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METHODOLOGICAL APPROACHES TO HYGIENIC STANDARDS DERIVATION USING HEALTH RISK CRITERIA**N.V. Zaitseva, P.Z. Shur, N.G. Atiskova, M.R. Kamaltdinov**FBSI "Federal Scientific Center for Medical and Preventive Health Risk Management Technologies",
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Abstract. Methodological approaches to hygienic standards derivation using health risk criteria are presented. As examples of these approaches implementation risk-based standards development for ambient air nickel and ractopamine residues in livestock products are described.

Keywords: health risk assessment, harmonization, risk-based standards.

Accession of the Russian Federation to the WTO, participation in the Customs Union within the Eurasian Economic Community puts convergence of the sanitary legislation, and in particular, harmonization of the environmental and products sanitary standards with the international standards among the highest priorities.

At present, the development of indicators of the environmental and product quality includes mandatory use of public health risk assessment methodology in accordance with its basic principles, such as safety priority; non-zero (acceptable) risk concept; transparent evaluation and description of uncertainties; stage-by-stage approach to risk assessment procedures; consideration of singularities of the regulated parameters and risk recipients; revision of standards as new scientific data comes in [6,7,11].

Following the stage-by-stage approach to health risk assessment, the process of quality standards development based on risk criteria includes the following: Hazard Identification, Dose-Response Assessment, Exposure Assessment and Risk Characterization, which, in accordance with the objective of validation of the hygienic standards, are characterized by a number of features.

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At hazard identification stage, not all the hazards are identified since risk-based standards are developed for specific risk factors only. The main focus at this stage is on the analysis of available information on the physical, chemical, biological and other characteristics of the studied factors, sources of its origin and actual levels in the environment. It is also considered necessary to examine the availability of hygienic norms and standards in the global practice, to determine possible effects of exposure, primarily those used to establish the standard (critical organs and systems), and to examine whether the health risk criteria were used. A separate issue is to identify the most sensitive contingents which can vary depending on the socio-economic situation, lifestyle, national characteristics, and behavioral characteristics. For those contingents, it is advisable to establish potential health disorders based on the principle of exposure scenarios.

The following criteria are provided to determine the priority of risk factors which require the establishment of hygienic standards based on health risk criteria:

- Differences between the values of standards used in the Russian Federation and abroad;
- Results of the ranking of risk factors in order of hazard to human health;
- Presence of priority pollutants in the international and national lists;
- Data on the environmental occurrence.

Based on the criteria, we developed a list of air pollutants in chronic inhalation exposure which should be considered a priority for health risk criteria standardization hygiene standards harmonization [1].

After the hazard is identified, we decide whether further validation of risk-based standards is necessary. If there are international hygienic standards that are based on risk assessment and acceptable risk criteria, meet the RF requirements, take into account the characteristics of the risk groups, and are drawn on adequate expertise, then it is possible to adopt the existing standard and use it in Russia.

At this stage, it is also necessary to determine whether additional toxicological and/or epidemiological studies are needed. This can change during later stages of validating the hygienic standards based on risk criteria.

At the dose-response assessment stage for the chemical factors and the hazard characterization stage for the microbiological factors, it is important to determine no-effect and/or threshold exposure levels in the toxicological and epidemiological studies for the factors with known threshold type of exposure.

The following values are usually considered as such levels: no-observed-effect-exposure-level (NOAEL), low-observed-effect-exposure-level (LOAEL) and reference exposure levels (benchmark dose (BMD) and concentration (BMC) [8,9,11,13].

At the dose-response assessment stage, it is also very important to analyze and, when necessary, build mathematical models that can quantitatively describe those dependencies. Those models can be used to determine an exposure level at which health risks do not exceed the permissible level; they must to the full extent describe quantitatively describe the dependency of the critical effects (responses) versus standardized factor.

To validate risk-based standards with the purpose of conducting exposure assessment, we develop a series of exposure scenarios. As a rule, detailed scenarios are developed that include the maximum, standard and real exposure levels. A standard exposure scenario is based on the use of standard (recommended) values, for example, water and food consumption, time spent outdoors and inside, etc. Real exposure scenarios are based on the use of similar parameters determined through research and sometimes forecast values. For scenarios based on the standard and actual exposure level, it is reasonable to analyze the features of exposure development for the most sensitive population groups, for example, the diet of pregnant and breastfeeding women is different from the regular diet; elderly people spend more time indoors, etc.

Assessment of exposure level for the purpose of validating the hygienic standards based on the health risk criteria can be conducted directly and indirectly; and here, the methods directed at studying exposure markers are particularly popular [13].

The main task at the risk characterization stage when validating the risk-based standards of environmental quality is to determine the level of exposure at which the health risk level is reliably permissible. For this purpose, based on the uncertainty analysis of risk assessment, it is necessary to determine the assurance factors / modifying factors which will be used as a denominator to the threshold or no-effect exposure levels. These factors take into account the scope of studies, animal specimen in the toxicological studies, the structure of epidemiological studies, and a number of toxicological parameters. The value of the uncertainty factor is determined with consideration for possible impact of a number of factors on the reliability of the assessment. When selecting the values of the uncertainty factor components, it is recommended taking into consideration extrapolation from one threshold level to another (from LOAEL to NOAEL), interspecies and intraspecific extrapolation, inflation of the results obtained under short-term exposure to longer-term exposure, impact on a developing body, extrapolation from one route of entry to another, transfer from a minimal to a full database, etc. [4].

Risk characterization is conducted on a step-by-step basis for the scenarios analyzed at the exposure assessment stage with the use of the parameters and models selected when assessing the 'exposure-response (effect)' relationship. If the maximum exposure level does not result in impermissible health risk, other scenarios then should be disregarded.

When developing risk-based standards, it is important to identify permissible health risk. Today, death or serious disease probability at $1 \cdot 10^{-4}$ is considered permissible health risk. For less serious effects, it is advisable to apply less strict values.

The risk characterization stage allows determining the health risk levels for the environment and products that provide the maximum exposure values that determine acceptable (permissible) health risk level. These values are regarded as risk-based standards.

The standards developed on the basis of epidemiological studies are preferable when setting hygienic standards or using health risk analysis methods. In this respect, it is necessary to determine the quality standards harmonized by the health risk criteria using a harmonized methodology which calls for validating the reference risk factor levels on the basis of the results of epidemiological analysis with the use of internationally acknowledged methods, for example, Benchmark Dose Technical Guidance (US EPA, 2012).

It is noteworthy that validating the hygienic environmental quality standards based on health risk criteria is one of the key elements of harmonization with the international standards.

New Russian standards harmonized with the international standards with validation based on the risk criteria may be maintained without any change; adjusted over time; recommended to serve as a basis for a new standard drawing upon international standards. In this case, it is necessary to conduct a comparative analysis of the information sources (with the account for their reliability, availability of expert opinions and citations), quality of the conducted studies (adequacy of the observation objects, sufficient sample size, duration of the experiment, etc.), and results of the studies (traceability, and reproducibility of the method).

The result is determined values of the harmonized standard and critical effects associated with the determined level and duration of exposure to the analyzed compound.

Applicability of the above methodological approaches is exemplified by the development of risk-based standard of the content of nickel in atmospheric air and validation of a safe level of ractopamine in food products.

Nickel was selected as a development target for a risk-based standard due to significant differences between its standardized content in the atmospheric air under chronic exposure in the Russian Federation and other countries (the content characteristic varies from 0.000014 mg/m^3 (OEHHA) [10] to 0.001 mg/m^3 (RF) [2]); nickel is classified as carcinogenic by the RF standards, the IARC (group 2B – possibly carcinogenic to humans), and the US EPA (group A – carcinogenic to humans) [4]; nickel is included in the international (e.g. ATSDR, EU, etc.) and Russian lists of top pollutants; additionally, nickel is included in sample collection under a national socio-hygienic monitoring program.

To assess exposure, it is necessary to use the calculated data on air pollution in an industrial city, in the areas of residence of the analyzed population group, approximated based on the results of instrumental surveys. The range of nickel content in atmospheric air is 0.0000067 – 0.000073 mg/m³.

The reference levels of nickel content in atmospheric air were determined based on the results of a cross-sectional epidemiological study of 382 children aged 3-7 residing in an industrial city. Health assessment of the group under study was conducted with the use of long-term studies of medical referrals.

Nosological entities from five classes of diseases by ICD-10 (II – new growths, III – blood and blood organ diseases and individual disorders that involve the immune mechanism; VI – nervous diseases; X – respiratory diseases; XII – diseases of the skin and subcutaneous tissue) corresponding to the critical organs and systems under chronic inhalation exposure to nickel [2], as well as prenosological effects were used as responses in modeling of the ‘nickel content in atmospheric air – chance ratio’ relationship.

We developed and assessed 32 nickel content in atmospheric air – chance ratio’ relationship models. Models for some respiratory diseases and lab tests were selected as most adequate for the purposes of the research. The reference levels of nickel in atmospheric air were calculated as: for asthma with a dominating allergic component (J 45.0), chronic tonsillitis (J 35.0), increased phagocytosis ratio, increased phagocytic number, decreased superoxide dismutase in blood – 0.00002 mg/m³; vasomotor rhinitis (J 30.0) – 0.00003 mg/m³; decreased serotonin in blood – 0.00004 mg/m³.

Based on the criterion of a limiting indicator as a reference level of nickel in atmospheric air under chronic exposure, a value of 0.00002 mg/m³ may also be considered. However, uncertainties associated with the presence in the atmosphere of the area under study of a number of pollutants which have the same effect as nickel affect the reliability of the results of epidemiological studies used to determine the reference levels.

To minimize uncertainties, when determining the value of a risk-based standard of nickel content in atmospheric air, we built models of risk development which is considered one of the most adequate methods of forecasting and assessment of possible effects of environmental factors on public health. Within that study, modeling of the health risk development was conducted with the use of linear non-threshold model, calculation of the quotient that reflects the power of the factor impact on the speed of risk development, and determination of nickel content in atmospheric air corresponding to the value of acceptable risk equal or less than 0.05 which is regarded as negligible (permissible, acceptable) and no different than everyday risks [3].

Based on the results of mathematic modeling of risk development for asthma, with a prevailing allergic component as specific response to chronic inhalation exposure to nickel, the concentration at which health risk is considered negligible equaled 0.00005 mg/m³, which may be regarded as non-active and used for further determination of risk-based standards of atmospheric quality.

We calculated the final value of the risk-based standard of atmospheric quality for nickel with the use of the non-active concentration determined based on evolutionary modelling and the cumulative uncertainty quotient.

Within the current study, we reviewed the following uncertainty factors: uncertainty factors that takes into account interspecies extrapolation – 1; uncertainty factor that takes into account intraspecific extrapolation – 1; uncertainty factor associated with the translation of the study results from high to low exposure levels – 1.

As a result, the value of the atmospheric quality standard for nickel determined on the basis of health risk assessment equals 0.00005 mg/m³, and respiratory disorders were used as critical effects.

When validating the maximum permissible content of ractopamine in food product based on risk criteria, we took into account both carcinogenic and non-cancer effects on public health.

The data on uterine leiomyoma in mice [14] was used as raw information to develop a ‘dose – effect’ relationship model to calculate the level of carcinogenic risk. The calculation of carcinogenic risk associated with exposure to ractopamine in food products at the level recommended by the Codex Alimentarius Commission (1 mcg/kg body mass per day) showed that the level of top 95% border of carcinogenic risk totals 1.32×10^{-6} , which is classified as maximum permissible risk level.

In terms of non-cancer effects, the ‘dose-effect’ modeling was conducted on the basis of FAO/WHO data [5, 14]. The dynamic model of the risk accumulation associated with cardiovascular disorders described in the guidelines “Quantitative Assessment of Non-Cancer Risks under Chemical Exposure Based on Dynamic Models” [3]. Exposure assessment was carried out for two scenarios: the content of ractopamine at the levels recommended as Codex MRL (scenario 1) and the quantification limit concentration of ractopamine in meat products (scenario 2). The modeling of cardiovascular disorders determined that in both scenarios, the normalized risk index for cardiovascular disorders equaled 0.47 and 0.141 respectively and is classified as impermissible [3] which may result in reduced life expectancy due to additional cases of cardiovascular diseases (diseases related to higher blood pressure and IHD).

Consequently, testing of the suggested methodological approaches to validating the

hygienic standards based on health risk criteria showed their applicability for the development of risk-based standards of environmental and food product quality.

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