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CRITERIA ELIGIBLE FOR ESTABLISHING REFERENCE CONCENTRATIONS OF ADVERSE CHEMICALS UNDER CHRONIC INHALATION EXPOSURE BY EXTRAPOLATION OF THE EXISTING PARAMETERS

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Some chemicals emitted into ambient air do not have eligible parameters for assessing associated non-carcinogenic health risks under chronic inhalation exposure. Therefore, it is relevant to extend the list of reference concentrations (RfC), among other things, to perform health risk assessment within implementation of the Clean Air Federal Project. The same reference concentrations and critical organs and systems can be fixed for different compounds of the same chemical in accordance with the Guide R 2.1.10.3968-23. This makes it possible to establish non-identified RfC values by extrapolating the existing parameters from a donor to an acceptor.

The article suggests eligible criteria for establishing reference concentrations under chronic inhalation exposure by extrapolation of the existing parameters. They include identity of chemicals per selective toxicity towards target organs and / or systems upon chronic exposure, identical critical organs and systems, identical specific effects (sensitizing and mutagenic effects and reproductive toxicity) and similar physiochemical properties.

Use of extrapolation criteria allowed suggesting RfC of cadmium oxide equal to $2 \cdot 10^{-5}$ mg/m^3; cadmium was employed as a donor for extrapolation. Verification results confirmed that the conventionally substantiated RfC value was consistent with the value obtained by extrapolation. At the same time, we found that it was unacceptable to establish RfC of cadmium sulfate by extrapolation from cadmium since the former chemical was more toxic in accordance with the suggested criteria as regards its mutagenic effects and reproductive toxicity. In addition, its physiochemical properties were different from those of cadmium.

Keywords: *parameters for health risk assessment, risk assessment, reference concentration, non-carcinogenic risk, extrapolation, extrapolation criteria, cadmium.*

According to the State Report 'On Quality and Protection of the Environment in the Russian Federation in 2022'[1], the total emissions of pollutants into ambient air from stationary sources reached 17,173.9 thousand tons in 2022. They included more than 100 chemicals and their compounds. Health risk assessment is required to minimize negative outcomes due to use of chemicals, both for human health and for providing chemical safety of the country population [1, 2].

The health risk assessment methodology is an important instrument eligible for providing sanitary-epidemiological wellbeing of the population in the Russian Federation through optimization of control and surveillance activities, social-hygienic monitoring, inspections and accomplishing well-grounded prevention activities [2–4].

As stated in the RF President Order 'On the Basics of the RF State Policy in the Sphere of Providing Chemical and Biological Safety for the Period up to 2025 and beyond', it is necessary to create such protection for the country population and the environment from negative effects produced by hazardous

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[1] O sostoyanii i ob okhrane okruzhayushchei sredy Rossiiskoi Federatsii v 2022 godu [On Quality and Protection of the Environment in the Russian Federation in 2022]: the State Report. Moscow, the RF Ministry of Natural Resources and Environment; M.V. Lomonosov's Moscow State University, 2023, 686 p. (in Russian).

chemicals that ensures permissible levels of chemical risks[2].

The methodical base available in the Russian Federation suffices for application of the health risk assessment methodology within providing sanitary-epidemiological wellbeing of the country population. Still, it is necessary to make supplements to some aspects, among other things, to extend the list of reference concentrations (RfC) under chronic inhalation exposure [5, 6].

According to the Federal Law No. 195-FZ 'On accomplishing the experiment on setting quotas for emissions of pollutants and making alterations into specific legal acts of the Russian Federation regarding reduction of ambient air pollution', the federal executive authority responsible for the federal sanitary-epidemiological surveillance is obliged to calculate and assess risks for human health[3]. Relevance of health risk assessment upon exposure to chemicals in ambient air is also emphasized by tasks set within the Clean Air Federal Project of the Ecology National Project[4].

Lists of chemicals contained in emissions from stationary and mobile sources were analyzed in four cities participating in the Clean Air Federal Project (Bratsk, Krasnoyarsk, Norilsk, and Chita) under supervision by the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies. As a result, it was found that RfC were not established in conformity with the Guide R 2.1.10.3968-23 Health Risk Assessment upon Exposure to Chemical Pollutants in the Environment (hereinafter the Guide) for more than a half of emitted chemicals[5]. Lists of priority chemical pollutants for 18 territories included in the Clean Air Federal Project were analyzed; as a result, RfC were found to be missing for 18 chemicals and 56 mixtures in them including cadmium oxide, sodium hydroxide, diiron trioxide (iron oxide), nickel sulfate, kerosene, and some others[6]. It is note-

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[2] Ob osnovakh gosudarstvennoi politiki Rossiiskoi Federatsii v oblasti obespecheniya khimicheskoi i biologicheskoi bezopasnosti na period do 2025 goda i dal'neishuyu perspektivu: Ukaz Prezidenta RF ot 11.03.2019 № 97 [On the Basics of the RF State Policy in the Sphere of Providing Chemical and Biological Safety for the Period up to 2025 and beyond: The RF President Order dated March 11, 2019 No. 97]. *KonsultantPlus*. Available at: https://www.consultant.ru/document/cons_doc_LAW_319787/ (September 10, 2024) (in Russian).

[3] O provedenii eksperimenta po kvotirovaniyu vybrosov zagryaznyayushchikh veshchestv i vnesenii izmenenii v otdel'nye zakonodatel'nye akty Rossiiskoi Federatsii v chasti snizheniya zagryazneniya atmosfernogo vozdukha: Federal'nyi zakon Rossiiskoi Federatsii ot 26 iyulya 2019 goda № 195-FZ [On accomplishing the experiment on setting quotas for emissions of pollutants and making alterations into specific legal acts of the Russian Federation regarding reduction of ambient air pollution: The Federal Law issued on July 26, 2019 No 195-FZ]. *KomsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_329955/ (September 10, 2024) (in Russian).

[4] Natsional'nyi proekt «Ekologiya». Federal'nyi proekt «Chistyi vozdukh» [The Ecology National Project. The Clean Air Federal Project]. Available at: https://mnr-air.ru/home (October 11, 2024) (in Russian).

[5] Guide R 2.1.10.3968-23. Rukovodstvo po otsenke riska zdorov'yu naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh sredu obitaniya; utv. Federal'noi sluzhboi po nadzoru v sfere zdravookhraneniya ot 5 sentyabrya 2023 g. [Health Risk Assessment upon Exposure to Chemical Pollutants in the Environment; approved by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on September 5, 2023]. *GARANT: information and legal support*. Available at: https://base.garant.ru/408644981/ (September 10, 2024) (in Russian).

[6] O vnesenii izmenenii v prilozheniya 1 i 2 k prikazu Ministerstva prirodnykh resursov i ekologii Rossiiskoi Federatsii ot 6 oktyabrya 2022 g. № 657 «Ob utverzhdenii metodik rascheta tselevykh pokazatelei «Snizhenie sovokupnogo ob"ema vybrosov», «Snizhenie sovokupnogo ob"ema vybrosov opasnykh zagryaznyayushchikh veshchestv v gorodakh-uchastnikakh proekta» federal'nogo proekta «Chistyi vozdukh» natsional'nogo proekta «Ekologiya»: Prikaz Minprirody RF ot 05.07.2023 № 418 [On making alterations into Appendixes 1 and 2 to the Order by the RF Ministry of Natural Resources and Environment dated October 6, 2022 No. 657 On Approval of the methods for calculating performance indicators 'Reduction in total emission volumes' and 'Reduction in emissions of hazardous pollutants in cities included in the Project' for the Clean Air Federal Project of the Ecology National Project: the Order by the RF Ministry of Natural Resources and Environment dated July 05, 2023 No. 418]. *Rosstat*. Available at: https://rosstat.gov.ru/storage/mediabank/MET_120013_1.pdf (October 10, 2024) (in Russian); Perechni prioritetnykh zagryaznyayushchikh veshchestv dlya territorii g. Bratsk, g. Nizhnii Tagil, g. Cherepovets: pis'mo Rospotrebnadzora ot 23.11.2020 № 02/23971-2020-23 [The lists of priority pollutants for Bratsk, Nizhniy Tagil, and Cherepovets: the Letter by Rospotrebnadzor dated November 23, 2020 No. 02/23971-2020-23] (in Russian); Perechni prioritetnykh zagryaznyayushchikh veshchestv dlya territorii eksperimenta (g. Noril'sk g. Lipetsk, g. Chelyabinsk, g. Krasnoyarsk): pis'mo Rospotrebnadzora ot 11.12.2020 № 02/25401-2020-23 [The lists of priority pollutants for the experiment territories (Norilsk, Lipetsk, Chelyabinsk, and Krasnoyarsk): the Letter by Rospotrebnadzor dated December 11, 2020 No. 02/25401-2020-23] (in Russian); Perechni prioritetnykh zagryaznyayushchikh veshchestv dlya territorii eksperimenta (g. Magnitogorsk, g. Omsk, g. Chita, g. Mednogorsk, g. Novokuznetsk): pis'mo Rospotrebnadzora ot 21.12.2020 № 02/26092-2020-23 [The lists of priority pollutants for the experiment territories (Magnitogorsk, Omsk, Chita, Mednogorsk, and Novokuznetsk): the Letter by Rospotrebnadzor dated December 21, 2020 No. 02/26092-2020-23] (in Russian).

worthy that RfC may be established for some compounds of a certain chemical in the Guide and be missing for others. For example, an RfC is established for cadmium but lists for chemicals that are priority for control include cadmium oxide and not cadmium; RfC are established for sodium dichromate and sodium fluoride, but a RfC for sodium hydroxide is actually needed; RfC are established for silicon dioxide (SiO_2 content below 20 %) silicon dioxide (SiO_2 content above 70 %), but lists of chemicals for control include inorganic dust that contains between 20 and 70 % of silicon dioxide etc.

Absence of several RfC does not allow complete health risk assessment in practice. This makes it necessary to extend a list that contains RfC of chemicals, effects of which on population health should be given priority in estimation.

In accordance with the Guide, the same numerical RfC values are fixed for some chemical compounds, which is indirect evidence of possibility to extrapolate parameters from one compounds to others to perform non-carcinogenic health risk assessment. For example, identical RfC and critical organs and systems are identified for compounds of barium, manganese, copper, lead, antimony, hydrazine, and some others.

It is reasonable to assume that compounds of the same chemical can have similar effects on human health. This assumption is confirmed by the fact that the US Environmental Protection Agency (US EPA) uses values established by experimental research that involves using compounds of a chemical, for which a safe standard is being established, as points of departure to determine RfC. For example, when an RfC was established for manganese, experts relied on using a point of departure identified in toxicological studies of manganese dioxide[7]. When establishing minimal risk levels (MRL), the Federal Agency for Toxic Substances and Disease Registry (ATSDR)) of the US Public Health Service also relies on results of studies accomplished using chemical compounds for which MRL are developed. This approach was implemented, for example, for hydrazine (based on 1,1-dimethyl hydrazine and 1,2-dimethyl hydrazine), cadmium (based on cadmium oxide and cadmium sulphide), nickel (using results obtained by research of effects produced by nickel oxide, nickel chloride, nickel sub-sulphide, and nickel sulfate hexahydrate) etc.[8] A point of departure was selected in all foregoing cases on the basis of LOAEL or NOAEL, which were the lowest out of those identified for all analyzed chemicals.

It is worth noting that development of toxic effects is directly related to a structure of an affecting chemical. By now, several studies have reported dependence between biological activity of a chemical and structure and composition of its molecules, available substitutes and their types, a type and multiplicity of a chemical bond. For example, polar molecules are more prone to be soluble in water and to interact with biological molecules. This may raise their toxicity since they penetrate into cells more easily and thus interact with cell structures. A molecule with double or triple bonds can have higher reactivity and be more toxic. As a molecular weight grows, it becomes more difficult for a toxicant to enter the body and spread in organs and tissues. Unstable chemicals that are prone to breakdown can

[7] Roels H.A., Ghyselen P., Buchet J.P., Ceulemans E., Lauwerys R.R. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. *Br. J. Ind. Med.*, 1992, vol. 49, no. 1, pp. 25–34; Manganese (CASRN 7439-96-5): Chemical Assessment Summary. *Integrated Risk Information System (IRIS), U.S. Environmental Protection Agency, National Center for Environmental Assessment*. Available at: https://iris.epa.gov/static/pdfs/0373_summary.pdf (October 15, 2024).

[8] Toxicological profile for cadmium. Draft for Public Comment. *U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry*, Atlanta, 2012, 487 p.; Toxicological profile for nickel. Draft for Public Comment. *U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry*, Atlanta, 2023, 422 p.; Hydrazines. *Agency for Toxic Substances and Disease Registry*. Available at: https://wwwn.cdc.gov/TSP/substances/ToxSubstance.aspx?toxid=89 (October 28, 2024); Cadmium. *Agency for Toxic Substances and Disease Registry*. Available at: https://wwwn.cdc.gov/TSP/substances/ToxSubstance.aspx?toxid=15 (October 28, 2024).

be more toxic since if a chemical is unstable, then a developing toxic effect may be associated with exposure to products of its transformation, which can be more toxic. Certain functional groups in a chemical composition, for example, when organic nitro groups (–N02) and nitroso groups (–NO) are introduced into a molecule, usually make a chemical more toxic. But introduction of a hydroxyl group, as a rule, weakens chemical toxicity, which is explained by higher solubility in biological media, etc.[9] [7, 8]. This indicates that it is physiochemical properties of a chemical that ultimately determine its toxicity.

Therefore, it is relevant to make supplements to the database that comprises RfC of chemicals applied in assessing non-carcinogenic health risks under chronic inhalation exposure. This can be done by extrapolating parameters from chemicals / compounds with identical characteristics of toxic effects. Given that, it is advisable to suggest certain criteria that allow selecting relevant parameters eligible for extrapolation.

In this study, our aim was to suggest criteria for establishing reference concentrations applicable in assessing non-carcinogenic health risks under chronic chemical inhalation exposure by extrapolation of the existing parameters.

Materials and methods. Within extrapolation, chemicals (donors) were identified, numerical RfC values of which can be extrapolated for other chemical compounds (acceptors).

Criteria of extrapolation parameters applied in non-carcinogenic health risk assessment under chronic chemical inhalation exposure were developed relying on data about toxicological and physiochemical properties. Several documents were considered in the process including State Standard GOST 32419-2022 Classification of Hazards Posed by Chemical Products. General Requirements (hereinafter the GOST)[10] that classifies chemicals per their effects on health and globally approved Globally Harmonized System of Classification and Labeling of Chemicals (hereinafter the GHS), which was created by the UN in order to provide the unified standard of criteria for assessing chemical hazards employed in different countries. The GHS allows classifying chemicals per their hazards basing on available data about hazardous properties of chemicals including their impacts on the human body [9][11].

When testing the suggested criteria, we used data about cadmium (CAS 7440-43-9), cadmium oxide (CAS 1306-19-0), and cadmium sulfate (CAS 10124-36-4) available in such databases as PubChem, European Chemicals Agency (ECHA), CAMEO Chemicals, Haz-Map (Information on Hazardous Chemicals and Occupational Diseases), Hazardous Substances Data Bank (HSDB), Toxin and Toxin Target Database (T3DB), Agency for Toxic Substances and Disease Registry (ATSDR), and eChemPortal. In addition, we used the results of a system review that covered 112 published toxicological and epidemiological studies in Russian and English. A source being indexed in Scopus / Web of Science / HAC / RSCI and statistically authentic data about impact of analyzed chemicals on occurrence of health outcomes in population were applied as criteria fir including data from a source.

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[9] Bradbury S.P. Predicting modes of toxic action from chemical structure: an overview. *SAR QSAR Environ. Res.*, 1994, vol. 2, no. 1–2, pp. 89–104. DOI: 10.1080/10629369408028842; R 1.2.3156-13. Otsenka toksichnosti i opasnosti khimicheskikh veshchestv i ikh smesei dlya zdorov'ya cheloveka: rukovodstvo, utv. Glavnym gosudarstvennym sanitarnym vrachom RF 27 dekabrya 2013 g. [Assessment of toxicity and hazard of chemicals and their compounds for human health: Guide, approved by the RF Chief Sanitary Inspector on December 27, 2013]. *GARANT: information and legal support*. Available at: https://base.garant.ru/71315562/?ysclid=m3cxgawtqp386048885 (October 18, 2024) (in Russian); WHO Human Health Risk Assessment Toolkit: Chemical Hazards, second edition. *WHO*, 2021, 112 p.

[10] GOST 32419-2022. Klassifikatsiya opasnosti khimicheskoi produktsii. Obshchie trebovaniya; vved. v deistvie 01.01.2023 [State Standard GOST 32419-2022 Classification of Hazards Posed by Chemical Products. General Requirements; enacted on January 01, 2023]. Moscow, FGBU RST, 2022, 40 p. (in Russian).

[11] GHS Classification (Rev.10, 2023) Summary. *PubChem*. Available at: https://pubchem.ncbi.nlm.nih.gov/ghs/ (October 18, 2024).

To verify RfC of cadmium oxide, we used approaches based on the methodology for establishing reference concentrations developed by the US Environmental Protection Agency[12] [10]. Uncertainty factors were established relying on approaches described in the International Program on Chemical Safety issued by the World Health Organization[13] [11].

Results and discussion. We developed a system of extrapolation criteria relying on assessing similarities of toxicological and physiochemical properties. It included assessment of similarities in selective toxicity towards target organs and / or systems under chronic exposure; comparison of critical organs and systems and specific effects (sensitizing and mutagenic effects and reproductive toxicity); analysis of physiochemical properties that can cause differences in toxicokinetics and mechanisms of actions of different chemicals.

Selective toxicity towards target organs and / or systems under chronic exposure describes capability of a chemical to produce toxic effects on specific target organs and / or biological systems without affecting other organs and / or systems through prolonged or repeated exposure. To compare an acceptor and a donor per this criterion, a chemical is assigned into hazard classes 1–2 according to GOST basing on sufficient or limited evidence of toxicity for a target human or animal organ and / or system relying on analyzing and assessing results obtained by toxicological and / or epidemiological studies as well as ranges of affecting concentrations in toxicological experiments. In addition, GHS codes and / or categories are assigned based on specific toxicity for target organs through repeated exposure: H372 (Category 1) means a chemical causes damage to organs through prolonged or repeated exposure; H373 (Category 2) means a chemical may cause damage to organs through prolonged or repeated exposure. Simultaneously, target organs should be established both for donor and acceptor[14] [9].

Critical organs and systems are those that have been proven to be authentically the first to react to LOAEL of analyzed chemicals. To perform an assessment per this criterion, critical organs and systems should be identified for an acceptor and compared with those established for a donor by the Guide. Extrapolation can be accomplished only if both donor and acceptor have the same critical organs and systems.

An assessment criterion per *sensitizing effects* determines whether a chemical is able to induce allergic reactions, that is, increased sensitivity of the body to repeated contacts with it. Both donor and acceptor should belong to the same hazard class / sub-class of chemicals upon inhalation exposure in conformity with the GOST (class 1, sub-class 1A or 1B) based on available evidence of developing allergic reactions in humans such as asthma, rhinitis / conjunctivitis, alveolitis, and manifestations of immunological mechanisms of allergic reactions in humans and animals depending, among other things, on frequency of introduction into the body. According to the GHS as regards description of respiratory sensitization, both acceptor and donor should be analyzed to established whether they have or do not have H334 code, than means a chemical may cause allergy or asthma symptoms or breathing difficulties if inhaled, and also whether they belong to the same hazard Category 1, which means a chemical is a respiratory sensitizer, subcategory 1A or 1B (a chemical is described with high or low / moderate frequency or likelihood of developing allergic reactions in humans based on animal or other studies).

[12] Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F). *U.S. Environmental Protection Agency*. USA, North Carolina, Research Triangle Park Publ., 1994, 389 p.

[13] Harmonization Project Document, No. 2. Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration-response assessment. Geneva, World Health Organization, 2005, 100 p.

[14] GHS Classification (Rev.10, 2023) Summary. *PubChem*. Available at: https://pubchem.ncbi.nlm.nih.gov/ghs/ (October 18, 2024).

The criterion related to *mutagenic effects* determines whether a chemical is able to cause changes in genetic material. When a donor and acceptor are compared using this criterion, they should be assigned into a hazard class / sub-class per mutagenic effects in accordance with the GOST (1 (A and B) or 2) based on criteria established in it. They include available data on mutations or mutagenic activity in germ cells of humans or mammals, mutagenicity of somatic cells, etc. At the same time, both donor and acceptor should have the same GHS codes that describe whether a chemical may have mutagenic effects. They are H340 and H341, which means this chemical may cause or is suspected of causing genetic defects. Both donor and acceptor should be assigned to relevant hazard categories for mutagens, which are Category 1 (chemicals known for their ability to cause heritable mutations or should be considered able to cause mutations in germ cells), subcategory 1A (chemicals able to cause heritable mutations in human germ cells) and subcategory 1B (chemicals that should be considered as causing heritable mutations), or Category 2 (chemicals that cause concern for human health due to their possible capability of causing heritable mutations in human germ cells).

The criterion related to *reproductive toxicity* is used to establish whether analyzed chemicals have teratogenic, gonadotropic and / or embryotropic effects. Both donor and acceptor should be assigned into the same hazard class / sub-class for chemicals that affect the reproductive function in conformity with the GOST (1 (A and B) or 2, chemicals that affect lactation or the body through it). This is identified based on available evidence of impacts on the human or animal reproductive functions, likelihood of a chemical occurring in breast milk in potentially toxic levels, or of hazards for breast-fed children. In the GHS, reproductive toxicity is described with several codes including H360 (may damage fertility or the unborn child), H361 (suspected of damaging fertility or the unborn child), and H362 (may cause harm to breast-fed children). Here each code has some subcategories encoded by different letters that describe specific effects of a chemical. For example, H360F means a chemical may damage fertility; H360D, may damage the unborn child; H360FD, may damage fertility, may damage the unborn child; H360Fd, may damage fertility, is suspected of damaging the unborn child, etc. In addition, both donor and acceptor should be assigned to a specific hazard category of reproductive toxicants including Category 1 (known or presumed human reproductive toxicants, 1A (based on evidence from humans) and 1B (largely based on animal studies)) and Category 2 (suspected human reproductive toxicant).

A donor and acceptor should be comparable both per a general hazard class and a sub-class (in case it is established) in accordance with the GOST as well as have the same code and belong to the same category within the GHS.

Per the criterion of *physiochemical properties that can cause differences in toxicokinetics and mechanism of action,* both donor and acceptor should have similar properties able to influence their capability to penetrate through cell membranes, interact with enzymes and other cellular structures as well as their distribution and excretion from the body. These properties can include an aggregate state, solubility in water and lipids, volatility, chemical reactivity, etc.

Therefore, it is possible to extrapolate reference concentrations from a donor to acceptor only if they belong to the same hazard classes according to the GOST; have the same codes and hazard categories in the GHS that describe their influence on health under chronic inhalation exposure considering their specific effects; the same critical organs and systems are established for exposure to them; they do not have crucial differences in their physiochemical properties.

Cadmium oxide and cadmium sulfate are relevant for RfC extrapolation since they are found in emissions in the cities included in the Clean Air Federal Project. Cadmium oxide also belongs to priority pollutants. Both chemicals do not have parameters established for them to perform risk assessment under

chronic inhalation exposure in accordance with the Guide[15].

Cadmium was selected as a probable donor since this chemical has an RfC established for it in accordance with the Guide.

After the donor and acceptors were compared using the suggested extrapolation criteria, the following results were obtained:

1. Both donor and acceptors belong to the hazard class 1 according to the GOST per their selective toxicity towards target organs and / or systems under chronic inhalation exposure[16] [12–14]. Within the GHS, they have the same code H372 (Category 1) (causes damage to organs through prolonged or repeated exposure, specific toxicity for target organs upon repeated exposure)[17]; the same target organs are the kidneys, respiratory organs, and the skeleton system.

2. The kidneys and respiratory organs are established as critical for cadmium oxide and cadmium sulfate under chronic inhalation exposure since no effects on the skeleton system are established for cadmium in accordance with the Guide. Given that, this system cannot be included into the extrapolation area[18].

3. Both donor and acceptors belong to the hazard class 1 per their sensitizing effects according to the GOST without any sub-classes established for them due to lack of relevant data in available Russian and foreign studies. H-code and categories according to the GHS are not identified either[16, 17].

4. Both donor and acceptors belong to the hazard sub-class 1B per their mutagenic effects (positive results obtained by in vivo tests aimed at establishing mutagenicity of mammal somatic cells together with evidence of potential ability to cause germ cell mutations) [15, 16]. Cadmium and cadmium oxide have H341 code in the GHS (Category 2).

Cadmium sulfate is not identical to cadmium per its mutagenic effects since it is more toxic, which is evidenced by this chemical's code being H340 (Category 1B) [17][19].

5. Both donor and acceptors belong to the hazard class 2 per their reproductive toxicity (limited positive evidence of effects on human and / or animal reproductive functions, which are not convincing enough to assign the chemical to the hazard class 1) [18, 19]. In the GHS, cadmium and cadmium oxide have

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[15] Ob utverzhdenii perechnya zagryaznyayushchikh veshchestv, v otnoshenii kotorykh primenyayutsya mery gosudarstvennogo regulirovaniya v oblasti okhrany okruzhayushchei sredy i priznanii utrativshimi silu nekotorykh Postanovlenii Pravitel'stva RF: Rasporyazhenie Pravitel'stva RF № 2909-r ot 20.10.2023 g. (s izmeneniyami na 5 iyunya 2024 goda) [On Approval of the list of chemicals that are subject to state regulation in environmental protection and on declaring invalidity of some RF Government Orders: The RF Government Order No. 2909-r issued on October 20, 2023 (last edited as of June 5, 2024)]. *KonsultantPlus*. Available at: https://www.consultant.ru/document/cons_doc_LAW_460257/ (October 11, 2023) (in Russian); Perechni prioritetnykh zagryaznyayushchikh veshchestv dlya territorii g. Bratsk, g. Nizhnii Tagil, g. Cherepovets: pis'mo Rospotrebnadzora ot 23.11.2020 № 02/23971-2020-23[The lists of priority pollutants for Bratsk, Nizhniy Tagil, and Cherepovets: the Letter by Rospotrebnadzor dated November 23, 2020 No. 02/23971-2020-23] (in Russian); Perechni prioritetnykh zagryaznyayushchikh veshchestv dlya territorii eksperimenta (g. Noril'sk g. Lipetsk, g. Chelyabinsk, g. Krasnoyarsk): pis'mo Rospotrebnadzora ot 11.12.2020 № 02/25401-2020-23 [The lists of priority pollutants for the experiment territories (Norilsk, Lipetsk, Chelyabinsk, and Krasnoyarsk): the Letter by Rospotrebnadzor dated December 11, 2020 No. 02/25401-2020-23] (in Russian); Perechni prioritetnykh zagryaznyayushchikh veshchestv dlya territorii eksperimenta (g. Magnitogorsk, g. Omsk, g. Chita, g. Mednogorsk, g. Novokuznetsk): pis'mo Rospotrebnadzora ot 21.12.2020 № 02/26092-2020-23 [The lists of priority pollutants for the experiment territories (Magnitogorsk, Omsk, Chita, Mednogorsk, and Novokuznetsk): the Letter by Rospotrebnadzor dated December 21, 2020 No. 02/26092-2020-23] (in Russian).

[16] Toxicological profile for cadmium. Draft for Public Comment. *U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry*. Atlanta, 2012, 487 p.

[17] Cadmium oxide. *PubChem*. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/14782 (October 20, 2024); Cadmium *PubChem*. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/23973 (October 20, 2024); Cadmium sulfate. *PubChem*. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/24962 (October 20, 2024).

[18] Cadmium oxide. *ECHA: European Chemicals Agency*. Available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/52656 (October 20, 2024); Cadmium. *ECHA: European Chemicals Agency*. Available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/51061 (October 20, 2024); Cadmium sulfate. *ECHA: European Chemicals Agency*. Available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/79772 (October 20, 2024).

[19] Cadmium sulfate. *PubChem*. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/24962 (October 20, 2024)

H361 code (suspected of damaging fertility or the unborn child) + H361fd (suspected of damaging fertility; suspected of damaging the unborn child), Category 2.

Cadmium sulfate is more toxic than cadmium per its reproductive toxicity and is given H360fd code in the GHS (may damage fertility, may damage the unborn child) (Category 1B).

6. Analysis of physiochemical properties established that cadmium, cadmium oxide and cadmium sulfate are in a solid aggregate state under standard conditions (25 °C and 1 atmosphere), have low molecular weight (cadmium = 112.41 g/mole, cadmium oxide = 128.41 g/mole, cadmium sulfate = 208.47 g/mole), are not soluble in lipids, are stable under normal conditions[20].

Cadmium and cadmium oxide are not soluble in water whereas cadmium sulfate has high water solubility. These differences in solubility between cadmium and cadmium sulfate can affect toxicokinetics and toxicodynamics of these chemicals since higher water solubility of cadmium sulfate makes it more available upon introduction into the body. Cadmium sulfate is not identical to cadmium per its physiochemical properties.

The accomplished analysis established cadmium and cadmium oxide to be identical per all the suggested criteria. Consequently, the numeric RfC value established for cadmium can be extrapolated to cadmium oxide and applied in assessing non-carcinogenic health risks upon chronic inhalation exposure. Therefore, RfC of cadmium oxide established by using the suggested extrapolation criteria amounts to $2 \cdot 10^{-5}$ mg/m^3.

It is impossible to extrapolate a reference concentration from cadmium to cadmium sulfate since the latter is more toxic per its mutagenic effects and reproductive toxicity and its physiochemical properties are not identical with the donor.

An RfC was developed for *cadmium oxide* to verify the value obtained by using the suggested extrapolation criteria. LOAEL = 1.8 μg/m^3 for cadmium oxide was taken as a point of departure. This value was established by using prediction models for cadmium levels in ambient air based on an internal dose that led to an elevated creatine level in urine. This level of 0.5 μg/g was established for occupational exposures by the ATSDR based on a study by L. Järup with colleagues[21]. [20, 21]. The total uncertainty factor amounted to 100 (2 is for extrapolation from controlled exposure to real-world conditions, 5 is the intraspecies extrapolation factor that considers a study group, 10 is the factor that considers the point of departure).

A calculated reference concentration of cadmium oxide was:

$$\text{RfC} = 0.0018 / 100 = 0.000018 = \\ = 0.00002 \text{ mg/m}^3$$

The verification results confirmed the RfC concentration of cadmium oxide established by using the suggested extrapolation criteria, which gives solid evidence of their eligibility for solving the outlined tasks.

Therefore, the suggested criteria make it possible to assess whether analyzed chemicals have identical toxicological properties considering specific effects and physiochemical properties. Use of them ensures reliable extrapolation of the existing reference concentrations under chronic inhalation exposure to other compounds. When performing extrapolation, it is advisable to select a donor that is based on the same chemical element as an acceptor.

The suggested extrapolation criteria can be used in creating databases for neural net-

[20] Cadmium oxide. *Cameo Chemicals*. Available at: https://cameochemicals.noaa.gov/chemical/4895 (October 20, 2024); Cadmium. *Cameo Chemicals*. Available at: https://cameochemicals.noaa.gov/chemical/16143 (October 20, 2024); Cadmium sulfate. *Cameo Chemicals*. Available at: https://cameochemicals.noaa.gov/chemical/8376 (October 20, 2024).

[21] Toxicological profile for cadmium. Draft for Public Comment. *U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry*. Atlanta, 2012, 487 p.; Järup L., Elinder C.G. Dose-response relations between urinary cadmium and tubular proteinuria in cadmium-exposed worker. *Am. J. Ind. Med.*, 1994, vol. 26, no. 6, pp. 759–769. DOI: 10.1002/ajim.4700260605; NTP Technical Report on Toxicity Studies of cadmium oxide (CAS No. 1306-19-0). Administered by inhalation to F344/N rats and B6C3F1 mice. *United States Department of Health and Human Services*, 1995, 144 p.

work training and subsequent recognition of chemical images; they are also eligible for digitalizing the process of reference concentration extrapolation.

Conclusion. The study suggests eligible criteria for establishing reference concentrations of chemicals by extrapolating the existing parameters to be used in assessing non-carcinogenic health risks under chronic inhalation exposure. These criteria include identical selective toxicity towards target organs and / or systems under chronic exposure; the same critical organs and systems; identical specific effects (sensitizing and mutagenic effects, reproductive toxicity); similar physiochemical properties.

Use of the suggested extrapolation criteria allowed suggesting RfC of cadmium oxide equal to $2 \cdot 10^{-5}$ mg/m^3; cadmium was employed as a donor for extrapolation. The verification results confirmed that the conventionally substantiated RfC value was consistent with the value obtained by extrapolation.

At the same time, we found that it was impossible to establish RfC of cadmium sulfate by extrapolation from cadmium since the former chemical was more toxic in accordance with the suggested criteria as regards its mutagenic effects and reproductive toxicity. In addition, its physiochemical properties were different from those of cadmium.

The suggested extrapolation criteria can be used in neural network training and subsequent recognition of chemical images; they are also eligible for digitalizing the process of reference concentration extrapolation.

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