UDC 616.152.13-02: [613.31: 628.162.8]-0532-07
DOI: 10.21668/health.risk/2018.3.09.eng

Read online

ON DETERMINATION OF REFERENCE CHLOROFORM CONTENT IN CHILDREN'S BLOOD

K.V. Chetverkina

Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 82 Monastyrskaya Str., Perm, 614045, Russian Federation

The author showed that consumption of chlorinated drinking water from centralized water supply systems with chloroform concentration being equal to 0.49 mg/l caused unacceptable non-carcinogenic risk (HI being up to 3.13) of functional disorders in the liver, kidneys, central nervous system, hormonal system, as well as the circulatory system. Assessment of carcinogenic health risk born by children revealed that individual carcinogenic risk was equal to $1.64 \cdot 10^{-5}$ under such concentration; this value corresponds to the upper limit of acceptable risk. Morbidity analysis revealed that children who consumed chlorinated drinking water from water supply systems suffered from pathologies in the nervous system, digestive organs, urogenital and endocrine systems authentically more frequently. The results coincided with those obtained in non-carcinogenic health risk assessment. Epidemiologic assessment of children morbidity revealed an authentic cause-and-effect relationship between oral exposure to chloroform introduced with drinking water and diseases in critical organs and systems (according to Guide P. 2.1.10.1920-04). The calculations showed that if population consumed drinking water with chloroform, morbidity among then could possibly grow by 10.41 times against population who didn't consume chlorinated water. The author performed in-depth research on population health via examining changes in clinical and laboratory markers that described functional disorders in critical organs and systems caused by oral introduction of chloroform. Basing on the obtained data, the author modeled 34 mathematical relationships "chloroform contents in blood – clinical and laboratory marker of a response" and chose 3 most relevant models that reflected changes in clinical and laboratory markers in accordance with chloroform contents in blood. They were an increase in alanine aminotransferase and aspartate aminotransferase which meant there were functional disorders in the liver, and a decrease in hemoglobin contents that was a sign of circulatory system disorders. Reference chloroform content in blood was fixed as per limiting hazard index principle and was equal to 0.0004 mg/dm^3 that corresponded to aspartate aminotransferase marker and confirmed that the liver was a critical organ under oral introduction of chloroform.

Key words: *chloroform, concentration, blood, drinking water, communal drinking water supply, children, reference level, critical organs, marker of exposure.*

Quality of drinking water consumed by people every day is a significant factor that determines health and life quality of any person. Drinking water is to conform to safety requirements as per its sanitary-chemical, microbiological, and parasitological parameters. But when safety is provided as per a certain parameter, it can lead to greater contamination as per another one; thus, to provide population with drinking water which conforms to all the microbiological safety parameters, it is necessary to apply disinfection [1]. Application of chlorine and chlorine-containing compounds (CCCs) as disinfectants is the most efficient and widely spread technique for water disinfection [2–4]. However, the technique has a serious drawback as it results in synthesis of highly toxic chlorinated organic compounds (COCs) due to a chemical reaction between chlorine ions and organic compounds that occur in initial water [1,5,6]. The most widely spread COCs are chloroform, tetrachloromethane (TCM), dibromchloromethane (DBCM), bromdichloromethane (BDCM) and others [7–9].

C.F. Tumasonis et al. (1987) [10], L.W. Condie et al. (1983) [11], De Salva et al. (1975) [12], F.J.C. Roe et al. (1979) [13], and A.E. Munsonetal. (1982) [14] detected in their research that chlorinated organic compounds (chloroform, tetrachloromethane, BDCM, and others) exert adverse impacts on the digestive organs, urinary excretion organs, the circulatory, nervous, and hormonal systems under oral exposure. Some COCs are carcinogenic [15–19]. When entering a body, chlorinated organic compounds are ab-

Kristina V. Chetverkina – junior researcher at Laboratory for Environmental Risks Analysis (e-mail: romanenko@fcrisk.ru; tel.: +7 (342) 238-33-37).

sorbed in the gastrointestinal tract, then penetrate blood and are distributed all over a body with it (primarily damaging the parenchymal organs); they are also partially deposited in adipose tissue [20,21].

Damaging effects produced by chlorinated organic compounds are mostly determined by their metabolic transformations; as a result, highly toxic compounds occur and they can activate lipid peroxidation. It causes damage to cellular membranes and induces cells death. As a result, dystrophic and necrotic changes occur in the parenchymal organs; hemolytic disorders develop in blood cells, the nervous system suffers as neurons cellular membranes are damaged and, consequently, disorders in neural transmission occur. It confirms that impacts exerted by chlorinated organic compounds on human health are significant and it is vital to explore the subject more profoundly. Taking into account that COCs contents in water are by 70-90% determined by chloroform, its concentration in water is considered to be an indicator of chlorination products contents [22]. At the same time, M.A. Zemlyanova (2015) and D.M.Desiderio et al. (2010) state in their works that chloroform content in blood is a marker of exposure to chloroform consumed with drinking water [23,24].

Given all the above mentioned, the author chose the following **research goal:** to detect impacts exerted by chloroform in drinking water taken from centralized water supply systems (CWSS) on health of children in order to determine a reference level of chloroform content in their blood.

Data and methods. We performed hygienic assessment of water quality on territories in Perm region where drinking water was distributed and supplied to consumers via centralized water supply systems. Test and control groups were made up as per a criterion of specific chlorination techniques applied at water treatment stations prior to it being supplied to population. We examined data collected during monitoring research performed by the Center for Hygiene and Epidemiology in Perm region.

Quality of water taken from centralized water supply systems was analyzed over a period of 2012-2016. Water samples were taken at 5 different points in a water supply network: a reservoir with purified water, a pumping station of the 2nd hoist, a station for additional pumping, a stand-pipe, and a water tap. There were no authentic discrepancies in chloroform contents in water taken at all the examined points in a water supplying network ($p>0.05$). 345 samples of drinking water taken from centralized water supply systems were analyzed for the test group over 2012-2016; 387 ones, for the control group. Chloroform concentration in drinking water was determined in accordance with State Standard (GOST) 31951-2012[1]. Analysis of drinking water contamination included calculation of average parameters (upper 95% confidence limit) and their conformity with the maximum permissible concentrations fixed in Sanitary-Epidemiologic Requirements 2.1.4.1074-01[2].

We assessed population health risks that occurred under chronic oral exposure in accordance with the Guide 2.1.10.1920-04[3]. At exposure assessment stage, we calculated average daily doses of chloroform consumed with drinking water, hazard quotients (HQ), and individual carcinogenic risk (CR). To analyze carcinogenic properties, we generalized both domestic and foreign data on validity of carcinogenic effects. We took data on carcinogenic properties of chloroform primarily from the SER 1.2.2353-08[4], materials by the U.S.EPA, and databases of the IARC (Table 1).

[1] State Standard 31951-2012. Drinking water. Determination of volatile halogen-organic compounds contents with gas liquid chromatography. *KODEKS: an electronic fund of legal and reference documentation*. Available at: http://docs.cntd.ru/document/1200097813 (access date 11.09.2018) (in Russian).

[2] SER 2.1.4.1074-01. Drinking water. Hygienic requirements to quality of water from centralized drinking water supply systems. Quality control. Hygienic requirements to providing safety of hot water supply systems. *KODEKS: an electronic fund of legal and reference documentation*. Available at: http://docs.cntd.ru/document/901798042 (access date 11.09.2018) (in Russian).

[3] G 2.2.1.10.1920-04. Guide for assessing population health risks under exposure to chemicals that pollute environment. Moscow, The Federal Center for State Sanitary and Epidemiologic Surveillance of the RF Public Healthcare Ministry Publ., 2004, 143 p. (in Russian).

[4] SER 1.2.2353-08. Carcinogenic factors and basic requirements to prevention of carcinogenic hazards. *KODEKS: an electronic fund of legal and reference documentation*. Available at: http://docs.cntd.ru/document/902101545 (access date 11.09.2018) (in Russian).

Table 1

Data on hazards of carcinogenic and non-carcinogenic effects under oral exposure to chloroform

Chemical	CAS	Carcinogenic effects				Non-carcinogenic effects	
		U.S.EPA	IARC	Russia	SFo	RfD, μg/kg	Critical organs and systems
Chloroform	67-66-3	B2	2B	–	0,0061	0,01	Liver, kidneys, CNS, hormonal system, blood

We analyzed morbidity among children applying data taken from the Report Form 12 "Data on a number of morbid events registered in patients living on a territory served by a medical organization" issued in 2016 as per nosologic categories (according to ICD-10) which corresponded to critical organs and systems mentioned in the Guide 2.1.10.1920-04 for oral exposure to chloroform.

We compared maximum morbidity levels detected on various territories. We analyzed health of children aged 3-12 profoundly; the analysis examining biochemical blood parameters that reflected impacts exerted by chloroform on state and functions of critical organs and systems:

¨ liver and bile-excreting system (activity of alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), and alkaline phosphatase; content of highly sensitive C-reactive protein (CRP), total protein, albumin, total and direct bilirubin);

¨ kidneys (creatinine and b_2-microglobulin content);

¨ central nervous system (contents of glutamate, γ-aminobutyric acid (GABA), serotonin, and hydrocortisone);

¨ blood (contents of erythrocytes, thrombocytes, and hemoglobin in whole blood, mean corpuscular hemoglobin concentration (MCHC), ratio of erythrocytes to blood plasma volume, anisocytosis erythrocytes);

¨ oxidation processes (lipid hydroperoxides, malonic dialdehyde (MDA) in blood serum), antioxidation processes (activity of glutathione peroxidase (GPO), Cu/Zn-superoxide dismutase (Cu/Zn-SOD), glutathione-S-transferase (GST), glutathione peroxidase and antioxidant activity), cytolytic, inflammatory, and dysmetabolic processes (contents of leucocytes, dextrose, eosinophils, plasma cells, and erythrocytes sedimentation rate in whole blood); cellular immunity (lymphocytes and monocytes contents in whole blood).

We detected chloroform concentration in children's blood taking into account State Standard GOST R 8.563-96[5] via analyzing equilibrium vapor phase on "Kristall-5000" gas chromatographer with DB-624 capillary column and selective electron-capture detector (ECD) in accordance with Methodical Guidelines 4.1.2115-06[6]. All the examinations were performed in full conformity with Helsinki Declaration issued in 1975 and supplemented in 1983 and the RF National Standard GOST R 52379-2005 "Good Clinical Practice" (ICH E6 GCP).

We performed epidemiologic assessment of population morbidity via calculating odds ratio (OR) and 95% confidence interval (CI). If there was a correlation (OR>1), we considered it to be authentic in case the bottom limit of the confidence interval was higher than 1. We calculated risk parameters (R) for those nosologies for which we detected a statistically authentic relationship [25].

В качестве модели исследования использована зависимость содержания хлороформа в крови от концентрации хлороформа в питьевой воде $y = 0{,}00188 + 0{,}01782X$ ($R^2 = 0{,}263$ $p < 0{,}05$) [22].

We applied a dependence of chloroform content in blood on chloroform concentration in drinking water y=0.00188+0.01782X (R^2=0.263 p<0.05) as our research model [22].

The obtained results were statistically processed with Statistica 6.0 software and Microsoft Excel applied packages.

[5] State Standard GOST R 8.563-96. Amendment No. 2 to GOST R 8.563-96. State System for Ensuring the Uniformity of Measurements. Procedures of Measurements. *KODEKS: an electronic fund of legal and reference documentation.* Available at: http://docs.cntd.ru/document/1200030346 (access date 11.09.2018) (in Russian).

[6] Methodical Guidelines 4.1.2115-06. Determination of mass concentrations of chloroform, 1,2-dichloroethane, and tetrachloromethane in biological media (blood) via gas chromatographic analysis of equilibrium vapor. *KODEKS: an electronic fund of legal and reference documentation*. Available at: http://docs.cntd.ru/document/1200065247 (access date 11.09.2018) (in Russian).

If distribution of values was normal, we determined mean value (M) and a standard error of the mean (m) and assessed validity of discrepancy between them with Student's test (t). In case there was no normal distribution law, we applied Mann-Whitney test (U). Discrepancies were considered to be authentic at $p<0.05$.

Results and discussion. We detected that there were authentic discrepancies in chloroform concentrations in drinking waters between territories where chlorination was applied to treat water and territories where chlorine-containing compounds (CCCs) were not used as disinfectants (Table 2).

We detected that average annual chloroform concentrations in drinking water amounted up to 1.15 MPC on territories where drinking water was chlorinated.

Morbidity as per all the nosologies, excluding diseases of the blood, was authentically higher in children who consumed chlorinated drinking water (Table 3).

Epidemiologic assessment of morbidity among children confirmed the validity of discrepancies between the test and control groups, including diseases of the blood (Table 4).

Consumption of drinking water that contains chloroform leads to 10.41 times higher risk of the diseases of the blood; 2.94 times higher risks of diseases in the kidneys; 2.67 times higher risk of the nervous system diseases; 1.49 times higher risk of the digestive organs diseases; 1.25 times higher risk of the hormonal system diseases against people who consume non-chlorinated drinking water.

We determined unacceptable non-carcinogenic risk (HQ>1) under exposure to drinking water contaminated with chloroform; it was up to 3.13 HQ in the test group (Table 5).

Table 2

Average annual concentrations and values of 95-th quantile of chloroform drinking water samples (on territories with and without chlorination), 2012–2016

Year	Average annual chloroform concentration in water, mg/l				Validity of discrepancy (p)
	Test group (drinking water is chlorinated)	95% quantile	Control group (drinking water is not chlorinated)	95% quantile	
2012	0,013 ± 0,02	0,38	0,0158 ± 0,0020	0,030	<0,05
2013	0,20 ± 0,03	0,41	0,0113 ± 0,0018	0,024	<0,05
2014	0,23 ± 0,03	0,49	0,0091 ± 0,0020	0,019	<0,05
2015	0,20 ± 0,03	0,38	0,0043 ± 0,0015	0,020	<0,05
2016	0,087 ± 0,01	0,17	0,0031 ± 0,0012	0,010	<0,05
2012–2016	0,172 ± 0,01	0,39	0,0068 ± 0,0007	0,024	<0,05

Table 3

Morbidity among children who live on territories where drinking water is chlorinated (test group) and where it is not chlorinated (control group) in 2016 (per 1,000 people)

Code as per ICD-10	Nosology as per ICD-10	group		Validity of discrepancy (*p*)
		Test	Control	
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	35,13	33,26	0,19
E00-E90	Endocrine, nutritional, and metabolic diseases	41,0	13,75	<0,05
G00-G99	Diseases of the nervous system	64,82	23,76	<0,05
K00-K93	Diseases of the digestive organs	111,36	73,43	<0,05
N00-N99	Diseases of the genitourinary system	36,0	28,70	<0,05

Table 4

Epidemiologic assessment of morbidity among children who live on territories where drinking water is chlorinated (test group) and where it is not chlorinated (control group) in 2016

Code	Nosology as per ICD-10	Group	Response to exposure		*OR*	95% CI	Risk ratio
			yes	no			
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	test	6520	179 089	10,93	8,45–14,13	10,41
		control	59	17 708			
N00-N99	Diseases of the genitourinary system	test	7610	177 999	3,07	2,34–4,02	2,94
		control	53	3801			
G00-G99	Diseases of the nervous system	test	943	13 605	2,85	2,48–3,26	2,67
		control	276	11 339			
K00-K93	Diseases of the digestive organs	test	20 669	164 940	1,58	1,40–1,79	1,49
		control	283	3571			
E00-E90	Endocrine, nutritional, and metabolic diseases	test	6682	178 927	1,26	1,15–1,38	1,25
		control	510	17 257			

Table 5

Assessment of non-carcinogenic risk for children's health under oral exposure to chloroform consumed with drinking water

Year	Concentration, mg/l	*HQ*	95-th quantile	*HQ*	RfD, mg/kg	Critical organs and systems
Test group (consume chlorinated drinking water)						
2012	0,013 ± 0,02	0,08	0,38	2,43	0,01	Liver, kidneys, CNS, hormonal system, blood
2013	0,20 ± 0,03	1,28	0,41	2,62		
2014	0,23 ± 0,03	1,47	0,49	3,13		
2015	0,20 ± 0,03	1,28	0,38	2,43		
2016	0,087 ± 0,01	0,56	0,17	1,09		
2012–16	0,172 ± 0,01	1,10	0,39	2,49		
Control group (consume drinking water that is not chlorinated)						
2012	0,0158 ± 0,0020	0,1	0,030	0,19	0,01	Liver, kidneys, CNS, hormonal system, blood
2013	0,0113 ± 0,0018	0,07	0,024	0,15		
2014	0,0091 ± 0,0020	0,06	0,019	0,12		
2015	0,0043 ± 0,0015	0,03	0,020	0,13		
2016	0,0031 ± 0,0012	0,02	0,010	0,06		
2012–2016	0,0068 ± 0,0007	0,04	0,024	0,15		

When chloroform concentration in drinking water is equal to 0.49 mg/l, carcinogenic risk amounts to 1.64×10^{-5}, and it is the upper limit of acceptable risk so no activities aimed at its reduction are required.

We analyzed blood samples taken from children and detected chloroform in blood of 342 children, its concentrations varying from 0 to 0.02 mg/dm^3 (Table 6). Chloroform contents were authentically higher in children from the test group than in those from the control one.

We applied mathematical modeling to describe a relationship between changes in laboratory parameters of health and chloroform concentration in blood and obtained 8 biologically plausible mathematical models (Table 7).

The obtain results correlate well with scientific research data taken from various literature sources; according to them, chronic oral exposure to chloroform leads to disorders in enzymatic activity of the liver and blood system disorders. Basing on the designed models, we determined reference levels for chloroform contents in blood; the lowest one was detected at an increase in aspartate aminotransferase contents in blood (Figure).

Table 6

Average concentrations and values of 95-th quantile of chloroform contents in children's blood (test group)

Year	Average chloroform concentration in blood, mg/dm^3				Validity of discrepancies (p)
	Test group (consume chlorinated drinking water)	95% quantile	Control group (consume drinking water that is not chlorinated)	95% quantile	
2013	0,0035 ± 0,0009	0,009	–		–
2014	0,0007 ± 0,00008	0,002	0,00039 ± 0,0001	0,00019	<0,05
2015	0,0009 ± 0,0002	0,004	0,00020 ± 0,0001	0,0007	<0,05
2013–2015	0,0011 ± 0,0001	0,004	0,00027 ± 0,0002	0,0007	<0,05

Table 7

Parameters of models that describe a relationship between changes in clinical-laboratory indexes and chloroform concentration in blood

Direction of change	Index in blood	Laboratory index	Reference level of chloroform contents in blood, mg/dm^3	Validity of discrepancies, p	Coefficient of determination (R2)
Higher	Chloroform in blood	ALAT	0,00465	<0,05	0,02
Higher	Chloroform in blood	ASAT	0,00042	<0,05	0,90
Lower	Chloroform in blood	Hemoglobin	0,00075	<0,05	0,35
Higher	Chloroform in blood	Dextrose	0,00101	<0,05	0,39
Higher	Chloroform in blood	Glutathione peroxidase	0,00134	<0,05	0,51
Lower	Chloroform in blood	Total protein	0,07782	<0,05	0,07
Higher	Chloroform in blood	Lymphocytes	0,1355	<0,05	0,13
Higher	Chloroform in blood	Leukocytes	0,0834	<0,05	0,08

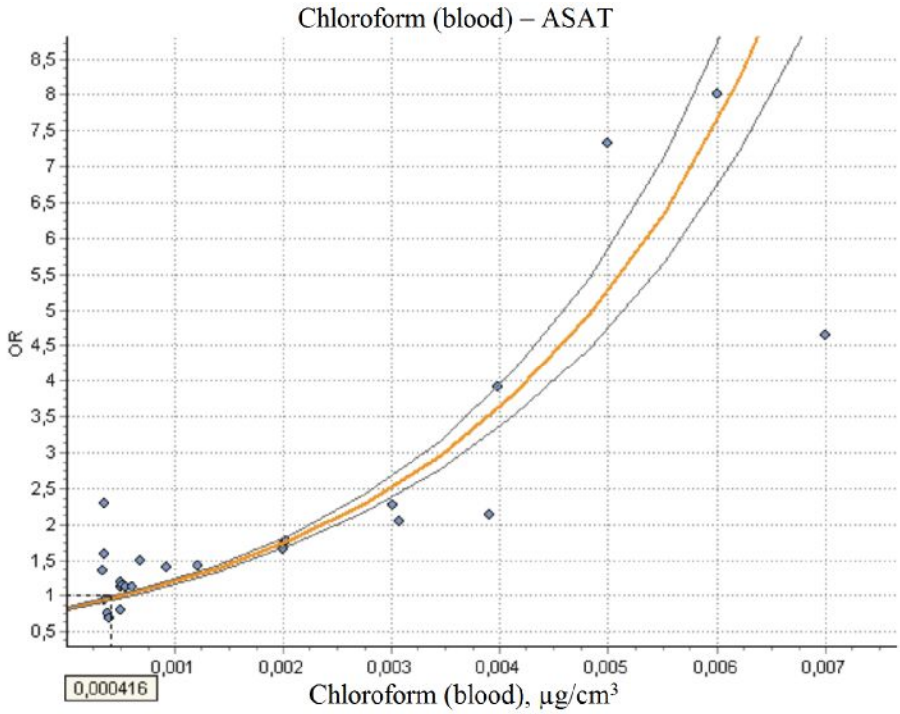

Figure 1. A model showing a dependence of odds ratio (OR) for an increase in aspartate aminotransferase contents on chloroform concentration in blood

Therefore, taking into account application of limiting hazard parameter, we can suggest to consider 0.0004 mg/dm^3 to be a reference level of chloroform contents in blood. This value corresponds to ASAT index that characterizes functioning of the liver and it confirms that the liver is a critical organ under oral exposure to chloroform.

Conclusion.

We detected an authentic discrepancy related to contamination of drinking water taken from centralized water supply systems; water was contaminated with chloroform on territories where it was disinfected with chlorine-containing compounds but there was no or insignificant chloroform contamination on territories where chlorination was not applied.

Morbidity among children assessed as per data on patients who applied for medical health due to diseases of the genitourinary system, nervous system, endocrine system, and the digestive organs was authentically higher on territories where population consumed chlorinated drinking water. Epidemiologic data are well in line with assessment of health risks among children (HQ being up to 3.13). Average long-term contamination of drinking water with chloroform that is equal to 0.172 mg/l causes unacceptable risk of diseases in the liver, kidneys, nervous system, endocrine system, and blood; it can result in higher morbidity on territories where drinking water is chlorinated. It can grow by 1.25 to 10.41 times.

We found out that contamination of drinking water taken from centralized water supply systems with chloroform that doesn't exceed 0.49 mg/l doesn't cause unacceptable carcinogenic risks (CR is not higher than 1.64×10^{-5}).

We determined a reference level of chloroform contents in blood (0.0004 mg/dm^3) as per an increase in aspartate aminotransferase contents in blood; it confirms that the liver is a critical organ under chronic oral exposure to chloroform. In future this parameter can be applied in solving tasks on fixing standards for safe chloroform concentrations in drinking water.

Funding. Our research was not granted any sponsors' support.

A conflict of interests. The authors state there is no conflict of interests.

References

1. Tul'skaya E.A., Rakhmanin Yu.A., Zholdakova Z.I. Obosnovanie pokazatelei bezopasnosti dlya kontrolya za primeneniem khimicheskikh sredstv obezzarazhivaniya vody i neobkhodimosti garmonizatsii ikh s mezhdunarodnymi trebovaniyami [Justification of both safety indices for control over the use of chemicals for water disinfection and need to harmonize them with international requirements]. *Gigiena i sanitariya*, 2012, no. 6, pp. 88–91 (in Russian).

2. Miftakhova K.R., P'yankova O.G., Rudakova L.V., Glushankova I.S. Khlorirovanie kak osnovnoi metod obezzarazhivaniya pit'evoi vody [Chlorination is the main method of disinfection of drinking water]. *Ekologiya i nauchno-tekhnicheskii progress. Urbanistika*, 2015, vol. 1, pp. 233–242 (in Russian).

3. Malkova M.A. Nekotorye problemy obrazovaniya trigalogenmetanov pri khlorirovanii pit'evoi vody [Some problems of formation of trigalogenmetans in chlorinated drinking water].*Vestnik molodogo uchenogo UGNTU*, 2016, no. 3, pp. 68–74 (in Russian).

4. Bahir V.M. Dezinfektsiya pit'evoi vody: problemy i reshen [Disinfection of drinking water: problems and solutions]. *Pit'evaya voda*, 2003, no. 1, pp. 13–20 (in Russian).

5. Onishhenko G.G., Zaitseva N.V., May I.V. [et al.]. Health risk analysis in the strategy of state social and economical development. In: G.G. Onishhenko, N.V. Zaitseva eds. Perm', Publishing house of the Perm National Research Polytechnic University, 2014, 738 p. (in Russian).

6. P'yankova O.G., Kuchukbaeva A.V., Glushankova I.S., Rudakova L.V. Analiz faktorov, vliyayushchikh na obrazovanie khloroforma v protsesse vodopodgotovki [Analysis of factors that influence formation of chloroform during water treatment]. *Modernizatsiya i nauchnye issledovaniya v transportnom komplekse*, 2015, no. 1, pp. 283–287 (in Russian).

7. Vozhdaeva M.YU., Cypysheva L.G., Kantor L.I., Kantor E.A. Vliyanie hlorirovaniya na sostav ogranichenno-letuchih organicheskih zagryaznitelej vody [Influence of chlorination on the composition

of partly volatile organic contaminants of water]. *Zhurnal prikladnoi khimii*, 2004, vol. 77, no. 6, pp. 952–955 (in Russian).

8. Mazaev V.T., Korolev A.A., Shlepnika T.G. Kommunal'naya gigiena [Communal Hygiene]. In: V.T. Mazaeva ed. The 2rd ed. Moscow, GEOTARMedia Publ., 2005, 304 p. (in Russian).

9. Rakhmanin Yu.A., Mikhailova R.I., Kir'yanova L.F., Sevost'yanova E.M., Ryzhova I.N., Savronskii A.Yu. Aktual'nye problemy obespecheniya naseleniya dobrokachestvennoi pit'evoi vodoi i puti ikh resheniya [Important problems of high quality drinking water supply, and the ways of their solution]. *Vestnik Rossiiskoi akademii meditsinskikh nauk*, 2006, no. 4, pp. 9–17 (in Russian).

10. Tumasonis C.F., McMartin D.N., Bush B. Toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. *Journal of Environmental Pathology, Toxicology and Oncology*, 1987, vol. 7, no. 4, pp. 55–64.

11. Condie L.W., Smallwood C.L., Laurie R.D. Comparative renal and hepatotoxicity of halomethanes: Bromodichloromethane, bromoform, chloroform, dibromochloromethane and methylene chloride. *Drug Chemical Toxicology*, 1983, vol. 6, no. 6, pp. 563–578.

12. De Salva S., Volpe A., Leigh G. [et al.]. Long-term safety studies of a chloroform-containing dentifrice and mouth-rinse in man. *Food and Cosmetics Toxicology*, 1975, vol. 13, no. 5, pp. 529–532. DOI: 1016/0015-6264(75)90007-3

13. Roe F.J.C., Palmer A.K., Worden A.N. Safety evaluation of toothpaste containing chloroform. I. Long-term studies in mice. *Journal of Environmental Pathology, Toxicology and Oncology*, 1979, vol. 2, pp. 799–819.

14. Munson A.E., Sain L.E., Sanders V.M. [et al.]. Toxicology of organic drinking water contaminants: Trichloromethane, bromodichloromethane, dibromochloromethane, and tribromomethane. *Environmental Health Perspectives*, 1982, vol. 46, pp. 117–126. DOI: 10.1289/ehp.8246117

15. Iksanova T.I., Malysheva A.G., Rastyannikov E.G., Egorova N.A., Krasovskii G.N., Nikolaev M.G. Gigienicheskaya otsenka kompleksnogo deistviya khloroforma pit'evoi vody [Hygienic evaluation of the combined effect of portable water chloroform]. *Gigiena i sanitariya*, 2006, no. 2, pp. 8–12 (in Russian).

16. Chernichenko I.A., Balenko N.V., Litvichenko O.N. Kantserogennaya opasnost' khloroforma i drugikh pobochnykh produktov khlorirovaniya pit'evoi vody [Carcinogenic hazard of chloroform and other drinking water chlorination by-products]. *Gigiena i sanitariya*, 2009, no. 3, pp. 28–33 (in Russian).

17. Sankpal U.T., Pius H., Khan M. [et al.]. Environmental factors in causing human cancers: emphasis on tumorigenesis. *Tumor Biology*, 2012, vol. 33, pp. 1265–1274. DOI: 10.1007/s13277-012-0413-4

18. Sciacca S., Conti G.O. Mutagens and carcinogens in drinking water. *Mediterranean Journal of Nutrition and Metabolism*, 2009, vol. 2, pp. 157–162.

19. Prokopov V.A., Gulenko S.V. Rol' khlorirovannoi pit'evoi vody v razvitii onkologicheskoi patologii [Role of chlorinated drinking water quality in cancer pathology development]. *Zdorov'e i okruzhayushchaya sreda*, 2013, no. 22, pp. 85–59 (in Russian).

20. Mikhailova D.L., Kol'dibekova Yu.V. Otsenka vozdeistviya khloroforma pri postuplenii v organizm s pit'evoi vodoi na sostoyanie zdorov'ya detei [Children health assessement from effect of chloroform entering in the organism with potable water]. *Vestnik Permskogo universiteta. Seriya: Biologiya*, 2012, no. 2, pp. 85–88 (in Russian).

21. U.S. EPA. Health Risk Assessment/Characterization Of The Drinking Water Disinfection Byproduct Chloroform. Prepared by Toxicology Excellence for Risk Assessment, Cincinnati, OH, under Purchase Order No. 8W-0767-NTLX. Washington, 1998, 52 p. Available at: https://www.tera.org/Publications/Chloroform.PDF (05.06.2018).

22. Dushkin S.S., Blagodarnaya G.I. Razrabotka nauchnykh osnov resursosberegayushchikh tekhnologii podgotovki ekologicheski chistoi pit'evoi vody: monografiya [Scientific substantiation for resource-saving technologies that are applied to obtain ecologically clean drinking water: Monograph]. Khar'kov, KhNAGKh Publ., 2009, 94 p. (in Russian).

23. Zemlyanova M.A., Peskova E.V. Otsenka narushenii biokhimicheskikh pokazatelei funktsii TsNS i pecheni u detei, potreblyayushchikh vodu s povyshennym soderzhaniem khlororganicheskikh soedinenii [As-

sessment of violations of biochemical indicators of central nervous system and liver in children consuming water with high content of organochlorine compounds]. *Vestnik Permskogo universiteta. Seriya: Biologiya*, 2015, no. 3, pp. 259–263 (in Russian).

24. Desiderio D.M., Nibbering N.M. White's Handbook of Chlorination and Alternative Disinfectants: Fifth Edition. New Jersey, John Wiley & Sons, Inc., 2010, 36 p. DOI:10.1002/9780470561331

25. Charles P. On the Origin of Risk Relativism. *Epidemiology*, 2010, vol. 21, no. 1, pp. 3–9. DOI: 10.1097/EDE.0b013e3181c30eba

Chetverkina K.V. On determination of reference chloroform content in children's blood. Health Risk Analysis, 2018, no. 3, pp. 85–93. DOI: 10.21668/health.risk/2018.3.09.eng

Received: 19.06.2018
Accepted: 20.09.2018
Published: 30.09.2018