

MEDICO-BIOLOGICAL RESULTS OF DIOXIN EXPOSURE

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Introduction

Problem of environmental pollution by dioxins appeared in the 1960-1970's with the first information about these xenobiotics influence on people and animals' organisms. These compounds are considered to have a wide spectrum of biological effect in extremely low doses on all the aerobic organisms including a human being. Being by-products in chemical, paper, metallurgic, electrotechnical and other industries they are spread widely enough in the environment and are formed in burning many industrial and life wastes, rubbish, benzine etc. In many towns of Russia there are industries whose technologies produce dioxins (1,2). By now almost all the scientific medical literature on dioxins concerns for the major part experimental works, where its immunodepressive, mutagenous, teratogenous and embriotoxic effects are described. There are few data about dioxin influence on people, they are of episodal character and are connected with production accidents in Saveze (Italy), war actions in Vietnam where herbicide 2,4,5-T with high dioxin content was used, and also with the use of food oils contaminated with dioxins in U-Sho (Japan) and U-Chenge (Taiwan).

Material and Methods

However, there are some large-scale enterprises with chlororganic syntheses on the territory of Bashkortostan and hence the importance of the dioxin problem for the Republic. On this basis to evaluate the character of dioxin effect on the human organism we analysed health state of people who had been working in dynamics in the production of 2,4-D. The main purpose of our investigation was retrospective and prospective evaluation of health state of people having contacts with dioxins for the determination of possible toxic effects and scientific bases for the system of preventive treatment. In accordance with our purpose and investigation tasks a programm was worked out including 3 stages of retro- and prospective investigation of people who had been working in the production of the herbicide 2,4,5-T and having contact-with high dioxin concentrations and working on in the same shop after its re-equipment for the production of 2,4-D under the conditions of low dioxin concentration. They comprised the main cohort investigation group. For the comparison the second group was formed consisting of workers producing 2,4-D but who had not had any contacts with high dioxin concentration in the past. The third control group consisted of clerks working at the same plant but having no contacts with chemical substances. Special statistical cards were worked out and compiled which showed the results of clinical examination by doctors of different specialization. Established clinico-functional, hematological, biochemical and immunological investigations were carried out. Evaluation of the results obtained was based on their comparison with the commonly supported ones and the data obtained from the comparison groups. Collective health indices were also analysed: diseases with temporary loss of working ability, oncological diseases and mortality as a result, cardiovascular diseases and mortality from them and indices of common mortality. With V.G.Shakhbasov method biological age determination of workers who had had contacts with high dioxin concentration as compared to their real age by 1994-1995 was carried out. Cytogenetic investigations aimed at finding genotoxic effect were fulfilled and chromosome aberrations frequency in peripheral blood lymphocytes was studied. Reproductive ability in the families of the main cohort group workers was evaluated by their questionnairing taking into account the number of their pregnancies, their course

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and outcome. On evidence of questionnaires and clinical examination the health state and reproductive function of the second generation and workers' grandchildren' diseases were studied. All the investigation results were processed by modern mathematical statistics methods on "IBM-486" computers with "Microsoft Works" and "Statgrafics" programme. Well-known methods of finding mean arithmetical value (M) and its standard error (m), evaluation of probability integral (t) and, on the bases of Student criterion, verification' of the difference between them were used. The results obtained were compared to those of the other two workers' groups and of the population.

Results and discussion

In 1965 a shop producing the most promising by that time herbicide 2,4,5-T was opened at the Chimprom plant in Bashkortostan. Relying on the survived technical documents the technological scheme of 2,4,5-T production was restored. The production was new, technological mode was not quite adjusted, breakages and accidental situations took place, maintenance often occurred with the equipment depressurization. Imperfection of the technological scheme, work in the high temperature mode-up to 300°C -led to the formation of great amount of the most toxic dioxin 2,3,7,8-TCDD. At that time measurements of dioxin content in the working area atmosphere and the end product were not conducted. Specially made by L. A. Fyodorov (2) calculations in 1993 showed that in the 1960s the content of the most toxic 2,3,7,8-TCDD in the herbicide 2,4,5-D came to not less than 30-40 mg/kg and reached 70 and even 100 mg/kg. The work was done in 3 stages. At the 1st stage 150 people who had been working in the shop producing herbicide 2,4,5-T were examined and of them a cohort group was formed consisting of 128 people with the revealed similar skin affections of ephoracne type and early signs of toxic melanoderma, in 85,3%/. Those were young people aged 20-29, predominantly men (92%) serving equipment 68.2%. In comparison with an analogous group of Chimprom workers of the same age where only 10% showed acneform eruption.

As the analyses of objective examinations by deematologists of those years (3) showed the cohort group revealed skin affections in the form of dryness, scaling, slight hyperemia, single acneform eruptions localizing mainly on the face and around eyes and often accompanied by itch. Cohort group patients underwent dermatological treatment during 6-12 months. There were more expressed skin affections noticed by characteristic multiple acne eruption in the form of acneform elements or folliculitis, comedones, milium. and moderately expressed hyperkeratosis which spread on breast, back, forearm, buttocks, thighs, external genitals. Besides ephoracne another indication of dioxin toxic action was in the form of early signs of toxic melanoderma revealed in 16.2% as brownish - aspid pigmentation on some face parts and around follicle opening. On the bases of retrospective analyses ; -of the results obtained during therapeutic and neurologic examination together with elimco-functional and laboratory investigations almost half of the examined patients (40%±6,1) revealed in parallel with skin affections signs of vegetovascular dysfunction of predominantly sympatheticoadrenal character, which expressed in high arterial pressure.

Major part of the cohort group 43.8±4.3% being about 23 years of age showed deflection of cholesterol level index in blood serum from the normal level (150-200 mm%). Besides, frequency of cholesterol indices deflections is higher in the cohort group in comparison with the second group of workers contacting with low dioxin concentrations and with the third control group.

Trend to cytopenia reaction in males mainly on the side of stab and segmented neutrophils, monocytes and lymphocytes from low norm limits is noted in the peripheric circulation.

At the second investigation stage health state of 39 people from the 128 cohort people was analysed retrospectively. In 1984 they were thoroughly examined in hospital (4). Clinical data analyses showed regression in skin affection development in spite of medical supervision and appropriate treatment during 4-6 years, though these people continued contacting with low dioxin concentrations. In comparison with the previous investigation more people 58.9±7.8% showed vegetovascular dysfunction of hypertension type. For 15.4±5.7% the diagnosis was made as hypertension, and for 13.0±5.3% it was myocardial ischemia. Attention was also paid to the changes in coagulative blood system, which were

characterised by the tendency to hypercoagulation in 40.7%. Content of prothrombin complex factors was increased in 27%. And 32.4% of the patients showed increased upper norm levels (4.0 ± 0.13) of fibrinogen A content. Frequency of positive fibrinogen p tests in 32.4% of patients proved the tendency to hypercoagulation. Decrease in the mean values of plasma tolerance to heparin in 43.2% and spontaneous fibrinolysis in 82.0% of the patients characterised anticoagulative system depression. Hematocrit indices in 35.1% of the patients exceeded the norms. All the obtained indices for certain differed from the control. Immunological investigations showed changes in the cellular immunity as a reliable decrease of mean values of T and B lymphocyte number in half of the patients ($p < 0.05$) in comparison with the control groups.

At the 3rd investigation stage we provided the rough clinical examination of 73 patients for their health state evaluation and drawing conclusions about distant outcomes of their contacts with high dioxin concentrations in the past. For comparison the same two groups of workers (producing 2,4rD and having contact with low dioxin concentrations and not contacting with chemical substances at all) were taken. Cohort group age by that time was 50-59 years old (mean 52 ± 1.4 years old). Increase in frequency of vegetovascular disturbances and also their transformation into hyper tension was observed in dynamics in patients with their aging ($p < 0.05$). Comparison studies of hematological indices results indicated as before increase of monocytes number in 33.8% of the patients and lymphocytosis appearance in 18,6%. Changes in the coagulative system were also evident in half of the patients and characterized by the tendency to hypercoagulation owing to activation of prothrombinforming and anticoagulative system depression. These changes might indicate the processes of organism aging and higher cholesterol levels (higher than 200 mg%) in 43.8% of the patients also testified to them. Evaluation of immunological status in dynamics noted, as at the second stage, cellular immunity depression, namely statistically reliable ($p < 0.05$) decrease of T and B lymphocytes in comparison with the second and the third control groups. Humoral immunity was characterized by some increase of M and G class immunoglobulins in 13.0% and 16.4%. What counted was the increase of the circulating immune complex level, the increase of auto-antibody titers to different organs tissues in 17% of the patients, which might indicate stimulation of autoimmune processes in organisms.

Thus, the results obtained from retro- and prospective investigations revealed in dynamics unidirectional form of functional disturbances and homeostasis indices in workers contacting in the past with high dioxin concentrations. It was characterised by skin affections of chloracne type: vegetovascular dystonia of sympathicoadrenal character, variability of hematologic indices, disturbances of biochemical and immunological hemostasis links.

To evaluate a detriment level of health state in workers having contact with high dioxin concentration in the past we studied collective health indices in the cohort group. It was found that disease indices with temporary loss of working ability and oncological diseases did not exceed the analogous indices both in work collectives and among the city population. Mortality rate and malignant tumor death indices were also not higher than among population (both on Ufa and in the Russian Federation) concerning frequency and structure. However, it should be noted that cohort patients died from oncological diseases being about 54.2 ± 5.8 years old and this was 8 years less than the mean Ufa mortality index in 1994 which was 63.7 ± 0.1 years. It means that people who came through dioxin intoxication died from oncological diseases' at an earlier age than other oncological patients in Ufa. Besides, biological age of people in the cohort group appeared to be higher than that in the control group.

In medical literature there is information about possible teratogenic and embryotoxic action. In this connection reproductive function of the cohort group people was studied.'

In the absence of statistical reliability just a tendency was noted to a greater number of spontaneous abortions in the studied group ($6.9 \pm 2.0\%$) than among the population ($5.7 \pm 5.9\%$) of Ufa. Sexual disproportion of infants with girls' share usually predominating was also revealed. Among the first infants of the first generation there were 120 girls and 100 boys. Among the following infants there was

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gradual equalization of sex relationship. Cytogenetic investigation revealed a tendency toward disturbance in chromosome aberrations frequency of chromatid and chromosome types in the genetic apparatus of peripheral blood lymphocytes. Number of middle molecules in blood serum of cohort people was also studied at the third stage. These results might be a good indication of dioxin toxic action. Reliable increase of middle molecules in 70% of people was found. It testified to inadequate function of organism detoxication and marked endogenous intoxication of organism having any origin. It is not improbable that endogenous intoxication was due to dioxin circulation in the patients' organisms even 30 years after the contact with high dioxin concentration had been stopped. This assumption was supported by the results of selected investigations of dioxin content in cohort people blood pursued by an American scientist A. Schechter.

First children of the first generation showed more vivid and frequent health disturbances (mostly in the form of allergic reactions). With the passage of time, that is second and third children marked decrease in diseases. Among grandchildren (second generation) there was no deflection in health indices from the rest of the population.

Conclusions

1. On evidence derived from retrospective analyses a symptom - complex characteristic for high concentration dioxin effect was worked out: skin affections, vegetovascular disturbances, tendency to cytopenia reaction and lipid metabolism disbalance.
2. 30 year long observation dynamics showed that in parallel with skin affection regression there was increase in vegetovascular dystonia frequency predominantly of sympathicoadrenal character with its transformation into cardiovascular pathology, as well as a number of homeostatis disbalances on evidence of some hematologic, biochemical and immunologic indices.
3. Observed disbalances of lipid metabolism and coagulative blood system, increase of vascular disturbance frequency, increase in biological aging allowed definite assumptions, that dioxins in high concentrations could be one of the risk factors in early organism aging, which was supported, and in earlier common mortality and mortality from oncological diseases.
4. Revealed tendency to chromosome aberration disbalance in blood lymphocytes, increase in spontaneous abortions and infant sexual disproportion with girls' share predominating could be accounted for the effects of high dioxin concentration on genetic and embryotoxic levels and called for further investigations.
5. Scientifically substantiated program of medico-biological monitoring of people exposed to dioxins and their offsprings was worked out and introduced.

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