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VERIFICATION OF AVERAGE DAILY MAXIMUM PERMISSIBLE CONCENTRATION OF STYRENE IN THE ATMOSPHERIC AIR OF SETTLEMENTS UNDER THE RESULTS OF EPIDEMIOLOGICAL STUDIES OF THE CHILDREN'S POPULATION

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We presented the materials on the verification of the average daily maximum permissible concentration of styrene in the atmospheric air of settlements performed under the results of own in-depth epidemiological studies of children's population according to the principles of the international risk assessment practice. It was established that children in the age of 4–7 years when exposed to styrene at the level above 1.2 of threshold level value for continuous exposure develop the negative exposure effects in the form of disorders of hormonal regulation, pigmentary exchange, antioxidative activity, cytolysis, immune reactivity and cytogenetic disbalance which contribute to the increased morbidity of diseases of the central nervous system, endocrine system, respiratory organs, digestion and skin. Based on the proved cause-and-effect relationships between the biomarkers of negative effects and styrene concentration in blood it was demonstrated that the benchmark styrene concentration in blood is 0.002 mg/dm^3. The justified value complies with and confirms the average daily styrene concentration in the air of settlements at the level of 0.002 mg/m^3 accepted in Russia which provides the safety for the health of population (1 threshold level value for continuous exposure).

Key words: styrene, average daily maximum allowable concentration, atmospheric air, epidemiological study, children's population, exposure marker, biomarkers of effect, target organs.

Styrene (vinylbenzene, phenylethylene, ethylbenzene) belongs to the condensed aromatic compounds having one benzene ring in their molecule (C_8H_8). It is the colorless liquid with specific smell. It is used mainly for the production of different polymerizing plastics (polystyrene, foamed plastic), synthetic copolymer rubbers and plastics included to the composition of construction and packing materials. Main manufacturing countries are: USA, Japan, Germany, and Russia. According to the data of the Federal State Statistics Service of the Russian Federation the production volume of styrene in Russian for 2014 was 4371.2 thous. tons.

Main route for styrene intake to the human body is inhalation. For the most of population the intake of styrene is carried out with the air of closed premises of residential and public buildings. The average concentrations in the air of residential premises are from 0.0003 to 0.05 mg/m^3 due to its intake from construction materials, domestic means and tobacco smoke [17]. Total daily exposure to styrene for population is 0.0003-0.0008 mg/kg/day (per 70 kg of body weight) [17].

According to the data of domestic and foreign authors, at the chronic exposure the styrene is charazterized by the polytropic impact on the human body. Together with general toxic it has the irritative, mutagenic, embriotoxic and carcinogenic effect as well as the high cumulative degree [13, 14, 16, 17]. Chronic styrene exposure stipulates the impact on the central nervous system (nerve conduction velocity reduction, weakening of neurobehavioral reactions), endocrine system (hormonogenesis disorder), liver (disorder of enzymic, protein-forming, pigmental function), blood system and

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blood-forming processes (marrowy hematopoiesis reduction), gastrointestinal tract (stomach acidity reduction), immune system (inhibition of phagocytic activity), kidney [13, 17]. According to ATDSR recommendations [17], the styrene exposure biomarkers are its presence in urine, blood as the qualitative indicator of exposure, fat tissue, as well as the presence of amygdalic acid in urine. The control of styrene content in the atmospheric air was performed using the gas chromatography with sensitivity of 0.0015 mg/m^3. Quantitatively the blood styrene was determined using the high-performance liquid chromatography (HPLC) with sensitivity of 0.0001 mg/dm^3.

According to the data of the U.S. Environmental Protection Agency the styrene is included to the list of hazardous contaminants of atmospheric air [15]. Herewith the hygienic standards for the content of styrene in the atmospheric air in Russian and abroad differ by 130-500 times. In USA the maximum styrene concentration ensuring the acceptable level of risk for the chronic inhalation impact (*RfC*) [15] is 1 mg/m^3 under the criterion of impact on the central nervous system [14]. WHO recommends 0.26 mg/m^3 as the minimum active styrene concentration [5]. In Russia the average daily maximum permissible concentration (MPC) of styrene in the atmospheric air of population clusters is 0.002 mg/m^3 [7] under the criterion of reflectory, general resorptive and specific effects (carcinogenic, mutagenic, embriotoxic, gonadotropic, allergenic).

Recently the role of hygienic standards is not always assessed unambiguously. There is the opinion on the imperfection of these values as the criteria of quality for the living environment objects [1]. Within the development of methodology for harmonizing the hygienic standards with the requirements of international organization and increasing the efficiency of measures on mitigating the unacceptable risk for population stipulated by the living environment factors it is urgent to extend the methodical approaches to the hygienic standardization in order to increase the reliability and credibility of initial materials forming the basis for MPC of the same substances in Russia and abroad [3].

The purpose of this study was the verification of the average daily MPC of styrene in the atmospheric air of population clusters under the results of epidemiological studies of the children population.

Materials and methods. The hygienic assessment of the quality of atmospheric air at the territories with location of source of emissions of styrene to the atmospheric air is performed on the example of Perm under the materials of monitoring observations of Rospotrebnadzor Administration for the Perm Territory and field studies of FBSI "Federal Scientific Center for Medical and Preventive Health Risk Management Technologies" for 2002–2013, implemented in accordance with RD 52.04.186–89 [8]. The information is generalized in ccordance with GN 2.1.6.1338–03 [7]. The exposure was assessed based on the calculation of the average daily dose of chronic exposure at the inhalation route of intake in accordance with guidance R 2.1.10.1920–04 [9].

The own in-depth epidemiological studies performed according to the principles of the international risk assessment practice in 2002-2013 covered 2248 persons. The observation group included the children from Perm in the age of 4-7 years of both sexes (in total 1892 persons, average age – 5.5±0.6 years, girls – 51%, boys – 49%). The children lived and visited for not less than 1 year the children organized institutions located in the residential area of the surveyed territory exposed to styrene (0.3 to 3.0 km from the source). The control group included the children from Kungur of the Perm Territory in the age of 4-7 years (in total 356 persons, average age – 5.8±0.3 years, girls – 50.5%, boys – 49.5%) living in the conditions not exposed to styrene. The examined groups were compared by:

– the character and frequency of prevalence of pathology in the perinatal and infant period and the babyhood period: observation group – 10%, control group – 12%;

– the social and domestic living conditions – comfortable accommodation and the average level of material security in relation to the average per capita minimum living wage: observation group – 85%, control group – 82%;

– the frequency and character of heavy hereditary history in the relatives of the 1 and 2 line: observation group – 15%, control group – 14%;

– the frequency and character of vicious habits and occupational hazards of the parents: observation group – 17.5%, control group – 15.0%.

As of examination the children did not have acute infectious diseases not less than during 4 weeks before the beginning of study, the infectivity index is 0.2–0,5, did not take the drugs having the expressed impact on hemodynamics, function of liver, etc. (barbiturates, omeprazole, cimetidine, etc.) не not less than 30 days before the beginning of study.

Each legal representative of child included into sampling provided the writted informed consent for the voluntary participation in the examination performed by the specialists of FBSI "Federal Scientific Center for Medical and Preventive Health Risk Management Technologies" based on the mobile consulting and diagnosting department and clinic, according to the mandatory compliance with ethical standards specified in Helsinki Declaration of the World Medical Association in 1964 (as amended as of 2008).

The chemical and analytical studies included the determination of blood styrene using HPLC methods in accordance with MUK 4.1.2116–06. The clinical examination is performed according to the specially developed clinical examination cards. The hematological (hemoglobin, erythrocytes, color index, reticulocytes, leukocytes, monocytes, lymphocytes), biochemical (activity of aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase (γ-GTF), glutathione peroxidase (GPO); content of hydroperoxides of lipides, malonic dialdehyde (MDA), totlal and direct bilirubin, total protein, albumin in the blood serum), indicsstors of hormonogenesis (content of thyrotropic hormone, adrenocorticotropic hormone in the blood serum) are studied using the unified methods [4]. The cytogenic disorders indication is performed using the polyorganic micronucleus test on the exfoliative buccal epithelial cells [6].

The *t*-criterion of Student (comparison of the studied samplings under the absolute values of feature) and *Z*-test of Fisher (comparison of the indicators of studied samplings under the shares of feature) was used to assess the credibility of differences in the obtained results. The differences of obtained results were statistically significant at $p \leq 0.05$ [2]. The condition of the health of children was assessed based on the clinical and laboratory data in accordance with MKB-10.

The styrene exposure marker justification is performed based on the established reliable relationship of styrene concentration in blood with exposure. The mathematical model describing the analyzed dependence in the conditions of low concentrations represents the following linear equation: $x = b_1 D + b_0$, where D is an average daily styrene concentration in the atmospheric air, mg/m^3, x is an average styrene concentration in blood, mg/dm^3; b_0, b_1 are the parameters of model characterizing the intial level of styrene concentration in blood and absorption velocity [2]. The justification of biomarkers of non-carcinogenic effects was performed under the calculation of the odds ratio indicator (*OR*) characterizing the relationship of styrene concentration in blood with the indicators of response reactions in children. The availability of relationship was assessed under criterion $OR>1$ [10]. The establishment of styrene benchmark concentration (BMC) in blood which provides the 10% exceeding of risk among the individuals located below the 2 or above the 98 percentile in case of normal distribution of responses from the side of health [18] is performed by simulation of dependence for change in the odds ratio indicator on the change in styrene concentration in blood (exposure marker) for each marker of effect. The assessment of dependence parameters was performed using the building of regression model in the form of exponential function [12]: $OR = e^{a_0 - a_1 x}$, where *OR* is an odds ratio indicator; x_0 is a styrene concentration in blood, mg/dm^3; a_0, a_1 are the parameters of model determined by the regression analysis method. The appropriatness of the obtained model was assessed under Fisher criterion ($F>3.63$) and the coefficient of determination (R^2) [12]. The analysis of information under the results of studies and assessment of the parameters of model was performed using the set of applied programs Statistica 6.0 and special program products associated with MS-Office applications.

The benchmark level of styrene in blood (x_0) for each marker of effect was calculated based on the condition $OR=1$ (the absence of relationship of the marker of effect with styrene concentration in blood) under the following formula: $x_0 = \frac{a_0}{a_1}$, where x_0 is a styrene concentration in blood, mg/dm^3; a_0, a_1 are the parameters of model determined by the regression analysis method. From the obtained range of 95% upper confidence borders of styrene concentrations in blood for each marker of effecr we determined the lowest which was recommended as thebenchmark level for the chronic exposure conditions. Based on the dependence of styrene concentration in blood on its content in the atmospheric air we calculated the level of styrene in the atmospheric air corresponding to the benchmark concentration of styrene in blood.

Results and their discussion. The average daily styrene concentration in the residential buildings of the observation territory (Perm) for the studied period is registered at the level of 0.0015–0.0043 mg/m^3 that corresponds to 0.8–2.2 of the maximum average daily permissible con-

centration or 0.0015–0.004 RfC_{cr}. The content of styrene in the atmospheric air of control territory did not exceed the lower limit of measurement (0.02 mg/m^3) performed using the gas chromatography. The chronic exposure at the observation territory was characterized by the aggregate average daily dose of styrene from 0.0002 to 0.0005 mg/(kg day). The exposed sub-population includes 360 thous. of population, including 42 thous. of children in the age 0-14 years.

The blood styrene as the marker of exposures within the range of concentrations from 0.0001 to 0.009 mg/dm^3 is identified in the children of observation group. The samples registration frequency with availability of styrene in blood was 55% of the total number of examined samples. In the children of control group the blood styrene is identified in none of the cases exceeding the lower limit of measurement performed by HPLC. In the observation group we established the reliable dependence (R^2=0.33, F=460.74, p=0.000) of styrene concentration in blood of children on the average daily concentration of substance in the atmospheric air which is described by the following equation: $y = –0.003 + 2.45x$ (fig. 1).

The results of in-depth study of the response reactions of the body of children in the observation group to the styrene exposure allowed for distinguishing the biomarkers characterizing the development of negative effects which have the reliable dependence on the styrene concentration in blood. The reliable cause-and-effect relationships (p<0.05) of the biomarkers of negative effects with styrene content in blood are not established in the children of conrol group.

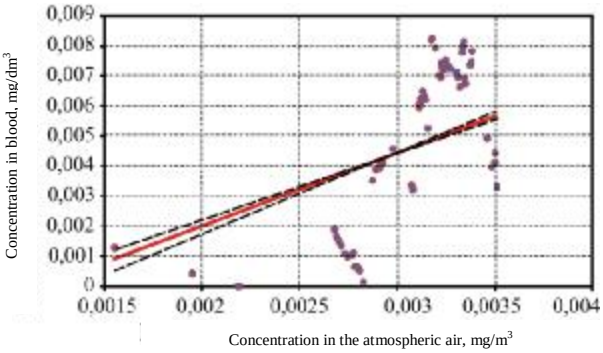

Fig. 1. Dependence of styrene concentration in blood of children on the average daily styrene concentration in the atmospheric air

The childred with styrene concentration in blood at the level of 0.002 mg/dm^3 and lower corresponding based on the established dependence of styrene concentration in the atmospheric air 1 of average daily MPC did not demonstrated the indicators of the response body reactions having the reliable deviations with the same indicators in the children of control group and reliable relationships with styrene concentrations in blood.

For the children with styrene concentration in blood at the level of 0.003-0.004 mg/dm^3 that corresponds to styrene concentration in the atmospheric air 1.2-1.4 of average daily MPC the biomarkers of effect was the increase in the level of adrenocorticotropic hormone and thyrotropic hormone in the blood serum by 1.3 and 1.2 times, respectively, in relation to the control group indicator (F=18.19÷170; 8; R^2=0.16÷0.56; p=0.000) that evidences the disorder in the synthesis of hormones in the anterior lobe of hypophysis and, as a result of it, the neuroendocrinal regulation (table 1).

In addition, in this subgroup of children we registered the increase in the level of total bilirubin in the blood serum by 1.4 times in relation to the control group indicator (F=2953.8; R^2=0.62; p=0.000) which characterizes the pigmental exchange disorder. This process is observed on the background of cytolysis activation established under the increased activity of aspartate aminotransferase and γ-GTF in the blood serum by 1.3-1.5 times compared to the control group indicators (F=200.7÷253.3; R^2=0.52÷0.69; p=0.000). We detected the increase in the level of monocytes and lymphocytes in the whole blood (F=11.28÷152.7; R^2=0.48÷0.60; p=0.000) which reflects the involvement of immunecompetent cells to the body response reaction when exposed to styrene. We established the decrease in the antioxidative activity ensured by the liver glutathione system in response to the increased peroxidation of the cell membrane lipids that is evidenced by the reliable increase in the content of lipids hydroperoxide, decrease in the activity of glutathione peroxidase and total antioxidative activity of blood serum (p=0.000÷0.016).

Table 1

Comparative analysis of hematological and biochemical indicators for children in the age of 4-7 years with styrene concentration in blood at the level of 0.003-0.004 mg/dm^3 stipulated by styrene exposure (on the example of Perm)

Indicator	Mean value (M±m)		Reliability of differences (p)
	Observation group	Control group	
Thyrotropic hormone, mcIU/cm^3	2,22±0,02	1,85±0,21	0,005
Adrenocorticotropic hormone, pg/cm^3	28,48±1,55	21,91±1,55	0,000
Aspartate aminotransferase, U/dm^3	30,78±0,55	23,68±1,29	0,000
y-GT, U/dm^3	26,26±2,34	17,51±0,73	0,000
Total bilirubin, mcmol/dm^3	10,05±0,38	7,20±1,09	0,000
Lymphocytes, %	43,03±2,51	39,94±0,48	0,030
Monocytes, %	6,58±0,38	4,44±0,11	0,000
Antioxidative activity, %	30,21±0,33	36,50±0,49	0,000
Hydroperoxide of lipides, mcmol/dm^3	461,1±20,4	194,2±24,2	0,000
Glutathione peroxidase, ng/cm^3	30,14±1,71	35,59±4,14	0,016

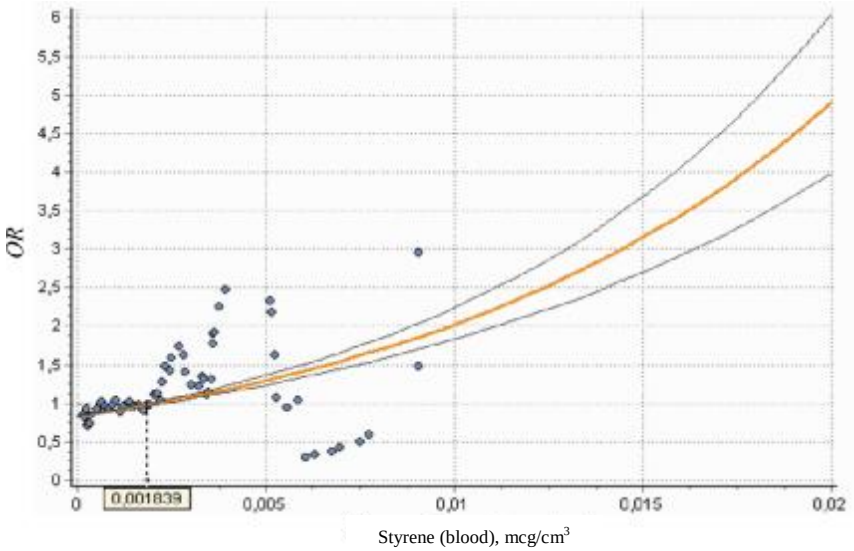

Fig. 2. Dependence of the odds ratio (*OR*) indicator for increase in the level of thyrotropic hormone in the blood serum on the styrene concentration in blood

The diseases of endocrine systems, malnutritions and metabolic disorders (code under MKB-10 – E00-E07, E65-E68) having the proved relationship with styrene concentration in blood are registered by 1.5 times more often in the children of described sampling. The example of graphical image of the reliable dependence of the odds ratio indicator for the increase in the level of thyrotropic hormone in the blood serum on the styrene concentration (F=868.0; p=0,000), described by equation $OR = e^{-0,180-88,5x}$ is shown in fig. 2.

In the provided example the benchmark concentration of styrene in blood is the concentration of 0.002 mg/dm^3; the upper confidence border of the benchmark styrene level in blood is 0.0018 mg/dm^3.

The children of described sampling (under the objective examination data) demonstrated the higher frequency of prevalence of the functional disorders of the central nervous system (by 2.2–3.0 times in relation to the control group) in the form of hyperresponsiveness syndrome and neurosis-like syndrome (code under MKB-10 – G93.8), strained headache (G44.8), other specified brain disorders; by 1.5–2.0 times more often – diseases of digestive organs in the form of biliary dyskinesia (K83.8), malabsorption syndrome (K90.0); by 1.3–1.7 times – diseases of respiratory organs in the form of hypertrophy of adenoids and tonsils (J35.0–J35.3),

chronic rhinitis (J31.0), diseases of bronchi (J40, J42). We established the reliable relationship of probability for the development of diseases of nervous system, digestive and respiratory organs with styrene concentration in blood (F=61.3÷1108.0; R^2=0.52÷0.69; p=0.000). The example of graphical image of the reliable dependence of the odds ratio indicator for the increase in the frequency of diseases of respiratory organs on the styrene concentration (F=405.91; p=0,000), described by equation $OR = e^{-0,198-124,6x}$ is shown in fig. 3.

In the provided example the benchmark concentration of styrene in blood is the concentration of 0.002 mg/dm^3; the 95% upper confidence border of the benchmark level is 0.0016 mg/dm^3.

The increased frequency (by 1.8 times in relation to the control group indicator) of the skin and hypoderm diseases in the form of atopic dermatitis (L20) was additionally registered in the children with styrene concentration in blood above 0.005 mg/dm^3 tha corresponds to the styrene concentration in the atmospheric air above 0.0032 mg/m^3 (or above 1.6 of the average daily MPC). The results of cytogenetic studies evidence the increased genetic instability fixed in the exfoliative cells of buccal epithelium of children with styrene concentration in blood above 0.003 mg/dm^3 (above 1.2 of the average daily MPC). We established the violation of the normal mitotic division cycle resulting in the formation of micronucleus and the cell division process activation characterized by the increase of the apoptotic activity and nuclear destruction. The frequency of cells with micronucleus and nuclear protrusions of type "tongue" and "broken egg" is up to 1.5 times higher the contrl group indicators (p=0.006÷0.022) and up to 3.0 times higher of the average Russian indicators [18]. The frequency of cells with apoptosic bodies and the cell nucleus vacuolation is up to 1.6 times higher of the control group indicators (p=0.003÷0.012) (table 2).

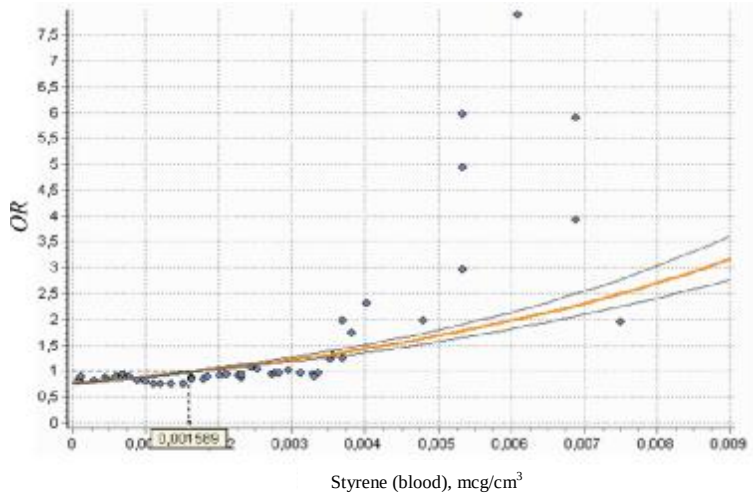

Fig. 3. Dependence of the odds ratio indicator (*OR*) of the increase in the frequency of morbidity with respiratory diseases on the styrene concentration in blood

Table 2

Frequency of changes in the exfoliative buccal epithelial cells for children in the age of 4-7 years with styrene concentration in blood above 0.003 mg/dm3, ‰ (p≤0.05)

Indicator	Observation group (M±m)	Control group (M±m)	Reliability of differences (p)
Cytogenetic indicators			
Micronucleus	0,86±0,16	0,64±0,09	0,022
Nuclear protrusions of type "tongue"	0,45±0,09	0,31±0,06	0,010
Nuclear protrusions of type "broken egg"	0,14±0,02	0,09±0,03	0,006
Indicators of destruction			
Nucleus with vacuolation	12,09±1,50	9,86±0,19	0,003
Cells with apoptotic bodies	0,95±0,24	0,59±0,15	0,012

The established biomarkers of cytogenetic disorders have the reliable relationship with styrene concentration in blood (F=55.4÷1558.0; R^2=0.54÷0.62; p=0.000).

As a result, we determined the benchmark styrene concentrations in blood for each marker of effect (represented in the change of laboratory indicator or increase in the frequency of diseases) at the chronic exposure of atmospheric air within the range of 0.002–0.005 mg/dm^3. Among the available number of the benchmark styrene concentrations in blood the lowest is 0.002 mg/dm^3 which corresponds to the average daily styrene concentration in the atmospheric air at the level of 0.002 mg/m^3 that confirms the value of the average daily styrene MPC in the atmospheric air of population clusters applicable in Russia.

Conclusions. Generalizing the results of epidemiological studies of the children population performed in accordance with principles of the international risk assessment practice in order to verify the average daily styrene MPC in the atmospheric air of population clusters demonstrated:

– at the content of styrene in the atmospheric air of population clusters at the level of 0.002 mg/m^3 and more the chidren of residential territories located in the areas of exposure had the blood styrene at the level of 0.002 mg/dm^3 and more;

– at the styrene concentration in blood at the level of 0.002 mg/dm^3 and below we did not detect the reliable differences in the indicators of the body response reactions with the same in the children of control group and reliable relationships with styrene concentration in blood;

– at the styrene concentration in blood at the level of 0.003-0.004 mg/dm^3 and more that corresponds to styrene concentration in the atmospheric air equal to 1.2-1.4 of the average daily MPC and more we established the health disorders in the children population stipulated by exposure to styrene (atmospheric air) in the form of increase of morbidity with diseases of the central nervous system, endocrine system, respiratory and digestive organs, skin and development of negative effecrs in the form of cytolysis, pigmental exchange disorders, hormonal regulation, antioxidative activity, involvement of immunecompetent cells and cytogenetic disbalance;

– the concentration of 0.002 mg/dm^3 which corresponds to the average daily styrene concentration in the atmospheric air – 0.002 mg/m^3 (or 1 of the average daily MPC) is the benchmark styrene concentration in blood;

– the styrene concentration in the atmospheric air of 0.002 mg/m3 adopted in Russia ensures the safety to the health of population.

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