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Review

UNCERTAINTIES IN RISK ANALYSIS AND MODERN APPROACHES TO THEIR REDUCTION

E.A. Saltykova[1,2], O.N. Savostikova[1]

[1]Centre for Strategic Planning and Management of Biomedical Health Risks, 10 Pogodinskaya St., bldg 1, Moscow, 119121, Russian Federation
[2]Kharkevich Institute for Information Transmission Problems of the Russian Academy of Sciences, 19 Bolshoy Karetny pereulok, bldg 1, Moscow, 127051, Russian Federation

The article analyzes the most common approaches to the risk assessment procedure and focuses on uncertainties at each stage of risk analysis. These uncertainties not only impede risk analysis but are also able to skew its results. The greatest impact on reliability of final risk assessments is caused by uncertainties associated with assessment of exposure, in particular, with establishing toxicological parameters in experiments and their extrapolation onto assessed population groups. An effect of a selected toxicant on a test animal sample is identified with an expected negative effect produced by it on a real human population. In addition, in laboratory experiments, in contrast to natural conditions, a population is affected only by controlled factors in small amounts.

Next, the article describes some uncertainties that arise at the stage of assessing the dose-effect relationship; in studies aimed at reducing uncertainties at this stage, it is almost impossible to detect a link between pollution and diseases not declared for research purposes. The problem of toxicological assessment of mixtures is described; the article highlights that at the moment there are no data on effects produced by most known mixtures on human health or any data on possible interactions between different chemicals either. The concept of exposome is described, which is an analysis of impacts of all environmental factors on an individual throughout his lifetime.

It is concluded that the existing concepts of risk assessment are applicable mainly for comparing hypothetical benefits and hypothetical damage at the population level. Given that, it seems quite relevant to develop such a concept of risk assessment that can be additionally used in planning preventive measures aimed at reducing morbidity and mortality and increasing life expectancy. At the same time, this concept should include a comprehensive assessment of mixtures affecting the body, considering the influence of natural and climatic conditions and non-specific reactions of the body.

Keywords: *risk analysis, risk assessment, uncertainty, exposure, "dose – effect", influence of natural conditions, mixtures of chemicals, the exposome concept.*

Research literature provides us with several basic definitions of "public health risk". Risk is described as a set of adverse outcomes for people's life and health due to various exposures or as likelihood of adverse effects on people's life or health considering their severity, or as likelihood of outcomes caused by a certain hazardous event[1] [1–3]. The WHO (World Health Organization) World Health Report 2002 defines a risk as "a probability of an adverse outcome, or a factor that raises this probability". In the Russian Federation,

Elena A. Saltykova – Candidate of Biological Sciences, Junior Researcher at the Department of Physical and Chemical Research and Ecotoxicology; Researcher (e-mail: rammka89@yandex.ru; tel.: +7 (903) 005-64-58; ORCID: https://orcid.org/0000-0003-3180-4370).

Olga N. Savostikova – Candidate of Medical Sciences, Head of the Department of Physical and Chemical Research and Ecotoxicology (e-mail: OSavostikova@cspfmba.ru; tel.: +7 (926) 814-59-35; ORCID: https://orcid.org/0000-0002-7032-1366).

[1] Guide R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals. Moscow, The Federal Center for State Sanitary and Epidemiological Surveillance of the RF Ministry of Health, 2004, 143 p. (in Russian).

the legislation has the following definition of risk: "Risk is likelihood of harm to citizens' lives or health, property of physical or juridical persons, state or municipal property, the environment, lives or health of animals and plants considering severity of this harm" (the Federal Law 'On Technical Regulation' issued on December 27, 2002 No. 184-FZ[2]).

Conventionally, the health risk assessment methodology applied to assess risks caused by chemical exposures consists of four main stages[1] [1, 2]: 1) hazard identification (screening investigation of all possible exposure sources, identification of key pollutants), 2) exposure assessment (establishing what quantities of a chemical entered the body by various introduction ways due to contacts with various environmental factors), 3) detection of a 'dose-effect' relationship (a relationship between a dose and intensity of harm caused by exposure to a chemical), 4) risk characteristics (risk quantification, risk analysis and description of uncertainties, and data generalization). The risk assessment procedure has been repeatedly described in literature in a similar way [1, 2, 4].

The aim of this review was to analyze approaches to reducing uncertainties that occur in risk analysis as well as the existing concepts of health risk assessment.

Many authors have noted that uncertainties can occur at any stage in risk analysis. They not only impede risk analysis but are also able to skew research results [1, 5, 6]. Uncertainties associated with exposure assessment have the greatest influence on validity of ultimate risk assessment [1]. There are several major sources of uncertainties that can occur at this stage in risk analysis. For example, some ways through which pollutants affect the human body can be excluded from analysis; monitoring results might be incomplete; a selected mathematical model does not characterize an exposure comprehensively. One more source is mistakes made by researchers such as descriptive mistakes, mistakes in choosing an expected exposure scenario, mistakes at any stage in quantitative analysis including sampling and sample preparation. Reduction in some of these uncertainties can be achieved by using models of pollutants distribution and by estimating a structure of various social population groups.

Mathematical methods, in particular, regression models, cluster analysis, and fuzzy set theory, are actively employed in contemporary studies that concentrate on health risk assessment [5, 7–9]. For example, J.P. Fabisiak with colleagues [10] rely on land use regression (LUR) to describe distribution of black carbon and nitrogen dioxides, their major sources being diesel exhausts, point industrial sources, as well as residential wood burning. The authors estimate increased mortality and hospitalization from coronary heart disease as a specific health endpoint of interest. They examine a linear dose-effect relationship over the range of pollutant concentrations expressed in the study, although they assume there may be significant departure from linearity at extremes of exposures. Still, the authors mention some limitations in employing LUR. It is noteworthy that these limitations can be extrapolated onto use of any other model for health risk assessment. In particular, the exposure estimates reflect projections of long-term average exposure concentrations; hence they ignore short-term fluctuations in concentrations that may also play a role in initiating untoward cardiovascular events. Besides, the LUR model described by J.P. Fabisiak with colleagues [10] incorporates mobile source plume analysis but may underestimate the contribution from fixed point sources.

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[2] O tekhnicheskom regulirovanii: Federal'nyi zakon № 184-FZ ot 27.12.2002, prinyat Gosdumoi 15.12.2002 [On Technical Regulation: the Federal Law No 184-FZ issued on December 27, 2002, approved by the State Duma on December 15, 2002]. *KonsultantPlus*. Available at: https://www.consultant.ru/document/cons_doc_LAW_40241/ (April 02, 2023) (in Russian).

Also, when building any mathematical model for health risk analysis, we should consider previously diagnosed diseases in research participants as well as a stage of a disease they have at the moment a research is conducted. It is necessary for identifying any possible impacts exerted by these factors on an effect of environmental pollution.

Many researchers point out that high uncertainty at the exposure assessment stage might be caused by toxicological parameters being established predominantly in experiments [11–13]. In particular, a reference dose, which is considered safe, is calculated based on results of various animal experiments performed on rats, mice, or rabbits [14–18] and then recalculated for the human body using some coefficients [19–22]. However, the US Food and Drug Administration (US FDA) conducted some studies to compare results of experimental pre-clinical and clinical investigations. As a result, it was established that approximately 90 % of analyzed chemicals, which had been declared safe in pre-clinical investigations, turned out to be highly toxic in clinical ones. Toxic effects on the human body were identified for 20 % of these chemicals [11, 23, 24]. There are several basic reasons for this inefficiency in transferring experimental results onto actual conditions. First, an effect produced by an analyzed toxicant on an animal test sample is identified with an expected negative effect produced by it on a real human population. Second, a test population is affected by a controlled factor in laboratory conditions whereas several factors affect a population simultaneously in natural ones and not all of them can be controlled. In addition, it is noteworthy that toxicological studies make it possible to derive a dose-effect relationship primarily for determined effects (radiation sickness, chemical burns, poisoning, etc.). The most reliable data for stochastic effects (cancer, cardiovascular diseases, etc.) can be derived by epidemiological studies[3]. At the same time, transferring results of epidemiological studies on an analyzed exposed population can be a considerable source of uncertainties at the stage when a dose-effect relationship is assessed.

Epidemiological studies usually concentrate on finding a relationship between pollution and specific diseases, for example, cardiovascular diseases [25], cancer [26], or non-communicable diseases in general [27]. However, it is almost impossible to detect a link between pollution and diseases not declared for research purposes in such studies. For example, J.P. Fabisiak with colleagues [10] chose increased mortality and hospitalization from coronary heart disease as a specific health endpoint of interest. In their study, the authors did not analyze any relationships with other diseases, for example, respiratory ones.

In addition to that, uncertainties occur at the stage of assessing a dose-effect relationship from such sources as identification of critical organs / systems; lack of knowledge on mechanisms of interactions between different components in chemical mixtures or peculiar kinetics and dynamics under different ways by which a chemical enters the body and under its simultaneous introduction by various ways; difference in the risk assessment methodology in Russian and foreign studies [1].

Numerous studies focus on reducing uncertainties at the stage of assessing a dose-effect relationship. Their actual aim is to predict a number of new disease cases due to an analyzed exposure [5, 10, 28, 29]. In particular, we should mention The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) as one of the most extensive studies aimed at systematizing and assessing

[3] Demin V.F. Analiz riska v obespechenii bezopasnosti cheloveka v chrezvychainykh situatsiyakh [Risk analysis in providing safety for people in emergencies]: Dissertation … for the Doctor of Technical Sciences Degree. Moscow, 2016, 221 p. (in Russian).

health risks (including those caused by environmental pollution). The authors make the following conclusion: ambient air pollution causes respiratory infections and tuberculosis, neoplasms, maternal and neonatal disorders, diabetes and kidney diseases, chronic respiratory diseases, and cardiovascular diseases (which are prevalent) [30]. However, the GBD researchers face certain difficulties since some countries are often unable to provide them with sufficient necessary data for analysis [31]. It is due to this reason that the methodology developers tried to consider many factors to compare a burden of various diseases using mathematic modeling. These factors are prevalence of some diseases and their symptoms, age at death, etc. However, this modeling is still not optimal and this can be illustrated by such an example as assessment of the DALY (disability-adjusted life year) parameter in Russia where it has the same value for the whole country [30]. But we should remember that Russia is the largest country in the world located across three different climatic zones and with apparent differences both in living standards and healthcare availability.

Conventionally employed health risk assessment methodologies that deal with chemical exposures are predominantly based on assessing exposure to some specific chemicals (and their maximum permissible levels); however, at present, some existing rules in the European Union include requirements that cover chemical mixtures as well [32]. The main problem of toxicological assessment of mixtures is absence of any data on effects produced by most known mixtures on human health [33–39]. Another serious issue is possible interactions between chemicals (that is, synergetic or antagonistic effects) and influence produced by these effects on hazards posed by a chemical mixture. Separate chemicals in a mixture can interact with each other thereby influencing each other's absorption, metabolism, excretion, or toxic dynamics. This may change a scope or sometimes even essence of a toxic effect [40, 41]. Several authors developed the Adverse Outcome Pathway (AOP) model [42–45]. It is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment. This model provides substantiation for mapping relevant data on toxicity of specific chemicals thus making it possible to identify which chemicals can produce combined effects. In case no data are available, the model demonstrates the necessity to conduct further research. Therefore, AOP helps integrate data derived by different testing methods (in vitro, in silico and in vivo) at different levels of biological organization and thereby facilitates elimination of gaps in data on toxicity [43].

The well-known phrase "genetics loads the gun environment pulls the trigger" illustrates a complex relationship between human diseases and the environment. This famous analogy by Dr. Judith Stern, Distinguished Professor of Nutrition and Internal Medicine at the University of California, Davis, conveys the message that disease phenotypes are not only a result of interaction between different genes within the host but also between genes and the environment [46]. An attempt to integrate environmental parameters when calculating an individual risk of diseases was made when the exposome concept was developed. According to the definition by C.P. Wild [47], the exposome encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards. The exposome concept is similar to the genome concept and was developed to quantify environmental exposures. The exposome model includes three broad categories of environmental exposures: internal, specific external and general external [48, 49]. The internal environment is considered an internal chemical environment of the body; that is, exposure partici-

pants are biologically active substances in the body formed due to usual vital activities, physical activity, gut microflora activity, inflammation, and oxidative stress. Specific external exposures are caused by, in particular, infectious agents, smoking, and alcohol abuse. Finally, general external exposures in the exposome include a socioeconomic status, mental exposures, and climate [50]. However, despite some promising postulates, the exposome model has not yet brought about any specific methods for health risk assessment. Nevertheless, many researchers share the opinion that adverse effects are often produced by a whole variety of heterogeneous factors and by each separate factor [5]. Typically, many people are simultaneously under exposure and they tend to have different responses to effects of negative factors [51–55].

To sum up all the aforementioned, we can conclude that all the existing studies strive not to create a new scheme for risk assessment but rather to reduce uncertainties. A considerable part of uncertainties occurring within health risk assessment is not given enough attention in the available studies and even within research trends in general. It is noteworthy that the existing methodologies for assessing health risks caused by chemical exposures are predominantly based on assessing exposure to specific chemicals. Any data on an exposure to the entire mixture are available for a limited number of them; any information on a dose-effect relationship and a mechanism of action typical for a specific component is often absent for many chemical classes. Conventional methods of health risk assessment practically never consider additional influence exerted by weather and climate (for example, cold temperatures). These methods are also unable to estimate nonspecific body reactions induced by pollutants (in particular, oxidative stress). All the abovementioned methods do not allow establishing clear relationships between pollution and morbidity / mortality. Approaches that are suggested for assessing effectiveness of population health risk mitigation make it possible to estimate whether planned or implemented protection activities are sufficient or relevant. But these approaches do not involve developing methods of adaptation to living in a polluted environment for population.

In our opinion, as well as in some other authors' opinion [11], at present, the risk assessment methodology in Russia should be updated to guarantee relevant health risk assessment; it is also necessary to perform a comprehensive analysis of foreign experience in the sphere including establishment of DNEL (Derived No-Effect Level and DMEL (Derived Minimal Effect Levels) in the REACH (Registration Evaluation Authorization and Restriction of Chemicals) international system [56], to revise maximum permissible levels (MPLs), and to revise identification of target organs and systems. It is worth noting that in Russia, just as in any other large country, it is necessary to consider substantial differences in effects produced by natural factors on population living in different climatic conditions. Different annual mean temperatures, wind rose, precipitations and other meteorological conditions have substantial influence on morbidity and mortality [57–60].

Most epidemiological criteria that have been developed so far and are actively used in health risk assessment reflect an expected growth in frequency of health disorders per a unit of influencing concentration. Although these criteria are, as a rule, based on results derived by several independent epidemiological investigations, it is still wrong to use them to predict changes in mortality or morbidity rates of a specific population living in a specific area. Just as any other risk assessments, they are only relative values, which describe comparative priority of these or those pollutants, their sources in the environment, etc. To sum up all the aforementioned, we can conclude that the existing risk assessment concepts are applicable mostly for comparing

hypothetic benefits and hypothetic damage at the population level. Given that, it seems quite relevant to develop such a concept of risk assessment that can be additionally used in planning preventive measures aimed at reducing morbidity and mortality and increasing life expectancy. At the same time, this concept should include a comprehensive assessment of chemical mixtures affecting the body, considering the influence of natural and climatic conditions and non-specific reactions of the body.

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