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Research article

ESTABLISHING INDICATORS FOR ASSESSING NON-CARCINOGENIC RISKS UNDER CHRONIC INHALATION EXPOSURE TO BENZENE AND AVERAGE ANNUAL MPC FOR BENZENE AS PER HEALTH RISK CRITERIA

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Recently multiple new toxicological and epidemiologic data on negative effects produced by chemicals have become available; given that, it is necessary to improve quantitative criteria applied in health risk assessment. It is advisable to revise previously established reference concentrations and to make more precise lists of organs and systems affected by a chemical in concentrations which are either equal to reference one or exceed it. Our research aim was to establish a reference concentration for benzene and additional quantitative indicators of its effects (additional reference concentrations) on specific organs and systems under chronic inhalation exposure; another aim was to determine average annual MPC verified as per permissible lifetime carcinogenic risk using evolution models. The research allowed recommending 0.005 mg/m^3 to be used as a reference concentration under chronic inhalation exposure to benzene; a decrease in quantity of B-lymphocytes was recommended as a critical effect since this decrease might produce negative effects on the blood and immune system. Additional reference concentrations for benzene were fixed at 0.007 mg/m^3 for the liver as a critical organ and 0.012 mg/mg^3 for violated process of organism development as a critical effect. They can be used as additional indicators for assessing non-carcinogenic health risks under chronic inhalation exposure to benzene in its elevated concentrations. Our research results were used to substantiate average annual MPC for benzene in ambient air; its recommended value was 0.005 mg/m^3 since it provided safety (absence of impermissible (unacceptable) lifetime health risk), probable carcinogenic effects taken into account.

Key words: *reference concentration, additional reference concentrations, average annual MPC, benzene, health risk, indicators for health risk assessment.*

The methodology for assessing health risks caused by exposure to chemicals that pollute the environment is an effective up-to-date tool that allows assessing a probability of harm to health depending on a scope of adverse impacts produced by a chemical [1–3]. The Guide R 2.1.10.1920-04 "Human Health Risk Assessment from Environmental Chemicals" is the policy document in risk assessment[1]. In accordance with the Guide, assessment of risks caused by chronic exposure to adverse chemicals in ambient air involves comparing all the established concentrations with reference ones (RfC). A reference concentration is a daily

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[1] R 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu [The Guide R 2.1.10.1920-04. Human Health Risk Assessment form Environmental Chemicals]. Moscow, The Federal Center for the State Sanitary and Epidemiologic Surveillance of the RF Public Healthcare Ministry, 2004, 143 p. (in Russian).

lifetime exposure to a chemical that can probably fail to cause unacceptable health risks for sensitive population groups[1, 2]; it should be established taking into account all the available latest scientific data

According to the Guide R 2.1.10.1920-04 RfC are fixed for a wide range of chemicals. Also, the Guide determines critical organs and systems for each chemical, that is, organs or systems that are primarily influenced by a given chemical. Some chemicals have quite a wide list of critical organs and systems under chronic inhalation exposure, for example, 1,3-butadiene (critical organs and systems: the reproductive system, respiratory organs, cardiovascular system, blood, and carcinogenic effects), acetone (the liver, kidneys, blood and the CNS), benzene (development, blood, red bone marrow, the CNS, immune, cardiovascular and reproductive systems), dioxins (overall systemic effects, development, liver, the reproductive and hormonal systems, respiratory organs, and blood) and some others. However, our preliminary analysis of literature data on action mechanisms typical for various chemicals has revealed that in most cases adverse effects initially occur in an organ or a system under a certain exposure and this exposure level is then used as grounds for establishing a reference concentration. When exposure grows beyond this reference concentration, other organs and systems also become involved into pathological processes. Given that, it is necessary to determine such exact exposure levels that produce adverse effects on the specified critical organs and systems; when risks of exposure to combined effects are estimated within the previously applied approach with using hazard quotients and indexes, it results in overestimation of created risk levels. It is also advisable to determine critical effects more precisely according to action mechanisms typical for chemicals bearing in mind critical organs and systems specified for them.

On the other hand, according to results described in several latest research works, statistically authentic effects produced by certain chemicals can be observed under exposure to concentrations lower than RfC, including effects on organs and systems that are not specified as critical and this can results in risks being underestimated as per the existing methodology. This might be due to new data becoming available thanks to the latest toxicological and epidemiological studies on effects produced by chemicals. Given that, it seems advisable to review previously established RfC following a principle of renewal fixed in the Guide R 2.1.10.1920-04 and in some foreign documents on establishing reference values [4–5]. According to this principle all established values are to be revised after occurrence of new data that can be used in developing and substantiating them.

Therefore, it is necessary to establish more precise quantitative criteria (reference concentrations) used in assessing non-carcinogenic health risks caused by chemical contamination of the environment. The obtained results may be applied to substantiate average annual MPC ($MPC_{av.an.}$) of chemicals in ambient air, carcinogenic effects also taken into account.

This approach seems appropriate to be tested on the example of benzene since the list of critical organs and systems specified for this chemical under chronic inhalation exposure in the Guide R 2.1.10.1920-04 is among the widest; this chemical is a carcinogen; and also there are several relevant toxicological and epidemiologic studies focusing on benzene that contain renewed data on its effects [6–10]. Besides, benzene is among chemicals mentioned in priority lists of ambient air pollutants such as the Air Quality Standards of European Commission and ATSDR's Substance Priority List; it is also included into a list of priority pollutants in accordance with the Letter "On

[2] Onishchenko G.G., Zaitseva N.V., May I.V. [et al.]. Analiz riska zdorov'yu v strategii gosudarstvennogo sotsial'no-ekonomicheskogo razvitiya: monografiya [Health risk analysis in the strategy of the state social and economic development: monograph]. In: G.G. Onishchenko, N.V. Zaitseva eds. Moscow, Perm, Perm National Research Polytechnic University Publ., 2014, 738 p. (in Russian).

the list of priority pollutants in the environment and their influence on population health" No. 11/109-111 dated August 07, 1997[3] [11–13]. Benzene is listed among priority environmental factors that cause medical and demographic losses in the State Report "On sanitary-epidemiologic welfare of the population in the Russian Federation in 2020"[4].

Our research aim was to establish a reference concentration for benzene and additional quantitative indicators of its effects on specific organs and systems under chronic inhalation exposure (additional reference concentrations); another aim was to determine average annual MPC for the chemical.

To achieve this aim, the following tasks were set:

1. To establish exposure levels that could be used as initial ones to substantiate RfC and additional RfC of benzene.

2. To substantiate RfC of benzene under chronic inhalation exposure and relevant critical organs and systems.

3. To substantiate additional quantitative indicators (additional reference concentrations) under exposure to which benzene would produce effects on other organs and systems apart from those specified as critical ones in establishing RfC.

4. To substantiate $MPC_{av.an}$ for benzene and verify it as per carcinogenic risk criteria and using evolution models.

Materials and methods. NOAEL (non-effective dose), LOAEL (threshold value), BMC (benchmark concentration) and BMCL (lower confidence limit of BMC) for effects produced by benzene on various organs and systems were taken as exposure levels that could be used as initial ones in substantiating RfC and additional RfC [14–15]. To do that, we performed an analytical review of domestic and foreign research works that focused on examining effects produced by benzene on various organs and systems, were cited in internationally acknowledged databases including Scopus, Research Gate, Web of Science, CyberLeninka, NCBI PubMed, eLibrary, Google Scholar, Elsevier, and were relevant to the present research. All the results obtained in this analysis were combined to build tables that provide data on effects produced by benzene on specific organs and systems. The tables provide data on a type of a study (toxicological / epidemiologic), research object, properties of a sampling, exposure (duration and intensity), research designs / experimental conditions, data on effects / responses, procedures applied to collect and analyze data, models of "exposure – effect" relationships, NOAEL / LOAEL, limitations in a study, and data sources. The next step was profound analysis aimed at estimating whether we had enough data for establishing statistically authentic minimal exposure levels that produced certain adverse effects on specified organs and systems; these minimal exposure levels gave grounds for further development of quantitative indicators for exposure to benzene. Overall, we carefully revised more than 150 published works and report.

RfC and additional RfC of benzene were established in conformity with approaches applied by the US Environmental Protection Agency (US EPA) [4–5, 16]. They were calculated as per the formula 1:

$$RfC = POD / \prod MF, \qquad (1)$$

where *RfC* is a reference concentration of benzene in ambient air, mg/m^3; *POD* is point of departure (concentration), mg/m^3; *MF* is a value of the total uncertainty factor.

Uncertainty factors in substantiating reference concentrations were established and $MPC_{av.an}$ for benzene was substantiated and

[3] O spiske prioritetnykh veshchestv, soderzhashchikhsya v okruzhayushchei srede i ikh vliyanii na zdorov'e naseleniya [On the list of priority pollutants in the environment and their influence on population health]. The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being. Available at: https://www.rospotrebnadzor.ru/documents/details.php?ELEMENT_ID=838 (November 15, 2021) (in Russian).

[4] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2020 godu: Gosudarstvennyi doklad [On sanitary-epidemiologic welfare of the population in the Russian Federation in 2020: the State Report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being, 2021, 256 p. (in Russian).

verified in accordance with the principles stated within the scientific research entitled "Developing methodical approaches to substantiating MPC of chemicals in ambient air as per health risk criteria", the State Register No. NIOKTR AAAA-A19-119060390099-5[5].

The formula (2) was applied to verify $MPC_{av.an}$ for benzene in ambient air as per carcinogenic risk since it allowed calculating such a concentration of a chemical in ambient air that provided an acceptable carcinogenic risk level:

$$MPC_{av.an.}^{carc} = \frac{(CR)}{(UR)}, \qquad (2)$$

where *CR* is acceptable carcinogenic risk level ($1 \cdot 10^{-4}$); UR is unit risk, m/mg^3 (calculated in accordance with the Guide R 2.1.10.1920-04[1]).

$MPC_{av.an}$ for benzene that corresponded to acceptable lifetime risk was verified based on principles stipulated in the Methodical Guidelines MR 2.1.10.0062-12 "Quantitative assessment of non-carcinogenic risks under exposure to chemicals based on building up evolution models"[6]; the verification was performed by experts from the Department for Mathematical Modeling of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies.

Results and discussion. Data obtained by analyzing the relevant research works allowed revealing that exposure to benzene in various concentrations produced adverse effects on several organs and systems in the body including the blood system, immune system, nervous system, cardiovascular system, respiratory organs, liver, reproductive system, skin and eyes; benzene also exerted negative influence on a developing organism, produced genotoxic and apparent carcinogenic effects [6–10, 16, 17].

Profound analysis provided us with sufficient relevant data for determining exposure levels regarding the blood system, the liver, and influence on a developing body; these exposure levels could be used as initial ones in substantiating RfC and additional RfC for benzene. Few research works that concentrated on estimating potential effects produced by chronic inhalation exposure to benzene on other organs and systems could not be used in our research due to multiple limitations, such as absence of qualitative and/or quantitative descriptions of exposure levels and effects, research being not designed properly, simultaneous exposure to benzene and other chemicals examined in a study etc. [7–10, 16, 17].

We selected several studies that established statistically authentic effects produced by benzene on the blood system under chronic inhalation exposure to lower doses of the chemical than those examined in all other works available at the moment. These studies included works by Scnhatter et al. [18], Rothman et al. [19], and Lan et al. [20]. Additional searching allowed revealing BMCL levels were calculated by USEPA and OEHHA based on the results described in these studies [16, 17]. These levels were used as points of departure in calculating various reference levels and establishing relevant uncertainty factors (Table 1).

We calculated three variants of RfC characterizing the exposure that might result in adverse effects produced on the blood system under chronic inhalation exposure to benzene; these concentrations amounted to 0.005, 0.07 and 0.09 mg/m^3. The minimal calculated concentration 0.005 mg/m^3 was taken as a reference one and the critical effect was a decrease in a number of B-lymphocytes. Since this effect characterizes both disorders in the blood and the immune system, these two systems were specified as critical ones for this RfC.

[5] Zaitseva N.V., Shur P.Z. Razrabotka metodicheskikh podkhodov k obosnovaniyu PDK khimicheskikh veshchestv v atmosfernom vozdukhe po kriteriyam riska zdorov'yu naseleniya: otchet o nauch.-issled. rabote [Developing methodical approaches to substantiating MPC of chemicals in ambient air as per health risk criteria: the report on the accomplished scientific research]. Perm, The Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 2019, 145 p. (in Russian).

[6] MR 2.1.10.0062-12. Kolichestvennaya otsenka nekantserogennogo riska pri vozdeistvii khimicheskikh veshchestv na osnove postroeniya evolyutsionnykh modelei: metodicheskie rekomendatsii [The Methodical Guidelines MR 2.1.10.0062-12. Quantitative assessment of non-carcinogenic risks under exposure to chemicals based on building up evolution models]. Moscow, The Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2012, 36 p. (in Russian).

Table 1

Calculations of benzene RfC under chronic inhalation exposure based on key studies focusing on effects produced by this chemical on the blood system

	Study (year)		
	Rothman et al. (1996)	Lan et al. (2004)	Scnhatter et al. (2010)
Research object	44 people	250 people	928 people
Exposure	Occupational exposure, on average 6.3 years	Occupational exposure, on average 6.1 years	Occupational exposure, on average 6.5 years
Critical effect	A decrease in absolute number of lymphocytes	A decrease in number of B-lymphocytes	A decrease in number of neutrophils and declining volume of thrombocytes
Threshold concentration	LOAEL = 7.6 ppm (24.8 mg/m^3)	LOAEL = 0.57 ppm (1.86 mg/m^3)	LOAEL = 7.8 ppm (25 mg/m^3)
Recalculation into BMCL (Source)	BMCL = 8.2 mg/m^3 (US EPA, 2003) [16]	BMCL = 0.204 ppm (0.665 mg/m^3) (OEHHA, 2014) [18]	BMCL = 3.3 ppm (10.8 mg/m^3) (OEHHA, 2014) [18]
Point of departure (POD)	BMCL = 8.2 mg/m^3	BMCL = 0.665 mg/m^3	BMCL = 10.8 mg/m^3
Total uncertainty factor (MF)	MF = 120 10 is intraspecific extrapolation factor; 2 is a factor taking into account extrapolation form controlled mode onto real life; 6 is a factor taking into account a scope of initial database	MF = 120 10 is intraspecific extrapolation factor; 2 is a factor taking into account extrapolation form controlled mode onto real life; 6 is a factor taking into account a scope of initial database	MF = 120 10 is intraspecific extrapolation factor; 2 is a factor taking into account extrapolation form controlled mode onto real life; 6 is a factor taking into account a scope of initial database
Calculated RfC	RfC = 0.07 mg/m^3	RfC = 0.005 mg/m^3	RfC = 0.09 mg/m^3
Selected RfC	RfC = 0.005 mg/m^3		

We also selected several studies that focused on effects produced by benzene on the liver; these studies established statistically authentic effects produced by the chemical in lower doses than those examined in all other available research works. These studies were performed by Perez et al. [21, 22] and Uzma et al. [23]. They gave grounds for establishing threshold benzene concentrations that produced various adverse effects and relevant uncertainty factors; these concentrations were used as points of departure in calculating various reference levels (Table 2).

We calculated two additional RfC characterizing an exposure level that might result in adverse effects on the liver under chronic inhalation introduction of benzene; they amounted to 0.007 and 0.016 mg/m^3. The minimal value out of two, 0.007 mg/m^3, was selected as an additional reference concentration. This value can be applied as an additional quantitative indicator of effects produced by benzene on the liver when health risks are assessed under elevated exposure.

Having analyzed all available studies focusing on impacts exerted by chronic inhalation exposure to benzene on a developing organism, we selected two key works, namely Chen et al. [24] and Lupo et al. [25]. Minimal exposure levels that caused adverse effects were determined based on the results described in these two works and applied as point of departure for substantiating reference concentrations (Table 3).

We calculated two additional RfC that might produce negative effects on a developing organism under chronic inhalation exposure to benzene; they amounted to 0.012 and 0.015 mg/m^3. The minimal value out of two, 0.012 mg/m^3, was selected as an additional reference concentration characterizing an exposure level that might exert negative influence on a developing organism. This value can be applied as an additional quantitative indicator of effects produced by benzene on a developing organism when health risks are assessed under elevated exposure.

Table 2

Calculations of additional benzene RfC under chronic inhalation exposure based on key studies focusing on effects produced by this chemical on the liver

	Study (year)	
	Perez et al. (2006)	Uzma et al. (2008)
Research object	Human	Liver cells
Exposure	Occupational, 9 months	Experimental (liver cells were cultivated during 8 hours with different concentrations of benzene)
Critical effect	Hypertransaminasemia	Hepatocytes viability going down by 30 %
Threshold concentration	Benzene concentration in ambient air is 4.7 mg/m^3	1 ppm (3.26 mg/m^3)
Point of departure (POD)	4.7 mg/m^3	3.26 mg/m^3
Total uncertainty factor (MF)	MF = 300 10 is intraspecific extrapolation factor; 5 is a factor taking into account point of departure; 6 is a factor taking into account a scope of initial database	MF = 480 10 is intraspecific extrapolation factor; 6 is a factor taking into account a scope of initial database; 8 is a factor taking into account extrapolation of research results obtained under short-term exposure onto chronic (long-term) exposure
Calculated additional RfC levels	0.016 mg/m^3	0,007 mg/m^3
Selected additional RfC	Additional RfC_{liver} = 0.007 mg/m^3	

Table 3

Calculations of additional benzene RfC under chronic inhalation exposure based on key studies focusing on effects produced by the chemical on a developing organism

	Study (year)	
	Chen et al. (2000)	Lupo et al. (2011)
Research object	Pregnant women	Pregnant women
Exposure	Chronic, 9 months	Chronic, 9 months
Critical effect	Lower body weight at birth	Spina bifida (the spinal column not fully formed)
Threshold concentration	Average effective concentration is 0.36 mg/m^3	Effective concentration starting from 0.45 mg/m^3
Point of departure (POD)	0.36 mg/m^3	0.45 mg/m^3
Total uncertainty factor (MF)	MF = 30 10 is a factor taking into account point of departure; 3 is a factor taking into account a scope of initial database	MF = 30 10 is a factor taking into account point of departure; 3 is a factor taking into account a scope of initial database
Calculated additional RfC levels	0.012 mg/m^3	0.015 mg/m^3
Selected additional RfC	Additional $RfC_{development}$ = 0.012 mg/m^3	

All the obtained results on substantiating benzene RfC under chronic inhalation exposure allowed suggesting that $MPC_{av.an}$ should amount to 0.005 mg/m^3 for this chemical.

Since benzene is a proven carcinogen [6], this calculated value has been also verified as per a carcinogenic risk criterion:

$$MPC_{av.an.}^{carc} = (1 \cdot 10^{-4})/(0.027 \cdot 1/70 \cdot 20) = 0.1 \text{ mg/m}^3$$

This result indicates that the suggested value provides health safety as per carcinogenic risk.

We applied evolution models to establish that exposure to benzene in a concentration equal to 0.005 mg/m^3 would result in addi-

tional risk that didn't exceed $2 \cdot 10^{-5}$ by an age of 70 and it means that lifetime inhalation exposure to benzene in this concentration is quite safe.

Therefore, since this suggested concentration provides life and health safety (absence of impermissible (unacceptable) risk) for a whole life span, carcinogenic effects taken into account, it can be applied as average annual MPC for benzene in ambient air.

Conclusion. We have established that a reference concentration of benzene should amount to 0.005 mg/m^3 under chronic inhalation exposure and a decrease in a number of B-lymphocytes should be considered a critical effect; this decrease can determine negative effects occurring in the blood and immune systems. We have also determined additional quantitative indicators (additional reference concentrations) for benzene, 0.007 mg/m^3, the liver as a critical organ, and 0.012 mg/m^3, violated process of organism development being a critical effect.

These additional RfC can be used as additional indicators when non-carcinogenic health risks are assessed under chronic inhalation exposure to elevated concentrations of benzene.

We suggest average annual MPC for benzene to be equal to 0.005 mg/m^3 since the value is verified to provide life and health safety (absence of impermissible (unacceptable) risk) for a whole life span, probable carcinogenic effects taken into account.

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