UDC 614.7
DOI: 10.21668/health.risk/2023.3.06.eng

Read online

Research article

THE THRESHOLD OF TOXICOLOGICAL CONCERN FOR INSUFFICIENTLY EXPLORED CHEMICALS OCCURRING IN DRINKING WATER DURING TRANSPORTATION

A.V. Alekseeva, O.N. Savostikova

Centre for Strategic Planning and Management of Biomedical Health Risks, 10 Pogodinskaya St., build. 1, Moscow, 119121, Russian Federation

Finding solutions to issues of drinking water safety is a significant component in activities aimed at public health protection. In accordance with sanitary-epidemiological requirements, drinking water, in particular, should be harmless as regards its chemical composition and have favorable organoleptic properties. It is especially vital to identify risk factors for public health associated with drinking water quality. Supplying high-quality drinking water to population is a relevant problem associated, among other things, with use of new materials and reagents. The major challenge posed by their hygienic assessment is a potential growth in human health risks caused by consuming tap drinking water contaminated with migrating organic compounds. Although each of them has been detected in low concentrations, they can cause adverse chronic health outcomes.

The Threshold of Toxicological Concern (TTC) is a powerful tool of risk assessment. It is based on identifying a threshold value of effects produced on human health by chemicals for which no hygienic standards have been developed so far. Below such a threshold, there is very low (95 %) likelihood of a health risk being higher than its acceptable levels. An idea of some exposure levels unable to cause adverse health outcomes is embedded in establishing maximum permissible levels (MPLs) for chemicals with known toxicological profiles. The TTC enlarges this concept by assuming that the minimum value can be identified for many chemicals based on their composition even if there is no comprehensive database on their toxicity. The TTC can be used for evaluating up-to-date materials applied in drinking water supply in order to detect risks for human health caused by consumption of drinking water that had contacts with them. Such risk assessment relies on the results of examining water extracts and involves identifying priority chemicals for their further investigation and control.

Keywords: *water supply, drinking water, hygienic assessment of polymer materials, threshold of toxicological concern, polymers, migration, water-related risk.*

Exposures to environmental factors are considered a strategic social risk in Russia. But quite often they are either neglected or comprehended incorrectly by the society due to absence of adequate and reliable data on them.

Multiple studies have established anthropogenic pollution of drinking water, together with ambient air and soil pollution, to be a substantial factor able to affect human health [1–7]. Ongoing pollution and constant development of analytical methods result in discovering new anthropogenic chemicals in drinking water sources as well as in water that has been treated until it is safe for drinking. Finding solutions to issues of drinking water safety is a significant component in activities aimed at public health protection. In accordance with sanitary-epidemiological requirements, drinking water, in particular, should be harmless as regards its chemical composition and have favorable organoleptic properties. It is especially vital to identify risk factors for public health associated with drinking water quality [1, 7]. At present, supplying high-quality drinking water to population is a relevant problem associated, among other things, with use of new materials and reagents in drinking water supply. Drinking water contains some admixtures represented by a heterogeneous group of anthropogenic compounds (for example, alkylphenols, pharmaceuticals, and microplastics); although each compound is usually identified

Anna V. Alekseeva – Candidate of Medical Sciences, Head of the Hygiene Department (e-mail: AAlekseeva@cspmz.ru; tel.: +7 (495) 540-61-71 (ext. 1661); ORCID: https://orcid.org/0000-0002-0422-8382).

Olga N. Savostikova – Candidate of Medical Sciences, Head of the Department for Physical and Chemical Research Methods and Ecotoxicology (e-mail: OSavostikova@cspmz.ru; tel.: +7 (495) 540-61-71; ORCID: https://orcid.org/0000-0002-7032-1366).

in low concentrations, exposure to such mixtures can cause chronic adverse health outcomes [8–11]. In fact, even if all the components of a mixture occur in quantities, which separately are unable to cause any observed adverse effects, people still might be affected due to chronic low-level exposures able to produce additive effects thereby becoming more toxic [12, 13].

At present, the system for hygienic regulation exists in the Russian Federation. Within the system, the threshold principle covers all the exposure effects and compliance with the hygienic standards (maximum permissible levels or MPL, some others) guarantees absence of any adverse effects on human health. However, more and more chemicals are being identified worldwide, which are not covered by the established hygienic standards (they have no MPL determined for them). The concept that exposure thresholds or safe exposure levels can be identified for certain chemicals is widely used nowadays in routine practices of regulatory authorities in western countries. They rely on it when establishing acceptable daily intakes for chemicals with known chemical structure [14, 15]. The concept proposes that a low level of exposure with a negligible risk can be identified for many chemicals, including those of unknown toxicity, based on knowledge of their chemical structures [16]. Munro with colleagues used a database containing information about 613 chemical compounds explored in sub-chronic and chronic animal studies including certain industrial chemicals, pharmaceuticals, food chemicals, protection chemicals, and consumer chemicals. Later on, new studies were added into the database and now it is employed in software tools such as Toxtree (TT) and OECD Toolbox. The database is used to identify a threshold of acceptable human exposure for three structural classes and can be applied in the absence of specific toxicity data on a substance within one of them. The Threshold of Toxicological Concern (TTC) method was first introduced in the 90ties last century to facilitate assessment of hazards and risks caused by chemicals [17, 18].

The threshold of toxicological concern (TTC) is a risk assessment tool that is based on the principle of determining a human exposure threshold value for all chemicals, which do not have hygienic standards established for them. Below such a threshold, there is a very low probability of an appreciable risk to human health (95 % likelihood that any chemical belonging to a specific class does not produce any adverse effects on human health) [19, 20]. The concept that there are levels of exposure that do not cause adverse effects is inherent in setting acceptable daily intakes (ADIs) for chemicals with known toxicological profiles. The TTC principle extends this concept by proposing that a *de minimis* value can be identified for many chemicals, in the absence of a full toxicity database, based on their chemical structures and the known toxicity of chemicals, which share similar structural characteristics [21]. The TTC method compares information about a chemical dose with a threshold, below which any observed adverse effects are highly unlikely. Some chemical groups are excluded from the TTC approach, namely, heavy metals, compounds with extremely long half-life time, chemicals that have huge interspecies differences in bioaccumulation and are strong genotoxic carcinogens (aflatoxin-like substances, N-nitrosamines, azoxy compounds, steroids and polyhalogenated dibenzo-p-dioxins, polyhalogenated dibenzofurans), and proteins [20–22].

The TTC approach employs Cramer classification of chemicals to assign a chemical into one of three structural classes depending on its structure. Initially, the approach relied on a database [23] that contained results obtained for 613 chemicals in subchronic and chronic animal studies. For each substance, the 5^{th} percentile was calculated from the empirical cumulative distributions of No observed (adverse) effect level (NOAEL) (concentration) values. Subsequent application of an uncertainty factor of 100 accounting for inter- and intraspecies differences and a default adult body weight of 60 kg resulted in TTCs representing exposure levels at which a 95% chance exists that any chemical belonging to the same class does not elicit adverse human health effects. The threshold human exposure levels identified for these three structural classes are 1800, 540 and 90 μg/person per day respectively [24–26] (Table 1).

That is, if a chemical belongs to Class 1, exposure to it in a dose lower than 1800 μg/day does not create any health risks even if there are only limited data on toxicological properties of this chemical. Body weight of an adult person is assumed to equal 60 kg; therefore, the threshold value can also be given as 30 μg/kg of body weight per day.

Exposure thresholds identified for each TTC level are based on evaluations of available data on chemicals toxicity at each level. However, it is generally accepted that those chemicals without any available data on their toxicity can be assigned to a relevant TTC level based on their chemical structure.

Researchers determined the lowest TTC levels to be equal to 0.15 μg/day (0.0025 μg/kg of body weight per day). Any chemical, for which there is information about its toxicity / mutagenic effects, is assigned into this category [24, 27].

Chemicals that are not potential mutagens and / or carcinogens, organic fluorine compounds or carbamates are assigned into one of three structural classes based on Cramer Decision tree[1]. The tree includes 33 questions that employ established ways of metabolic deactivation and activation and data on toxicity. The Decision tree was created in such a way so that chemicals not covered by the TTC approach are excluded at an early stage. Use of the Decision tree ensures the well-structured approach that makes it possible to sequentially apply the TTC method to assess chemical risks. The databases are constantly updated [28, 29] but since they can fail to include certain chemicals, the latter should not be considered as per this principle.

Cramer structural classes were identified in the following way: Cramer class 1 includes substances of simple chemical structure with known metabolic pathways and low potential toxicity. Cramer class 2 includes substances that are intermediate; they possess structures that are less innocuous than those in Class 1 but they do not contain structural features that are suggestive of toxicity like those in Class 3. Cramer class 3 contains substances with chemical structures that permit no strong initial impression of safety and may even suggest a significant toxicity. Therefore, assigning a chemical into one of these three Cramer classes is an important step in maintaining risk assessment reliability.

Several software platforms were based on the obtained information. They allow achieving minimal subjectivity and sequentially applying Cramer Decision tree for any chemical that should be assessed. The Decision tree was employed in software tools including Toxtree (TT) [30] and OECD Toolbox (TB) [31]. There were certain inconsistencies between TT and TB. In total, 165 chemicals (16 %) turned out to have different results in these two programs. Crucial control points are being revealed in the Decision tree; there are ongoing discussions as regards strategies and recommendations on how to identify a Cramer class for various chemicals [31, 32].

Table 1

TTC values within classification of chemicals

Classification	TTC, μg/day	TTC, μg/kg of body weight per day
Potential mutagens and /or carcinogens	0.15	0.0025
Organic fluorine compounds and carbamates with anti-cholinesterase activity	18	0.3
Cramer class 3	90	1.5
Cramer class 2	540	9.0
Cramer class 1	1800	30

[1] TOXNET Databases. Available at: https://toxnet.nlm.nih.gov/cpdb/ (February 15, 2023).

Toxtree is a user-friendly open source application. Its development was ordered by the European Chemical Agency of the Joint Research Center of the European Commission exclusively for determining a Cramer class of a chemical substance and estimating its relative toxic hazard. Later Toxtree versions included some additional options such as mucosa irritation, BfR / SICRET and Verhaar [33].

OECD QSAR Toolbox was ordered by the Organization for Economic Cooperation and Development (OECD). Cramer classification was included into it as a module. Although both these systems were developed based on the same Cramer Decision tree, each rule might be interpreted differently in each of them[2].

Some foreign organizations such as Health Canada[3], Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS)[4], and Food Standards Australia New Zealand (FSANZ) [34] consider TTC a powerful tool for identifying priorities and performing risk-based screening. The Toxic Substances Control Act (TSCA) obliges the US Environmental Protection Agency (US EPA) to determine priority of chemicals in trade based on risks posed by them and then assess health risks caused by high-priority substances. Such assessments combine data obtained by toxicological studies and information about exposures [22]. The TTC approach can be used as a filter to determine the necessity of a toxicological study and its order of priority and avoid conducting such studies if an exposure level of a chemical in humans is far below the concentration needed for it to have any biological effect. Such a situation is labeled as 'negligible exposure' in the REACH legislation. The studies [19, 35] highlight a likely decrease in animal studies as a result of active TTC use.

The TTC approach is applied to evaluate safety of cosmetic ingredients and ingredients in personal and household products [36–38]. The European Food Safety Agency relies on TTC to evaluate levels of pesticides in groundwater [39]. Independent non-food Scientific Committees (SCCP, SCHER, and SCHENIHR) assessed potential TTC use and concluded that the approach was scientifically eligible for assessing non-carcinogenic risks for human health caused by exposure to chemicals in trace quantities [40]. The TTC approach is also used to assess food products safety (flavoring agents); for mixtures of substances; to identify internal exposure to chemicals (iTTC) [41]; for plant extracts (Botanical-TO); to identify the ecological threshold of toxicological concern (eco-TTC) [42–44].

In the Netherlands a clear and consistent approach called 'Drinking Water Quality for the 21st century (Q21)' has been developed within the joint research program of the drinking water companies. Target values for anthropogenic drinking water contaminants were derived by using the Threshold of Toxicological Concern (TTC) approach [45]. The target values for individual genotoxic and steroid endocrine chemicals were set at 0.01 μg/l. For all other organic chemicals the target values were set at 0.1 μg/l. The target value for the total sum of genotoxic chemicals, the total sum of steroid hormones and the total sum of all other organic compounds were set at 0.01, 0.01 and 1.0 μg/l, respectively.

The studies [46, 47] set the following chemical levels for drinking water supply: 37 μg/l for Cramer class 1 substances and 4 μg/l for Cramer class 3 substances; for Cramer class 3 substances with reproductive toxicity, 3 μg/l. The authors believe it is essential to assess toxicological risks posed by pollutants in drinking water sources since it helps identify potential health risks and determine priority of chemicals for further investigation and monitoring. Calculations performed in the studies [45–47] either rely on a person consuming 2 liters of water per day, or consider 10 % admissible daily contribution made by water for substances with threshold effects, or non-threshold lifetime risk of cancer reaching $10^{(-6)}$.

[2] The OECD QSAR Toolbox. Available at: https://www.oecd.org/chemicalsafety/oecd-qsar-toolbox.htm (March 17, 2023).

[3] Health Canada. *Government of Canada*. Available at: https://www.canada.ca/en/health-canada.html (March 18, 2023).

[4] Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Available at: https://www.nicnas.gov.au/ (March 18, 2023).

Therefore, **the aim of this study** was to test whether it was possible to apply the TTC approach to evaluate materials used in drinking water supply. The task was to reveal likely risks for public health caused by consumption of drinking water that had contacts with a polyethylene coated woven hose used within reconstruction of drinking water pipelines. To do that, we evaluated the results yielded by examining water extracts.

Materials and methods. In this study, we examined a polyethylene coated woven hose designed for reconstruction of drinking water pipelines, thermal water supply, communal and industrial sewage networks. Its use was examined by analyzing water extracts derived from samples under aggravated conditions.

Ready samples were represented by white hose cuts with a smooth inner polyethylene coated surface and an outer surface made of a synthetic woven material. The samples were evaluated considering the Unified Requirements[5]; we also examined some indicators that were not mandatory within assessment of polymer materials used in drinking water supply.

Prior to any tests, the samples were prepared in accordance with the Methodical Guidelines MU 2.1.4.2898-11 Sanitary-Epidemiological Examinations (Tests) of Materials, Reagents, and Equipment used for Water Treatment[6]. The ratio of a surface of an examined material and a contacting water volume was 1 cm^2 per 1 cm^3. Distilled water was used as initial one to prepare water extracts. The extracts were derived under +20 °C and +37 °C. The aforementioned water types were used as controls to ensure adequacy of hygienic assessment. Samples of test (water extracts) and control water were examined to identify and quantify low volatile organic compounds on the 5th and 7th day of the experiment by using chromato-mass-spectrometry.

Results and discussion. Our analysis of a 5-day water extract from a polyethylene coated woven hose identified 22 organic compounds under 37 °C and 15 organic compounds under 20 °C. Most compounds were identified in low concentrations; maximum permissible levels in water were not established for some of them. The identified compounds mostly belonged to oxygen-containing ones; it is noteworthy, that we detected phenols and aldehydes, ketones, organic acids, complex ethers, and phthalates. Moreover, we identified nitrogen- and fluorine-containing compounds used in chemical industry, such as benzotiazol in a level equal to 0.102 mg/l. According to chromato-mass-spectrometry data, the following substances were identified in the highest concentrations, apart from benzotiazol: tetrahydrofurfuryl ether (0.437 mg/l under 37 °C and 0.088 mg/l under 20 °C) and di-tert-butyl-oxaspiro-decadiendion (0.345–0.136 mg/l), both substances not standardized in drinking water.

Our analysis of a 7-day water extract identified 15 organic compounds under 37 °C and 12 organic compounds under 20 °C. The identified substances were in low concentrations and maximum permissible levels in drinking water were not established for most of them. According to chromato-mass-spectrometry data, the following substances were identified in the highest concentrations: pentadecanols, hexadecanols, 2,4 di-tert-butylphenol, di-tert-butyl-oxaspiro-decadiendion, di-tert-butyl benzochinon; all these substances were not standardized in drinking water.

Therefore, chromato-mas-spectrometry identified a wide range of chemicals in water extracts, most of them though in low levels; still,

[5] Edinye sanitarno-epidemiologicheskie i gigienicheskie trebovaniya k produktsii (tovaram), podlezhashchei sanitarno-epidemiologicheskomu nadzoru (kontrolyu), utv. Resheniem Komissii Tamozhennogo soyuza ot 28 maya 2010 goda № 299 [The Unified Sanitary-Epidemiological and Hygienic Requirements to products (goods) subject to sanitary-epidemiological surveillance (control), approved by the Decision of the Customs Union Commission on May 28, 2010 No. 299]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902249109 (April 11, 2023) (in Russian).

[6] MU 2.1.4.2898-11. Sanitarno-epidemiologicheskie issledovaniya (ispytaniya) materialov, reagentov i oborudovaniya, ispol'zuemykh dlya vodoochistki i vodopodgotovki: metodicheskie ukazaniya, utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii i vvedeny v deistvie 12.07.2011 [Sanitary-Epidemiological Examinations (Tests) of Materials, Reagents, and Equipment used for Water Treatment: Methodical Guidelines, approved by the Head of the Federal Service for Surveillance over Consumer Rights Protection, the RF Chief Sanitary Inspector; came into force on July 12, 2011]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200089967 (April 11, 2023) (in Russian).

it is noteworthy that maximum permissible levels in drinking water are not established for most of them. Our tests also showed that intensity of migration is influenced by many factors; in our case, the experiment involved different time of contacts with water and different temperatures.

The next task was to determine possible effects on health produced by the chemicals identified in water extracts from a polyethylene coated woven hose designed for reconstruction of drinking water pipelines. To do that, we determined Cramer classes of the identified chemicals without any hygienic standards established for their level in drinking water using Toxtree and OECD Toolbox software (Table 2).

Table 2

Cramer's classes of the chemicals identified in the analyzed water extracts determined by using Toxtree and OECD Toolbox

No.	Chemical	CAS	Cramer class, Toxtree	Cramer class, Toolbox
1.	Tetradecene	1120-36-1	Low (Class 1)	Low (Class 1)
2.	Trimethyl-1-dodecanol	6750-34-1	No data available on the chemical	No data available on the chemical
3.	Phenoxyethanol	122-99-6	Intermediate (Class 2)	Intermediate (Class 2)
4.	2,4- di-tert-butylphenol	96-76-4	Low (Class 1)	Low (Class 1)
5.	Cyclopentanone	120-92-3	Intermediate (Class 2)	Intermediate (Class 2)
6.	2-cyclopentyl cyclopentanone	4884-24-6	No data available on the chemical	Intermediate (Class 2)
7.	2-cyclopentiliden-cyclopentanone	825-25-2	No data available on the chemical	Intermediate (Class 2)
8.	Tributyl acetylcitrate	77-90-7	Extended Cramer rules with Low (Class 1). Updated Cramer Decision tree High (Class 3)	Low (Class 1)
9.	Methyl ether of 3-oxo-2-pentylcyclopentane-acetic acid	24851-98-7	Intermediate (Class 2) Updated Cramer Decision tree Low (Class 1)	High (Class 3)
10.	Diisobutyl phthalate	84-69-5	Low (Class 1) skin-irritating	Low (Class 1)
11.	Oxaspirodecadiendion-di-tert-butyl	82304-66-3	No data available on the chemical	No data available on the chemical
12.	2,5-di-tert-butyl-1,4-benzochinon	2460-77-7	No data available on the chemical	Intermediate (Class 2)
13.	4-methyl-8-aminochinoline	62748-01-0	No data available on the chemical	High (Class 3)
14.	Tetramethylindol	27505-79-9	No data available on the chemical	No data available on the chemical
15.	Nitrosomethane	865-40-7	No data available on the chemical	High (Class 3)
16.	(3 5-dimethyl-1-piperidinyl) (4-mopholil)methanone	349118-92-9	No data available on the chemical	No data available on the chemical
17.	Benzotiazol	95-16-9	High (Class 3) Updated Cramer Decision tree Intermediate (Class 2)	High (Class 3)
18.	Tetradecane	629-59-4	Low (Class 1)	Low (Class 1)
19.	5-tridecene	25524-42-9	No data available on the chemical	No data available on the chemical
20.	2,4-di-tert-butylphenol	96-76-4	Low (Class 1)	Low (Class 1)
21.	3,5-di-tert-butyl-4-hydroxybenzaldehyde	1620-98-0	No data available on the chemical	High (Class 3)
22.	Hexadecane acid	57-10-3	Low (Class 1)	Low (Class 1)
23.	Butoxyethoxy ethyl acetate	124-17-4	Low (Class 1)	Low (Class 1)
24.	Propylene carbonate	108-32-7	High (Class 3) Revised Cramer Decision tree Low (Class 1)	High (Class 3)
25.	Complex ether of propionic acid	74381-40-1	No data available on the chemical	No data available on the chemical
26.	1 6-dioxacyclododecane-7 12-dione	777-95-7	No data available on the chemical	Low (Class 1)

We did not find any information about 6 substances that would allow assigning them into one of the aforementioned classes. These chemicals are not included into the IARC classification of carcinogens either.

Tables 3 and 4 provide results of comparisons between the levels of the chemicals identified in the analyzed water extracts and the threshold of toxicological concern, below which there is a very low probability of an appreciable risk to human health. The detected concentrations (mg/l) were recalculated into dose values (µg/day) basing on the assumption that a person on average consumes 3 liters of water per day (as established in the Methodical Guidelines MU 2.1.5.720-98 Substantiation of Hygienic Standards for Chemicals in Drinking and Household Water[7]). The concentrations of the identified chemicals were taken from the series of tests conducted under 37 °C as the most aggravated conditions. In a situation, when use of two different software packages, Toxtree and OECD Toolbox, yielded different results, a substance was assigned into a higher Cramer class out of two.

Table 3

Indicators that describe quality of water (water extracts) in a statics experiment in comparison with the threshold of toxicological concern for these substances (distilled water; in a contact with the analyzed material for 5 days; water temperature is 37 ± 0.5 °C)

No.	Chemical	CAS	Level, mg/l	Cramer class	TTC, µg/day, not higher than	Intake with drinking water, µg/day
1	Tetradecene	1120-36-1	0.005	Low (Class 1)	1800	15
2	Trimethyl-1-dodecanol	6750-34-1	0.008	No data available on the chemical		
3	Phenoxyethanol	122-99-6	0.023	Intermediate (Class 2)	540	69
4	2,4- di-tert-butylphenol	96-76-4	0.014	Low (Class 1)	1800	42
5	Cyclopentanone	120-92-3	0.007	Intermediate (Class 2)	540	21
6	2-cyclopentyl cyclopentanone	4884-24-6	0.092	Intermediate (Class 2)	540	276
7	2-cyclopentiliden-cyclopentanone	825-25-2	0.046	Intermediate (Class 2)	540	138
8	Tributyl acetylcitrate	77-90-7	0.012	High (Class 3)	90	36
9	Methyl ether of 3-oxo-2-pentylcyclopentane-acetic acid	24851-98-7	0.015	High (Class 3)	90	45
10	Diisobutyl phthalate	84-69-5	0.051	Low (Class 1)	1800	153
11	Oxaspirodecadiendion-di-tert-butyl	82304-66-3	0.345	No data available on the chemical		
12	2,5-di-tert-butyl-1,4-benzochinon	2460-77-7	0.014	Intermediate (Class 2)	540	42
13	4-methyl-8-aminochinoline	62748-01-0	0.032	High (Class 3)	90	96
14	Tetramethylindol	27505-79-9	0.017	No data available on the chemical		
15	Nitrosomethane	865-40-7	0.01	High (Class 3)	90	30
16	(3 5-dimethyl-1-piperidinyl) (4-mopholil)methanone	349118-92-9	0.091	No data available on the chemical		

[7] MU 2.1.5.720-98. Obosnovanie gigienicheskikh normativov khimicheskikh veshchestv v vode vodnykh ob"ektov khozyaistvenno-pit'evogo i kul'turno-bytovogo vodopol'zovaniya, utv. i vved. v deistvie Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 15 oktyabrya 1998 goda [Substantiation of Hygienic Standards for Chemicals in Drinking and Household Water, approved and put in force by the RF Chief Sanitary Inspector on October 15, 1998]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200006903 (April 12, 2023) (in Russian).

Table 4

Indicators that describe quality of water (water extracts) in a statics experiment in comparison with the threshold of toxicological concern for these substances (distilled water; in a contact with the analyzed material for 7 days; water temperature is 37 ± 0.5 °C)

No.	Chemical	CAS	Level, mg/l	Cramer class	TTC, µg/day, not higher than	Intake with drinking water, µg/day
1	Tetradecene	629-59-4	0.015	Low (Class 1)	1800	45
2	5-tridecene	25524-42-9	0.028	No data available on the chemical		
3	Pentadecanols (3 isomer compounds)	629-76-5	0.050	Low (Class 1)	1800	150
4	Hexadecanol (2 isomer compounds)	36653-82-4	0.049	Low (Class 1)	1800	147
5	2,4- di-tert-butylphenol	96-76-4	0.034	Low (Class 1)	1800	102
6	3,5-di-tert-butyl-4-hydroxybenzaldehyde	1620-98-0	0.008	High (Class 3)	90	24
7	6,8-dioxapentadecane	-	0.018	No data available on the chemical		
8	Hexadecane acid	57-10-3	0.043	Low (Class 1)	1800	129
9	Butoxyethoxy ethyl acetate	124-17-4	0.012	High (Class 3)	90	36
11	Propylene carbonate	108-32-7	0.037	High (Class 3)	90	111
12	Complex ether of propionic acid	74381-40-1	0.033	No data available on the chemical	-	-
13	Methyl ether of 3-oxo-2-pentylcyclopentane-acetic acid	24851-98-7	0.032	High (Class 3)	90	96
14	Oxaspirodecadiendion-di-tert-butyl	82304-66-3	0.050	No data available on the chemical	-	-
15	2,5-di-tert-butyl-1,4-benzochinon	2460-77-7	0.037	Intermediate (Class 2)	540	111
16	1 6-dioxacyclododecane-7 12-dione	777-95-7	0.005	Low (Class 1)	1800	15
17	Hexadecane acid	57-10-3	0.014	Low (Class 1)	1800	42

Our analyses of the test data revealed that levels of some chemicals in water extracts, including 4-methyl-8-aminochinoline (in tests on 5-day extracts), propylene carbonate, and methyl ether of 3-oxo-2-pentylcyclopentane-acetic acid (in tests on 7-daty extracts) were higher than the threshold of toxicological concern after the identified concentrations were recalculated into dose values. These findings are evidence of likely health risks. Chemical concentrations higher than TTC indicate the necessity to search for new data and to conduct toxicological experiments to collect an evidence base proving their safety. Therefore, our study findings do not allow absolute certainty in confirming it is safe to use the examined polyethylene coated woven hose in drinking water supply.

Conclusion. The major challenge in hygienic assessment of up-to-date materials is a potential growth in health risks associated with drinking tap water, which is polluted with migrating organic compounds [48, 49]. It is impossible to achieve complete absence of any pollutants in supplied drinking water since modern analytical procedures allow identifying even very low concentrations; it hardly seems possible to prevent migration completely either given the contemporary levels of industrial development. New plasticizers are being developed at the moment; there is ongoing search for compounds able to provide good mechanical properties of a material but with limited or even zero migration, resistance to extraction, and low volatility.

At present, the TTC use to evaluate materials applied in drinking water supply allows identifying possible health risks for human health caused by consuming drinking water that had contacts, among other things, with polymers. Such evaluations are based on analyzing results obtained by examining water extracts.

The issue of calculating a dose of a chemical intake with water remains open for discussion. In this study, we calculated intake doses relying on likely consumption equal to 3 liters of water per day in accordance with the Methodical Guidelines MU 2.1.5.720-98 Substantiation of Hygienic Standards for Chemicals in Drinking and Household Water[7]. Therefore, the upper limit of TTC-based levels in drinking water is 30 µg/liter for chemicals assigned into the high Class 3. Given possible effects on the reproductive function and likely long-term health outcomes, the threshold for drinking water should be set at 0.03 µg/liter. The Guide Human Health Risk Assessment from Environmental Chemicals (R 2.1.10.1920-04[8]) calculates health risks relying on daily water consumption of 2 liters, therefore, the upper limit of chemical levels will grow.

In this study, we conducted hygienic assessment of a polyethylene coated woven hose; as a result, it is not deemed to comply with the EAEU Unified Sanitary-Epidemiological and Hygienic Requirements to Goods Subject to Sanitary-Epidemiological Surveillance (Control). It is not safe to use it in drinking water pipelines due to migration of organic compounds without any hygienic standards established for their levels in drinking water as well as due to elevated turbidity and inadequate color of the examined water extracts (the latter indicators were not analyzed in this study).

Basic uncertainties in the present study are as follows. First, extracts from polymer pipes can be considered similar to drinking water only conditionally. Second, we relied on using standard exposure factors for a general population without considering the most sensitive population groups. Third, we used maximum levels of the analyzed chemicals in our calculations and this might result in risk overestimation. On the other hand, we did not consider summated exposure to all the analyzed chemicals in this study; due to this fact, a health risk caused by combined exposure to all the analyzed chemicals is considered negligible.

Therefore, the TTC approach is a quite simple practical tool that allows assessing health risks caused by exposure to unregulated and understudied chemicals compounds with unknown toxicological properties occurring in drinking water. It also draws attention to chemicals with expected high toxicity and allows more precise evaluation of materials, reagents and equipment for water treatment, which considers likely health risks caused by their use.

Funding. The study was conducted within the R&D State Task, the Registration No. 123040500002-3, at the Centre for Strategic Planning and Management of Biomedical Health Risks of the Federal Medical-Biological Agency of the RF.

Competing interests. The authors declare no competing interests.

[8] The Guide 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals, approved and put into force by G.G. Onishchenko, the First deputy to the RF Minister of Health, 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 (April 12, 2023) (in Russian).

References

1. Rakhmanin Yu.A. Pollution of the water ecosystems and the problems of the drinking water quality. *Vestnik RAEN*, 2022, vol. 22, no. 4, pp. 38–44. DOI: 10.52531/1682-1696-2022-22-4-38-44 (in Russian).
2. Rakhmanin Yu.A. Updating the problems of human ecology and environmental health and the ways of solving them. *Gigiena i sanitariya*, 2012, vol. 91, no. 5, pp. 4–8 (in Russian).
3. Rakhmanin Yu.A., Mikhailova R.I., Alekseeva A.V. Butilirovannye pit'evye vody kak faktor povysheniya kachestva zhizni [Bottled drinking water as a factor in improving the quality of life]. *Kontrol' kachestva produktsii*, 2015, no. 9. pp. 14–19 (in Russian).
4. Rakhmanin Yu.A., Levanchuk A.V., Kopytenkova O.I., Frolova N.M., Sazonova A.M. Determination of additional health risk due to pollutants in ambient air during operation of road-vehicles complex. *Gigiena i sanitariya*, 2018, vol. 97, no. 12, pp. 1171–1178. DOI: 10.18821/0016-9900-2018-97-12-1171-1178 (in Russian).
5. Kuzmin S.V., Dodina N.S., Shashina T.A., Kislitsin V.A., Pinigin M.A., Budarina O.V. The impact of atmospheric pollution on public health: diagnosis, assessment, and prevention. *Gigiena i sanitariya*, 2022, vol. 101, no. 10, pp. 1145–1150. DOI: 10.47470/0016-9900-2022-101-10-1145-1150 (in Russian).
6. Rakhmanin Yu.A., Ivanov S.I., Novikov S.M., Revazova Yu.A., Rusakov N.V. Topical problems of the comprehensive hygienic characterization of urban environmental factors and their influence on the population's health. *Gigiena i sanitariya*, 2007, no. 5, pp. 5–7 (in Russian).
7. Rakhmanin Yu.A., Onishchenko G.G. Hygienic assessment of drinking water supply of the population of the Russian Federation: problems and the way their rational decision. *Gigiena i sanitariya*, 2022, vol. 101, no. 10, pp. 1158–1166. DOI: 10.47470/0016-9900-2022-101-10-1158-1166 (in Russian).
8. Kurwadkar S., Dane J., Kanel S.R., Nadagouda M.N., Cawdrey R.W., Ambade B., Struckhoff G.C., Wilkin R. Per- and polyfluoroalkyl substances in water and wastewater: A critical review of their global occurrence and distribution. *Sci. Total Environ.*, 2022, vol. 809, pp. 151003. DOI: 10.1016/j.scitotenv.2021.151003
9. Xue J., Samaei S.H., Chen J., Doucet A., Ng K.T.W. What have we known so far about microplastics in drinking water treatment? A timely review. *Front. Environ. Sci. Eng.*, 2022, vol. 16, no. 5, pp. 58. DOI: 10.1007/s11783-021-1492-5
10. Acarer S. Abundance and characteristics of microplastics in drinking water treatment plants, distribution systems, water from refill kiosks, tap waters and bottled waters. *Sci. Total Environ.*, 2023, vol. 884, pp. 163866. DOI: 10.1016/j.scitotenv.2023.163866
11. Wee S.Y., Aris A.Z., Yusoff F.M., Praveena S.M. Occurrence of multiclass endocrine disrupting compounds in a drinking water supply system and associated risks. *Sci. Rep.*, 2020, vol. 10, no. 1, pp. 17755. DOI: 10.1038/s41598-020-74061-5
12. de Aquino S.F., Brandt E.M.F., Bottrel S.E.C., Gomes F.B.R., de Queiroz Silva S. Occurrence of Pharmaceuticals and Endocrine Disrupting Compounds in Brazilian Water and the Risks They May Represent to Human Health. *Int. J. Environ. Res. Public Health*, 2021, vol. 18, no. 22, pp. 11765. DOI: 10.3390/ijerph182211765
13. Lazofsky A., Buckley B. Recent Trends in Multiclass Analysis of Emerging Endocrine Disrupting Contaminants (EDCs) in Drinking Water. *Molecules*, 2022, vol. 27, no. 24, pp. 8835. DOI: 10.3390/molecules27248835
14. Maertens A., Golden E., Luechtefeld T.H., Hoffmann S., Tsaioun K., Hartung T. Probabilistic risk assessment – the keystone for the future of toxicology. *ALTEX*, 2022, vol. 39, no. 1, pp. 3–29. DOI: 10.14573/altex.2201081
15. Patlewicz G., Wambaugh J.F., Felter S.P., Simon T.W., Becker R.A. Utilizing Threshold of Toxicological Concern (TTC) with High Throughput Exposure Predictions (HTE) as a Risk-Based Prioritization Approach for thousands of chemicals. *Comput. Toxicol.*, 2018, vol. 7, pp. 58–67. DOI: 10.1016/j.comtox.2018.07.002

16. Kroes R., Kleiner J., Renwick A. The threshold of toxicological concern concept in risk assessment. *Toxicol. Sci.*, 2005, vol. 86, no. 2, pp. 226–230. DOI: 10.1093/toxsci/kfi169

17. Munro I.C. Safety assessment procedures for indirect food additives: an overview. Report of a workshop. *Regul. Toxicol. Pharmacol.*, 1990, vol. 12, no. 1, pp. 2–12. DOI: 10.1016/s0273-2300(05)80042-x

18. Munro I.C., Ford R.A., Kennepohl E., Sprenger J.G. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. *Food Chem. Toxicol.*, 1996, vol. 34, no. 9, pp. 829–867. DOI: 10.1016/s0278-6915(96)00049-x

19. Hartung T. Thresholds of Toxicological Concern – Setting a threshold for testing below which there is little concern. *ALTEX*, 2017, vol. 34, no. 3, pp. 331–351. DOI: 10.14573/altex.1707011

20. Kroes R., Renwick A.G., Cheeseman M., Kleiner J., Mangelsdorf I., Piersma A., Schilter B., Schlatter J. [et al.]. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chem. Toxicol.*, 2004, vol. 42, no. 1, pp. 65–83. DOI: 10.1016/j.fct.2003.08.006

21. US EPA Strategic Plan to Promote the Development and Implementation of Alternative Test Methods. *Regulations.gov*. Available at: https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPPT-2017-0559-0584&contentType=pdf (March 03, 2023).

22. Reviewing New Chemicals under the Toxic Substances Control Act (TSCA). Statistics for the New Chemicals Review Program under TSCA. *US EPA*. Available at: https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/statistics-new-chemicals-review (March 05, 2023).

23. Cramer G.M., Ford R.A., Hall R.L. Estimation of toxic hazard – a decision tree approach. *Food Cosmet. Toxicol.*, 1978, vol. 16, no. 3, pp. 255–276. DOI: 10.1016/s0015-6264(76)80522-6

24. Nelms M.D., Patlewicz G. Derivation of New Threshold of Toxicological Concern Values for Exposure via Inhalation for Environmentally-Relevant Chemicals. *Front. Toxicol.*, 2020, vol. 2, pp. 580347. DOI: 10.3389/ftox.2020.580347

25. Munro I.C., Renwick A.G., Danielewska-Nikiel B. The Threshold of Toxicological Concern (TTC) in risk assessment. *Toxicol. Lett.*, 2008, vol. 180, no. 2, pp. 151–156. DOI: 10.1016/j.toxlet.2008.05.006

26. EFSA Scientific Committee. Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC). *EFSA Journal*, 2012, vol. 10, no. 7, pp. 2750. DOI: 10.2903/j.efsa.2012.2750

27. Snodin D.J., McCrossen S.D. Mutagenic impurities in pharmaceuticals: a critique of the derivation of the cancer TTC (Threshold of Toxicological Concern) and recommendations for structural-class-based limits. *Regul. Toxicol. Pharmacol.*, 2013, vol. 67, no. 2, pp. 299–316. DOI: 10.1016/j.yrtph.2013.08.014

28. Patel A., Joshi K., Rose J., Laufersweiler M., Felter S.P., Api A.M. Bolstering the existing database supporting the non-cancer Threshold of Toxicological Concern values with toxicity data on fragrance-related materials. *Regul. Toxicol. Pharmacol.*, 2020, vol. 116, pp. 104718. DOI: 10.1016/j.yrtph.2020.104718

29. European Food Safety Authority and World Health Organization. Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree. *EFSA Supporting Publications*, 2016, vol. 13, no. 3, pp. 1006E. DOI: 10.2903/sp.efsa.2016.EN-1006

30. Patlewicz G., Jeliazkova N., Safford R.J., Worth A.P., Aleksiev B. An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. *SAR QSAR Environ. Res.*, 2008, vol. 19, no. 5–6, pp. 495–524. DOI: 10.1080/10629360802083871

31. Bhatia S., Schultz T., Roberts D., Shen J., Kromidas L., Api A.M. Comparison of Cramer classification between Toxtree, the OECD QSAR Toolbox and expert judgment. *Regul. Toxicol. Pharmacol.*, 2015, vol. 71, no. 1, pp. 52–62. DOI: 10.1016/j.yrtph.2014.11.005

32. Nelms M.D., Pradeep P., Patlewicz G. Evaluating potential refinements to existing Threshold of Toxicological Concern (TTC) values for environmentally-relevant compounds. *Regul. Toxicol. Pharmacol.*, 2019, vol. 109, pp. 104505. DOI: 10.1016/j.yrtph.2019.104505

33. Lapenna S., Worth A. Analysis of the Cramer classification scheme for oral systemic toxicity – implications for its implementation in Toxtree. *JRC Scientific and Technical Report*. Luxembourg, Publications Office of the European Union, 2011, 39 p. DOI: 10.2788/39716

34. Risk profile – Proposal P1034. Chemical Migration from Packaging into Food. *EFSA, WHO*, 2016. Available at: http://www.foodstandards.gov.au/code/proposals/Documents/P1034%20Packaging%201CFS%20SD3%20Risk%20Profile%20Mar2016.pdf (March 17, 2023).

35. Middleton A.M., Reynolds J., Cable S., Baltazar M.T., Li H., Bevan S., Carmichael P.L., Dent M.P. [et al.]. Are Non-animal Systemic Safety Assessments Protective? A Toolbox and Workflow. *Toxicol. Sci.*, 2022, vol. 189, no. 1, pp. 124–147. DOI: 10.1093/toxsci/kfac068

36. Blackburn K., Stickney J.A., Carlson-Lynch H.L., McGinnis P.M., Chappell L., Felter S.P. Application of the threshold of toxicological concern approach to ingredients in personal and household care products. *Regul. Toxicol. Pharmacol.*, 2005, vol. 43, no. 3, pp. 249–259. DOI: 10.1016/j.yrtph.2005.08.007

37. Yang C., Barlow S.M., Muldoon Jacobs K.L., Vitcheva V., Boobis A.R., Felter S.P., Arvidson K.B., Keller D. [et al.]. Thresholds of Toxicological Concern for cosmetics-related substances: New database, thresholds, and enrichment of chemical space. *Food Chem. Toxicol.*, 2017, vol. 109, pt 1, pp. 170–193. DOI: 10.1016/j.fct.2017.08.043

38. Kroes R., Renwick A.G., Feron V., Galli C.L., Gibney M., Greim H., Guy R.H., Lhuguenot J.C., van de Sandt J.J. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.*, 2007, vol. 45, no. 12, pp. 2533–2562. DOI: 10.1016/j.fct.2007.06.021

39. Terry C., Rasoulpour R.J., Knowles S., Billington R. Utilizing relative potency factors (RPF) and threshold of toxicological concern (TTC) concepts to assess hazard and human risk assessment profiles of environmental metabolites: a case study. *Regul. Toxicol. Pharmacol.*, 2015, vol. 71, no. 2, pp. 301–317. DOI: 10.1016/j.yrtph.2014.12.010

40. Autrup H., Calow P., Dekant W., Greim H., Wojciech H., Janssen C., Jansson B., Komulainen H. [et al.]. SCCP/SCHER/SCENIHR preliminary report on: the Use of the Threshold of Toxicological Concern (TTC) Approach for the Safety Assessment of Chemical Substances. *Scientific Committee on Health and Environmental Risks*, 2008.

41. Ellison C.A., Blackburn K.L., Carmichael P.L., Clewell H.J. 3rd, Cronin M.T.D., Desprez B., Escher S.E., Ferguson S.S. [et al.]. Challenges in working towards an internal threshold of toxicological concern (iTTC) for use in the safety assessment of cosmetics: Discussions from the Cosmetics Europe iTTC Working Group workshop. *Regul. Toxicol. Pharmacol.*, 2019, vol. 103, pp. 63–72. DOI: 10.1016/j.yrtph.2019.01.016

42. Plugge H., Das N., Kostal J. Toward a Universal Acute Fish Threshold of Toxicological Concern. *Environ. Toxicol. Chem.*, 2021, vol. 40, no. 6, pp. 1740–1749. DOI: 10.1002/etc.4991

43. Rizzi C., Villa S., Cuzzeri A.S., Finizio A. Use of the Species Sensitivity Distribution Approach to Derive Ecological Threshold of Toxicological Concern (eco-TTC) for Pesticides. *Int. J. Environ. Res. Public Health*, 2021, vol. 18, no. 22, pp. 12078. DOI: 10.3390/ijerph182212078

44. Baderna D., Faoro R., Selvestrel G., Troise A., Luciani D., Andres S., Benfenati E. Defining the Human-Biota Thresholds of Toxicological Concern for Organic Chemicals in Freshwater: The Proposed Strategy of the LIFE VERMEER Project Using VEGA Tools. *Molecules*, 2021, vol. 26, no. 7, pp. 1928. DOI: 10.3390/molecules26071928

45. Mons M.N., Heringa M.B., van Genderen J., Puijker L.M., Brand W., van Leeuwen C.J., Stoks P., van der Hoek J.P., van der Kooij D. Use of the Threshold of Toxicological Concern (TTC) approach for deriving target values for drinking water contaminants. *Water Res.*, 2013, vol. 47, no. 4, pp. 1666–1678. DOI: 10.1016/j.watres.2012.12.025

46. Melching-Kollmuss S., Dekant W., Kalberlah F. Application of the "threshold of toxicological concern" to derive tolerable concentrations of "non-relevant metabolites" formed from plant protection products in ground and drinking water. *Regul. Toxicol. Pharmacol.*, 2010, vol. 56, no. 2, pp. 126–134. DOI: 10.1016/j.yrtph.2009.09.011

47. Baken K.A., Sjerps R.M.A., Schriks M., van Wezel A.P. Toxicological risk assessment and prioritization of drinking water relevant contaminants of emerging concern. *Environ. Int.*, 2018, vol. 118, pp. 293–303. DOI: 10.1016/j.envint.2018.05.006

48. Alekseeva A.V., Savostikova O.N. Problems of the safe use of modern cement materials in the practice of drinking water supply. *Gigiena i sanitariya*, 2022, vol. 101, no. 12, pp. 1458–1463. DOI: 10.47470/0016-9900-2022-101-12-1458-1463 (in Russian).

49. Alekseeva A.V., Savostikova O.N. Hygienic assessment of the possibility of using polyurethane coatings in the practice of drinking water supply. *Gigiena i sanitariya*, 2022, vol. 101, no. 5, pp. 487–492. DOI: 10.47470/0016-9900-2022-101-5-487-492 (in Russian).

Alekseeva A.V., Savostikova O.N. The threshold of toxicological concern for insufficiently explored chemicals occurring in drinking water during transportation. Health Risk Analysis, 2023, no. 3, pp. 49–61. DOI: 10.21668/health.risk/2023.3.06.eng

Received: 31.05.2023
Approved: 19.09.2023
Accepted for publication: 25.09.2023