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Analysis of promising directions for improving the methodological part of the biological monitoring system at potentially hazardous chemical facilities (analytical review)

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ABSTRACT

Introduction. Currently in the Russian Federation, the practice of industrial medicine does not use methods of biological monitoring of organic compounds – an addition to industrial control, which consists in regularly measuring the content of biomarkers of harmful chemicals in the body of workers.

The purpose of the study is to analyze available scientific publications and methodological documents on biomarkers of harmful organic substances, to draw conclusions about the directions for the development of methodological support for biological monitoring of organic compounds in the Russian Federation.

Material and methods. Available scientific publications, methodological guidelines of Rospotrebnadzor, materials of the Russian Register of Potentially Hazardous Chemical and Biological Substances, and foreign methodological documents, in particular from the Agency for Toxic Substances and Disease Registry, USA, were used.

Results. A list of the most common harmful organic substances circulating at hazardous chemical facilities, their biomarkers and methods for measuring them in biological media was compiled. An analysis of domestic and foreign hygienic standards for the content of toxicants or their markers in biological media was performed.

Limitations. The analytical review of biological monitoring methods was carried out only for organic compounds and does not include inorganic substances.

Conclusion. The analytical review made it possible to identify the following necessary methodological elements for the implementation of biological monitoring in the Russian Federation: the development of at least 9 chemical-analytical methods for determining biomarkers in the biological environments of workers, the introduction of immunochromatographic methods when conducting biological monitoring of workers to clarify the reliability of anamnesis data on attitudes towards alcohol, smoking and medications, experimental studies on the detection and identification of biomarkers of exposure to a number of organic compounds, experimental substantiation of hygienic standards for the content of 15 substances in the air of the working area.

Keywords: *biomonitoring; biological control; chemical risks; toxic chemicals*

Compliance with ethical standards. The study does not require the submission of a biomedical ethics report.

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Introduction

According to methodological guidelines 2.1.10.3165–14, the central place in the assessment of chemical risk is assigned to “measuring a chemical substance (exposure marker) in the body of a patient (group of patients)” using biological monitoring methods reflecting the total content of harmful substances or their markers in the body when ingested from the environment by inhalation, through water, food, soil and consumer goods.

In the field of occupational medicine or occupational hygiene, biomonitoring should be understood as the study of biological materials of workers for the quantitative determination of harmful substances, their metabolites or their biochemical and/or biological parameters [1].

The development of the concept of biomonitoring is the transition to biological control, the main points of which were established in the methodological recommendations on biological control [2]. The key difference between biological monitoring and biological control is the existence of standards for the content of biomarkers in biological media, and, accordingly, the requirement of sensitivity to the biomarkers used [3].

Objective: to analyze the list of substances circulating at potentially chemically hazardous facilities and chemical risk markers and assess the possibility of their biological monitoring. To do this, it is necessary to inventory certified methods (measurement methods – MM, methodological guidelines – MG) for measuring substances or their biomarkers, domestic and foreign hygienic standards for the content of toxicants or their markers in biological media, evaluate, according to literature data, the suitability of certified methods for biological monitoring and formulate the main directions for the development of biological monitoring in the Russian Federation.

Results and their discussion

In the course of the work, data on controlled chemical factors at potentially chemically hazardous facilities serviced by the FMBA of Russia were analyzed.

The study had limitations: an analytical review of biological monitoring methods was performed only for organic compounds and does not include inorganic substances.

The field of application of biological monitoring methods is inorganic (for which appropriate chemical and analytical support has been developed and reference ranges of content in biological media), organic and organoelement compounds,

the determination of which is impossible when analyzing the elemental composition of a biological sample (emission and absorption spectral methods). However, a clear boundary between these classes of compounds cannot be established. Since some inorganic compounds that do not contain a carbon atom in the molecule form many biologically active condensation products with aldehydes and ketones in biological media [4], and their determination by inductively coupled plasma spectrometry or other methods characteristic of inorganic compounds is impossible in biological samples.

Considering the above, we conducted an inventory of methods, biomarkers and reference values suitable for biomonitoring personnel exposure to substances of hazard classes 1–4 according to GOST (State Standard) 12.1.007–76 (Tables 1–4), with the exception of inorganic elements, including “heavy metals”.

The exposure biomarkers in the table are divided into 6 conditional categories:

1. “Direct” biomarkers – the content of the non-metabolized form in biological media.
2. Biomarkers of the 1st phase of metabolism – products of interaction with oxidoreductases, hydrolases, etc.
3. Biomarkers of the 2nd phase of metabolism – glucuronides and sulfates.
4. Adducts with glutathione – products of interaction with glutathione (including acetylcysteine adducts, the so-called mercapturic acids) should be separated into independent group due to their prevalence and high significance as markers.
5. Adducts with deoxyribonucleic acid nucleotides (hereinafter referred to as DNA).
6. Adducts with biological macromolecules, in particular including hemoglobin, blood proteins, mainly albumin, and lipids.

The analysis of the data presented in Table 1 shows that biological monitoring methods have already been developed or may be developed for only 2 out of 9 extremely dangerous substances. However, for an extremely dangerous compound – 2,3,7,8-tetrachlorodibenzo-para-dioxin, which acts in such low concentrations, the required limits for the quantitative determination of a direct biomarker are unattainable at this technological level.

Biological monitoring of only 3 substances from Table 1 (benz[a]pyrene, UDMH and vinyl chloride) can be carried out without additional studies. To improve the chemical and analytical support for biological monitoring of extremely dangerous compounds at facilities serviced by the FMBA of Russia, it is necessary to develop methods for measuring biomarkers of propylene oxide, nitroglycerin, 2,4-toluene diisocyanate, ozone and dioxins.

Table 1

Inventory of methods, biomarkers and reference values suitable for biomonitoring of personnel exposure to extremely dangerous substances

Substance	Validated methods of biomonitoring	Candidate biomarkers
Benzo[a]pyrene	3-hydroxybenzo[a]pyrene in urine (FR.1.31.2018.32029) from 1.0 to 100 ng/L	<i>Straight biomarkers:</i> benzo[a]pyrene in urine 0.01–4.0 mkg/L (MG 4.1.3041–12) benzo[a]pyrene in blood 0.02–2.00 mkg/L (MG 4.1.3040–12) <i>DNA adducts</i> [5]
Ozone (O ₃)	None	<i>Biomarkers of exposure:</i> 3 α -hydroxy-5-oxo-5,6-secocholestan-6-al and 3 β -hydroxy-5-oxosecocholestan-6-oic acid in blood or urine [6, 7]
1,1-Dimethylhydrazine (UDMH)	Pyridoxal dimethylhydrazone in urine [8] (FR.1.31.2023.47016)	<i>Phase 1 biomarkers:</i> Dimethylhydrazones of pyridoxal and pyruvic acid in urine
N-Nitrosodimethylamine (NDMA)	NDMA in urine (MG 4.1.3231–14)	<i>Biomarkers of methylating agents:</i> methyl mercapturic acid in urine methylated nucleotides in the blood: N ₇ -methylguanine (main), N ₃ -methyladenine and O ₄ -methylthymine, antibodies to 7-methylguanine [9]
Vinyl chloride	Thiodiacetic acid in urine according to MG 4.1.3475–17 [10, 11]	<i>Straight biomarker:</i> Vinyl chloride in the blood (MG 4.1.3056–13) <i>Phase 1 biomarkers:</i> Chloroacetic acid in urine (MG 4.1.3477–17) <i>Adducts with glutathione:</i> Thiodiglycolic acid* (MG 4.1.3474–17) N-acetyl-S-(2-hydroxyethyl)cysteine** S-formylmethylcysteine S-carboxymethylcysteine S-(2-hydroxyethyl)cysteine <i>Adducts with DNA:</i> 7-(2-oxoethyl)guanine (basic), N _{2,3} -ethenoguanine – a marker of genotoxic effect. Adducts with hemoglobin are unknown.
2,4-Toluene diisocyanate	None	<i>Albumin adducts in the blood at a lysine residue</i> (expected concentrations 29 to 269 fmol/mg albumin) N-[(3-amino-4-methylphenylamino)carbonyl]lysine N-[(5-amino-2-methylphenylamino)carbonyl]lysine N-[(3-amino-2-methylphenylamino)carbonyl]lysine <i>Albumin adducts in urine based on a lysine residue:</i> N-4-[(4-aminobenzyl)phenylamino]carbonyllysine N-4-[(4-acetylaminobenzyl)phenylamino]carbonyllysine Antibodies (IgG and IgE) to albumin adducts (antiTDI-HAS)
Nitroglycerine	None	<i>Phase 1 biomarker:</i> 1,2-dinitroglycerol in the blood [12]
Propylene oxide	None	<i>Adduct with hemoglobin at a valine residue:</i> N-(R,S)-2-hydroxypropylvaline [39] – the expected concentration is 80 pmol/g globin <i>Adducts with glutathione:</i> N-acetyl-S-(2-hydroxypropyl)-L-cysteine in urine [13] <i>Adducts with DNA:</i> adducts with DNA – N ₇ -(2-hydroxypropyl)guanosine N ₃ -(2-hydroxypropyl)adenosine N ₆ -(2-hydroxypropyl)adenosine in the blood [14]
Dioxins	None	The most promising biomarkers of the effect are markers of oxidative stress [15]

Note. * – common biomarker for vinylidene chloride, ethylene oxide and 2,2-dichloroethyl ether; ** – common biomarker with acrylonitrile.

Table 2

Inventory of methods, biomarkers and reference values suitable for biomonitoring of personnel exposure to highly dangerous substances

Substance	Validated methods of biomonitoring	Candidate biomarkers
Formaldehyde	None	<i>Biomarkers of the 1st phase:</i> Hydroxymethylurea Bis-(hydroxymethyl)-urea <i>Абдукты с ДНК:</i> N6-hydroxymethyldeoxyadenosine N2-hydroxymethyldeoxyguanosine <i>Phase 2 biomarkers:</i> Thiazolidinecarboxylic acid Thiazolidinecarbonylglycine [18]
Hydrogen sulfide (H ₂ S)	None	<i>Biomarkers of the 1st phase:</i> Thiosulfate in urine
Styrene	None	<i>Adducts with hemoglobin at valine and cysteine residues:</i> N-(2-hydroxyethyl)-valine (most sensitive biomarker) <i>DNA adducts:</i> with guanine at N ₂ with adenine at N ₆ with cytosine at O ₂ with thymidine at N ₃ [19] <i>Interference:</i> ethylbenzene
Benzene	Benzene in blood according to MG 4.1.765–99	<i>Phase 1 biomarkers:</i> E,E-muconic acid in urine (outdated standard – 500 mcg/g creatinine) <i>Adducts with hemoglobin and albumin</i> [21] <i>Adducts with DNA:</i> 3,4-dihydroxyphenyladenine [22] (unstable)
Epichlorohydrine	None	<i>Phase 1 biomarkers:</i> α-chlorohydrin in urine <i>Glutathione biomarkers:</i> 3-chloro-2-hydroxypropyl-mercapturic acid in urine [23] 2,3-dihydroxypropylmercapturic acid in urine [23] <i>Adducts with hemoglobin:</i> N-(3-chloro-2-hydroxypropyl)valine [24]
Acrolein	Acrolein in blood according to MG 4.1.3158–14 [25]	<i>Glutathione biomarkers:</i> N-acetyl-S-(3-hydroxypropyl)-L-cysteine in urine N-acetyl-S-(carboxyethyl)-L-cysteine in urine [26] <i>Adducts with proteins:</i> IgG antibodies to acrolein adducts with proteins [27] IgG specific to acrolein [25] <i>Adducts with DNA:</i> Deoxyguanosine adduct [28]
Phenol	Phenol in urine MG 4.1.2107–06 Phenol in blood MG 4.1.2108–06	<i>Interference:</i> phenol is a metabolite of benzene and a product of the metabolism of certain proteins. It is possible to discriminate between exposure to benzene based on a specific metabolite – <i>trans-trans</i> -muconic acid
Trichloromethane	Chloroform in blood MG 4.1.2112–06	<i>Adducts with proteins:</i> Adducts of the most toxic metabolite of trichloromethane, phosgene, with histones [29], globin and albumin [30]
Carbon tetrachloride	Carbon tetrachloride in urine according to MG 4.1.2113–06 and in blood according to MG 4.1.2112–06	According to EPR spectroscopy data, carbon tetrachloride (the most reactive intermediate is the trichloromethyl radical) forms adducts with proteins, lipids and nucleotides [31], however, studies on the detection and identification of biomarkers could not be found in the available literature
N,N-dimethylformamide	None	<i>Adducts with glutathione:</i> N-acetyl-S-(N-methylcarbamoyl)cysteine (ACGIH limit set at 40 mg/L) <i>Adducts with hemoglobin:</i> N-methylcarbamoylvaline N-methylcarbamoyl-lysine [32]

Continuation of Table 2 on page 155.

Continuation of Table 2. Beginning on page 154.

Substance	Validated methods of biomonitoring	Candidate biomarkers
Acrylonitrile	Acrylonitrile in blood and urine according to MR FMBA of Russia 4.1.23–2014 [37]	<i>Adducts with glutathione:</i> Thiocyanate in urine N-acetyl-S-(2-cyanoethyl)-l-cysteine N-acetyl-S-(1-cyano-2-hydroxyethyl)-l-cysteine N-acetyl-S-(2-hydroxyethyl)-l-cysteine N-acetyl-S-(carboxymethyl)-l-cysteine [38] <i>Adducts with hemoglobin:</i> N-2-cyanoethylvaline [39] <i>Adduct with DNA:</i> 7-(2-oxoethyl)deoxyguanosine [40]
Ethanethiol	None	Unknown
Dimethylamine	None	Trimethylamine oxide ¹ <i>Interference:</i> formaldehyde
Tetrachlorethylene	None	<i>Straight biomarkers:</i> Tetrachlorethylene in the blood (maximum concentrations not more than 0.5 mg/L) <i>Phase 1 biomarkers:</i> Trichloroacetic acid in urine (limit concentrations not more than 3.5 mg/L) 2,2,2-Trichloroethanol <i>Adducts with glutathione in urine:</i> S-trichlorovinylglutathione N-acetyl-S-trichlorovinyl-L-cysteine (expected concentration 2.2–14.6 pmol/mg creatinine) <i>Adducts with proteins:</i> N-(dichloroacetyl)-L-lysine [41]
2-chloroprene	None	<i>Adducts with glutathione in urine:</i> S-3-chloro-2-hydroxy-3-butenyl-L-cysteine (expected concentration 6.1 µg/g creatinine) N-acetyl-S-3,4-dihydroxybutyl-L-cysteine (limit concentrations not more than 400 µg/g creatinine) N-acetyl-S-4-chloro-3-oxobutyl-L-cysteine, N-acetyl-S-4-chloro-3-hydroxybutyl-L-cysteine N-acetyl-S-4-hydroxy-3-oxobutyl-L-cysteine and N-acetyl-S-3,4-dihydroxybutyl-L-cysteine [42] <i>Phase 1 biomarkers:</i> 3-chlorobut-3-ene-1,2-diol; 1-chlorobut-3-en-2-one; 2-chlorobut-2-en-1-ol
Aniline	None	<i>Phase 1 biomarkers:</i> <i>p</i> -aminophenol in urine N-acetyl-4-aminophenol ² Acetanilide (N-acetylaniline) <i>Phase 2 biomarkers:</i> N-acetyl-2-aminophenol in the form of glucuronides and sulfates. <i>Adducts with glutathione in urine:</i> N-acetyl-4-aminophenolmercapturic acid [43]. <i>Biomarker of effect:</i> Methhemoglobin [44]
Formic acid	None	Biogenic compound: 13.6 µg/ml (1.0–95 µg/ml) ³ <i>Interference:</i> formaldehyde and methanol
1,2,4-Trimethylbenzene	None	<i>Phase 1 biomarkers:</i> Dimethylbenzoic acid in urine [45] <i>Adducts with glutathione in urine:</i> N-acetyl-S-(2,4-, 2,5- and 3,4-dimethylphenyl)-L-cysteines [46]
Butyl acrylate	None	<i>Phase 1 biomarkers:</i> 3-hydroxypropionic acid <i>Adducts with glutathione in urine:</i> N-acetyl-S-(2-carboxyethyl)-cysteine and N-acetyl-S-(2-carboxyethyl) cysteine sulfoxide [47] <i>Interference:</i> acrylic acid derivatives
Methylbenzene-1,4-dicarbonatamide	None	Unknown

Note. ¹ Dimethylamine [MAK Value Documentation, 1996] 1996. Documentations and Methods.

² Used as a medicine Paracetamol.

³ https://www.testcatalog.org/show/FORAU

Table 3

Inventory of methods, biomarkers and reference values suitable for biomonitoring of personnel exposure to moderately dangerous substances

Substance	Validated methods of biomonitoring	Candidate biomarkers
Toluene	Toluene in urine (MG 4.1.764–99)	<i>Straight biomarkers:</i> Toluene in urine (30 µg/l at the end of the shift) <i>Phase 1 biomarkers:</i> Total ortho-cresol (0.3 mg/g cre at end of shift) Benzyl alcohol <i>Phase 2 biomarkers:</i> Hippuric acid <i>Adducts with glutathione in urine:</i> S-benzyl- and S-para-toluyll mercapturic acids [50]
Acetaldehyde	None	<i>Adducts with DNA:</i> N2-ethylidene-deoxyguanosine [18] N2-ethyl-2'-deoxyguanosine N6-ethyl-2'-deoxyadenosine [51] <i>Adducts with glutathione in urine:</i> Methylthiazolidinecarboxylic acid Methylthiazolidinecarbonylglycine [52] <i>Adducts with proteins:</i> Antibodies (IgG) to acetaldehyde adducts with proteins [53] <i>Interference:</i> ethanol
Butanol-1	Butanol in blood (MG 4.1.772–99)	Biogenic compound [54] <i>Interference:</i> butane [55]
Dimethylbenzene (mixture of ortho-, meta-, para-isomers)	None	<i>Phase 2 biomarkers:</i> 2-Methylhippuric acid (from o-xylene) 3-Methylhippuric acid (from m-xylene) 4-Methylhippuric acid (from p-xylene) Expected concentrations are 16.5 ng/ml at 4-hour exposure 27 mg/m ³ , 9.9 ng/ml at 13.5 mg/m ³ [56] <i>Adducts with glutathione:</i> Minor metabolites unsuitable for monitoring: N-acetyl-S-xylylcysteines [57]
Isopropanol	Acetone in urine (MG 4.1.763–99)	<i>Phase 1 biomarker:</i> Acetone in urine (dependence on exposure to isopropanol has been established: acetone concentration in urine (mg/l) = 0.031 • isopropanol concentration in air (ppm) + 0.608 [58]
Ethylbenzene	None	<i>Phase 1 biomarkers:</i> Mandelic acid Phenylglyoxalic acid <i>Interference:</i> styrene
Acetic acid		The level of acetate content in human blood is 3.0–3.6 mg/L [59]
Mixture of saturated hydrocarbons C ₆ H ₁₄ –C ₁₀ H ₂₂		<i>Phase 1 biomarkers:</i> 2,5-hexanedione (3 mg/g creat. at an average daily hexane concentration in the air of 50 ppm) Hexanon-2 Hexanol-1 Heptanone-2 (from heptane) Octanol-1 (from octane) [60] <i>Adducts with proteins:</i> Dimethylpyrrolnorleucine in urine is a selective and specific marker of chronic exposure n-hexane [61]

Continuation of Table 2 on page 157.

Continuation of Table 3. Beginning on page 156.

Substance	Validated methods of biomonitoring	Candidate biomarkers
Methyl methacrylate	Methyl methacrylate in blood and urine (MR FMBA of Russia 4.1.23–2014)	<i>Straight biomarker:</i> Methyl methacrylate in blood and urine (rapidly eliminated from blood [62]) <i>Phase 1 biomarkers:</i> Methacrylic acid Methanol [63] There is little data on the content of people in biological environments to establish the suitability of the measurement technique. <i>Interference:</i> methanol
Distillate (petroleum) hydrotreated	None	Unknown
Shale phenols	Phenol in urine (MG 4.1.2107–06)	See phenol
2,4,6-Trinitrotoluene	None	<i>Phase 1 biomarker:</i> 4-amino-2,6-dinitrotoluene in urine (major) 2-amino-2,6-dinitrotoluene in urine <i>Adducts with proteins:</i> Adducts with hemoglobin (HPLC and ELISA) [64] Adducts of 4-amino-2,6-dinitrotoluene with globin (522 ng/g globin after hydrolysis) [65]
Hexanoic acid	Hexanoic acid in blood (MG 4.1.2773–10)	High biogenic level. There is insufficient data on the content in biological media under industrial conditions. Normal: 0.035–0.2 mmol/mol creatinine in urine and 17 (0–105) µM in blood (0–12 µg/ml)
Pentanoic acid	Pentanoic acid in blood from 0.5 to 16 µg/ml (MG 4.1.2773–10)	High biogenic level. There is insufficient data on the content in biological media under industrial conditions. Normal: 0.6 (0.3–1.2) µM (according to HMDB) (30–122 ng/ml) and 4.0 ± 4.5 µmol/mmol creat.
Trichlorethylene	None	<i>Straight biomarker:</i> Trichlorethylene in the blood (1 mg/L at the end of the shift) <i>Phase 1 biomarkers:</i> Trichloroacetic acid in urine (100 mg/g creat.) Trichloroethanol in the blood (4 mg/L in the USA, 5 mg/L in Germany) The amount of trichloro derivatives in urine (300 mg/g creat.) [66]

MG 4.1.2110–06, MG 4.1.2111–06 and MG 4.1.2771–10 are not suitable for biomonitoring of formaldehyde in biological media, since the expected background concentrations are 31–58 mcg /L of urine, which is below the limits of determination [48]. MG 4.1.2116–06 are not suitable for the determination of styrene, since the expected concentrations in urine are below the limit of quantitative determination, similarly, MM aniline in the blood in the range of 0.035–0.2 mcg/cm (MG 4.1.767–99) and aniline in urine in the range of 0.045–2.0 mcg/mL (MG 4.1.766–99) do not allow biomonitoring: the expected concentrations of aniline are 22 ng/mL in workers after shift [49] at TWA of 19 mg/m³.

Common highly dangerous substances at facilities serviced by the FMBA of Russia are sulfuric and hydrochloric acids (at the 98th and 21st facilities, respectively), which were not included in

Table 2 due to their inorganic nature. However, it is impossible to determine them in biological media by methods of elemental analysis. Biomarkers of exposure to them are unknown. A possible direction in the search for approaches to their biological monitoring is the search for highly sensitive biomarkers of the effect.

Biological monitoring of 6 of the 22 substances from Table 2 (benzene, phenol, acrolein, chloroform, carbon tetrachloride and acrylonitrile) can be carried out without additional studies. To improve the chemical and analytical support for biological monitoring of highly hazardous compounds at facilities serviced by the FMBA of Russia, it is necessary to develop methods for measuring biomarkers of formaldehyde, styrene, epichlorohydrin, dimethylformamide, dimethylamine, tetrachloroethylene, aniline, trimethylbenzene and butyl acrylate.

Table 4

Inventory of methods, biomarkers and reference values suitable for biomonitoring of personnel exposure to low-hazard substances

Substance	Validated methods of biomonitoring	Candidate biomarkers
Gasoline (petroleum, low sulfur)	None	See hydrocarbons C ₆ –C ₁₀
Acetone	Acetone in urine (MG 4.1.763–99)	High nutrient background: 10 mg/L in unexposed healthy people <i>Interference:</i> propane, isopropanol
Ethanol	Ethanol in blood (MG 4.1.772–99) and urine (MG 4.1.771–99)	<i>Straight biomarker:</i> Ethanol in blood and urine <i>Phase 1 biomarkers:</i> Ethyl esters of fatty acids; Phosphatidylethanol <i>Phase 2 biomarkers:</i> Ethyl glucuronide in urine <i>Adducts with proteins:</i> Acetaldehyde adducts with hemoglobin (including ELISA for IgA to adducts) [67] <i>Biomarker of effect:</i> Change in CDT concentration ¹ <i>Interference:</i> acetaldehyde
Butyl acetate	None	<i>Straight biomarker:</i> Butyl acetate in urine [68] <i>Interference:</i> 1-butanol and acetic acid
Methane	None	Exposure biomarkers are unknown
Alkanes C ₁₂ –C ₁₉ (converted to C)	None	Unknown
Ethyl acetate	None	<i>Straight biomarker:</i> Ethyl acetate in urine [68]
Mixture of saturated hydrocarbons C ₁ H ₄ –C ₅ H ₁₂	Acetone in urine (MG 4.1.763–99)	<i>Phase 1 biomarkers:</i> Acetone (from propane); <i>Tret</i> -butanol (from isobutane); Butanone (from butane); Butanol-1 (from butane) [55] <i>Interfering influence:</i> acetone, isopropanol, butanol-1
Odorant	None	Unknown
White Spirit	None	See hydrocarbons C ₆ –C ₁₀
Dichloromethane	None	<i>Straight biomarker:</i> Dichloromethane in blood and urine. <i>Biomarker of effect:</i> Methemoblin

Note. ¹ Carbohydrate-deficient transferrin is a biomarker of chronic alcohol consumption (more than 60 grams of ethanol per day). Reference values: 0–1.6%.

For biological monitoring of methylbenzene-1,4-dicarbonate amide, ethanol and formic acid (biogenic compound), experimental studies are required to detect and identify possible exposure biomarkers.

The certified method of measuring acetaldehyde in bile (MG 4.1.2771–10) is an invasive procedure and, according to this criterion, is not suitable for continuous biomonitoring. The estimate of the expected content of xylenes in the blood (32 ng/mL) slightly exceeds the lower limit for the quantitative determination of MM xylenes in the blood of 0.014–0.1 mcg/mL (MG 4.1.765–99).

Common moderately dangerous substances at facilities serviced by the FMBA of Russia are nitrogen dioxide (NO₂), sulfur dioxide and monoxide nitrogen. Biomarkers of exposure to them are unknown.

Biological monitoring of 4 of the 18 substances from Table 3 (methyl methacrylate, isopropanol, butanol-1 and toluene) can be carried out without

additional studies. Certified methods are known for the determination of acetic, pentanoic and hexanoic acids, but there is no data on their toxicokinetics in production conditions, therefore, it is difficult to assess the suitability of the methods. To assess the suitability of the method for determining phenol in urine for biological monitoring of the effects of a complex mixture of variable composition “shale phenols”, additional studies of biological samples of personnel of potentially chemically hazardous facilities are necessary.

Experimental studies on the detection and identification of exposure biomarkers will be required to develop methods for biological monitoring of a complex mixture of “distillate (petroleum) hydrotreated”.

To improve the chemical and analytical support for biological monitoring of moderately hazardous compounds at facilities serviced by the FMBA of Russia, it is necessary to develop methods for

measuring biomarkers of acetaldehyde, xylenes, styrene, C₆–C₁₀ hydrocarbons, trinitrotoluene and tetrachloroethylene.

The most common low-hazard substance at facilities serviced by the FMBA of Russia is carbon monoxide, for biological monitoring of which the determination of carboxyhemoglobin in the blood is used, which is both an exposure biomarker and an effect biomarker.

Biological monitoring of 3 of the 11 substances from Table 3 (mixtures of marginal hydrocarbons C₁H₄–C₅H₁₂, ethanol and acetone) can be carried out without additional studies.

Methane does not undergo biotransformation and has no biomarkers.

To improve the chemical and analytical support for biological monitoring of low-hazard compounds at facilities serviced by the FMBA of Russia, it is necessary to develop methods for measuring biomarkers of hexane-containing substances: gasoline (petroleum, low-sulfur), white spirit, C₆–C₁₀ hydrocarbons, butyl acetate, ethyl acetate and dichloromethane. Experimental studies on the detection and identification of exposure biomarkers will be required to develop methods for biological monitoring of complex mixtures: "odorant" and "alkanes C₁₂–C₁₉".

The maximum concentrations of biomarkers of organic compounds in biological media, established or proposed by domestic or foreign regulatory documents, are known only for 2 extremely dangerous organic compounds (2,4-toluene diisocyanate and nitroglycerin), 7 highly dangerous (formaldehyde, styrene, benzene, phenol, 2-chloroprene, tetrachloroethylene and N,N-dimethylformamide), 8 moderately hazardous (dimethylbenzenes, ethylbenzene, toluene, trichloroethylene and hexane-containing substances) and 2 low-hazard (acetone and dichloromethane).

Conclusions

Based on the completed review, it is possible to identify the following promising areas for improving the methodological part of the biological monitoring system at facilities serviced by the FMBA of Russia:

1. Development of 8 chromatomass spectrometric methods:

- determination of 5 mercapturic acids in urine by HPLC-MS: N-acetyl-S-(2-hydroxypropyl)-L-cysteine; 3-chloro-2-hydroxypropyl mercapturic acid, N-acetyl-S-trichlorovinyl-L-cysteine, N-acetyl-S-3,4-dihydroxybutyl-L-cysteine, N-acetyl-S-(2-carboxyethyl)-cysteine in urine, methyl mercapturic acid;
- definitions of pyridoxal dimethylhydrazone;

- 3 α -hydroxy-5-oxo-5,6-secocholestane-6-ala and 3 β -hydroxy-5-oxosecocholestane-6-ovoy? acids in the blood or urine;
- determination of 2-, 3- and 4-methylhyppuric, trichloroacetic, dimethyl benzoic, almond and phenylglyoxalic acids in urine;
- determination of 1,2-dinitroglycerin in the blood;
- determination of total toluene diamine, N-methylformamide, dimethylamine, para-aminophenol, total 2,5-hexanedione, 4-amino-2,6-dinitrotoluene, butyl acetate, ethyl acetate and dichloromethane in urine;
- determination of thiosulfate in urine;
- determination of markers of methylating agents (including NDMA) in the blood: N₇-methylguanine (basic), N₃-methyladenine and O₄-methylthymine.

2. Development of enzyme immunoassay methods for the determination of antibodies to albumin adducts with formaldehyde and toluene diisocyanate, proteins with acetaldehyde, 7-methylguanine and antibodies to proteins oxidized with hypochlorous acid (antiHOP) [34].

3. The introduction of an immunochromatographic method for determining the metabolite of nicotine (cotinine) during biological monitoring of personnel to clarify the reliability of anamnesis data on attitudes to tobacco smoking. Combined exposure to tobacco smoke may affect the reliability of biological monitoring: benz[a]pyrene, acrolein and acrylonitrile, as well as a number of inorganic compounds.

4. The introduction of a study based on the principle of a sample of unknown composition in accordance with the Methodological recommendation of the FMBA of Russia 4.1.23–2014 during the biological monitoring of personnel to identify the combined effects of a chemical factor, as well as drugs. For example, the use of paracetamol will distort the data of biological monitoring of aniline, and a number of other drugs can change the toxicokinetics of biomarkers of harmful substances in the human body.

5. Conducting research to determine the content of markers of acetic, pentanoic, hexanoic acids, shale phenols, in the biological environments of personnel of potentially chemically hazardous facilities and to evaluate the suitability of certified methods for biological monitoring.

6. Experimental studies on the detection and identification of biomarkers of exposure to methylbenzene-1,4-dicarbonatamide, ethanethiol, formic acid, as well as complex mixtures "odorant", "alkanes C₁₂–C₁₉" and "distillate (petroleum) hydrotreated".

7. Experimental substantiation of the hygienic standards missing in Sanitary rule 1.2.3685–21 for the content of 15 substances in the air of the working

area: benz[a]pyrene, N-nitrosodimethylamine, 2,4-toluylenediisocyanate, dioxins, methylbenzene-1,4-dicarbonatamide, mixtures of marginal hydrocarbons $C_{14}H_{10}$ – $C_{15}H_{12}$, alkanes C_{12} – C_{19} , distillate (petroleum) hydrotreated, odorant, shale phenols, 1,4-dimethylbenzene, isopropanol, 1,2-dimethylbenzene, 1,3-dimethylbenzene and 2,4,6-trinitrotoluene.

8. Development of a method for the determination of nitro derivatives of polyaromatic hydrocarbons to discriminate against the negative effects of vehicles.

9. Substantiation of the direction of biological monitoring of common inorganic compounds undetectable by elemental analysis methods: nitrogen dioxide (NO₂), sulfur dioxide (SO₂), nitrogen monoxide (NO), sulfuric acid and hydrochloric acid.

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