TOXICOLOGY[1]

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The rapid development of the chemical industry and the extensive use of various chemicals in industry, agriculture, and transport make it necessary to assess the toxicity of a great number of final, intermediate, and by-products, and to define their potential hazards to people. The main task is to work out measures to prevent poisoning from various chemical compounds.

The development of chemistry challenges the increased importance of toxicology, and the number of scientific works in this field of science has increased as well.

Thus, to review all the achievements in toxicology over the recent years is rather a complex task. This article deals with only some of the most important aspects of toxicology and the problems of agricultural toxicology, sought and worked out by the authors of this review.

Some Methodical Questions and Quantitative Criteria of Toxicity

One of the main tasks of toxicology is to obtain data concerning toxicity of new chemical compounds before they are widely used in practice (1, 2). This task is carried out in the USSR where no new chemical is permitted to be used as a pesticide without the approval of the Sanitary-Epidemiological Department of the Ministry of Public Health of the USSR, to which the Committee of Study and Regulation of Pesticides is attached. This Committee directs the research work of more than 50 scientific-medical institutions.

To accelerate the toxicological investigations, some necessary conditions are listed: (*a*) precise sequence of investigations; (*b*) experimental-toxicological and occupational-hygienic research work; (*c*) definition of criteria needed for toxicological experiments and establishment of tolerance limits of chemicals; (*d*) recommendation of special techniques of investigations (3).

The sequence of investigations provides for a possible decision not to continue further studies of chemicals because of their high toxicity.

For instance, in the USSR, such organophosphorous pesticides as: tetraethyl pyrophosphate (TEPP), tetraethyl monothiopyrophosphate, O,O-diethyl-S-ethyl mercaptomethyldithiophosphate (Thimet), O,O-diethyl-S-ethyl mercaptoethyldithiophosphate (Disyston), chlorinated hydrocarbons of diene synthesis—endrin and isodrin, and some others were forbidden at the first stage of investigation because of their high toxicity.

[1] The survey of the literature pertaining to this review was concluded in March 1965.

Having been approved at the second stage, the chemical compounds are investigated further with the aim of establishing the maximum permissible concentrations in the air and in biological media. The hygienic conditions of pesticides used in agriculture are studied as well, and preventive measures are worked out.

When a new pesticide has been accepted for production, a new detailed study of its fundamental physiological and biochemical effects is carried out, and special, suitable measures for prevention and treatment of poisoning are worked out (3).

The unification of the investigation programs, involving the solution of specific problems associated with the need to assess the toxicity and hazards of new chemical substances, and the realization of a strict order in the research work, not only permit a decision on practical problems in a short time, but also promote the collection of information on theoretical questions of toxicology. To obtain comparable data, it is necessary to have a unified plan for the experimental investigations and to apply identical criteria for the estimation of toxic effects. Some investigations devoted to these problems resulted in the following: "Some methodical instructions on hygienic and toxicological assessment of the new chemicals recommended for use in agriculture" (4), and "Tentative methodical instructions for experimental investigations for determining maximum permissible concentrations of hazardous substances in the working atmosphere" (5). Both documents give the necessary minimum requirements, but they do not restrain the investigators' creative initiative.

The instructions provide for problems concerning the gradual study of chemicals, the choice of laboratory animals, the routes of administration of chemicals into an animal's body, the choice of exposure under inhalation, the determination of the upper and lower toxicity levels, the range of toxic effects, cumulative properties of a substance, the minimum periods of chronic experiments, etc.

Special attention is paid to the determination of the probability of quantitative criteria of toxicity. The necessity of the correct statistical approach, involving probability of the criteria of toxicity, is also stressed in some further papers (6–12, 35). The characteristics of the relationship "dosage—effect" is available for quantitative analysis of mutual reaction of the poison and the organism. LD_{50} and LC_{50} are commonly defined by means of probit analysis (13, 14, 15) or by means of areas (16). However, the techniques of "the least squares" (15) and "the areas" have proved to be the most objective. The lower toxic levels (thresholds of dosages and concentrations) are defined by means of the most sensitive, specific, or any integral (if the former is absent) evidence of toxicity. The determination of cholinesterase activity of blood erythrocytes and serum may serve as an example for a specific test to establish threshold dosages and concentrations of organophosphorous compounds and some derivatives of carbamates (17, 18). As an integral physiological test to determine the threshold dosages and concentrations of poisons, the method of conditioned reflexes is widely used in the USSR (19–24). The data concerning methods of conditioned reflexes applied in toxicology are summarized in a review by Medved, Spynu & Kagan (25).

Some other physiological and biochemical methods, revealing early changes in physiological systems of the organism, are widely used. These methods include the gathering of impulses, the estimation of characteristics of flexor unconditioned reflexes in rabbits (26, 27) the determination of the work capacity of animals (28, 29, 30), the investigations concerning interchange of gases in small laboratory animals (28), the application of different functional difficulties (31), and others.

The survey of methods applied in the USSR to determine threshold dosages and concentrations of toxic substances is adduced in methodical handbooks by Pravdin (28) and Rilova (31).

A number of papers stress the necessity for probable determination of threshold dosages and concentrations of poisons (6, 7, 32).

With the upper and the lower toxic levels given, it is possible to define the range of toxic effect as the ratio LD_{50}/ED_{50} lim or LC_{50}/EC_{50} lim, i.e., the ratio of the lethal dosages or concentrations to thresholds (28, 38). The range of toxic effect is also well defined by the slope of the line expressing the ratio "dosage—effect" (7, 23). As an index for toxicity which gives the value LD_{50} as well as the toxic effect range the following index is proposed: $1/LD_{50}$ slope.

The value expressing effective or two-phase toxicity, involving the product of toxicity ($1/LC_{50}$) and volatility (C sat), is used to define the rate of inhalant, poisoning hazards. This value expresses the ratio C sat/LC_{50}.[2] The higher the value, the greater the hazards of inhalant poisoning. The rate of dermal absorption can be expressed by the skin-intravenous coefficient LD_{50} on the skin/LD_{50} intravenously or by the skin-oral coefficient LD_{50} on the skin/LD_{50} per os. These coefficients were used to assess the dermal absorption of organophosphorous compounds (17, 33). The cumulative property of a substance is one of the important criteria of toxicity. To express it numerically, the cumulative coefficient is accepted, which presents the ratio LD_{50} estimated in a chronic experiment by giving daily a definite fraction of the LD_{50} acute (1/10, 1/20, 1/50) to animals, against LD_{50} acute (12, 34). The value of this coefficient depends upon the daily portion of the lethal dosage administered to the animals, and can be shown as a curve expressing the dependence of a cumulative coefficient upon the daily dosage. The critical dose, i.e., the maximum dose of some compounds (for example, organophosphorus), producing no toxic

[2] According to I. B. Sanotskij, coefficient of possibility of inhalant poisoning.

effect, has been established (17). Only some of the most efficient, quantitative criteria of toxicity have been mentioned above. More detailed information is presented in a number of papers (6–9, 11).

From this review alone, it is clear that the assessment of toxicity of the various compounds is not only established according to the value of LD_{50}, but also involves the toxicity of a compound, determined in acute and chronic experiments with poisons, administered by different routes to an organism and based on the threshold dosages and concentrations and the degree of their cumulative properties.

Criteria of Hazards and the Principles for Establishing Tolerance Limits of Chemicals in Environment

One of the main tasks of hygienic toxicology is to establish the maximum permissible content of chemical substances in the environment: in the air, in the working atmosphere, in the atmospheric air, in food products, in water reservoirs, and other media influencing man. The principal criteria in establishing hygienic standards must be to ensure full safety and complete guarantee for public health.

In the USSR, the maximum permissible dosages mean such concentrations of different chemical substances that do not cause any pathological changes or diseases under daily exposure during an unlimited period of time (36, 37, 38).

It is stressed that the establishment of tolerance limits for industrial toxicants not only provides for the prevention of acute and chronic poisoning, but also expresses physiological changes which can become pathological under prolonged exposure (39, 40). The problem of ranges within which the outer factors of the medium pass the *physiological limits* and become hazardous for man is very involved, as there are no strict differences between the norm and the pathology.

In the process of phylogenesis, man's organism has adapted itself to continuing changes of physical and chemical conditions of the environment, thus it is very difficult to define the border where the physiological reactions of adaptation change into pathological disturbances.

However, it is very important to determine these limits for various branches of hygiene, as it concerns not only the establishment of tolerance limits, but also in many cases the decision of the possibility of applying new, different physical and chemical factors, produced by practical and scientific activity of man, in man's environment. At present, there are no universally adopted points of view concerning the changes that should be considered as harmful. Kurlyandskaya & Sanotskij suggest that those reactions be considered harmful which, though being in the range of physiological changes, turn into pathological ones and respond to prolonged and constant exposure of different toxic agents. Statistically evident changes compared with control and with initial values of the most sensitive of physiological systems under chronic experiment, are considered by these authors as the threshold of harmfulness. These disturbances are on the verge of physiological changes, physiological defense measures, and pathological processes. Although this definition is not comprehensive enough, it calls upon the investigators to seek the most sensitive biochemical and physiological tests, showing the minimum effect produced by a toxic agent in an organism.

Some integral and specific tests applied in the USSR to determine the maximum allowable exposure have been described above. Lately, much attention has been paid to the use of functional tests to determine the minimum latent effect occurring in an organism under reduced adapting possibilities. The method of functional impairment has been successfully applied to determine obliterated forms of chronic intoxications from different chemicals, and to determine functional diseases which are still in a compensated state but indicate the development of a harmful effect of the poison.

Among the functional impairments applied, studies reveal the reduced adapting possibility of an organism to changes in environment (temperature, pressure, oxygen content in the air, and changes in sensitivity to different poisons, etc.).

Impairment is also provided by pharmacological agents, bleeding, or by injury to function of the liver, kidney, or other organs. The influence of chemicals on animals during the period of pregnancy or under any experimentally provoked pathological condition has been investigated. The detailed information on the methods of functional impairments is given in a book by Rilova (31) and in some reviews (39, 41, 42, 43).

To determine the chronic effect upon an organism by chemical agents of low toxicity, the study of their influence on the organism's immunobiological reactivity is widely used (44–56). These data testify that toxic substances developing no visible pathological effect can reduce the immunobiological reactivity of an organism and its resistance to different infectious and noninfectious pathological processes. Such concentrations are undoubtedly to be defined as hazardous and it is important to determine their permissible content in the environment. In addition to the tests characterizing the immunobiological reactivity of an organism for determination of threshold toxic effect, investigations have been made of functional changes of the hypophysis-adrenal system (43, 56), hematological and biochemical changes, and their specific and unspecific developed effect of exposure to chemical substances on an organism (57).

The application of a complex of all the mentioned methods makes it possible to determine the threshold of hazardous effect under chronic experiment, which is the basic criterion for establishing hygienic norms.

Some difficulties concern the choice of "reserve coefficient," i.e., the amount threshold concentrations must be reduced to get the maximum permissible concentrations. This coefficient varies to a great extent because of the peculiar toxic properties of chemicals, and to the sensitivity of effects chosen to determine the threshold concentration. Some special formulas for determining the reserve coefficient have been suggested. Tolokontsev (35) proposes to subtract the value of three standard deviations from the value of threshold concentration (ED_{50} lim). This deserves special attention. In such a case, the probability of the threshold effect is equal to 3.10^{-3}. But a more strict criterion can be chosen. The value of the reserve coefficient must be determined in any concrete case according to the toxicity, the extent of toxic effect, including the cumulative qualities and other peculiarities of the action of a chemical. Lately, some calculative methods for approximate determination of maximum permissible concentrations have been suggested (58–64). These methods are based on determining quantitative, correlative relations between toxic effect, chemical structure, and physicochemical properties of the substances. However, it is to be stressed that the calculative methods are used only as auxiliary ones, mainly in order to accelerate experimental investigations or for special tentative recommendations.

Maximum permissible concentrations of hazardous substances in an environment become official when accepted by a special commission for maximum permissible concentrations and then adopted by the Sanitary-Epidemiological Department of the Ministry of Public Health of the USSR.

Even after thorough experimental investigations on animals have been carried out, the maximum permissible concentrations of toxic substances are accepted only as tentative. Then prolonged, complicated clinical-hygienic investigations take place under normal working conditions in order to make the necessary correction from the standards estimated on animals under experiment. But even then, the maximum permissible concentrations are not established as unchangeable and forever. By obtaining new experimental and clinical-hygienic data, the standards may be revised if necessary (37).

In the USSR, the maximum permissible concentrations are the largest possible concentrations. They must not be exceeded and the local institutions of Sanitary Inspection are designed to ensure the realization of all the necessary, appropriate arrangements.

Such definitions of maximum permissible concentrations differ from those adopted in the USA and Czechoslovakia (65, 66). In Czechoslovakia, for example, the maximum permissible concentrations are defined as mean quantities of concentration variations with not more than five times possible excess (66).

The *International Symposium for Maximum Permissible Concentrations* (Prague, April 1959) stressed the fact that the maximum possible concentrations accepted in the USSR and the USA differ greatly. As a rule, the maximum possible concentrations in the USSR are much lower than those in the USA, the difference sometimes being several dozens. It can be assumed that these differences are due to different sensitivity of the methods used to determine the threshold of hazardous effect. In the USSR, the applied physiological and biochemical methods are very sensitive and investigations are performed over a considerable length of time. The experimental method of investigations on laboratory animals conforms as far as possible to clinical-statistical ones. However, in the USA, less sensitive criteria (the death of the animals, the changes of the organs, and the weight of a body) are chosen as a basis (67). When establishing maximum permissible concentrations in the USSR, medical factors are used, while in the USA the technical accessibility is taken into account as well. As mentioned in the article by Magnusson on the practice of determining maximum permissible concentrations in the USA, there are some cases where the tolerance limits are not sufficiently investigated.

The article by Kurlyandskaya & Sanotskij (39) presents some data stating that certain maximum permissible concentrations adopted in the USA are evidently exceeded. The concentrations of some chemicals (benzene, chlormethane, ethyleneimine), close to the standards adopted in the USA, produced a number of pathological changes in experimental animals and an incidence of sickness among employees.

The list of standardized substances has been extensively enlarged during recent years. Official standards of 1963 (SN-245-63) number 192 maximum permissible concentrations of gases and vapors and 83 maximum permissible concentrations of dusts and other aerosols (68).

At present, more than 300 substances in the working atmosphere have been standardized. The list of maximum permissible concentrations of hazardous chemicals in food products, water reservoirs, and the atmospheric air is being enlarged as well. Some papers discuss the principles and approaches for the establishment of tolerance limits of chemical substances especially of pesticides in food products (69–73) and in water reservoirs (74, 75, 76).

The importance of ensuring the harmlessness of consumer products is stressed. However, it is equally important that some additional factors be taken into account (i.e., changing of organoleptic properties of food products and water, the influence upon the sanitary standards of water reservoirs, etc.).

The most important criterion for determining maximum permissible concentrations is the one revealing the lesser concentrations of chemicals. Thus, if concentrations produce no toxic effect in an organism, but change the organoleptic properties of a product, this is regarded as a limiting criterion and the standardization is set according to this indication. As far as the working atmosphere is concerned, while carrying out seasonal work (e.g., with pesticides in agriculture), some excess of tolerance limits is permitted in agreement with the Sanitary Inspection. In each particular case, however, maximum permissible concentrations are being defined and may not be exceeded.

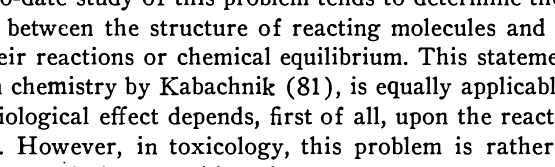
If some solvents or irritating gases evaporate in the air simultaneously, the design of general exchange ventilation must include the total of air volume values needed to dilute each substance separately in agreement with the norm (38).

Much attention is paid to the establishment of hygienic tolerance limits of hazardous substances in the environment, and Sanitary Institutions are in charge of the inspection to enforce these limits (74, 75, 77, 78, 79).

The Dependence of the Toxicity of Substances upon their Chemical Structure

The establishment of regulations basing the dependence of biological activity and, first of all, the toxicity of chemicals upon their chemical structure, is one of the principal problems of toxicology. This problem should be considered not only as necessary for determining particular dependences in some groups of compounds, but mainly as a development of a general theory of the dependence of the biological activity of a substance upon its chemical structure and its physicochemical properties and reacting ability.

Lazarev (80) suggests the following line of relationship between chemical structure, physicochemical properties of a substance, and their biological effect.



The up-to-date study of this problem tends to determine the quantitative relationship between the structure of reacting molecules and the rate constants of their reactions or chemical equilibrium. This statement, originally developed in chemistry by Kabachnik (81), is equally applicable to toxicology, as the biological effect depends, first of all, upon the reacting ability of a substance. However, in toxicology, this problem is rather involved, as many substances, before reaching the area under treatment, convert into more or less active compounds, and the physiological effect depends upon the actions of several compounds.

Nevertheless, some evidence testifies to a definite relationship between the biological activity of substances, including even toxicity and their chemical composition, and it has been made possible to express a number of more or less general principles together with determining the specific relationships of some groups of compounds.

In recent years, a considerable body of experimental data has been obtained regarding the dependence of biological activity upon composition in the group of organophosphorous compounds. First, investigations were made to estimate the role of separate chemical groupings in a molecule of a definite type of compound (82). These particular investigations alone do not reveal any proof that the detected relations are the only explanation for the mode of action of organophosphorous compounds upon cholinesterase (83–91). Discovering the mechanism of the inhibition of cholinesterase has developed the theory of the dependence of anticholinesterase activity of organophosphorous compounds upon their chemical structure. The majority of established relationships have been explained in the same way. In a number of articles, however, attention has been drawn to the fact that in many cases there is no conformity between the anticholinesterase activity of organophosphorous compounds *in vitro* and their toxicity (92–96). This is considered to be due to the peculiarities of distribution and conversion of organophosphorous compounds in an organism. Mihelson and his collaborators (92, 97, 98) showed the dependence of the distribution of organophosphorous compounds upon the rate of ionization of their molecules. Molecules of highly ionized compounds penetrate only slightly through the hematoencephalitic barrier. Sulfonic (including S^+) compounds with a positive charge do not penetrate at all (99, 100). The ionization rate of organophosphorous compounds also influences greatly their penetration through the skin (101). The rate of inhibition of cholinesterase depends greatly upon the position of the charge in a molecule of an organophosphorous compound (102). Compounds with the charge located on the atom, separated from etheric oxygen with two methyl groups, i.e., at the same distance as in an acetylcholine molecule, create the strongest anticholinesterase effect.

An important reason for the often detected discrepancy between the toxicity of organophosphorous compounds and their anticholinesterase activity is the rapid processes of conversion of these compounds taking place in an organism. Low anticholinesterase activity *in vitro* of many amides of phosphorous acids (octamethyl and others) and esters of thiophosphorous acid with high toxicity for insects and warm-blooded animals is associated with their ability to convert into more active, anticholinesterase agents in the appropriate organisms. On the other hand, low toxicity for warm-blooded animals of a number of active anticholinesterase chemicals depends upon their rapid detoxication in tissues (103–105). One of the most promising methods for finding selective compounds of low toxicity is to determine the groupings in a molecule of the compound providing for their rapid hydrolysis in the organism of warm-blooded animals and the absence of these in insects [Kagan and his collaborators (106)].

The toxicity of organophosphorous compounds depends mainly upon the structure of the molecule as a whole, and is not at all associated with the toxicity of elementary phosphorus; this is, however, quite different in the case of organomercury compounds. Investigation of toxicity of some compounds in this group, with different composition, showed that their toxicity (LD_{50}) varied within a comparatively narrow range (from ten to several hundred mg/kg). These data ascertain that toxicity of organomercury compounds is determined first of all by an available molecule of elementary mercury; the structure of the molecule influences the toxicity only within definite limits, mainly because of the variation of rate and kind of distribution (107, 108). This point of view is also confirmed by similarity of effects, by symptoms of poisoning caused by mercury and organomercury compounds, and by information obtained in experimental investigations, which showed that organomercury compounds as well as mercury blockade the SH-groups of enzymes. The differences in their action are more quantitative than qualitative [Medved (22)].

While studying the dependence of toxicity upon the structure of compounds, it should be kept in mind that this dependence is mainly due to the length of time the compounds remain in an organism. Some evidence has been obtained concerning certain dinitrophenol compounds (107). The lengthening of the carbonaceous chain in alkyl radical of dinitrophenol compounds up to three atoms, prolongs the time of chemical stay in an organism. However, a further lengthening of the carbonaceous chain (dinitrobutylphenol) produced decreased activity of circulation of the chemical. There is a definite relationship between the number of carbon atoms in an alkyl chain and the penetration of dinitrophenol compounds through the hematoencephalitic barrier—the lengthening of the alkyl chain leads to less penetration of dinitrophenol pesticides into the brain (108).

New data have been obtained regarding the dependence of toxicity upon the structure of chlorinated hydrocarbons of diene synthesis (109, 110). It has been stated that the toxicity of aldrin analogues can be reduced by changing the double bond into a simple one and also by introducing different substitutes into the side-chain of the cycle. Substitution of acid or ether residues for hydrogen in dehydroaldrin in a side-chain of the second bicyclic ring reduces the toxicity.

Considerable reduction of toxicity to warm-blooded animals has been produced by substituting hydrogen and fluorine for chlorine in the endomethylene bridge of the first bicyclic ring of aldrin. The introduction of oxygen at the place of the double bond of the second bicyclic ring does not reduce the toxicity. Stereoisomerism greatly influences the toxicity. Isodrin and endrin are much more toxic than their stereoisomers aldrin and dieldrin. Bicyclic derivatives (allodan, thiodan) involve less cumulative properties compared to the tetracyclic ones (aldrin, dieldrin, heptachlor).

Some evidence regarding the dependence of toxicity upon a chemical composition has been obtained in the group of chlorine derivatives of phenoxyacetic acid (111–117), derivatives of carbamate acid (116), and among the pesticides of some other groups (118).

Some papers discuss the dependence of toxicity upon the composition of silicones (119, 120), nitroparaffins (119), fluorine-containing alcohols (120), organic peroxides (121), and benzoquinones (122).

Golubev & Rusin (123) have presented a review on the dependence of toxicity of industrial poisons upon their structure (123).

Some Other Actual Problems

The size of this article does not permit elucidation of even the most actual problems of toxicology in detail. Therefore, we were obliged to name only some of them, indicating the appropriate broader investigations and reviews in this field. Much attention has been given to the development of the mode of action of different poisons. Classification of poisons according to their enzymatic mode of action has been successfully carried out (124, 125). The systems metabolizing poisons have been studied and the conversion of toxic substances in an organism investigated (126–129). In the toxicology of pesticides, some papers discuss the investigation of mechanisms of their selective toxicity. The most important results in this field have been achieved during the study of organophosphorous insecticides (17, 18, 93, 94, 103, 105). It has been shown that the low toxicity of some effective organophosphorous insectoakaricides on warm-blooded animals is associated with the metabolic detoxication by the tissues of these animals. Definite differences were found in rate and intensity of detoxication of these compounds in insects and warm-blooded animals and some structures concerning these differences have been found (92, 103, 105). The role of spatial conformation of a molecule in the mechanism of selectivity has also been defined (93).

The determination of a biochemical mode of action of organophosphorous, arsenic-containing, and organomercury pesticides enabled one to recommend the effective specific chemical and physiological antidotes for treatment of poisoning caused by these compounds (130).

The problem of combined action of poisons is being discussed by some investigators. A number of cases of synergetic and antagonistic effects of poisons have been determined (131–133), although in most cases, especially at the lower level of a chronic effect, additive effects occur with chemicals of one-directed action, and "independent effects" with chemicals of different-directed action (37, 38).

Some papers have discussed the combined action of chemicals and different factors of medium. It has been shown that the toxicity of organophosphorous and dinitrophenol pesticides, lead, mercury, and some other chemicals is higher in media of high temperatures (134, 135).

Research on blastomogenic, mutagenic, and teratogenic effects of poisons has recently been carried out (136–146). Together with investigations to determine the mechanism of blastomogenic, mutagenic, and teratogenic properties of poisons, attempts have been made to estimate the extent of hazards of different chemicals.

The research in this field has also been directed toward the problem of developing simple methods for determining mutagenic and blastomogenic properties of poisons in order to accelerate the determination of these properties and to find a quick solution to the problem of whether it is possible to use a specific chemical (142, 146).

Generalizing on the research work in the field of hygienic toxicology, it should be noticed that this work is characterized by the increase in experimental-theoretical studies, some important conclusions in toxicodynamics, elucidation of biochemical and physiological modes of action, quantitative estimation of hygienic hazards, and establishment of tolerance limits of poisons in the environment for the sake of public health.

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