological Development of the Russian Federation[2] create considerable risks for the society, economy and the system for state regulation. The most significant ones include demographic transition caused by declining birth rates, growing LEB and associated ageing of the country population; growing human impacts on the environment up to such level when they endanger reproduction of natural resources and associated growths in risks for people's lives and health. In the face of great challenges, scientific substantiation is required for actions that should be taken to deal with likely threats and response to new emerging challenges. Many studies focus on finding solutions to this problem; based on the succession principle, effective information and methodical support has been created that includes more than 50 developments. They develop scientific approaches to analytical health risk assessments at the individual, group, and population level established by leading Russian experts in preventive healthcare [1–5].

To prevent or reduce personalized and population health risks, the Prediction of Scientific and Technological Development of Russia up to 2030[3] has identified the necessity in the middle- and long-term outlook that encompasses comprehensive development of science-intense investigations with their focus on pathogenetic aspects of developing adverse effects. These effects are caused, among other things, by environmental exposures. It is important to study how a pathological process develops so that relevant preventive activities can be worked out. Within this context, it is especially interesting to investigate the molecular-genetic component of intracellular signaling pathways, structural and functional impairments of specific cells and tissues together with identifying potential molecular and cellular targets upon damaging exposure to environmental risks, including their combined introduction [6–15]. A wide range of highly hazardous chemicals that create chemical exposure are able to produce polytropic effects[4]. This creates elevated risks of multiple adverse health outcomes in population. To mitigate such risks, it is necessary to effectively regulate quality of environmental objects by activities within the state control that includes social and hygienic monitoring (SHM) and control and surveillance activities (CSA) [16, 17]. At the same time, in case a moratorium is introduced on control and surveillance activities, a list of chemicals subject to control can be minimized without any qualitative and information losses.

Given that, a relevant challenge for hygiene is to perform molecular profiling and investigation of cellular-molecular, metabolic, organ and systemic pathways of modifying effects produced by chemical environmental factors and to develop scientific and methodi-

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[1] O natsional'nykh tselyakh razvitiya Rossiiskoi Federatsii na period do 2030 goda i na perspektivu do 2036 goda: Ukaz Prezidenta RF ot 07.05.2024 № 309 [On National Development Goals of the Russian Federation for the period up to 2030 and further outlook up to 2036: The RF President Order issued on May 07, 2024 No. 309]. *GARANT.RU: information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/408892634/ (April 30, 2024) (in Russian).

[2] O strategii nauchno-tekhnologicheskogo razvitiya Rossiiskoi Federatsii: Ukaz Prezidenta RF ot 28.02.2024 № 145 [The Strategy for Scientific and Technological Development of the Russian Federation: The RF President Order issued on February 28, 2024 No. 145]. *GARANT.RU: information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/408518353/ (April 30, 2024) (in Russian).

[3] Prognoz nauchno-tekhnologicheskogo razvitiya Rossiiskoi Federatsii na period do 2030 goda, utv. Pravitel'stvom RF 03.01.2014 g [The Prediction of Scientific and Technological Development of Russian Federation up to 2030, approved by the RF Government on January 03, 2014]. *GARANT.RU: information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/70484380/ (April 29, 2024) (in Russian).

[4] Obshchaya toksikologiya [General toxicology]. In: B.A. Kurlyandskii, V.A. Filov eds. Moscow, Meditsina Publ., 2002, 608 p. (in Russian).

cal instruments on this basis to make numerical prediction of responses given by the human body upon exposure. It is very important to optimize the list of chemicals that are subject to immediate control to make regulation practices more effective.

The aim of this study was to develop scientific and methodological grounds for iterative numerical prediction of risk and harm to human health under chemical environmental exposures.

Materials and methods. To achieve the aim, the study design was based on the consistent implementation of an algorithm for system analysis of how negative effects develop upon a chemical environmental exposure, from molecular to the whole body level. The in-depth examination covered more than 1 million people (approximately 800 thousand children aged 4–7 years and 500 thousand adults aged 22–48 years) living under actual long-term combined inhalation exposure at doses of up to 5–10 reference concentrations established for chronic exposures (RfC)[5].

Molecular studies were conducted using proteome profiling of blood plasma of exposed children (approximately 300 proteome profiles, 180 quantified and identified expressed proteins). Contamination was examined and quantified in biological media (blood and urine) by using chemical and analytical methods fixed in the Rosaccreditaiton Register (18 chemicals including aluminum, copper, manganese, nickel, chromium, vanadium, cobalt, molybdenum, arsenic, mercury, fluorine-ion, benzo(a)pyrene, phenol, benzene, toluene, xylene, ethylbenzene, and acrolein)[6]. The results of proteome profiling obtained in real-world field conditions were verified with animal experiments when animals were challenged with an exposure equivalent to a real-world one. Experiments were performed on 300 Wistar rats and involved simulating inhalation exposures, both isolated and combined. Twenty-five bioinformation matrices were created relying on UniProt, Tissue expression DB, and DisGeNET to predict negative outcomes induced by transformation of the protein-peptide profile of blood plasma.

Cellular studies were conducted using scanning electronic microscopy, 3D cell reconstruction, and image analysis technologies. Morphological changes in tissues were examined with histological techniques. Specific cellular reactions were comparatively analyzed upon exposure to 9 metals in their micro- and nano-sized form (Al, Mn, Ni, Cr, Cu, Ca, Mg, Co, Mo).

Changes at the organ and systemic level were examined by biochemical, immunological, and hematological studies (approximately 100 indicators). Responses to exposure at the whole body level were estimated based on actual diagnosed diseases in exposed children and adults confirmed by a profound medical check-up (approximately 1500 diagnoses in accordance with ICD-10). Losses in life expectancy at birth (LEB) due to elevated expression of target proteins were estimated based on evolution modeling of health risk growth.

Cause-effect relations within the cascade model ‘Exposure – Biomarker of Exposure – Expressed Protein – Biomarker of Negative Effect – Response (an actual risk-associated disease)’, considering combined effects of exposure factors, were modeled using regression analysis that involved creating multiple logistic models. In general, the model that describes the relationship has the following outlook:

$$y = 1 / (1 + exp(-(b_0 + \sum b_i \cdot x_i + \sum\sum b_{ij} \cdot x_{ij}))).$$

Authenticity and adequacy of the modeling results were assessed using Fischer’s F-test, determination coefficient (R^2) and Stu-

[5] R 2.1.10.3968-23. Rukovodstvo po otsenke riska zdorov'yu naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh sredu obitaniya [Guide on assessing population health risks upon exposure to chemical pollutants in the environment]. Moscow, State Sanitary-Epidemiological Standardization of the Russian Federation, 2023, 221 p. (in Russian).

[6] Chemical were quantified in biological media by personnel of the Department of Analytical Chemistry Analysis (headed by T.V. Nurislamova, Doctor of Biological Sciences).

dent's *t*-test ($p \leq 0.05$). Overall, more than 450 parameterized relationship models were created (approximately 5000 coefficients)[7]. The list of chemicals that are subject to immediate control was substantiated based on solving the inverse problem using minimax evaluation and factor analysis with fixed profiles of exposure factors on the analyzed territories[8]. Intensity of a correlation between chemicals was estimated as per R^2.

Concrete examples of the results achieved by implementing the algorithm for system analysis are presented predominantly using the model of long-term real-world inhalation exposure due to harmful components in industrial emissions into ambient air, namely, aluminum oxide (Al_2O_3) and hydrogen fluoride (HF) in doses of 0.0006–0.003 mg/kg × day (0.1–2.2 RfC); benzo(a)pyrene (B[a]P), 0.000003 mg/kg × day (2.1 RfC). These chemical were selected due to being highly hazardous for human health (Class 1–2) and their simultaneous occurrence in emissions into ambient air from 13 large productions of primary aluminum and alumina in some RF regions. Spatial distribution of the results was analyzed using GIS-technologies[9].

Results and discussion. In this study, we implemented an algorithm for investigating risk-associated body responses at different levels of their initiation in exposed people from various age groups against non-exposed ones. As a result, transformation of the protein-peptide profile of blood plasma was identified at the molecular level. We established protein targets upon exposure to common exposure markers (Mn, Al, Cu, Ni, Cr, fluorine, and benzo(a)pyrene) and specific tissues where identified proteins were usually expressed. These tissues are found in the liver, brain, heart, small intestines, and lungs. For example, growing expression of 6 proteins out of 23 identified ones in children aged 4–7 years was proven to be associated with exposure to elevated contamination in biological media (1.5–1.8 times higher than the reference or background levels in blood/urine) upon combined exposure to Al_2O_3, HF, and B[a]P. Only two proteins were verified in an experiment on rats upon both isolated and combined exposure and identified as exposure targets. They are apolipoprotein A1 (encoded by the *APOA1* gene), which stimulates reverse cholesterol transport from the vessels, and transthyretin (encoded by *TTR*), which transports thyroxin to the liver and is a factor of molecular damage reparation [18–20]. These proteins are mostly expressed in hepatocytes, enterocytes, and neurons.

Safety levels of 10 contaminants in biological media (blood and urine) were substantiated for the first time relying on the proteome profiling results. These safe levels are considerably lower than reference ones for combined exposures. For example, the highest no-observed-adverse effect level identified per changes in apolipoprotein A1 expression equals 0.001 mg/dm^3 (RFL is 0.0065 mg/dm^3)[10] for aluminum in urine; 0.06 mg/dm^3 (RFL is 0.2 mg/dm^3) for fluorine-ion in urine[11]; 0.0 mg/dm^3 for benzo(a)pyrene.

Predictive structural-bioinformation matrices were built to identify changes in molecular-cellular events and their sequence associated with elevated expression of 25 identified proteins. They described the hierarchy of primary signaling-transport connections and pathways that occur at 5–12 levels, their localization points (40–100), and cell population responses (10–15 types), which in future determine the metabolome. This allowed clarifying how expressed proteins were involved into

[7] Cause-effect relations were modeled by personnel of the Department of Mathematical Modeling of Systems and Processes (headed by D.A. Kiryanov, Candidate of Technical Sciences).

[8] See previous footnote.

[9] Spatial distribution of the results was visualized by personnel of the Department of Sanitary and Hygienic Analysis and Monitoring Systemic Methods (headed by S.V. Kleyn, RAS Professor, Doctor of Medical Sciences).

[10] Tietz N. Clinical Guide to Laboratory Tests. In: V.V. Menshikov translation from English ed. Moscow, YuNIMED-press Publ., 2003, 960 p. (in Russian).

[11] See previous footnote.

pathogenesis of metabolic disorders, negative health outcomes of which could include hypertension, obesity, hepatosis, cognitive dysfunction, polyneuropathy, bronchial asthma, etc. In a specific example, when apolipoprotein A1 and transthyretin expression is activated, molecular interactions occur at 7–10 levels in intracellular signaling pathways. Lipoprotein metabolism, proliferative epithelial and endothelial reactions are involved starting from the level 3. Pathogenetically specific apolipoprotein A1 breakdown develops due to ligand-receptor interaction. This process is caused by activated oxidation and proteolytic properties of transthyretin. As a result, inverse sterol transport (cholesterol included) becomes less active. Anti-inflammatory and antioxidant apolipoprotein A1 properties are replaced with inflammatory and oxidant ones. We can expect metabolic disorders; their biochemical mechanisms manifest themselves as imbalance in lipoproteins and neuromediators as well as less active neurogenesis [21, 22].

In-depth examination of major pathways used in signaling transduction of molecular events established possible trends in pathogenesis of negative health outcomes. Changes in signal transmission were shown to deregulate cellular communication in variable ways. A launch is usually stimulation of protein expression, which induces changes in signal perception. This results in a whole chain reaction of signaling events and, consequently, incoordination of cell homeostasis. Figure 1 provides a concrete example of major pathways in signaling transduction of molecular events in case of elevated apolipoprotein A1 expression caused by simultaneous exposure to Al_2O_3, HF, and B[a]P. Oxidative activity by apolipoprotein A1 disrupts correct perception of a signal to start synthesis of high density lipoproteins. Lysosomal endocytosis of low density lipoproteins becomes slower and lipoprotein a secretion intensifies. There is a growth in synthesis of bilirubin as antioxidant as a response to elevated oxidative activity [23, 24]. The latter is associated with direct oxidative effects produced by toxicants and active apolipoprotein A1 breakdown.

As a result, cholesterol synthesis intensifies, which may create elevated risks of early atherosclerosis, diseases of peripheral vessels, coronary heart disease etc. as common causes of less qualitative active longevity.

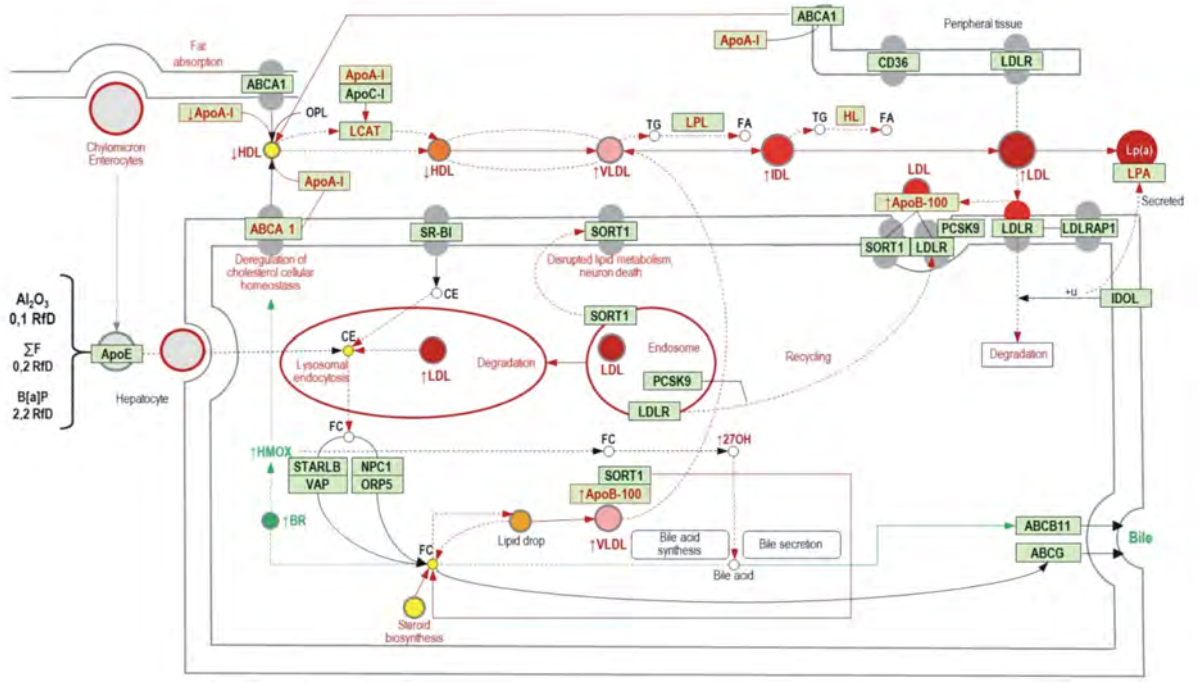


Figure 1. Major pathways in signaling transduction of molecular events in case of elevated apolipoprotein A1 expression caused by simultaneous exposure to Al_2O_3, HF, B[a]P (cell communication deregulation is colored red)

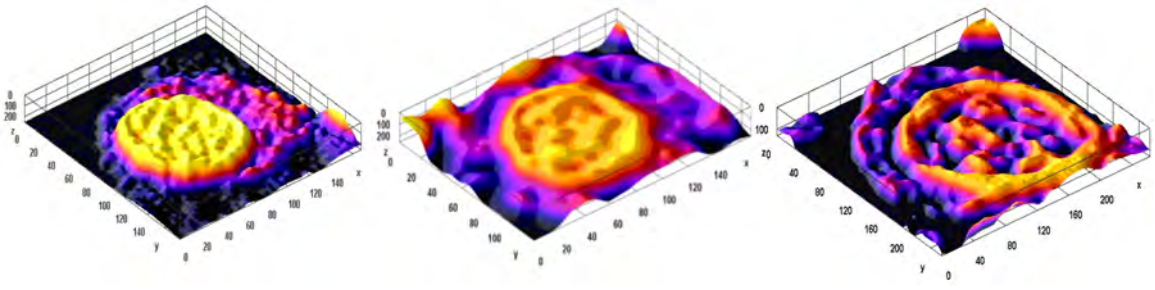
The suggested approach facilitates more precise prediction and ensures early diagnostics of metabolic disorders caused by proteome profile transformation upon chemical exposures, combined ones included. It also helps determine relevant correction and prevention activities.

Prediction of pathogenetic pathways was confirmed at the cellular-tissue level in animal experiments. Actual evidence was provided for elevated expression of identified proteins in predicted cells. Developing inflammation in cell population was established to be the common pathway, with peculiarities both per non-immune and immune-mediated damage. Additionally, a relationship was revealed between a type of inflammatory reaction (neutrophilic or eosinophilic) and size and specific surface area of affecting particles. It was established that the smaller were sizes and bigger specific surface area, the less favorable was the forecast. Thus, intratracheal exposure to nano-sized Al_2O_3 (13–20 nm) particles at the dose of 0.01 mg/kg per day, equivalent to real-world one (0.1 RfC considering extrapolation) caused a predominantly eosinophilic response of the cell population in bronchoalveolar lavage (BAL). The eosinophil count was 21–62 times (p = 0.0001) higher than in the control and reference groups, the latter being exposed to a micro-sized analogue (20–30 μm). Intratracheal exposure to the latter resulted in a predominantly neutrophilic response. Leukocyte count in BAL was 2–16 times higher (p = 0.0001) than in the control group.

Digital 3D reconstruction of surfaces of fixed cells in bronchoalveolar lavage is shown in Figure 2.

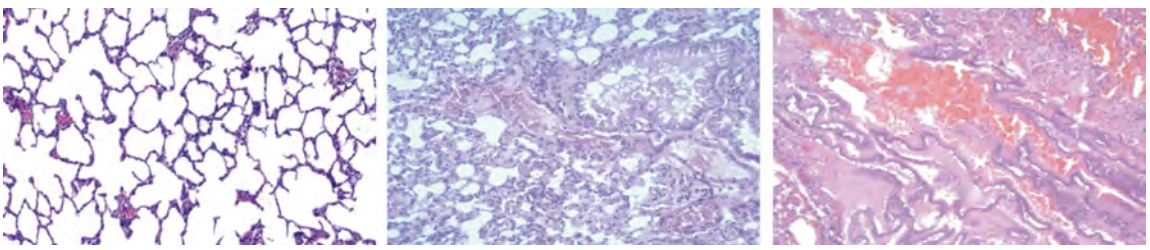
Electronic microscopy established structural and shape damage on alveolar macrophage surfaces such as ‘foaminess’ that increased as a size of affecting particles became smaller. Identified changes indicate damages to cellular membranes. The proportion of alveolar macrophages with structural damage to their surface and shape equaled 18 % upon exposure to nano-sized Al_2O_3 particles, which was 2.5 times as high than upon exposure to micro-sized particles (p = 0.02). Image analysis confirmed and provided a better insight into the relationship between a scope of cellular damage and morphometric structure of affecting chemicals.

The depths of tissue damage were confirmed by histology (Figure 3).



a *b* *c*

Figure 2. 3D reconstructed morphological parameters of alveolar macrophages in BAL of Wister rats upon intratracheal exposure to Al_2O_3 at the dose of 0.01 mg/kg per day, equivalent to real-world one (0.1 RfC): *a* is control, *b* is a group exposed to micro-sized particles, *c* is a group exposed to nano-sized particles



a *b* *c*

Figure 3. Morphological changes in lung tissues of Wistar rats upon inhalation exposure to aluminum oxide, × 1000: *a* is control, *b* is a group exposed to micro-sized particles, *c* is a group exposed to nano-sized particles

These experiments established different morphological changes in lung tissues in comparison with the control upon exposure to nano-sized and micro-sized particles. In the former case, there was apparent lymphoid tissue hyperplasia, eosinophilic infiltrates and hemorrhagic foci. In the latter case, hyperplasia and infiltrate were moderate and no hemorrhagic foci appeared; that is, damage to lung tissues was less intense than upon exposure to nano-sized aluminum oxide particles.

When we describe health outcomes occurring at the organ level, we should note that in real-world conditions, exposed people had confirmed metabolic disorders characterized with changes in organ-specific indicators. The latter were pathogenetically associated with exposure factors that caused elevated contamination in biological media (between 1.5 and 3.5 RfL). This is evidenced by lower levels of apolipoprotein A1, high density lipoproteins, elevated apolipoprotein B100 to A1 ratio, elevated levels of bilirubin, up to 1.5 times higher against reference indicators (p = 0.0001–0.001). Less active neurogenesis and imbalance in neuromediators occur due to hyposynthesis of neurotrophin-3, levels of glutamine acid, neuron-specific enolase and serotonin being 1.3–2.0 times higher against the control (p = 0.001–0.03). Imbalance of thyrotrophic hormones (TSH and free T4) and an authentic increase in activity of some specific enzymes, for example, glutamate dehydrogenase (by 1.3 times, p = 0.002) associated with elevated contamination in biological media are evidence of cytotoxic effects on hepatocytes and thyrocytes. In future, we can predict occurrence of amyloid plaques in neuronal cells and cholesterol plaques in vascular endothelium. This can also induce atherosclerotic and neurodegenerative changes as well as fatty changes in hepatocytes.

Intensity of protein expression and metabolically associated changes in biochemical indicators of negative effects were shown to depend on peculiar impacts exerted by a combination of chemicals. We developed 25 digital models that described relationships between biomarkers of negative effects and biomarkers of exposure (150 coefficients). This was done to assess combined exposure to chemicals including oxides of aluminum, copper, nickel, chromium, hydrogen fluoride, and benzo(a)pyrene. Sixty indicators of additional risk realization cases were obtained; they were 2–45 times higher than the acceptable level. These risks were associated with developing negative health outcomes in the immune, musculoskeletal, and nervous system, respiratory and digestive organs. The necessity to consider combined exposures in regulation practices was confirmed by a concrete example when intensity of elongation factor G (encoded by *EF1G*) expression was investigated upon isolated and combined exposure. Combined exposure was established to manifest itself under chronic simultaneous exposure to benzo(a)pyrene, aluminum oxide and hydrogen fluoride as not just summation of effects but predominantly as synergy that was 1.5 times as high against additivity effects (Figure 4). In addition to negative outcomes under isolated exposure, combined exposure created risks of negative outcomes in the immune and respiratory systems. Additional risk levels were up to 30 times higher than the acceptable level.

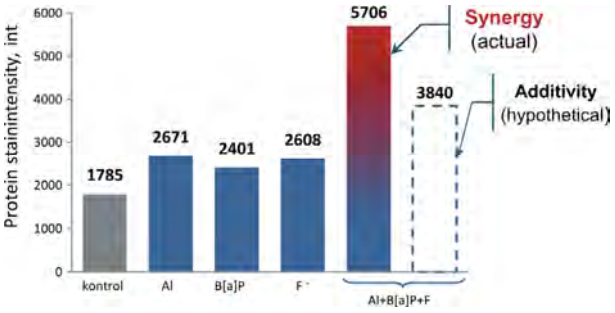
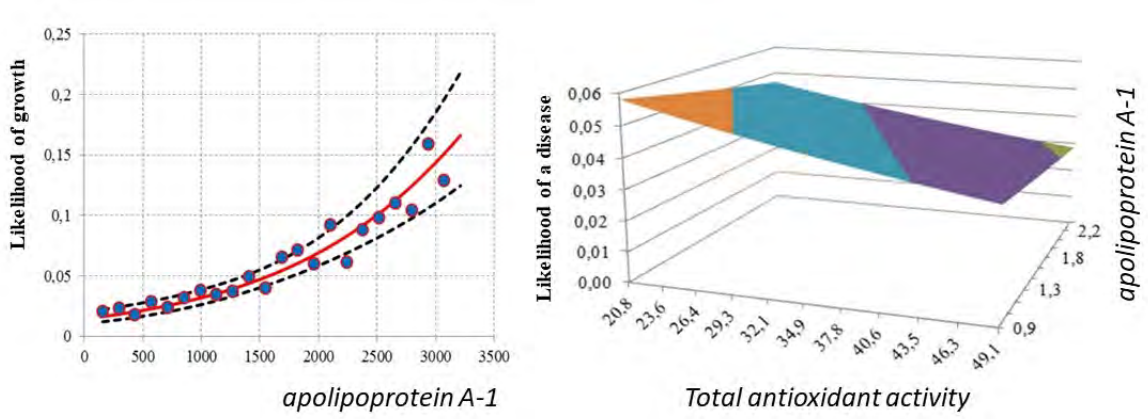


Figure 4. Intensity of elongation factor G (encoded by *EF1G*) expression in blood plasma of Wistar rats upon isolated and combined exposure

Profiles of predictors were identified considering peculiar effects of combined exposure at the organ and system levels. These predictors are eligible for early diagnostics of formalized risk implementation as health harm upon specific exposure. A profile includes target proteins and biomarkers of negative effects that are pathogenetically associated with them. Changes in these proteins make a specific disease more likely (Figure 5).



a *b*

Figure 5. Likelihood of overnutrition in children upon combined exposure to airborne Al_2O_3, HF, B[a]P: *a* is likelihood of elevated malonic dialdehyde levels upon apolipoprotein A-1 expression; *b* is likelihood of overnutrition in case of growing apolipoprotein A-1 levels and declining total antioxidant activity

For example, diagnostic profiles were identified for children aged 4–7 years who were exposed to components found in emissions of a large aluminum production. These profiles predict likely diseases of the nervous system and metabolic disorders. Early detection and prevention of overnutrition (hyperalimentation as per ICD-10, E67.8) associated with the analyzed exposure requires a profile of predictors that includes apolipoprotein A1 and associated biomarkers of imbalance in lipoproteins (total cholesterol and LDLP above the normal level; HDLP below the normal level) and oxidant-antioxidant activity (elevated levels of malonic dialdehyde and lower antioxidant activity). The multifactorial model that describes the relationship between likelihood of a disease and changes in biomarkers of effects has the following parameters: b_0 = -2.27, b_1 = -0.303–0.053 (R^2 = 0.41–0.50, p = 0.0001–0.002). Disorder of the autonomic nervous system (ICD-10: G90.8) is associated with transthyretin expression and associated increase in neuromediators (dopamine, glutamate), imbalance of cellular redox status (elevated levels of malonic dialdehyde, total antioxidant activity, glutathione peroxidase). The relationship model has the following parameters: b_0 = -1.93, b_1 = -0.16, b_2 = -0.16–0.07 (R^2 = 0.52, p = 0.0001). All this made it possible to create risk groups for further medical and preventive activities.

Predictive estimates obtained by implementation of the cascade model were fully confirmed at the whole body level by actually diagnosed diseases that were proven to be associated with exposure to airborne chemicals. Structural specificity of additional incidence is determined by territorial peculiarities of occurring contamination. For example, additional disease cases were diagnosed following in-depth medical examinations of children aged 4–7 years in a zone exposed to Al_2O_3, HF, B[a]P. These additional cases were mostly represented by diseases of the respiratory system such as allergic and chronic rhinitis, adenoiditis, and sinusitis (J30.4, J32, J35.9) (23.0 % of the total disease cases); disorders of the autonomic and central nervous system (G90.8) including inattention and overactivity (F90.0) (21.9 %); biliary dysfunction (K82.8) (18.6 %); hyperlipidemia and overnutrition (E67.8, E78.5) (13.3 %). Among adults of reproductive age (22–48 years), the most significant additional disease cases include obesity (24.8 %); diseases of the upper and lower airways (J32, J37, J42) such as chronic rhinitis, sinusitis, laryngitis, and bronchitis (23.0 % of the total disease cases). Priorities identified at the individual level create the whole profile of population health losses.

The obtained results made it possible to develop conceptual grounds and architecture of the iterative prediction of health risk and harm: from protein targets to risk-associated diseases. Figure 6 provides a simplified version.

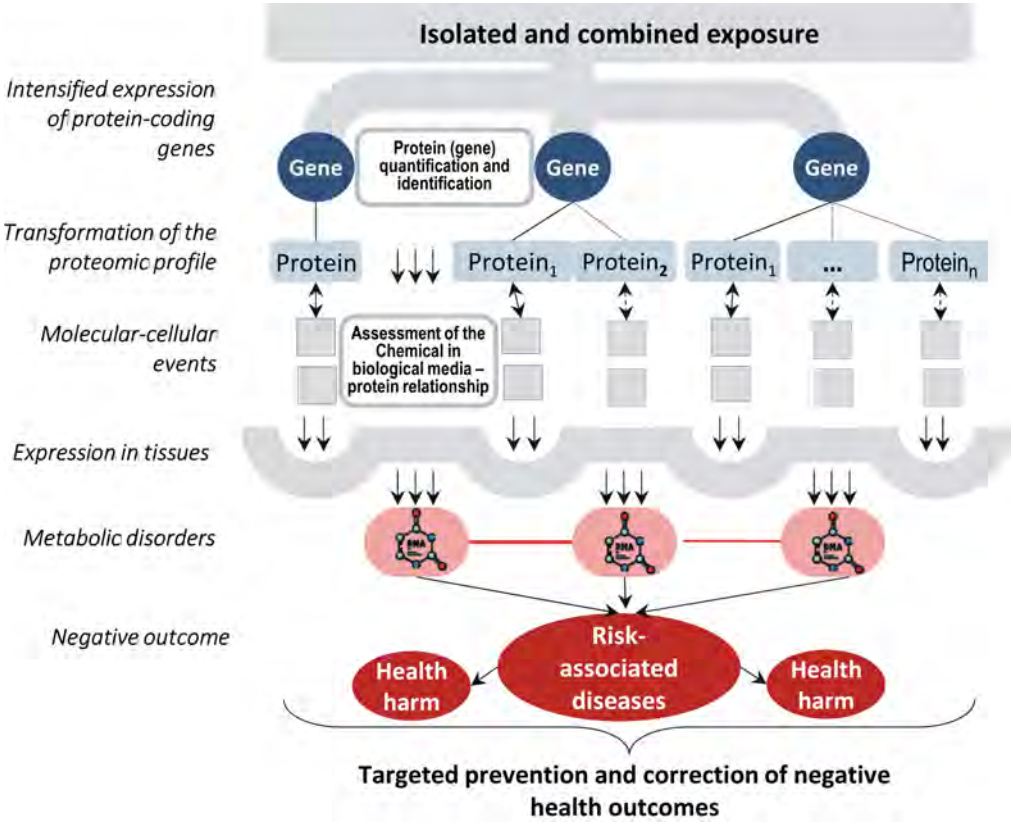


Figure 6. Conceptual grounds and architecture of the iterative prediction of health risk and harm: from protein targets to risk-associated diseases

Proteome signature, deregulation of intracellular signaling pathways, direct and mediated cytotoxicity, and oxidant activity of toxicants were shown to determine key components of modifying pathogenetic mechanisms. In its essence, the digitized version is a multi-level cascade model and an algorithm for scientific analysis of a hygienic situation with parameterized expected negative health outcomes.

Practical use of the suggested conceptual approaches allows estimating losses in life expectancy at birth based on evolution modeling of risk growth. Expression of just two proteins and associated metabolic disorders were established to result in expected decline in life expectancy at birth by almost 2 months. Integral health losses in this case have etiopathological significance and are represented by essential hypertension, obesity, polyneuropathy, and fatty hepatosis.

Fifty-four medical technologies were developed based on the analyzed mechanisms and established facts of occurring personalized health risks. They are eligible for preventing cellular-molecular and organ-system risk-associated negative effects and are needed by more than 45 % of the population under the analyzed exposure. Medical and preventive technologies were developed as regards specific risk-associated diseases per 8 classes of diseases including respiratory diseases, diseases of the cardiovascular and nervous system, endocrine disorders, etc. Personalized measures expand the existing healthcare standards until risks of diseases reach their acceptable level and do not manifest themselves as actual diseases in practical healthcare. These activities are divided into an etiotropic and pathogenetic block. The former is aimed at reducing chemical contamination in the body and its contents depend on levels of chemicals in biological media. The latter is targeted and involves several corrective and preventive activities differentiated as per prevention directions considering how apparent a pathogenetic process is and placing an emphasis on correction of possible cellular-molecular changes.

Figure 7. RF regions where exposed children and adults are provided with specialized targeted healthcare and prevention

Experience gained by providing exposed population with targeted healthcare and prevention in RF regions (approximately 800 thousand children and adults) gives evidence of its effectiveness (Figure 7). Effectiveness of prevention activities was evidenced by a decline in levels of toxic components by 1.5–30 times (benzo(a)pyrene, aluminum, fluorine-ion, benzene, xylene, phenol, and others) in biological media one year after treatment. Frequency of exacerbation and duration of diseases, for example, vegetative-vascular dystonia and biliary dysfunction, went down by 2.3–3.2 times in children.

Frequency of ARVI as a concomitant disease went down by 2.7 times. Economic effectiveness equaled approximately 6.5 rubles per 1 ruble of expenses on one person treated in outpatient care; 1.8 rubles per 1 ruble for inpatient treatment.

Based on accumulated findings, an electronic register was created and has been maintained ever since. This register contains combined data on each examined patient who is under actual chemical exposure (Figure 8). The logical structure of the register contains data on quality of the environment, patient's individual characteristics, contamination in biological media, proteome profile, laboratory and functional indicators, diagnoses, targeted healthcare and prevention activities and their effectiveness. So far, approximately 3 million information units have been input; they create an actual database and a pool of knowledge.

Analysis of digitized data on contaminant levels in biological media of examined people living in various RF regions allowed visualizing the spatial distribution of data on biomarkers of airborne exposures.

Analysis of the obtained results gave evidence of actual chronic exposure of population to highly toxic chemicals (hazard class 1 and 2),

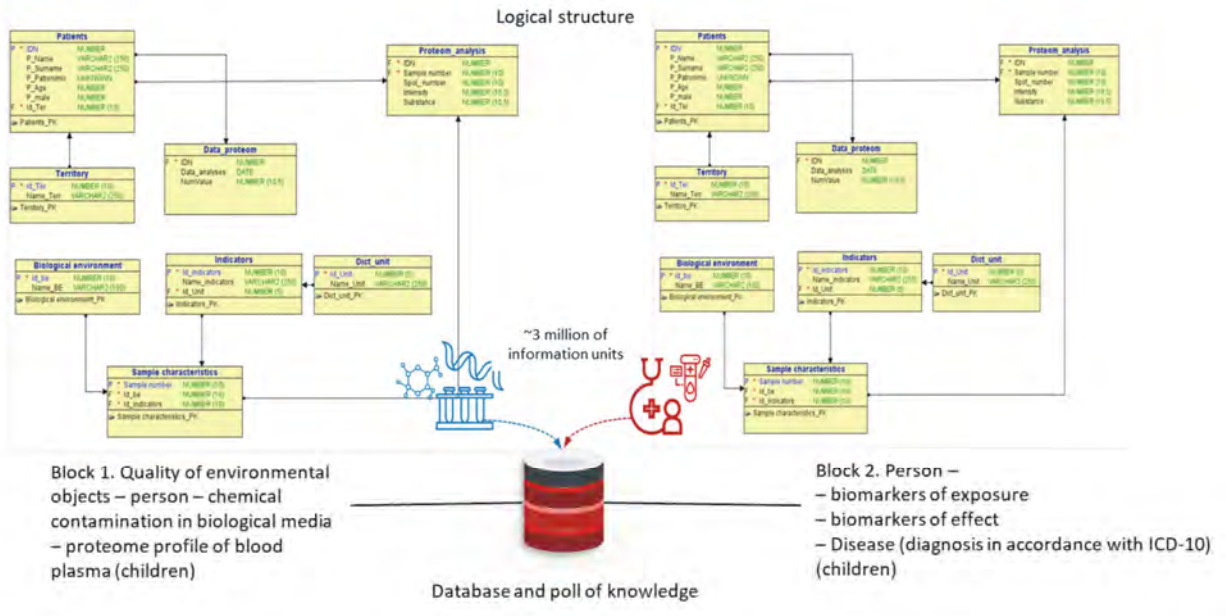


Figure 8. A scheme showing the component blocks of the electronic register with digitized authentic data combined within the Environment – Health system

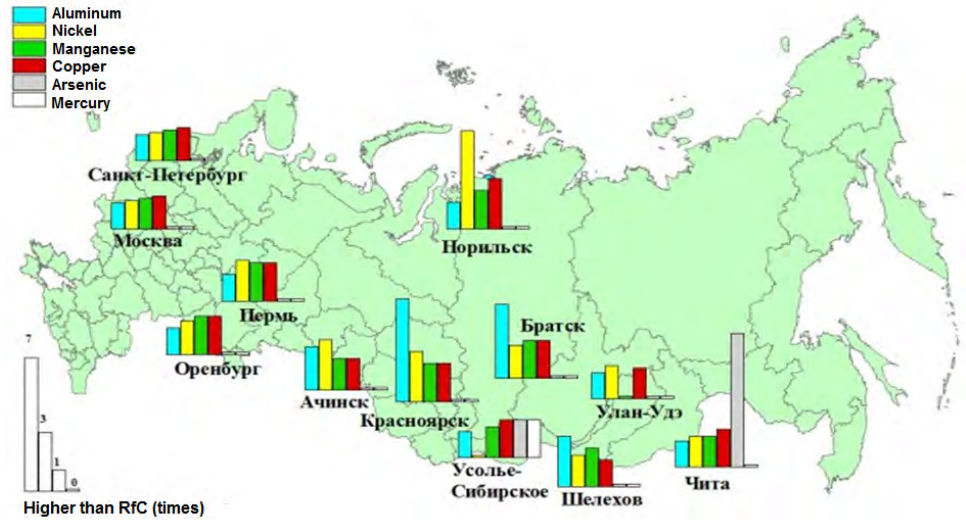


Figure 9. Metal contents in biological media of exposed population in various RF regions

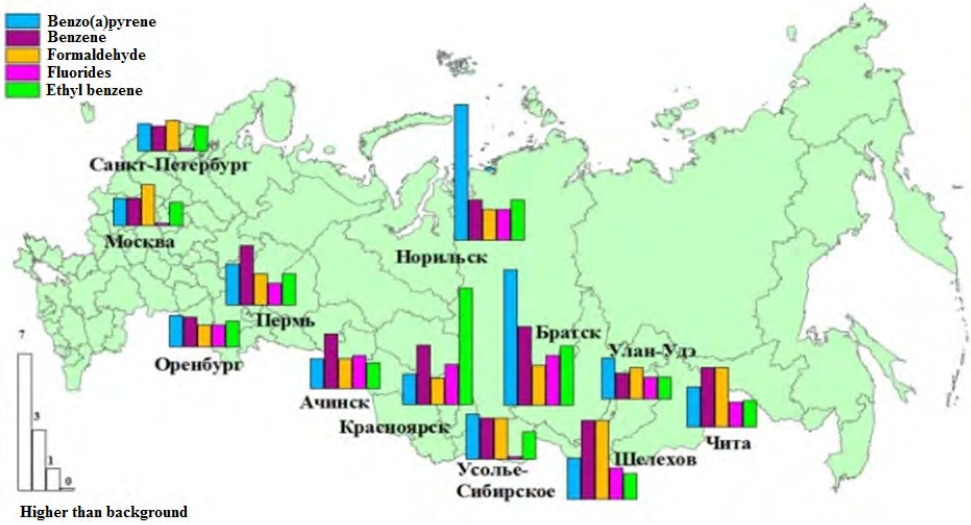


Figure 10. Levels of organic compounds in biological media of exposed population in various RF regions

in some cases, at levels up to 10 RfC. Levels of metals adequate to exposure factors (oxides of aluminum, manganese, chromium, nickel, copper, lead, etc.) are identified in biological media at levels reaching 8 RfC; organic compounds (benzene, toluene, zylene, ethyl benzene, phenol, benzo(a)pyrene, formaldehyde, etc.), up to 10 RfC (Figures 9 and 10). Approximately 10 chemicals, which were substantiated as biomarkers of exposure, were revealed to be commonly spread across the country. There are local zones where people are exposed to them and have their biological media contaminated with highly toxic chemicals (arsenic, mercury, fluorine, etc.).

Overall, considering uneven distribution over RF regions, 71.3 million people, children accounting for 14.3 million of them, live under exposure.

A science-based approach was implemented to identify highly hazardous chemicals that are subject to immediate control in an exposure area (on the example of a zone influenced by emissions from aluminum production). As a result, the priority minimally sufficient list was created, which included 3 out of 45 chemicals emitted into ambient air. They are aluminum oxide, hydrogen fluoride and solid fluorides, and benzo(a)pyrene. In case levels of these chemicals are above safety

Table

The list of airborne chemicals that are subject to control in an area influenced by emissions from aluminum productions

Priority airborne chemicals subject to immediate control					
Aluminum oxide		**Hydrogen fluoride and solid fluorides**		**Benzo(a)pyrene**	
Chemicals recommended as expansion of monitoring program					
Particulate matter	0.96*	Nitrogen oxide	0.82	Resins	0.76
Lead and its compounds	0.96	Dimethyl sulfide	0.76	Petroleum (mineral) oil	0.74
Manganese oxide	0.90	Hydrogen cyanide	0.75		
Inorganic dust SiO_2	0.89	Hydrochloride	0.74		
Copper oxide	0.84				
Heavy oil ash from TPS (Va)	0.77				
Iron oxide	0.59				

Note: * means determination coefficient (R^2).

standards, a monitoring program may be expanded to cover other 13 chemicals emitted into ambient air, which are most closely connected to the first three (confirmed statistically). Thus, for example, in case benzo(a)pyrene levels are above safety standards at control points, a monitoring program is expanded due to including two other chemicals into it, namely, resins and petroleum (mineral) oil. The list of airborne chemicals that are subject to control and are differentiated as per the order of this control is given in Table.

Representativeness of lists of priority chemicals subject to immediate control is evidenced by actual established disease cases associated with them among working age adults and children (totally up to 490 cases per 1000 people).

Therefore, results of scientific research that are presented in this study are completely devoted to providing wider opportunities to perform effective management of health risks and health harm. This is done to protect values that are guarded by law, namely, citizens' life and health, and to achieve key national goals of the RF development. The digitized version of the forecast (digital platform), as a multi-level cascade model, is a tool for scientific analysis of a hygienic situation with the parameterization of expected negative outcomes. It determines methods for their correction and prevention, which increases the reliability of hygienic assessments and the validity of management decisions.

Conclusions. We have developed and tested theoretical and methodical essentials and then created a digital platform for predicting risk-associated negative outcomes at different levels of the structure of a live organism, from molecular to population one.

Multi-level architecture of bioinformation recognition of a response ensures transition from a contact examination to a numeric experiment and quantitative prediction without any information losses.

Results obtained by investigating pathogenetic mechanisms with modifying effects produced by chemical contaminants on protein-genetic and organ-system components in a body response make hygienic assessment more reliable and help accomplish more effective SHM and CSA as regards achieving socially significant results.

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