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Modeling issues in experimental toxicology and medicine. Zero-order biomodels

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Introduction. The creation of adequate models for studying the processes of human interaction with the environment is a key problem of modern experimental biology and medicine. This is due to the fact that both the results of the conducted studies and the recommendations developed on their basis depend on the choice of the biological object and the characteristics of the factor directly affecting it. It should be noted that errors related to both the discrepancy between the developed experimental pathology and the simulated conditions for humans, and the choice of a method for assessing the safety of xenobiotics are critical and can lead to serious consequences.

The study aims to determine the existing trends in biomodeling and extrapolation of the results currently being implemented in experimental toxicology and medicine based on the analysis of literature data.

Materials and methods. We have used forty five domestic and foreign scientific publications as materials. The research method was the analysis and generalization of the materials presented in scientific publications.

Results. The scientists considered such components of extrapolation modeling as the creation of an adequate model, compliance with the principles of proper laboratory, as well as extrapolation of the obtained data to humans. We have given the definition of an experimental model of the disease as a condition developing in a laboratory animal under the influence of an etiological factor, which most fully reflects the main manifestations of the disease that arose on the basis of a common human and used biomodel of pathogenesis. We introduced the term "zero-order biomodels" and defined it as an object used for biomodeling and also presented a classification of zero-order biomodels.

Conclusion. *Currently, issues related to their standardization are of increasing importance in conducting biomedical research, which is reflected in the appearance of a large number of regulatory documents regulating not only the procedure for conducting them, but also the requirements for biological models used for these studies. However, despite the existing trends, the key point in conducting all studies was and still is the issues related to the extrapolation of the data obtained to humans.*

The conducted analysis suggests that new biological models (of the zero-order) are being actively introduced into the practice of biomedical research according to their characteristics fully corresponding to the prototype — human biological material obtained from various sources. A distinctive feature of these models is the absence of the need to extrapolate the results obtained to humans.

The analysis shows that at present there are all prerequisites for conducting preclinical studies using almost the entire spectrum of biological models of the zero-order specified in this publication within the existing legal framework.

Keywords: *biomodels; biomodeling; zero-order biomodels; classification; laboratory animals; good laboratory practice; extrapolation of data*

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Introduction. The creation of adequate models for studying the processes of human interaction with the environment is a key problem of modern experimental biology and medicine. This is due to the fact that both the results of the conducted studies and the recommendations developed on their basis depend on the choice of the biological object and the characteristics of the factor directly affecting it. We note that the errors associated with both the discrepancy between the developed experimental pathology and the simulated human condition, and with the choice of a method for assessing the safety of xenobiotics, are critical and can lead to serious consequences.

All specialists working in the field of experimental toxicology and medicine are aware of the difficulties that a researcher faces when extrapolating data obtained from biomodels to humans, even in the case of multilevel modeling, i. e., combined use of biomodels of various orders.

So, at present, researchers are considering a classic version of predictive research, which includes several successive stages:

- the theoretical choice of a biomodel(s) for modeling a condition/pathology for humans;
- development of a mathematical model of the condition/pathology for humans and prospective biomodels;
- trial modeling of the condition/pathology to select an adequate biomodel(s);
- conducting research on the selected biomodel(s);
- validation and verification of the selected model(s);
- extrapolation of the obtained data to humans using mathematical models.

However, as our experience shows, even in such a seemingly ideal variant, the error in extrapolating the data obtained to a person can be very significant. In this connection, in recent years, against the background of the growth of technical capabilities, as well as the emergence of new technologies, a number of new approaches have emerged that can help solve existing problems.

Modeling in biology and medicine is the creation and management of processes at the population, organismal,

systemic, tissue, cellular and subcellular levels in order to understand the essence of physiological and pathological conditions and their influence on their course. Modeling in experimental science implies the influence of a factor on the animal organism, on their functional systems or on cell cultures, followed by the transfer (extrapolation) of the information received to humans [1].

The adequacy of the model used means the maximum possible similarity of the state of the experimental animal caused by the influence of the factor with the processes, including pathological ones, detected in humans. The criteria for the adequacy of the experimental model can serve as various indicators of the functional systems of the body, primarily the central nervous system, cardiovascular, respiratory systems and homeostasis parameters.

The researchers justified the choice and creation of experimental models to study the influence of the factor (impact) taking into account the following criteria:

- similarity in humans and experimental models of biological parameters of systems reacting to a harmful factor;
- maximum possibility of reproduction on laboratory animals of the entire spectrum of manifestations of human exposure to the factor;
- proximity of sensitivity in terms of the response to the influence of the factor established for the person and the model, as well as the common characteristics of metabolic processes.

Currently, we reduce the problem of extrapolation modeling in a simplified form to three key points:

- creating an adequate model;
- compliance with the principles of good laboratory practice (NLP; GLP — good laboratory practice) in the course of work;
- extrapolation of the obtained data to a humans.

Creating an adequate model. Depending on the goal pursued by the experimenter, models can be explanatory, exploratory and predictive. Explanatory models are designed to understand a complex biological problem. Research models are designed to determine the biological mechanism of both fundamental and particular. While predictive models are designed to detect and quantify impacts. Most often, researchers use laboratory animals as biomodels to achieve their goals.

Laboratory animals are classical biological models of the first order, whose reactions to the action of factors are in many ways similar to their effects in humans. Animals as models are widely used in experimental research to increase knowledge about humans and solve a number of fundamental and applied problems in various fields of medicine [2].

Similarity criteria that determine the adequacy of modeling and reliability of extrapolation are:

- similarity in humans and experimental models of parameters of biological systems that respond to exposure;
- common characteristics of metabolic processes;
- proximity of sensitivity, that is, the values of quantitative indicators established for humans and laboratory animals.

However, the data that we obtained in the experiment, especially on small laboratory animals, must be transferred to the real circumstances of the development of pathology in humans with great caution [3].

Often, when studying the effectiveness of new medicines, as well as non-drug methods of treating various diseases, specialists model on first-order models not a specific nosological form of the disease, which stands out as an independent one, based on the established cause (etiology), features of development (pathogenesis) and typical external and internal manifestations, but a syndrome-like state.

This is due to the fact that, as a rule, it is impossible to simulate a specific nosological form of the disease on biological objects, and it is possible to simulate only its part, which includes elements of pathogenesis and a number of "typical" external and internal manifestations.

We explaine this approach by the fact that when creating an experimental model of a disease (pathology), the researcher is guided by the universality of the body's response to exposure, which manifests itself in the form of compensatory reactions and typical pathological processes. With this approach, instead of the etiological factor, another (similar — similar in characteristics, but more accessible) can be used, taking into account that the response of the biomodel will be identical or as close as possible to the prototype in terms of basic characteristics. In this case, we are dealing essentially with a "surrogate" (ersatz) model of pathology in humans. Thus, models of diseases (pathological conditions) according to modeling approaches we divide into etiotropic, pathogenetic and syndromic (syndrome-like).

I would also like to note that to date there is no clear definition of the concept of "experimental model of human disease". In our opinion, an experimental model of human disease should be understood as a condition that has arisen in a laboratory animal under the influence of an etiological factor, developing on the basis of a pathogenesis common to humans and the biomodel used, and which most fully reflects the main manifestations of the disease. In turn, if it is not possible to simulate the disease, a "surrogate" model of human pathology can be used as an experimental model for conducting research.

Besides biomodels of the first order (laboratory animals-mammals), there are biomodels of the second and third order. Currently, researchers apply alternative second-order models (various hydrobionts, bacteria, enzymes, cell cultures, etc.) are increasingly used in research [4]. At the same time, scientists often transfer the results directly from test objects to a person, which, as a rule, does not always have a detailed analysis and proof of the validity of such an approach [5–8]. Third order biomodels are mathematical models describing biological processes. It should be noted that their applicability in scientific research is also currently underdeveloped. At the same time, the results are often directly transferred from test objects to humans, which, as a rule, is not always accompanied by a detailed analysis and proof of the validity of such an approach [5–8]. Third-order biomodels are mathematical models describing biological processes. It should be noted that their applicability in research is also currently insufficiently developed.

It should be noted that none of these approaches claims to be comprehensive, since it does not cover all aspects of the human prototype.

However, biomodels of the first order most fully reflect the actual biological essence of a person, without claiming a social component, as well as derivatives of this type of activity of homo sapiens [9].

Compliance with the principles of good laboratory practice. Good laboratory practice is a system of norms, rules and guidelines aimed at ensuring consistency and reliability of laboratory research results [10].

Based on GLP standards, scientists plan and conduct research, as well as draw up protocols and reports. Compliance with the GLP rules ensures the reliability of research results and their reproducibility. The GLP rules primarily define the technology for conducting preclinical studies related to the study of the safety and/or efficacy of the substance under study.

The GLP rules include requirements for the organization of tests; the staff of researchers; the premises in which tests are carried out; laboratory equipment and its calibration; the test and control substance; the preparation and conduct of a detailed standard methodology for experimental work (SOP — standard operating procedure) and the procedure for conducting tests (protocol); data registration and report design; testing quality control service; standard methods of experimental work [10].

In addition, the principles of GLP include requirements for the selection of test systems (including experimental animals) and work with them, however, mainly when assessing the safety of chemical compounds in preclinical studies of new drugs [11]. When conducting preclinical studies of new medicines, researchers have recently paid a great attention to the validation of the biological models used, i. e., their verification for compliance with the requirements of the quality management system.

In fact, validity is a consequence of reliability, i. e., it indicates the repeatability and accuracy of measurements, and also confirms the conformity of what was measured to what should have been measured. However, in modeling, reliability is not a consequence of the similarity or accuracy of the correspondence of the model to the object, but only the basis for the subsequent correct extrapolation of the results obtained on the experimental model to a person.

According to N.N. Karkishchenko, "... validation is the "anatomy", and extrapolation is the "physiology" of biomodeling processes, since the first is a reflection of the structure of the process and the search for isomorphism, and the second is ... focused on finding primarily dynamic components in the criteria of similarity and transfer" [12].

Extrapolation of the obtained data to a person. Extrapolation of the obtained data in human obtained in experimental animal studies is one of the main tasks of modern biology and medicine. The problem of transferring experimental data to humans is usually solved in order to determine, firstly, the characteristics of the influencing factor that may or may not cause certain changes in humans similar to reactions in animals; secondly, in order to determine the dynamics of these changes (start time and duration); thirdly, to establish and account for qualitative differences in human reactions compared to other mammalian species [1].

Extrapolation of the obtained results to a person is a mandatory, complex and ambiguous stage of any experimental modeling. The principles of extrapolation are most fully developed in the field of assessment of acute and chronic toxicity of substances for humans on first-order models. Scientists use either direct data transfer from animals in human or introduce correlation coefficients [13–15].

In modern science, the basic principles of modeling and extrapolation are based on analogies, which we call structural-functional and functional-structural. In the first variant, researchers isolate an element or function from a prototype, a thing reproduced on an animal, and compare it with the original. The second option, that is, functional-structural analogies, can be characterized as an analogy of relationships. If any relation of variable units is transferred from the model to the prototype, then we are already dealing with a pure analogy of relationships, which can only be described in some cases by biomodels of the thirdorder [16].

Biological models of the second order can more or less fully represent data from the molecular to the cellular level. However, it is impossible to use these models to extrapolate processes related to the functioning of tissues, organs, and processes of higher nervous activity. For the absolute majority of xenobiotics, direct extrapolation of data from second-order models to humans is also impossible due to the lack of the necessary scientific justification [7].

When extrapolating, it is very important to take into account the fact that there are not only quantitative but also qualitative differences between the results of human observation and animal studies. In experiments on some animal species, it is impossible to reproduce individual biochemical and metabolic reactions occurring in the human body [17, 18].

Depending on the nature and objectives of the study, in each case it is necessary to choose a model that will most adequately recreate the corresponding process in humans. Therefore, biomodeling and extrapolation proceed from the following postulates, prerequisites and conditions:

- despite the existing specific features, the development of approaches to extrapolation is possible and necessary, since there is still a closeness of anatomical and physiological properties and biochemical processes of the human and animal body;
- the presence of identical organs, the uniformity of their functioning, the similarity of the main functions;
- similarity of chemical composition and structure of most body tissues;
- qualitative uniformity of the main biological processes;
- the main metabolic and energy reactions are qualitatively similar in animals and humans;
- similarity in the isotopic composition of water, air, organic and inorganic nutrients entering the body from the environment;
- the dynamics of the metabolism of substances entering the body is conditioned and quantitatively related to the main metabolic processes occurring in the body;
- the changes that develop in animals and humans after exposure to xenobiotics and various environmental factors are basically qualitatively the same.

The concept of "biomodeling" is the existence of two objects — a model and a prototype, that is, an animal and a human. Studying one allows us to draw conclusions about the other. The logical basis of the biomodeling method can be any conclusions in which the biological prerequisites relate to one object, and the scientific conclusion to another [1, 15].

Thus, by a biomodel we mean such a mentally imagined or materially realized system of vital activity of the studied animals, which, by displaying or reproducing the object of research, is able to replace it in such a way that its study provides new information about and for humans [19–21].

When comparing the features of a model with a prototype, the method of analogy is most often used [1, 16]. As a general condition for the validity of the conclusion by analogy, there is a requirement that the properties of the objects being compared with each other should be point-like. At the same time, they should be multiple, for example, the correspondence of biochemical, physiological, pharmacokinetic and pharmacodynamic parameters of humans and animals [1].

If the same linear or multidimensional properties are attributed to the compared objects, then their refinement can lead to different point properties.

If the properties being compared are point-like, then the refinement procedure is unnecessary, and the statement about the identity of these properties in different animals will not be in doubt, which allows us to proceed to the formulation of the rules of inference by analogy [16]. For the properties that are given in the messages it is important that they relate specifically to the phenomena being compared and are specific to the objects being compared. At the same time, the more concrete the fact, the less likely it is. We explain the meaning of this statement from the standpoint of information theory, according to which, the less likely the fact described by this statement is, the more information it contains.

Therefore, the considered condition for increasing the degree of plausibility of the conclusion by analogy is equivalent to the requirement that the messages contain as much information as possible about the objects being compared [16].

When using analogies of relations, the very concept of isomorphism of model and prototype structures is pushed into the background. The analogy of establishing isomorphism becomes not a prerequisite, but the result of the conclusion [22].

In biology and medicine, as well as in general in formal logical modeling, four criteria of spatial similarity are generally accepted:

1. Spatial similarity or commonality of morphofunctional characteristics of organs and systems in the human prototype and its biological or alternative model (extrapolation of the first level).

2. Unity or similarity of metabolic, neuroregulatory, motor, endocrine and exocrine functions or their analogues in alternative models (extrapolation of the second level).

3. The unity or maximum similarity of the effects of critical systems and organs in their response to the selected or studied impact (extrapolation of the third level).

4. Comparability of constants or other parameters quantified and mathematically described in a system of homogeneous functions in a prototype, animal or alternative object (extrapolation of the fourth level).

Compliance with these similarity criteria in the model allows for effective extrapolation from the model to the prototype and back. However, there are formulations of sufficient similarity conditions in which the concept of criteria is excluded. The concept of similarity can also be formulated as the similarity of unambiguity conditions with the identity of the main system of equations describing both phenomena. That is, for the similarity of phenomena, in addition to the identity of equations, geometric and temporal similarity, similarity of biological constants, initial and boundary conditions, functions and effects are sufficient. So, the fifth, temporal type of similarity (homochrony), is not included in any of the subsets of spatial similarity (extrapolation of the fifth level) [12].

Table 1 shows the main methods of "friendly" assessment of the main functions and some indicators of human and animal homeostasis.

The most important property of complex systems, which include biosystems, is their structural and functional heterogeneity and diversity. There is a multidimensional relationship between them, manifested in a large number of heterogeneous parameters, in a variety of connections

Table 1

Extrapolation approaches to the study of human functions and their modeling on laboratory

Evaluation criteria	Research methods	
	Human	**Animal**
Physiological reactions	– registration of body temperature, respiratory rate, blood pressure, heart rate, cardiointervalometry, ECG, external respiration, motor activity, heat exchange, oxygen consumption, basal metabolism, echography, etc.	
Clinical, laboratory and biochemical parameters	– assessment of somatic status, blood (ESR, number of erythrocytes, hemoglobin, shaped elements of white and red blood, etc.), urine (specific gravity, daily amount, microscopy of sediment, presence of protein, erythrocytes, leukocytes, etc.), biochemical parameters of blood and body media	
Higher nervous activity and neurodynamic reactions	– indicators of the development of classical conditioned reflexes (the rate of appearance, fixation, extinction time, stability in samples, the time of conditional and unconditional reaction, etc.); – indicators of the development of differentiation reflexes (the rate of appearance and fixation, extinction time, stability, etc.); – electroencephalographic and neurodynamic indicators:	
	– based on the reactions of the first and second signaling system	– based on the reactions of the 1st signal system
Performing targeted actions		
a) physical endurance	– cross-country running, treadmill running, bicycle ergometry, PWC-170, swimming, wrist and standing dynamometry, obstacle course overcoming	– treadmill running, PWC-170, swimming, high-speed Kiplinger swimming, measuring the strength of the flexors of the forelimbs, overcoming barriers, etc.
b) operator actions	– the results of performing targeted actions of a discrete (by signals) or integral (with tracking) nature	– the results of performing skills with the selection of a sample of operant (instrumental) skills in shuttle, jump, one- and two-pedal chambers, etc.

between single and heterogeneous parameters that characterize the operation of this biosystem. Another feature of biosystems is the dynamism of their interaction with the environment.

Therefore, extrapolating the results of experimental data to humans is very difficult, in many respects it is an unsolved task, which implies the need to take into account many factors that require the development of differentiated transfer algorithms depending on the nature of the biological effect [15]. Achieving a high level, quality and conformity of extrapolation in relation to humans should be based on models of various orders and the use of high-quality animal models.

Allometry (allos-other, different) deals with the systematization of comparative characteristics of various organisms in order to optimize the transmission of experimental data in human. Allometry includes not only and not so much mutual measurements, but first of all, the establishment of similarity of morphofunctional characteristics and other important parameters for the purpose of extrapolation [15, 16].

In turn, allometric equations are a regression expression that describes the change of one parameter depending on another (usually on body weight) and is determined by the method chosen to find them, being a statistical approximation, and not a function of mathematical dependence. In addition, they take into account such indicators as metabolic rate, anatomical parameters, heart rate and characteristics of the biochemical status of the body [12, 15].

However, despite the good theoretical foundations for the selection of model biological objects for research, the issues of modeling a specific experimental pathology, with the exception of preclinical safety assessment of new drugs, present significant difficulties.

Since the reaction to the selected effect may not be linear and may not obey the law of the normal Gaussian distribution, but proceed not according to one, but according to several scenarios in animals of the same group with the same exposure, while the "dose–effect" pattern is not always determined. As an optimal solution to this problem, we propose to develop mathematical models of pathology for a person and a selected biological object, followed by the calculation of indicators for the prototype based on the results of the studies conducted, which will be an extrapolation.

In addition, to assess both the impact itself and the methods of its correction, it is necessary to focus on "surrogate points", which also complicates the process of extrapolating the data obtained.

In this regard, recently there have been more studies in which researchers use non-standard approaches to modeling to achieve the goal.

Thus, in the work of T.V. Gorbacheva and co-authors (2018), when studying the biotransformation of ethylene glycol and its esters, as well as the effect of alcohol metabolism inhibitors on their metabolic rate, liver homogenates of nonlinear rats and humans were used as test systems [23].

In this case, the rat liver homogenate, in accordance with the requirements for the models, we refer to the first-order models, since they corresponded to the prototype both in qualitative and quantitative terms.

However, unlike classical first-order models, extrapolation of data obtained using rat liver homogenates to human liver homogenates and the prototype as a whole can be carried out only using recalculation coefficients, and not direct transfer [23].

In turn, to extrapolate data from first-order models to a person, either direct transfer or correction coefficients can be applied, while for second-order models we use only the latter [7, 13, 24, 25].

We note that the conversion coefficient reflects not qualitative, but quantitative differences between the prototype and the biomodel.

Researchers consider human liver homogenates in the study of alcohol metabolism inhibitors as models of the zero-order, since this test system itself is an element of the prototype [23].

Zero-order biomodels. Biomodels of the zero-order can include both the prototype itself and its individual elements (organs, tissues, cells, etc.).

Given the fact that a healthy person cannot be a biomodel, being a prototype, then, accordingly, in this case we are talking either about a corpse or about certain conditions, in which a person can be recognized as a "bio-object".

Such conditions may include the death of the brain stem (complete death), as well as a persistent vegetative state.

The death of the trunk implies an irreversible loss of the most important characteristics necessary for the existence of a living person (loss of the ability to maintain consciousness and independent breathing).

However, with the help of prosthetics of vital functions, scientists can artificially support cardiac activity, blood circulation and breathing, creating the appearance of life. In turn, in a patient in a chronic vegetative state, while maintaining independent breathing and other vital functions, the death of the brain stem does not occur [26].

As for the individual elements of the prototype (organs, tissues, cells, etc.), they can be obtained during the section, surgery, from a donor or grown in a test tube and can be used as biomodels, both in native form and after appropriate preparation.

In accordance with this, the following classification can be proposed for biomodels of the zero-order ***(Table 2)***.

Currently, state and commercial organizations that have the appropriate license for this type of activity are engaged in the collection of human biological material. In turn, biobanks specially created for these purposes are engaged in storage. A biobank is a structure created for the purpose of long–term responsible storage of biological samples of various origins and associated data for their further use in scientific and clinical research. The following requirements apply to the work of biobanks:

- strict compliance with ethical standards and responsible attitude to personal data of patients and donors;
- standardization of procedures for processing, transportation and storage of biomaterials;
- collection and responsible storage of information associated with biological samples.

We would like to elaborate in more detail on some issues of legal regulation when working with biomodels of the zero-order. Currently, there is no regulatory framework regulating the use of an integral organism for scientific research. However, despite the existing legal vacuum in this matter, there is a mechanism that allows both obtaining permission and conducting such studies. Such a mechanism may be a decision by the Scientific Council of the relevant National Medical Research Center [38] or the Scientific Council of the Ministry of Health of Russia [39] on the feasibility of conducting scientific research on an integral organism. After approval of the protocol of the

Table 2

Classification of zero-order biomodels

1. By degree of organization:	2. By origin
– the whole organism; – corpse; – after brain death; – being in a chronic vegetative state; – obtained in vitro (embryos) [27] – isolated organs [28, 29]; – insulated fabrics [30, 31]; – isolated cells or homogenates [32]; – isolated organelles [33]; – isolated enzymes [34, 35]; – other biological material [36, 37].	– cadaverous origin; – from a living donor; – from a living donor during surgery; – obtained in vitro (including 3D printing).
3. On issues of legal regulation arising when working with them (regulated):	
– by Federal Law No. 8-FZ of January 12, 1996 "On Burial and Funeral Business"; – the Law of the Russian Federation "On Transplantation of Human Organs and (or) tissues" of December 22, 1992 No. 4180-1 (as amended. dated 08.12.2020); – Federal Law "On Blood Donation and its components" dated July 20, 2012. No. 125-FZ; departmental legal acts; – not having a clear legal basis.	

proposed study by the Bioethics Commission, it is possible to proceed with their conduct.

Currently, the procedure for working with donor organs and tissues is regulated by the Law of the Russian Federation No. 4180-1 of 22.12.1992 (as amended. dated 08.12.2020) "On transplantation of human organs and(or) tissues".

To conduct research with this category of biological objects, a decision of the Scientific Council and the conclusion of the Ethical Commission of a scientific organization are also required, but in this case these may not be national medical research centers.

The right to human biological material, in accordance with the current legislation, belongs to the scientific (medical) organization in which it was separated from the donor's body, if it is not recognized as property or an object of ownership [40]. Currently, there are two generally recognized restrictions on such property rights in Russia — informed voluntary consent [41] and the right to protect the donor's personal data [42]. In some cases, the procedure for working with specific types of biomaterial (blood and its components, etc.) may be regulated by separate regulatory legal acts [43, 44].

Conclusion. *Currently, issues related to their standardization are of increasing importance in conducting biomedical research, which is reflected in the appearance of a large number of regulatory documents regulating not only the procedure for their conduct, but also the requirements for biological models used for these studies. However, despite the existing trends, the key point in conducting all the research was and still is the issues related to the extrapolation of the data obtained in human.*

The analysis shows that in the practice of biomedical research, scientists are actively introducing new biological models according to their characteristics that fully correspond to the prototype — human biological material obtained from various sources.

A distinctive feature of these models (zero order) is the absence of the need to extrapolate the results obtained in human. Another advantage of zero-order models when used as a comparison group is the possibility of using direct conversion coefficients of individual second-order models (structural elements of first-order models).

In addition, the analysis shows that currently there are all prerequisites for conducting preclinical studies using almost the entire spectrum of zero-order biological models specified in this publication, within the existing legal framework.

Taking into account the obvious advantages of the zero-order models over others, we can say that in the near future the use of the latter may become routine, which in turn will lead to a change in the currently existing standard approaches when conducting scientific research in experimental toxicology and medicine.

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