WATER MONITORING:
ESTIMATION OF BIOLOGICAL HAZARD OF ORGANIC XENOBIOTICS
(methodological aspects)

The problem of assessing the biological activity of organic xenobiotics using calculations like «structure – activity» is considered. This issue arises due to the fact that the number of anthropogenic and natural xenobiotics in environment exceed the maximum allowable concentrations. Examples of such calculations for xenobiotics detected in water bodies illustrate the practical solution of the problem.

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Introduction

The issues dealing with protection of natural water from effects of anthropogenic factors as well as the problems associated with recovery of polluted water to the initial natural status belong to the most important challenges in practical ecology. Resolving these issues should harmonize the living mankind in natural habitat and give a positive impetus into the sustainable development of international community.

Using one of the development models and carrying out a comparative analysis of the trends in increasing water consumption and pollution for the next one hundred years we can conclude that as early as in 2030 the basis of water consumption will be provided by polluted water (*Fig. 1*).

More optimistic pollution dynamics models defer this term by some 20-30 years. These generalized data does not reflect distribution of underlying components over geographic zones, continents and countries; some of them already feel this pressure, whereas others are about to face the pending water deprivation. For instance the majority of large Russian rivers including the Volga River are typically (sometimes pretty heavily) polluted either along the whole length of the river or locally [1].

High pollution level in natural sources of drinking water brings about the issue of protecting population and hydrobionts from negative effects of anthropogenic chemicals acting as water pollutants.

Results and Discussion

Formulation of the problem

Accounting for mentioned above, identifying polluting substances, determining their concentration in water and revealing their biological hazard is a task of ultimate practical importance. Let us consider some issues associated with these challenges. Let us start with a general outline of the set of chemical compounds.

The second half of the 20th century and the first decade of the 21st century were marked with intensive growth in the number of chemicals. The general magnitude of the size of this set is provided in *Fig. 2*; the Figure was compiled using the Chemical Abstract Service (CAS) data [2]; CAS is the service recognized as an international register (in addition there are other unique identifiers: InChI codes (project IUPAC – http://www.iupac.org/inchi/), project PubChem – http://pubchem.ncbi.nlm.nih.gov/).

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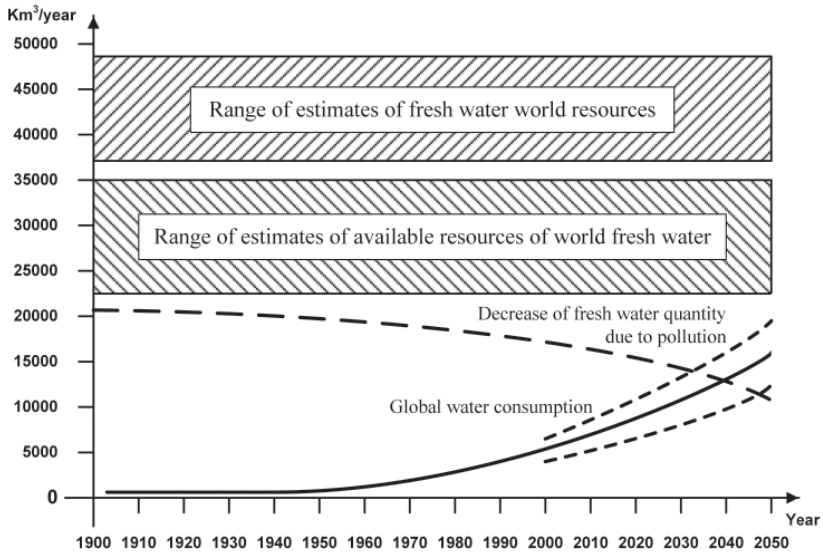


Fig.1. Water resources, water needs, decrease of fresh water quantity due to pollution (the average trend according to different scenarios) and global water consumption (according to three different models) [1]

During the last five years as many as 50 000 new chemicals [3] have been annually added to this list. This set is dominated by organic compounds.

In practice as many as 5 000 000 chemicals having anthropogenic origin are used among which the organic compounds are dominant [5].

All chemical – anthropogenic or natural alike – are potentially biologically active. The degree of this activity depends only on concentration and the type of biological target plus some other factors [4].

Xenobiotics can be represented by organic and inorganic compounds as well as by some chemical elements. These are organic substances that form the dominant part of xenobiotics. The major part of mutagens, carcinogens, embryotoxins and other types of toxic compounds belong to anthropogenic organic xenobiotics [4]. The degree of impact and the type of biological activity of a specific xenobiotic can vary depending on the influence of other chemicals (additivity, synergism or antagonism).

Given the magnitude of the chemical set and the number of compounds practically used, accounting for the share of xenobiotics in this set we should consider this set as a universal chemical «domain», which influences practically all biotic entities including humans [6]. Taking into account the biological activity of all chemicals and degree of spreading anthropogenic chemicals we can introduce the concept of «chemiosphere».

It is useful to classify the main constituting chemiosphere components accounting for their origin breaking them into two main groups:

1) chemicals of anthropogenic origin particularly including the following:

- chemicals used in industry, in power generation, in transportation, in agriculture, designed for communal and military use (except chemical war gases);
- chemicals produced as industrial waste materials;
- chemicals that provide the designated positive effect on humans (medicines, vitamins, food additives, etc.);
- chemicals that provide designated negative effect on humans (poisons, chemical war gases, etc.);
- chemicals used to study living objects in biology, medicine and other areas;
- chemicals used as reagents in fundamental research studies (outside living matter), intermediate and by-products of chemical synthesis, etc.;
- Other chemicals.

2) chemicals having natural anthropogenic and anthropogenic natural origin:

- Chemicals produced from natural objects and substances;
- Anthropogenic chemicals subject to natural transformation;

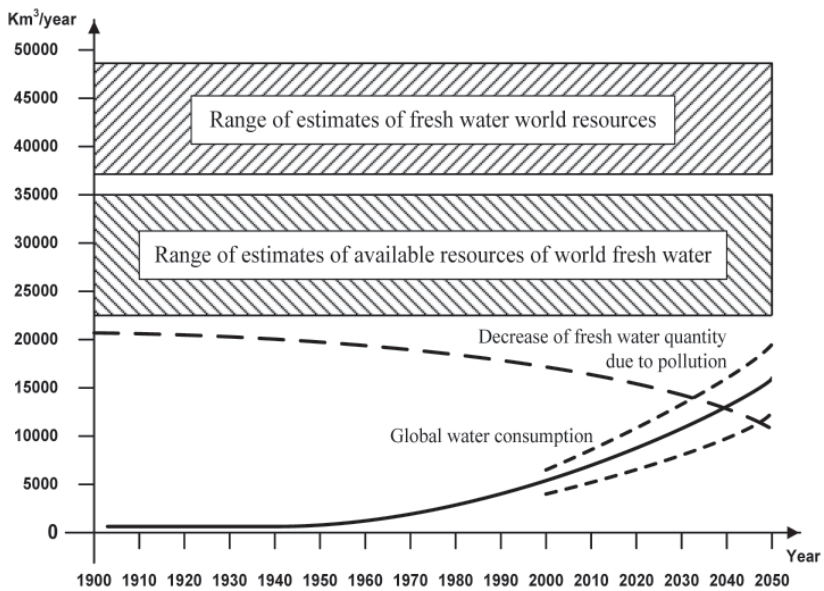


Fig. 2. Increase in the quantity of chemical compounds registered in CAS. [2-4]

- Chemicals synthesized as natural analogues;
- Other chemicals.

The effect of chemiosphere is applicable to the natural water as water is accessed by anthropogenic xenobiotics, including organic xenobiotics.

Physics chemical, chemical and biological transformation of initial polluting organic substances brings about the secondary pollutants or pollutants of the next order. Many of these secondary tier substances can potentially be new chemical structures not listed in CAS register.

It is obvious that the amount of the different organic substances acting as water polluting agents can be much larger than the existing pool for which the regulatory maximum allowed concentration is set out.

This concept is illustrated by the original data of one of the authors shown in *Table 1* (see also *Fig. 3*).

Therefore, in order to resolve the issues dealing with protection of the water bodies and secure water supply (free from organic xenobiotics) it is required to detect and then evaluate the biological hazard to be followed by recommendations to mitigate the potential ecological risks.

Developing methodological aspects to detect organic xenobiotics and determine their biological activity.

Area of study

There are several areas to look for organic xenobiotics in water, namely: 1) the search for specific substances; 2) the search broken down into chemical classes; 3) the search broken down into classes of functional designation of the substances; 4) the search accounting for pollutant profile (industrial area); 5) the search against the priority of hazardous substances; 6) total screening; 7) the search using other criteria. We should mention that the types of search often overlap.

For instance, when analyzing water bodies that are used to supply drinking water to Moscow, the following groups of substances were analyzed: 1) semi-volatile organic compounds of aromatic and cyclic series; 2) volatile chlorine organic substances; 3) chlorine organic substances (polychlorinated biphenyls, chlorophenols, etc.); 4) synthesized detergent substances (anionic and non-ionogenic); 5) petroleum hydrocarbons; 6) organic acids; 7) some other organic substances. In addition, the presence of

Table 1

Organic compounds detected in some in-land water bodies (illustrating examples)

Item	Water body	Medium analyzed		Content	Established MAC*
		Water	BS*		
1.	Volga River Cheboksary reservoir, area adjacent to Cheboksary water treatment plant	34	83	Phenols Hydrocarbons of oil refining origin, cyclic aromatics, chlorine and brome organics, organic acids etc.	4
2.	Volga River collecting area Sura River (meeting Cheboksary reservoir)	37	98		3
3.	Volga River Kujbyshevsk reservoir (downstream of Cheboksary Hydro Power Plant)	81	128		5

*List of abbreviations: MAC – maximum admissible concentration; BS – bottom sediments.

Fig. 3. Geographical location of water bodies mentioned in *Table 1*. On the map there are water bodies where samples were taken but not the exact sites of their sampling.

specific pesticide groups is analyzed within the scope of this methodology.

Stages of work.

The first stage to identify xenobiotics and to determine their biological activity began with choosing the water body to be assessed, setting forth the investigation goals, collecting the available relevant information including the pollution data. Specifically, this stage involves collecting existing information on the water body and the analytical data on the water quality. This information should contain the purpose of water use, the long term historical water pollution data, the list of experimental methods used to determine the pollution level, the list of main polluting sources. It is also necessary to compile the list of principal characteristics of the water body; it is recommended to get hold of the data on hydro-biological water assay, etc. As a result the representative data base is being formed.

On the second stage the organic xenobiotics are identified. In fact, this is a standard procedure that entails collecting samples, preparing samples for analysis, the analytical work itself which most often involves chromatography, chromatographic mass spectrometry and/or optical spectroscopy [7, 8]. At the end of this stage the comparison is made between the experimental spectra and published data borrowed from various data bases. One of the issues of application of this procedure deals with the right choice of extracting solvent having adequate polarity as well as determination of completeness degree of extraction process.

Key words:
water monitoring,
water pollution,
organic xenobiotics,
biological activity,
calculation
of "structure-activity"
relationships

To optimize the analytical work, the database (DB) was developed at this stage to give guidelines to determine classes of organic compounds. These methods were recommended in previous publications for as many as 200 substances belonging to different classes of compounds. As reference sources we took the registers outlining national methods, ISO, E – ISO, Regulations provided by Environmental Protection Agency (EPA, USA), The National Institute of Standards and Technology (NIST, USA), American National Standards Institute (ANSI, USA), Russian patents and patents in other countries, publications and Internet web sites.

At the third stage we determined the type of biological activity of identified organic chemicals for which – if possible – we assessed the maximum admissible concentration.

Determining biological activity.

There are many documents published and data bases compiled that provide the information on toxicity type of various substances, the levels of maximum admissible concentrations or, at least, ranking the potentially hazardous toxic substances.

Among these data sources we can mention the following:

a) regulatory documents of the Russian Federation and other countries giving the levels of the maximum or recommended admissible concentrations for various substances;

b) ranked lists of the hazardous substances (here we can refer to the lists published by EU,

USA, as well as the lists enclosed in various treaties, e.g. Stockholm conference of 2001);
c) regular bulletins covering specific toxic substances published by the World Health Organization (WHO), International Program of Chemical Safety (IPCS) and others;
d) various registers compiled by international and national organizations, including universities (e.g., registers issued by IPCS (International Chemical Safety Cards)), the data of the Belgian search system (ChemExper), the data base of the Cornell University (Cornell MSDS Search), the Russian register of potentially hazardous chemical and biological substances published by Rospotrebnadzor (Russian Agency to Protect Consumer Rights), etc.

All these data sources were merged into a unified automated system which is administered using specially developed software. The algorithm of this system is given in *Fig. 4*.

The developed scheme illustrates the first of the necessary procedures to assess water quality, and, in particular, to estimate availability of organic contaminants. In particular, it has been successfully tested to identify xenobiotic contamination of the snow cover [9, 10].

The search through this system can be stopped at each stage or a substance can be put through

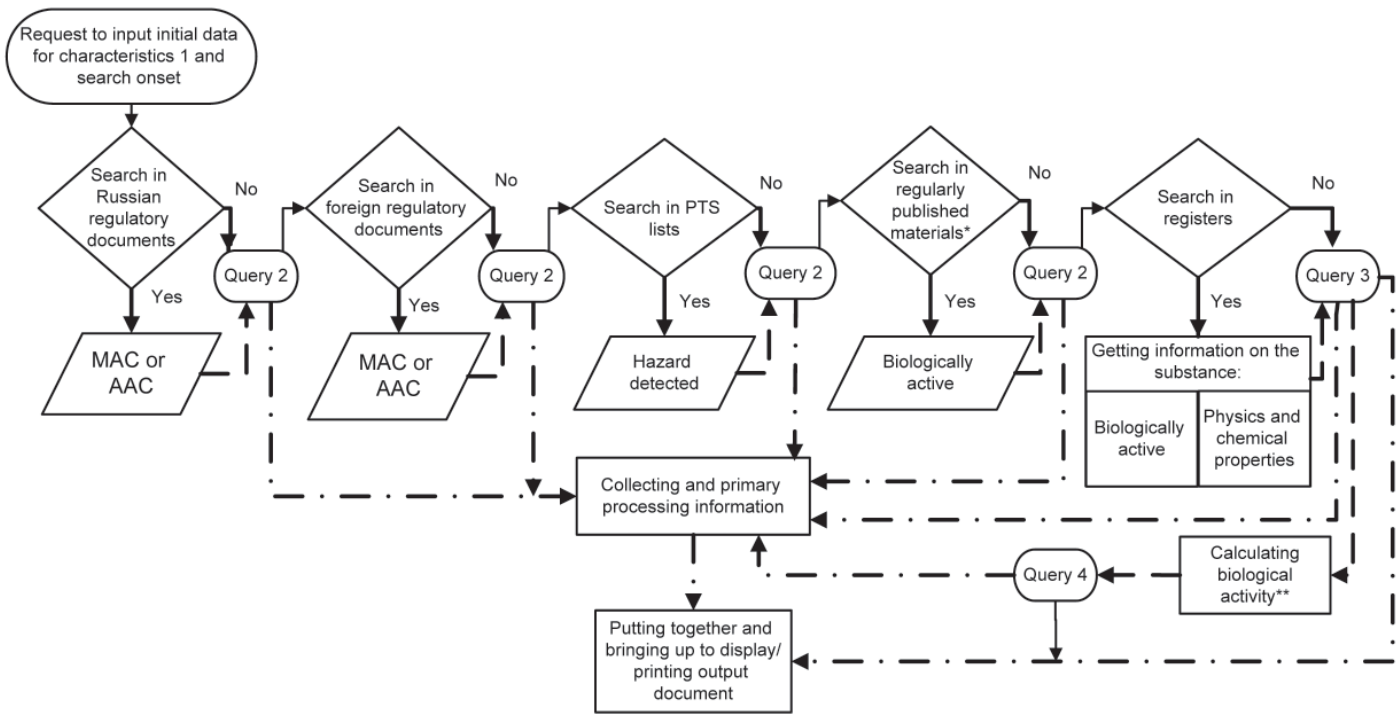


Fig. 4. Algorithm of Program to Estimate Biological Activity.

* Serial analysis:
- Environmental Health Criteria;
- Health and Safety Guide;
- Concise International Chemical Assessment Document.

** Calculating biological activity:
- structural-logical;
- quantum-chemical;
- Using «compound – target» type approach;
- Estimate of physics and chemical properties.

Query 1 – input characteristics: Chemical name of substance, commercial brand, structure, place and date of detecting, sample type, concentration, name of laboratory to conduct the analysis; MAC level for the substance as given by the laboratory.
Query 2 – to bring the data up on display/to print, to enter the information into the exit passport of the substance, to continue searching.
Query 3 – to bring the data up on display/to print, to enter the information into the exit passport of the substance, on calculating biological activity in PASS, on putting together and bringing up/printing exit passport.
Query 4 – to bring the data up on display/to print, to enter the information into the exit passport of the substance, on putting together and bringing up/printing exit passport.
Abbreviations: MAC and AAC – are maximum admissible and approximately admissible concentration, respectively; PTS – top priority toxic substances.

all the stages of the search. In case the required data is missing and in some cases when the data is available we recommend calculating the activity using a cross-plot «structure – activity» approach.

In general the different schemes are applied to calculate the biological activity of chemicals:

1) use of learning sample (descriptive analysis);
2) application of empirical, semi-empirical and other calculation formulas, based on physical and physico–chemical properties of compounds;
3) making quantum chemical calculations;
4) making expert evaluations;
5) modeling interaction of chemical substances with biological macromolecule-targets on molecular level.

The estimates of biological activity for compounds analyzed can be obtained using computer program PASS (Prediction of Activity Spectra for Substances) [11, 12].

Current version of a computer program PASS 10.1 predicts over 4000 kinds of biological activity with an average accuracy of about 95% (leave-one-out cross-validation). PASS 10.1 training set contains information on more than 260,000 pharmaceuticals and biologically active compounds, including the data on some chemical toxic substances.

Let us illustrate the virtual behavior of dibutyl phthalate (DBP) as provided by the search system (DBP is a placticizer used in production of polymer materials; it can be also used as repellent). DBP and other organic compounds were found during auditing a water treatment plant in Moscow. The search system outlined above found DBP-related entries in the Russian regulatory documents on the maximum admissible concentrations published for the fishery water bodies, in WHO regular publications and in registers. In addition the calculations in PASS were made with results partially shown in *Table 2*.

As a result, we compiled a final document that contained all information on DBP and gave relevant recommendations to mitigate risks.

In addition, after evaluating the biological activity, other search engines that contain synonyms of names of chemical substances (e.g., ChemIDplus, Chemical Lookup Service, etc.) can be used. This will allow identifying potential functions of the compound and, consequently, the sources of its supply into the environment. Using a database containing information on the metabolites of substances (e.g., SYMYX Metabolite) will allow identifying toxic metabolites in water. Further, this will allow searching for those substances in water from which these metabolites are formed.

Table 2

A portion of calculating dibutyl phthalate biological activity [$C_6H_4(COOC_4H_9)_2$], CAS No 84–74–2

Activity Prediction		
23 Substructure descriptors; 0 new.		
Teratogen		
67 of 3750 Possible Activities at Pa > 0.800		
Pa	Pi	for Activity:
0.946	0.004	Retinal oxidase inhibitor
0.938	0.003	Sugar-phosphatase inhibitor
0.928	0.004	Alkenylglycerophosphocholine hydrolase inhibitor
0.925	0.003	VCAM1 expression inhibitor
0.901	0.003	Phosphatidylcholine-retinol O-acyltransferase inhibitor
0.899	0.002	Gluconate 5-dehydrogenase inhibitor
0.909	0.003	Pullulanase inhibitor
0.899	0.003	Acaricide
0.915	0.025	Transferase stimulant
0.888	0.006	Antiseborrheic
0.879	0.003	All-trans-retinyl-palmitate hydrolase inhibitor
0.884	0.012	Polyporopepsin inhibitor
0.885	0.014	Signal peptidase II inhibitor
0.877	0.007	Acylglycerol lipase inhibitor
. . .		

Pharmaceuticals detected in natural water bodies.

A separate problem deals with finding organic compounds that possess pharmacological activity, including those known as drugs. This aspect is related to the fact that currently the growing concern is associated with polluting in-land water bodies with such specific substances as medicines. Until recently this issue was not high on agenda and the studies addressing the issue of the content of medicines in water bodies were almost non-existent. On the other hand during the last decade an elevated interest was hinged all over the world with the issue of the fate of medicines in environment, in water bodies in particular. It is important not only to detect these compounds but also to know about the degree of negative impact they provide on the human body and on polluted fresh water sources. This issue is especially important for antibiotics and hormones.

Initially the issue of pollution with medicines was raised in US back in the seventies; almost ten years later the same problem was addressed in England. Despite these pioneering studies only the progress with analytical techniques enabled getting important knowledge on environmental pollution with medicines in the mid-nineties [13]. The contemporary chromatographic detection techniques ensured high accuracy in detecting large number of components of medicines (for instance, narcotics and auxiliary substances) in natural environment. The fact of wide spread of low concentration medicines has been reliably established in water medium. For instance, these agents were discovered in waste water outlet streams at the sewage water treatment plants, in the open water bodies (rivers, lakes, streams, estuaries, etc.), in seawater, in underground water and in drinking water [14].

To search for medicines in the set of detected organic compounds we applied several techniques:

- Determining the brand name of an organic compound through comparison of its mass spectrum with the reference mass spectrum in case the latter not only contains the name of the substances per Geneva nomenclature, but also the synonym trade name (pharmaceutical in our case);
- Using the DB to look for synonyms for the chemical compound and singling out the synonym of the substances as a medicine using the DB (e.g., ChemIDplus DB);
- Searching for medical properties and the name of a substances as a drug using interactive search engines, inputting the substance name using chemical nomenclature and word «medicine» (in Russian and then in English);
- Doing search of pharmaceutical name and finding organic compound in pharmaceutical papers and/or specialized data bases «substance – pharmacological activity – medicine»;
- Searching for description of pharmacological activity of the found substances and potential of mentioning them as drugs in international and national registers describing physics and chemical and/or biological activity of the substance;
- Definition of biological activity of analyzed organic xenobiotic and determining its affiliation with medicines on the basis of belonging to the substances populating learning set having proven medical properties;
- The search for drug metabolites against the data bases using the logic «chemical compound (name of chemical structure) – metabolite of a specific drug»;
- Use of other data bases mentioned in this paper; finding new data bases suitable to solve the issue addressed.

«Register of medicinal products of Russia», a regularly updated guide on drugs and their manufacturers, with more than 11,000 articles [15] should be noted among the information guides on medicines in Russia. The directory «Vidal» containing fairly complete and useful information on drugs is notable, too [16].

ChemIDplus NLM [17] database contains more than 370,000 chemicals; it contains an extensive list of synonyms of substances having various functionalities. It can be searched by the chemical name, by CAS registration number, by the molecular formula for the classification code, etc. New features include search and display of toxicological and physico-chemical characteristics of compounds.

The database Metabolite (SYMYX) [18] mainly contains information on biotransformations of drug compounds. For some reactions there is also information given on enzymes involved in reactions. Database Metabolite 2001.1 contains information on 16,922 compounds and more than 55,000 reactions of biotransformation.

In general, the use of the algorithm Program to Estimate Biological Activity (Fig. 4) as an approach to detect drugs and their metabolites is outlined in *Fig. 5*.

As an example, we note that due to integrated use of above methodological approaches to the study of some water bodies in the Moscow

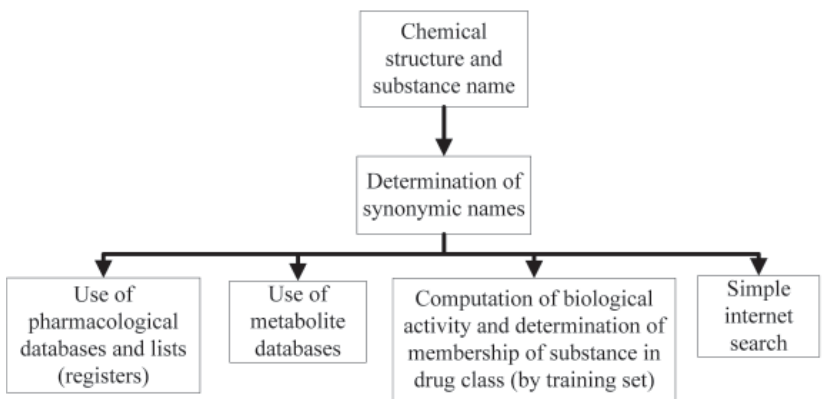


Fig. 5. The generalized scheme to determine whether detectable compounds belong to drugs.

region were detected substances included in composition of medicines as the main active ingredient or as a supporting component. For example, there are medical substances such as caffeine, linoleic acid, beta-sitosterol, glycerol, eritritol and others found [19].

In addition, it was found that many substances that could be substrates of detected organic compounds, i.e. their sources of occurrence, are the substances of known drugs; among them there are two de-worming drugs, one substance features antifungal activity, and five compounds are anticancer agents.

Thus, these substances belong to the class of drugs, whose presence in drinking water at low concentrations can cause resistance to worms and fungi, or to drugs used against vitally important indications with a trend to have relatively high toxicity (anticancer drugs).

In the course of comprehensive use of above approaches the studies of the water bodies in the Moscow region revealed substances that form medicines as a main acting agent or an auxiliary component. Among them we can mention such drugs as caffeine, octadenic acid, beta-sitosterol and others.

Application of screening systems.

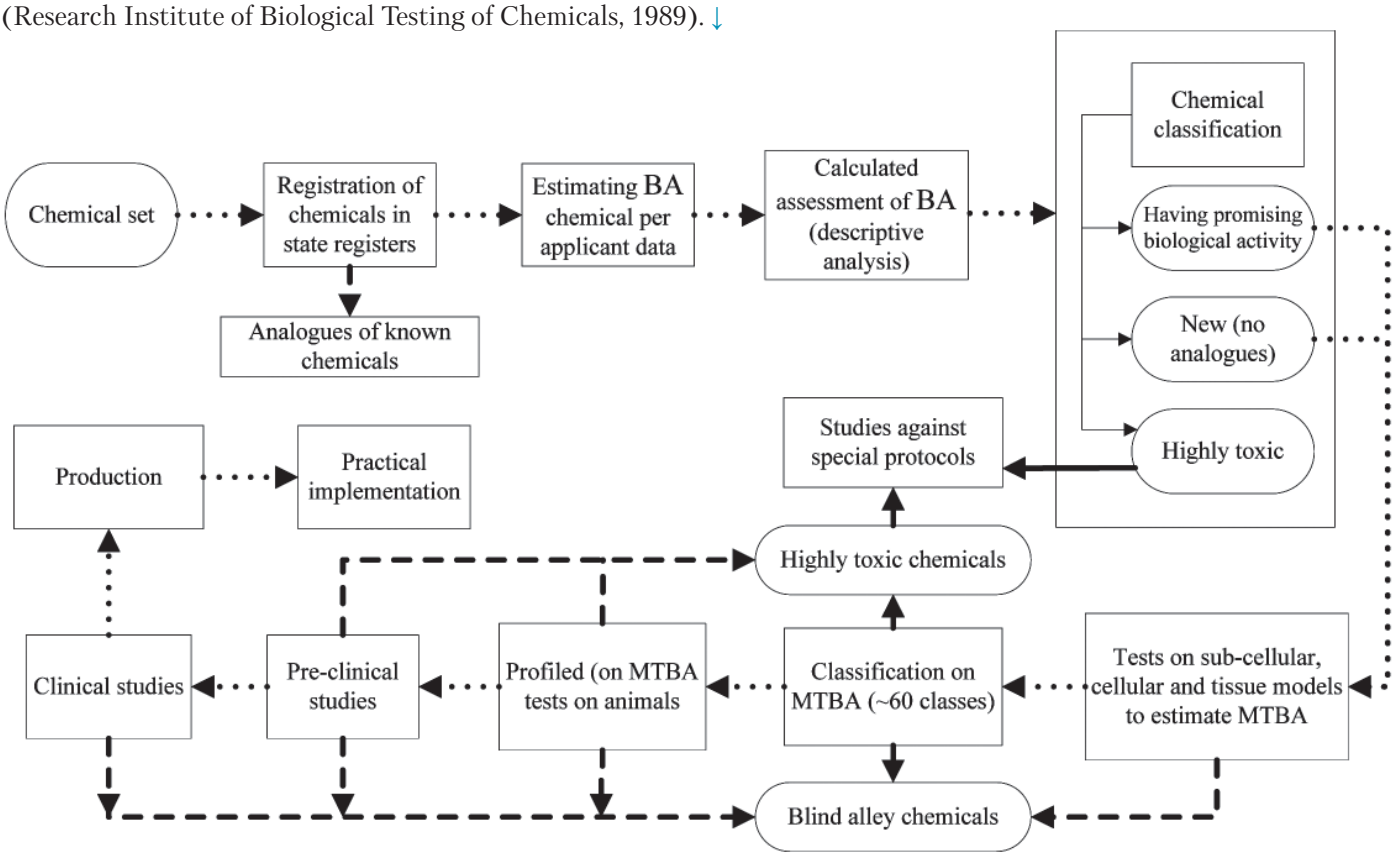
A unique situation occurs when an organic xenobiotic is found in water with locating its source but calculations of biological activity reveal the types of hazardous impact that require experimental verification. In addition the fact of estimating the biological activity does not stipulate the level of admissible safe concentration.

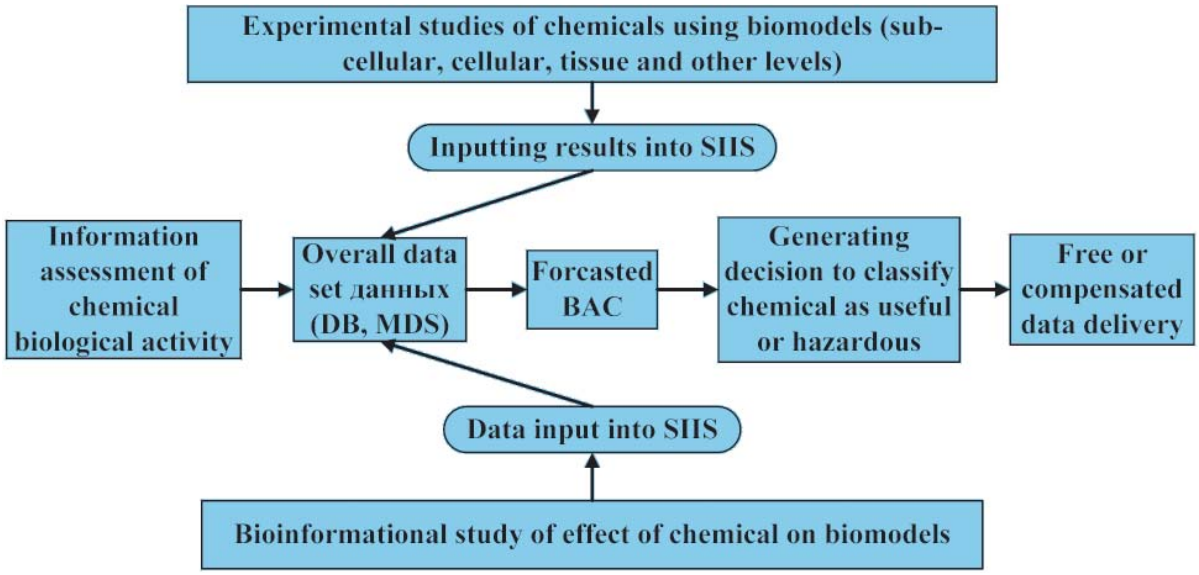
It is purposeful to apply the drug screening system that is both useful and gives information on detrimental properties provided the sample under investigation can be isolated from water. On proposal of Academician L.A. Piruzyan first time such system was developed in the Research Institute of Biological Studies of Chemical Compounds; we took part in that project [4]. Schematically the system can be represented as shown in *Fig. 6*.

The new classification of toxicity types was developed for this system. The classification is

List of abbreviations: chemicals – chemical compounds, BA – biological activity, MTBA – major types of BA

Fig. 6. System of biological testing (screening) of chemical compounds (Research Institute of Biological Testing of Chemicals, 1989). ↓





Abbreviations: DB – data base; MDs – managing data storage

Fig. 7. The search for new drugs and estimate of detrimental properties of chemical compounds (chemicals) based on INTERNET (a proposal to set up specialized international information system – SIIS).

based on the influence of a chemical on critical indicators of the life cycle of cells (biosynthetic capacity, energy processes, splitting, substance transport, etc.). The results obtained are then projected to higher organisms through developing epimorphic models.

In 2008 we proposed developing a comprehensive selection system to collect experimental and theoretical data on biological activity of chemicals, including hazardous properties based on specially set up internet portal to gather the data from international research groups (*Fig. 7*). This system could be ecologically advantageous; it can act as a screening system to look for new promising drugs [6].

In general, screening systems designed for selection of chemical compounds with potential pharmacological activity and already operating in different countries. They can serve as a valuable source of data in relevant databases and registers. At the same time obtaining the screening information about the hazardous properties of substances can make it unfit for its intended use as drugs. However, information about it being entered into the database or registry may play an important role in determining the biological activity of new substances.

Conclusion

Organic xenobiotics in water pose the major threat to humans and hydrobionts. They are also capable of providing detrimental effects on the grown of agriculture plants in irrigated areas, on animals using polluted water for drinking. The paper proposes a schematic approach to estimate the biological activity of these xenobiotics, hazardous types inclusive. Depending on the type of detected biological activity a practical recommendation can be given (discontinuing pollution or decreasing its level, finding conditions that restrict the use of polluted water, improving the purification degree, etc.). A special attention should be paid to water polluted with drugs and their metabolites. In case such substances are detected in water it makes sense to look for sources of such contamination.

Application of experimental screening medicines seems to be quite timely as it will provide the data on detrimental properties of these substances.

The fact that the process proposed involves addressing numerous data bases to identify and determine biological activity dictates setting up a unified information technology to automate and improve the efficiency of resolving above issues. The suggested methodological approaches provide a universal tool for all components of the environment: water, air and soil. We should bear in mind that water can contain a bigger number of secondary products than atmosphere. The soil is not as important as

drinking water sources in terms of impact on humans and hydrobiotics.

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