Translated from *Uspkhi Khimii* **60** 530–535 (1991)

Systematic treatment and assessment of the risks due to superecotoxicants

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At the dawn of his appearance 30 000–40 000 years ago, *Homo sapiens*, being a product of the overall evolution of the geosphere, depended on nature, but he soon (against the background of the 4 billion years of the existence of the planet) disturbed the essential balance of nature.

The scientific-technical revolution in the 20th century gave rise to the "explosive character" of the development of anthropogenic energy and mass exchange. As a result of the extremely rapid functioning of this process, in essence via a "chain mechanism", qualitative and quantitative changes have taken place in the geosphere of a kind such that their accumulation has been responsible for the conversion of the anthropogenic factor into a significant factor on not only a regional but also a global scale.

The long neglect of this objective consideration, the euphoria associated with gaining control of powerful types of energy, the synthesis and introduction of new substances and materials, and the "victories" over nature have in general suddenly and in an acute form faced humanity with the ecological problem as a problem of its survival.

Indeed the global climate, the ozone layer, the oceans, the forests, the biological species, and the natural resources are being increasingly considered with alarm.

A reliable answer to the question whether or not the equilibrium between the interactions in the geosphere has now been disturbed can be given on the basis of the solution of a fairly complete global model. Its main components are the dynamics of the processes, the establishment of the permissible limits to the structural, phase, and functional changes, and the estimation of the relationship between fact and norm. The development of such a model will apparently make it possible to find a satisfactory solution to the problem of the preservation of the global equilibrium. However, this requires international efforts by scientists for a long time.

At the same time, together with the development of a global model and large-scale studies within the framework of the biosphere and biological research at governmental and international levels under the auspices of the United Nations Organisation, UNESCO, and other organs, rapid assessments of signal systems in various fields, which might reveal negative trends requiring immediate action by the community, are needed without delay. One of the most important objects of such assessments should be man himself (and, by analogy, all the components of the flora, fauna, and the environment as a whole).

In the outcome of the evolution of man against the background of the manifestation of negative factors one may note undoubted positive aspects: the growth of population, the increased lifespan, development, etc. However, during the past 30 years an appreciable (severalfold) increase in congenital deformities, allergies, and other negative phenomena has been noted throughout various countries of the world. If these figures are objective, and there are no grounds for disbelieving them, then they may in fact serve as the signal indicator system indicating the exhaustion of not only the capacity for adaptation to changes in the environment inherent in man but also of the capacity of the compensating mechanisms underlying the basis of modern medicine with its system of total monitoring of persons, diagnosis, and prophylactic and therapeutic measures.

A relaxed approach to this situation is not permissible. Firstly, it is essential to estimate urgently and repeatedly the reliability of the occurrence and the growing incidence of persons with congenital deformities. The point is that, if only the growth of human lifespan is adopted as a factor measuring man's well-being and the changes in the gene stock are not analysed, then one is faced with the objective problem of the risk of the appearance after a short time of a new "destructive" population of persons, the development of which, after the attainment of a certain "critical mass", would acquire the character of a chain reaction.

It is entirely clear that it is essential and a matter of extreme urgency to alter fundamentally the general trend towards an increase in congenital deformities. After all, if even now decisive measures are adopted, the alteration of the general trend will require time and hence will involve new victims.

The solution requires the discovery of the new factor or several factors responsible for this jump in the degradation index of human gene stock. Naturally, it would be most correct to carry out research in numerous directions: the influence of the external background electromagnetic radiation, the growth of the consumption (provided that this has occurred objectively) of alcohol and drugs, as well as other negative factors.

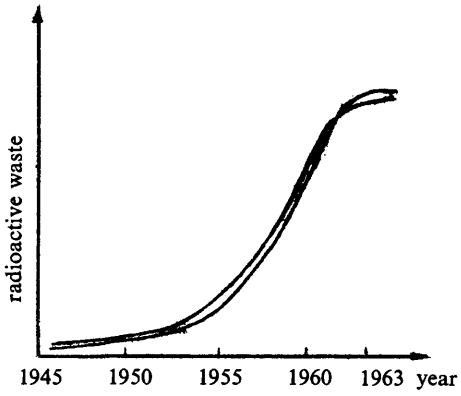


Figure 1. Approximate scale of the pollution forming the "dirty" background and exhibiting a polyfunctional biological activity. Fall-out $\Sigma(^{90}Sr$ and $^{137}Cs) \simeq 10^{18}$ Bq; amount in the stratospheric reservoir (fall-out continues) $\sim 10^{16}$ Bq.

Greenhouse effect: $\leftarrow CO_2 \rightarrow$ > 500 million tonnes (increment 0.3–0.5% annually), $SO_x \sim 300$ million tonnes, petroleum and petroleum products ~70 million tonnes, pesticides ~2 million tonnes, surfactants 10 million tonnes, solid waste ~4 billion tonnes, domestic waste (Moscow—2 million tonnes) ~50 million tonnes, liquid waste from animal husbandry (>100 thousand tonnes ha^{-1}) ~13 billion m^3.

An attempt at a comparative analysis of the radiation and chemical factors has been made. Fig. 1 illustrates the approximate scale of pollution, which, in terms of its regional and global

distribution, gives rise to a kind of constant qualitative and quantitative "dirty" background which exhibits objectively, by virtue of its nature, a polyfunctional biological activity. Hence arise the anomalies in the diseases of individual regions and, as the global "dirty" background grows, the biological response to it is manifested on a planetary scale.

The understanding of this approach makes it possible to formulate at the present time the fundamentally new problem of drawing maps of the planet, state, region, town, or village based on the index of the biologically harmful activity of samples of air, soil, water, and food in terms of an integral indicator of the activity of pollutants against a very small but chronic background.

Unfortunately world practice is directed at the present time to the investigation of biological activities of individual specific substances, involving the determination of the limiting permissible concentrations (LPC) of the latter. We believe that there are at present sufficient data to transfer the estimation of the biological activity of daily air, water, and food samples also to a new polyfunctional level.

Returning to the problem of the determination of the factors responsible for the increase in the number of persons with altered heredity, one cannot fail to pay attention to the chemical factor. Among the widely distributed "chemical pollutants", mention should be made of the mutagenic polyaromatic hydrocarbons (PAH), polychlorophenols (PCP), heavy metals, and other compounds. The present author has given the term superecotoxicants (SET) to substances small doses of which exhibit a powerful activity inducing or inhibiting enzymes (Fig. 2).

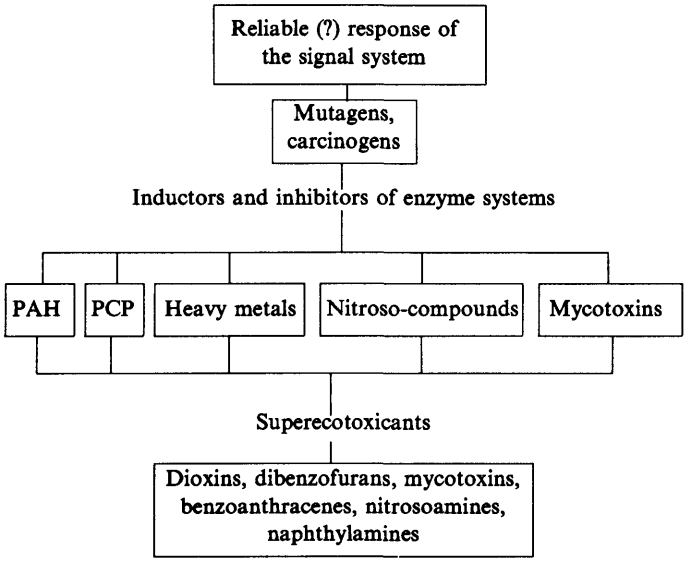


Figure 2. Chemical factors responsible for the increase in the number of persons with altered heredity.

Together with their inducing and inhibiting activities, superecotoxicants can also induce in man and animals a sharp increase in sensitivity to xenobiotics and other natural agents in the environment. It is essential to note also their natural stability and the absence of a toxicity limit (superaccumulative effect). The concept of the limiting permissible concentrations loses significance for virtually all superecotoxicants. The superecotoxicants circulate in all media and exhibit their activity through the components of the medium. Man is subject to their activity both via the aerobic pathway and perorally together with food products of plant and animal origin and water in which they accumulate from the soil and the hydrosphere. Thus yet another property is characteristic of superecotoxicants—an extremely high mobility in the ecosphere. These properties are in fact responsible for the complex toxic activity of various superecotoxicants, which can induce mutagenic, teratogenic, carcinogenic and porphyrogenic effects and can also suppress cell immunity, damage internal organs, and waste the organism.

The enormous experience gained in past toxicological studies made it possible to discover the normal logarithmic law governing the distribution of living organisms with respect to sensitivity to the action of harmful factors, including toxic substances. According to this law, the "dose–effect" relation can be in most cases fitted by monotonically increasing S-shaped curves, which are converted into straight lines when plotted on a logarithmic or a logarithmic probit grid. .

At the same time, in a number of instances experimenters have encountered significant deviations of the experimental data from the fitted S-shaped curves. The extreme case of such deviations are the so called paradoxical bimodal or two-phase effects where within a certain range an increase of dose leads not to an increase but to a decrease in the effect. The paradoxical dose relations have now been differentiated as a separate group, since they cannot be fitted by the known methods.

In our view, this shows that the methodology adopted fully takes into account all the features of the response of the organism as a complex system with numerous compensating and adaptive functions.

Theoretical treatment of the essential features of the response by living organisms to the effect of harmful factors suggests that toxic substances (superecotoxicants) act simultaneously or successively to a greater or lesser extent on virtually all the biotargets and systems of the organism, exerting their toxic action simultaneously via different mechanisms. The overall effect is then equivalent to the effect of the combined action of two or more substances involving summation (additivity), internal potentiation (synergism), and even autoantagonism.

On the basis of these features, a series of chemical substances inducing such two-phase effects have been specifically synthesised and investigated.

Analysis of experimental data on the dose relations for these compounds and of certain literature data made it possible to discover the rule governing the occurrence of "dose–effect" curves and to find a logical explanation in terms of which they can be fitted:

$$P = \frac{(D/X)^n \frac{1}{1+(D/Z)^k} + (D/Y)^m}{1 + (D/X)^n \frac{1}{1+(D/Z)^k} + (D/Y)^m},$$

where D is the dose of the substance, X and Y are the average lethal doses in the first and second phases, Z is the average effective

autoantagonistic ("antidote") dose, and n, m, and k are the corresponding coefficients for the intensity of the increase in the effect.

It has also been established that Z is a dependent quantity and can be expressed by the formula

$$\lg Z = \lg X + \frac{3.1}{m/n + k} \lg (Y/X).$$

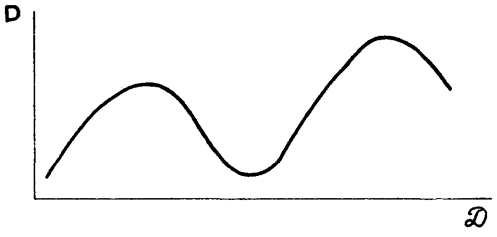


Figure 3. Two-phase dose relation.

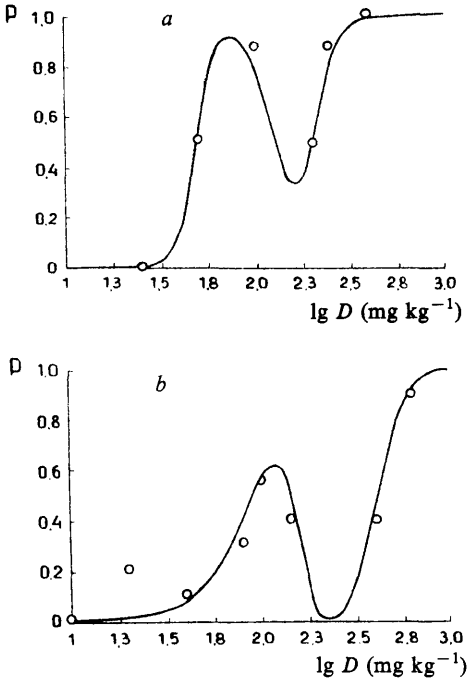


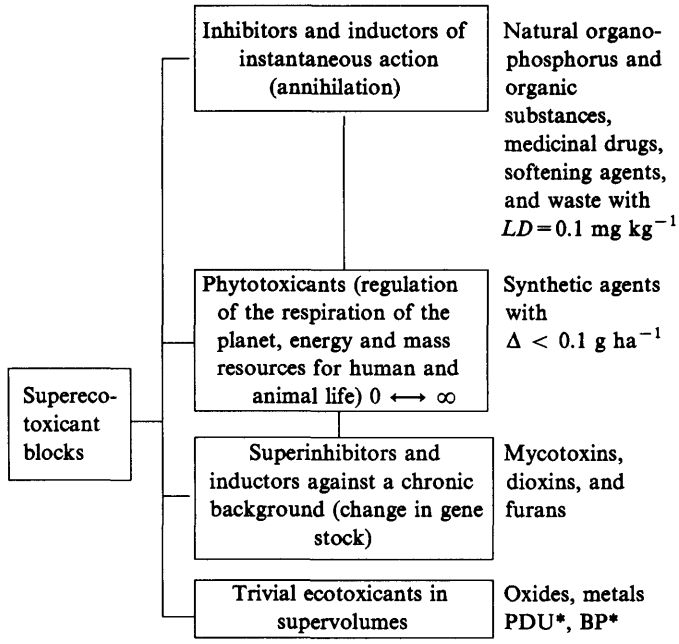
Figure 4. Experimental curves for the two-phase dose relation (composition based on dimethylbenzoanthracene) on the 45th day for white rats (*a*) and white mice (*b*).

A typical two-phase relation is presented in Fig. 3. The coefficients n, m, k, X, and Y as well as the standard deviation were determined by the multiple regression method on a computer.

An experimental confirmation of the validity of the relation is presented in Fig. 4 for dimethylbenzoanthracene (DMBA).

On the basis of the analysis carried out, it is suggested that for practical applications the superecotoxicants be treated systematically on the basis of four main blocks (they can be expanded in terms of substructures).

SCHEME



*Unidentified Russian abbreviation (Ed. of Translation).

It is striking that controls in relation to the first block have been adopted in a number of international conventions and agreements and in registers of medicinal drugs.

Controls in relation to the second block have not yet been organised although one cannot rule out the possibility that they will be included in the convention on chemical weapons.

As regards the third block, the methods of registration and control of submicro-amounts of the relevant substances and experimental estimation of their biological activity in combination with accompanying "pollutants" and "ordinary" substances require urgent tests and development on national and international levels.

The fourth block requires a more clear-cut formulation and control. Overall, the following problems come to the fore:

1. Detection, screening, systematic treatment, registration, and international control (Soviet and international systems).

2. Monitoring and local and remote control methods for chemical and express biological detection with a high sensitivity. Mapping of the planet, regions, and populated areas. Dynamics. Characteristic features. Predictions. Solutions. Practice.

3. Methods for the estimation of the integral "response" to multifactorial influences.

4. Detection, location, isolation, and abolition of sources of pollution.

5. Development of controlled cycles (waste-free technology, closed cycle manufacturing processes, absorption of absorbable gases, and the supercycle).

It is very important to note that overall, within the framework of the earlier estimate of the degree of risk associated with chemical factors, a systematic treatment and control of superecotoxicants and

the development of a methodology for their estimation should be prosecuted on a universal, international scale, since this would make it possible to obtain maps of the probable biological effects of various media (air, water, soil, food) for populated areas, regions, and the planet as a whole. This would in fact serve as a guide in the adoption of solutions.

It is necessary to go over to a new philosophy of the organisation of the life cycle of any article, any material, and any substance. This cycle must include in a unique whole the extraction of the raw material, transport, conversion of the raw material into the product, the utilisation of waste, ecologically clean employment of the product, and methods for its complete utilisation after the article has fulfilled its function (purpose). This in fact constitutes a closed "supercycle".

Translated from *Uspekhi Khimii* **60** 536–544 (1991)

Polychloropolycyclic xenobiotics

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Xenobiotics from a number of polychloropolycyclic compounds (PCPC) of the dioxin type such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), 2,3,7,8-tetrachlorodibenzofuran (2,3,7,8-TCDF), their more highly chlorinated derivatives and also 3,3',4,4'-tetra-3,3',4,4',5-penta- and 3,3',4,4',5,5'-hexachlorobiphenyls (Table 1) are some of the most dangerous ecotoxicants passed into nature from the production of the chloro-compounds and from technologies based on the use of chlorine and its compounds.

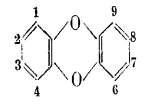
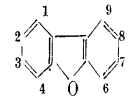
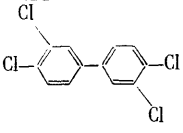
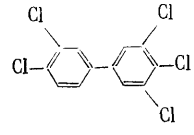
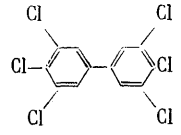
Some general properties of these xenobiotics (compiled in 1984) are given in a short review.[1] However, during the past five years the number of scientific publications on PCPC has more than doubled. Among the more than 1600 studies there are monographs, handbooks, and large reviews of the various aspects of the PCPC problem, summarising results on national and international programmes, results of national and international scientific meetings and conferences. New information, a significant part of which is presented in the proceedings of international symposia on 'Dioxin and Related Compounds',[2–5] has enabled a more ordered concept to be created of PCPC as poisons, ecotoxicants, on their influence on contemporary medicine and on the ecological situation. The most important conclusions are given below.

I. Toxic effects

Acute toxicity for warm-blooded animals is not now considered to be a criterion of the danger of PCPC for man. The primary and secondary effects of PCPC on an organism and their consequences, which depend substantially on the habitat and conditions of existence of the organism, have proved to be more important in this regard.

The primary effects of 2,3,7,8-TCDD and its analogues are linked with the high specificity of these xenobiotics towards the cytosolic A*h* receptor controlling primarily the activation of genes A1 and A2 (on the 15th human chromosome) and the set of non-specific monooxygenases, viz. cytochromes P-4501A1 and P-4501A2.[6] Recently a third locus activating the A*h* receptor has become apparent and has been investigated.[7] Participation of the complex of 2,3,7,8-TCDD with the receptor has also been shown in the suppression of a gene on the 16th human chromosome producing menadioneoxidoreductase.[8] A high affinity has been established for dioxin-type PCPC towards the nuclear thyroxine receptor and an increase in thyroxine receptor concentration has been shown in the nuclei of cells of animals poisoned with 2,3,7,8-TCDD.[9] These data suggest that the action of PCPC is directed towards a series of regulatory mechanisms of the living cell, selected in the course of evolution, started by receptor proteins with a single type of active centre. Haem, which is sterically accessible for planar PCPC, emerges as the most probable target, since of natural substances only the iron-porphyrins are capable because of their geometric and electronic parameters of interaction with all the known inducers of the dioxin type.[10]

Table 1. List and relative danger of polychloropolycyclic compounds.

Compound*	Relative danger	Compound*	Relative danger
			
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PCDD	0.5	1,2,3,7,8-PCDF	0.01
1,2,3,6,7,8-HxCDD	0.1	2,3,4,7,8-PCDF	0.5
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
octa-CDD	0.01–0.001	1,2,3,4,7,8,9-HpCDF	0,1
		octa-CDF	0.01–0.001
	0.001		0.3
	0.01		

Footnote. Relative danger is given for carcinogenic risk.
* HxCDD is hexachlorodibenzo-*p*-dioxin; HpCDD is heptachlorodibenzo-*p*-dioxin; HxCDF is hexachlorodibenzofuran; HpCDF is heptachlorodibenzofuran.

On passing into an organism PCPC act as inducers of extended false responses enabling the accumulation of a series of biocatalysts-haemoproteides in quantities dangerous for cell and organism function. Essentially, the regulatory mechanisms affected by these xenobiotics lead to a disturbance of the protective mechanisms of the