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Research article

PARAMETERS FOR HEALTH RISK ASSESSMENT ASSOCIATED WITH CHRONIC EXPOSURE TO HYDROGEN SULPHIDE IN AMBIENT AIR

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High levels of chemical pollution in ambient air due to industrial emissions can facilitate development of functional disorders in various organs and systems. They are a significant component to be considered when assessing health risks under exposure to combined multi-factorial pollution. However, the issue of methodical approaches to assessing possible effects on health under exposure to combinations of chemicals has not been studied enough as regards public health risk assessment. Given that, we suggest a trend to develop the methodology that involves revising and substantiating indicators applied in health risk assessment. This should be done as new research data on influence exerted by chemicals on health (including exposure to levels higher than reference ones) become available.

We have substantiated a system of quantitative indicators (including additional reference concentrations) for health risk assessment under chronic exposure to hydrogen sulphide in ambient air (including its elevated levels). Points of departure and modifying factors were established by analyzing studies on effects produced on health by hydrogen sulphide. On their basis, we developed parameters for non-carcinogenic health risk assessment.

The reference concentration equaled 0.002 mg/m^3 (the critical systems were respiratory organs and the nervous system). The additional reference concentration for risk assessment under elevated exposure to hydrogen sulphide was substantiated as equal to 0.07 mg/m^3 (impaired development being the critical system in the case).

The suggested system of quantitative indicators enhances and specifies parameters for health risk assessment. This makes it possible to perform more adequate assessment of health risks under combined exposure to chemicals in ambient air including those contained in levels higher than reference ones.

The suggested system of quantitative indicators was tested properly; as a result, the system was established to give an opportunity to obtain more comprehensive and accurate results of health risk assessment under combined exposure to chemical pollutants.

Keywords: *health risk assessment, hydrogen sulphide, chronic exposure, the system of quantitative indicators, reference concentration, respiratory system, nervous system, development.*

Environmental pollution and its influence on public health hold a significant place in the state policy in Russia; every year, issues arising in this sphere are given more attention and finding solutions to them is recognized as vital [1]. The methodology for assessing health risks caused by chemical pollution in the environment is a most significant instrument to explore this relationship. The health risk assessment methodology is applied both in fundamental research and in practical activities. However, the issue of methodical approaches to assessing possible effects on health under exposure to combinations of chemicals has not

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been studied enough as regards public health risk assessment. Given that, we suggest an obvious trend to develop the methodology that involves revising and substantiating indicators applied in health risk assessment. This should be done as new research data on influence exerted by chemicals on health (including exposure to levels higher than reference ones) become available.

It is common knowledge that at present health risk assessment that addresses risks caused by chemicals with threshold effects relies on reference levels. These levels have been developed based on NOAELs or LOAELs and systems and organs that are authentically the first to react to these levels are accepted as critical ones [2]. At the same time, under exposure to a concentration higher than these levels, a pathological process can additionally involve organs or their systems, which have not been considered in risk assessment, including that with its focus on combined exposures. As a result, occurring risk levels are underestimated.

Some documents confirm health outcomes under various levels of exposure to concentrations higher than reference ones. For example, the Agency for Toxic Substances and Disease Registry, when revising its toxicological profiles, provides detailed information about the results obtained by epidemiological and toxicological studies. It deliberately highlights statistically authentic results for various organs and systems that could be affected by an analyzed chemical.

Elevated levels of chemicals, hydrogen sulphide included, were established in ambient air in some cities in Russia within implementation of the 'Clean Air' Federal project of the 'Ecology' National project. These levels occur due to industrial emissions into ambient air in Lipetsk, Magnitogorsk, Nizhniy Tagil, Novokuznetsk, Bratsk, Norilsk, Omsk, Chelyabinsk and Chita and are higher than permissible ones[1] [3].

Respiratory organs are known to be the basic target under long-term exposure to hydrogen sulphide[2] [4–6] but the chemical is established to affect the nervous system and the development processes as well. However, at present the latter effects are not considered when risk assessment is performed under combined exposure to several chemicals.

Given that, **the aim of this study** was to identify a reference concentration more precisely and to substantiate a system of quantitative indicators (including additional reference concentrations) for health risk assessment under chronic exposure to hydrogen sulphide in ambient air (including its elevated levels).

To achieve this, the following tasks were formulated and solved:

To analyze research data on influence exerted on health by hydrogen sulphide to establish points of departure and modifying factors for further development of parameters for non-carcinogenic health risk assessment.

To specify the reference level of hydrogen sulphide and relevant critical organs and systems under chronic inhalation exposure to it.

To substantiate the system of quantitative indicators (including additional reference concentrations) for health risk assessment under chronic exposure to hydrogen sulphide in ambient air in levels higher than its reference concentration.

Materials and methods. We analyzed previously accomplished studies available in

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[1] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2019 godu: Gosudarstvennyi doklad [On sanitary-epidemiological welfare of the population in Russian Federation in 2019: The State report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2020, 300 p. (in Russian); O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2020 godu: Gosudarstvennyi doklad [On sanitary-epidemiological welfare of the population in Russian Federation in 2020: The State report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2021, 256 p. (in Russian).

[2] Guide R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals (approved and introduced by G.G. Onishchenko, the First Deputy to the RF Public Healthcare Minister and the RF Chief Sanitary Inspector on March 5, 2004). *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200037399 (November 22, 2022) (in Russian).

ATSDR and U.S. EPA databases as well as those stored in the Internet databases with open access and then selected key ones that contained the most relevant data.

The study designs were estimated in order to identify modifying factors and points of departure. They were later applied to establish parameters for health risk assessment under chronic inhalation exposure; the parameters were determined as a value of a selected point of departure to a value of the total (complex) uncertainty factor ratio [7].

The lowest value among the obtained ones was taken as a reference concentration; an organ (or a system) for which a reference indicator was established was considered a critical one.

The suggested methodical approaches were applied to develop a system of quantitative indicators (additional RfC) that characterized safe elevated exposure levels as regards specific disorders (excluding those that are critical for RfC).

Results and discussion. Having estimated the available research data, we established that studies addressing impacts exerted by hydrogen sulphide in ambient air were the most convincing as per validity and completeness of the relevant materials. These studies addressed influence, first of all, on the respiratory organs and nervous system as well as on a developing body (development abnormalities) exerted by the chemical within the range of levels comparable to actual pollution [8–12].

Effects produced by hydrogen sulphide on the respiratory organs were described the most comprehensively and precisely by Brenneman with colleagues [13] and by the CIIT [14]. Our analysis of the study designs made it possible to identify elements common for both studies; according to them, the key modifying factors and their values were determined.

The studies were established to involve animal experiments and this allowed selecting a modifying factor that considered interspecific extrapolation; its value equaled 10. Correctness of selecting this factor is validated by the fact that rats are obligate as per nose breathing and therefore more susceptible to the nasal cavity damages. In addition, rats' nasal cavity (50 %) has more olfactory epithelium than human one (5–10 %). This epithelium covers a complicated net of ethmoturbinates and this considerably increases a surface area where chemicals can be absorbed and slows down airflow thereby creating much more favorable conditions for effective deposition of inhaled toxicants [15, 16].

The experiments did not consider sensitive sub-populations; therefore, the next modifying factor was selected to allow for a specific population if intraspecific extrapolation was needed. Its value also equaled 10. Since only sub-chronic exposures were examined, the next modifying factor considered duration of chronic exposure and was taken as equal to 3. The total (complex) uncertainty factor for each study that addressed negative influence exerted by hydrogen sulphide on the respiratory organs was equal to 300.

At the same time, we can see certain differences in the experiment results. Thus, the study by the CIIT established a NOAEL equal to 43 mg/m^3. An initial NOAEL value (14 mg/m^3) was established by Brenneman with colleagues based on methodical approaches developed by the U.S. EPA; it was then recalculated into hydrogen sulphide level equivalent for the human body ($NOAEL_{HEC}$) considering weekly uninterrupted exposure and anatomic and physiological peculiarities related to development of an observed health disorder. The ultimate value equaled 0.64 mg/m^3. We established certain differences at the structural level of detected histological changes in the respiratory organs. Thus, Brenneman with colleagues identified certain disorders at the cellular level such as basal cell hyperplasia in the nasal cavity mucosa whereas the study by CIIT established some changes in tissues such as signs of inflammation in the nasal cavity mucosa.

Therefore, the study conducted by Brenneman with colleagues yielded more scientifically valid and precise results as regards establishing parameters that could provide absence of non-carcinogenic health risks.

Table 1 provides NOAELs for hydrogen sulphide effect on the respiratory system and relevant parameters for health risk assessment calculated on their basis.

The lowest no effect dose (NOAEL) that did not cause any health disorders of the respiratory organs such as basal cell hyperplasia in the nasal cavity mucosa was equal to 0.002 mg/m^3.

We examined research articles that addressed effects produced by hydrogen sulphide on the nervous system and spotted out two key studies, by Morgan with colleagues [19] and Dorman with colleagues [20]. Since both study designs were quite similar, we identified key modifying factors that provided their identical description. Both studies involved animal experiments with sub-chronic exposure to hydrogen sulphide and this made it possible to assuredly identify an interspecific extrapolation factor equal to 10, an intraspecific extrapolation factor equal to 10, and a factor to allow for duration of exposure equal to 3. The total (complex) modifying factor was equal to 300.

Certain differences between two studies were identified in the established points of departure and histopathology. The no effect doses applied in the studies were NOAEL equal to 420 mg/m^3 (Morgan with colleagues) and $NOAEL_{HEC}$ equal to 0.64 mg/m^3 (Dorman with colleagues). A point of departure recalculated as per a dose equivalent for the human body seems more eligible for establishing parameters for health risk assessment.

The experiments by Morgan with colleagues established behavioral and neurological effects such as weaker paw grip, hypotonia, loss of weight, necrosis and / or cavitation and / or bilateral symmetrical cerebral malacia of the parietal cortex, and impaired functioning of somatosensory neurons. All this indicates there are rather severe tissue damages in the nervous system. At the same time, changes established in the experiments by Dorman with colleagues indicated not so severe damages in the nervous system; they were only cell ones since certain signs of damage to olfactory neurons were identified.

Both studies give evidence of adverse effects on the nervous system but at different levels and with different severity of the established disorders. Table 2 provides parameters for health risk assessment under chronic inhalation exposure to hydrogen sulphide as per studies on its adverse effects on the nervous system.

Having analyzed the results of the aforementioned studies, we established the lowest exposure level (0.002 mg/m^3); any exposure to

Table 1

Calculation of parameters for health risk assessment under chronic inhalation exposure to hydrogen sulphide as per results of studies on its adverse effects on the respiratory organs

Parameter / study	Brenneman et al.	CIIT
Test group	Sprague – Dawley rats	$B_6C_3F_1$ mice
Duration of exposure	6 hours a day during 10 weeks	6 hours a day, 5 days a week, during 90 days
Adverse effect	Basal cell hyperplasia in the nasal cavity mucosa	Inflammation of the nasal cavity mucosa
Point of departure (POD)	NOAEL = 10 ppm (14 mg/m^3) $NOAEL_{ADJ}$ = 14 mg/m^3 × 6/24 h × 7/7 days/week = 3,5 mg/m^3 [17] $NOAEL_{HEC}$ = 3.5 mg/m^3 × 0.184 = 0.64 mg/m^3 [18]	NOAEL = 43 mg/m^3
Total (complex) uncertainty factor	MF = 300 10 – intraspecific extrapolation; 10 – interspecific extrapolation; 3 – a factor allowing for duration of exposure	MF = 300 10 – intraspecific extrapolation; 10 – interspecific extrapolation; 3 – a factor allowing for duration of exposure
Calculation	$NOAEL_{HEC}$ / MF = 0.64 mg/m^3 / 300 = 0.002 mg/m^3	NOAEL / MF = 43 mg/m^3 / 300 = 0.143 mg/m^3
Value	0.002 мг/м^3	0.143 mg/m^3

Table 2

Calculation of parameters for health risk assessment under chronic inhalation exposure to hydrogen sulphide as per results of studies on its adverse effects on the nervous organs

Parameter / study	Morgan et al.	Dorman et al.
Test group	Fischer 344 rats	Fischer-344 rats, Sprague – Dawley rats and $B_6C_3F_1$ mice
Duration of exposure	6 hours a day, 5 days a week, 12 weeks	6 hours a day, 5 days a week, not less than 90 days
Adverse effect	Weaker paw grip, hypotonia, slight weight loss, necrosis and / or cavitation and / or bilateral symmetric cerebral malacia of the parietal cortex, functional disorders of somatosensory neurons	Multifocal two-side symmetric loss of olfactory neurons
Point of departure (POD)	NOAEL = 420 mg/m^3	$NOAEL_{HEC}$ = 0.64 mg/m^3
Total (complex) uncertainty factor	MF = 300 10 – intraspecific extrapolation; 10 – interspecific extrapolation; 3 – a factor allowing for duration of exposure	MF = 300 10 – intraspecific extrapolation; 10 – interspecific extrapolation; 3 – a factor allowing for duration of exposure
Calculation	NOAEL / MF = 420 mg/m^3 / 300 = 1.4 mg/m^3	$NOAEL_{HEC}$ / MF = 0.64 mg/m^3 / 300 = 0.002 mg/m^3
Value	1.4 mg/m^3	0.002 mg/m^3

a higher concentration may result in adverse effects on the nervous system and such negative health outcomes as multifocal two-sided symmetric loss of olfactory neurons under chronic inhalation exposure to hydrogen sulphide.

Studies accomplished by Hayden with colleagues [21] and Skrajny with colleagues [22] provide the most convincing description of influence exerted by hydrogen sulphide on occurring development abnormalities. These studies involved animal experiments with sub-chronic inhalation exposure to hydrogen sulphide.

We established that both experiments used LOAELs as their points of departure but the values were different and equaled to 28 mg/m^3 (Hayden et al.) and 110 mg/m^3 (Skrajny et al.).

The studies also reported different adverse effects produced on development by hydrogen sulphide. Thus, Hayden and others detected an authentic subtle increase in time of ear detachment and hair development; Skrajny with colleagues established an authentic elevated level of serotonin and lower level of epinephrine in the cerebellum and frontal cortex on the 14th and 21st day postnatal. All this leads to the nervous system not developing properly in a fetus.

However, the beginning of a pregnancy and the beginning of poisoning is a vital moment in an experiment aiming to examine adverse effects produced on a developing fetus. Poisoning started on the 1st day of a pregnancy in the experiment performed by Hayden with colleagues whereas its start was only on the 5th day of a confirmed pregnancy in the experiment performed by Skrajny and others. This was a key difference in establishing a value of a modifying factor that allowed for duration of an exposure.

Having analyzed these studies, we established LOAELs for effects produced by hydrogen sulphide on occurring development abnormalities and parameters for health risk assessment calculated on their basis (Table 3).

The analysis revealed that LOAEL equal to 0.07 mg/m^3 was the lowest safe dose and any dose higher than it would induce development abnormalities (an increase in time of ear detachment and slower hair development in animals).

Table 3

Calculation of parameters for health risk assessment under chronic inhalation exposure to hydrogen sulphide as per results of studies on its adverse effects on a developing body (development abnormalities)

Parameter / study	Hayden et al.	Skrajny et al.
Adverse effect	An authentic slight increase in time of ear detachment and hair development	An authentic increase in a level of serotonin and a decrease in a level of norepinephrine in the cerebellum and frontal cortex on the 14th and 21st day postnatal
Point of departure (POD)	LOAEL = 28 mg/m^3	LOAEL = 110 mg/m^3
Total (complex) uncertainty factor	MF = 400 10 – intraspecific extrapolation; 10 – interspecific extrapolation; 4 – a factor allowing for duration of exposure	MF = 700 10 – intraspecific extrapolation; 10 – interspecific extrapolation; 7 – a factor allowing for duration of exposure
Calculation	LOAEL / MF = 28 mg/m^3 / 400 = 0.07 mg/m^3	LOAEL / MF = 110 mg/m^3 / 700 = 0.15 mg/m^3
Value	0.07 mg/m^3	0.15 mg/m^3

Therefore, our analysis of all the aforementioned studies allowed us to establish relevant parameters for assessing non-carcinogenic health risks under chronic inhalation exposure to hydrogen sulphide. The lowest identified dose, which is equal to 0.002 mg/m^3, is taken as the reference concentration. Any dose higher than this concentration can create risks for not only the respiratory organs (such as basal cell hypoplasia in the nasal cavity mucosa) but also for the nervous system with multifocal two-sided symmetrical loss of olfactory neurons. This fact not only confirms the existing RfC for hydrogen sulphide but also indicates that a list of critical organs and systems susceptible to the chemical should be expanded. The research data indicate that the airways and the nervous system are the most susceptible (critical) organs / systems under exposure to hydrogen sulphide.

We also established an additional RfC for hydrogen sulphide (0.07 mg/m^3). Any dose higher than it can produce adverse effects on a developing body and this should be considered when conducting health risk assessment under combined exposure to chemicals that can influence development in concentrations being higher than the basic reference one.

We comparatively assessed non-carcinogenic health risks associated with chronic inhalation exposure to hydrogen sulphide (0.028 mg/m^3) and several other chemicals (nitrogen dioxide, 0.03 mg/m^3; chloromethane, 0.03 mg/m^3; methanol, 3 mg/m^3) that produce adverse effects on critical organs and systems similar to those susceptible to hydrogen sulphide. The assessment revealed certain differences in a risk level (HI) under combined exposure (Table 4).

We established additional unacceptable non-carcinogenic risks for the nervous system ($HI = 14.33$) and intrauterine development ($HI = 1.15$) under the same levels of exposure to chemicals when the developed system of quantitative indicators was applied to test it. These testing results indicate that the suggested system of quantitative indicators makes it possible to obtain more comprehensive and accurate results of health risk assessment under combined exposure to chemical pollutants including elevated levels of exposure (higher than reference ones).

Conclusion. A suggested system of quantitative indicators for risk assessment includes a reference concentration and additional indicators under elevated levels of exposure. It is advisable to use it when assessing health risks associated with multicomponent chemical pollution in ambient air under chronic inhalation exposure.

Table 4

Comparative analysis of the results obtained by health risk assessment under combined chronic inhalation exposure to chemicals in accordance with the parameters stipulated in the Guide R 2.1.10.1920-04[3] and the developed system of quantitative indicators

Critical organ / system	In accordance with the parameters in R 2.1.10.1920-04			In accordance with the developed system of quantitative indicators		
	Chemical	HQ	HI	Chemical	HQ	HI
Respiratory organs	Nitrogen dioxide	0.75	14.75	Nitrogen dioxide	0.75	14.75
	Hydrogen sulphide	14.00		Hydrogen sulphide	14.00	
Nervous system	Chloromethane	0.33	–	Hydrogen sulphide	14.00	14.33
				Chloromethane	0.33	
Development	Methanol	0.75	–	Hydrogen sulphide	0.40	1.15
				Methanol	0.75	

To substantiate its use, this study describes the system of quantitative indicators for assessing health risks associated with chronic inhalation exposure to hydrogen sulphide. It includes the reference concentration, which is equal to the valid one and is 0.002 mg/m^3. Following the study, the list of critical organs and systems was enhanced for this reference concentration since any exposure to hydrogen sulphide in a dose higher than this level can produce adverse effects both on the respiratory organs and nervous system.

The additional reference concentration for risk assessment under elevated exposure to hydrogen sulphide was substantiated as equal 0.07 mg/m^3 with its critical effects produced on intrauterine development (development abnormalities).

The substantiated system of quantitative indicators enhances and specifies parameters for health risk assessment. This makes it possible to perform more adequate assessment of health risks under combined exposure to chemicals in ambient air.

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