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TRANSLATION:

CHARACTERISTICS OF THE EFFECT OF BENZENE ON THE REPRODUCTIVE FUNCTION OF ADULT AND YOUNG ANIMALS

Avilova, G. G., and I. P. Ulanova: Sravnitel'naia kharakteristika vliianiia benzola na reproduktivnuiu funktsiiu vzroslykh i molodykh zhivotnykh. Institute of Industrial Hygiene and Occupational Diseases of the USSR Academy of Sciences, Moscow.

The intensive development of the chemical industry and the involvement of a large contingent of students in trade and other technical training brought about an increase in the number of young persons exposed to chemical compounds.

Recent literature reports indicate the considerable vulnerability of young subjects both during exposure and at later dates after the poisoning. This especially applies to benzene, a toxic substance which is currently in wide use in various segments of the national economy (V. A. Doskin; Iu. D. Kalashnikov, etc.). I. A. Gribova and L. A. Zorina observed steady hematological changes during the late period of chronic poisoning with benzene in subjects who have been in occupational contact with this substance since adolescence.

V. R. Chevpetsov and A. A. Liapkalo demonstrated the effect of benzene on the reproductive function of animals. However, these effects were observed only in adult animals under the influence of high concentrations.

What remained unclear, and what consequently forms the subject of the present study, is the mode of the effect of benzene on the reproductive function of animals whose contact with this substance began during the period of sexual maturation, i.e., during the period of intense reorganization of the entire neuroendocrine system, rather than during adulthood.

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The experiment was carried out on animals of two different age groups: One group of adult animals was made up of four-month old strainless female albino rats with a body weight of 230-250 g, while the group of young animals comprised rats aged 1.5-2 months, with a body weight of 100-120 g, i.e., rats being in the period of sexual maturation. It was at this age that the four-month chronic exposure to benzene vapors in a concentration of 0.03 ± 0.003 mg/liter ($\sim Lim_{ch}$) and 0.005 ± 0.0003 mg/liter (MAC level) was started. The concentration in the inhalation chamber was determined by N. M. Mal'tseva by means of a "Khrom-3" chromatograph.

The functional status of the ovaries was assessed monthly throughout the entire experiment by calculating the overall duration of the estrous cycle and of its individual phases and by determining the number of the animals having rhythmic cycles. After the conclusion of the chronic experiment, the females were mated with intact males, and the reproductive function was assessed according to the methods recommended in the "Methodological Guidelines for Determining the Effect Threshold of Industrial Poisons on Reproductive Function."

Another group of the pregnant animals was left alive till spontaneous delivery occurred to study the characteristics of the offspring. The factors determined were the number of offspring, their weight, postnatal mortality, as well as the status of the central nervous system on the basis of the summation threshold parameter and of the status of the peripheral blood.

The general health status of the animals during exposure was assessed according to the following: body weight, value of the summation threshold parameter, reflex function of the central nervous system, peripheral blood picture (hemoglobin, erythrocyte, leukocyte, thrombocyte, and reticulocyte counts, phagocytic activity of the neutrophils), ability to perform static

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work, and permeability and resistance of the cutaneous capillaries. To detect possible latent changes, an ethanol loading test was performed on the nervous system, which was the most severely damaged system of the body, and the function of the hematopoietic system was tested by bloodletting; the amount of blood removed equaled 1.5% of the body weight. All results obtained were anlayzed statistically by the Student T-test or by the χ^2 method.

The study of the estrous cycle demonstrated an increase in the duration of estrus (1.46 $\pm$ 0.13 in the experiment vs. 1.15 $\pm$ 0.08 in the control; $P < 0.05$) in adult rats during the fourth month of exposure to a concentration at the $\sim Lim_{ch}$ level, while a reduction of the overall length of the cycle was observed in animals exposed to the MAC level (4.80 $\pm$ 0.16 in the experiment vs. 5.32 $\pm$ 0.18 in the controls; $P < 0.05$). Among the young animals exposed to benzene at the MAC level, a reduction in the number of rats with rhythmic cycles was observed during the third month of the experiment. The ability for conception did not show any changes from the controls either in the adults or in the young rats.

The parameters and results obtained upon examination of the sacrificed animals are presented in the Table. These findings show that there were no changes in the pregnant young rats that had been exposed to benzene concentrations at the $\sim Lim_{ch}$ and MAC levels, while increased embryonal weight and an increase in the relative number of fetuses with hemorrhages were observed in the adult animals exposed to a concentration at the $\sim Lim_{ch}$ level. The increased number of fetuses with hemorrhage in the latter group may be due to increased vascular permeability. Increased preimplantational mortality was observed in animals exposed to the MAC.

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TABLE. PARAMETERS OF THE REPRODUCTIVE FUNCTION OF RATS AFTER PROLONGED INHALATION OF BENZENE (M ± m).

Parameter	Dose of benzene (in mg/liter)			
	0.03 ± 0.003			
	Young animals		Adults	
	Experiment	Control	Experiment	Control
Absence of pregnancy	4/28 (14.3%)	5/30 (16.5%)	4/28 (14.3%)	8/27 (29.5%)
Fertility	9.7 ± 1.05	10.7 ± 1.19	10.5 ± 1.19	11.1 ± 0.91
Number of corpora lutea (per female)	14.4 ± 1.08	14.8 ± 0.65	15.0 ± 0.61	17.0 ± 0.79
Death of ovum before implantation	5.1 ± 1.84	4.0 ± 1.7	6.9 ± 1.6	4.25 ± 1.86
Embryonal mortality after implantation	2.5 ± 0.97	1.2 ± 0.54	1.6 ± 0.69	3.0 ± 1.19
Overall embryonal mortality (in %)	50.5 ± 10.8	34.3 ± 10.8	54.7 ± 8.6	42.6 ± 11.5
Length of fetuses (in mm)	27.6 ± 0.72	27.2 ± 0.62	27.9 ± 0.25	27.1 ± 0.54
Fetal weight (in g)	2.17 ± 0.08	2.26 ± 0.09	2.38 ± 0.08	2.09 ± 0.06
			$P < 0.01$	
Number of fetuses with (subcutaneous and intramuscular) hemorrhage	5/68 - 7.3%	11/95 - 11.6%	12.84 - 14.3%	4/78 - 5.1%

Left

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TABLE. PARAMETERS OF THE REPRODUCTIVE FUNCTION OF RATS AFTER PROLONGED INHALATION OF BENZENE (M ± m).

Parameter	Dose of benzene (in mg/liter)			
	0.005 ± 0.0003			
	Young animals		Adults	
	Experiment	Control	Experiment	Control
Absence of pregnancy	2/28 (7.15%)	5/30 (16.5%)	2/22 (9.1%)	8/27 (29.5%)
Fertility	11.0 ± 1.95	10.7 ± 1.19	9.9 ± 1.24	11.1 ± 0.91
Number of corpora Lutea (per female)	14.7 ± 1.67	14.8 ± 0.65	17.3 ± 1.29	17.0 ± 0.79
Death of ovum before implantation	6.0 ± 0.7	4.0 ± 1.7	10.2 ± 1.95	4.25 ± 1.86
			P < 0.05	
Embryonal mortality after implantation	1.33 ± 0.59	1.2 ± 0.54	1.7 ± 0.54	3.0 ± 1.19
Overall embryonal mortality (in %)	49.9 ± 11.9	34.3 ± 10.8	66.8 ± 9.38	42.6 ± 11.5
Length of fetuses (in mm)	27.5 ± 0.74	27.2 ± 0.62	26.4 ± 0.57	27.1 ± 0.54
Fetal weight (in g)	2.31 ± 0.09	2.26 ± 0.09	2.04 ± 0.07	2.09 ± 0.06
Number of fetuses with (subcutaneous and intramuscular) hemorrhage	7/65 - 10.7%	11/95 - 11.6%	1/54 - 1.9%	4/78 - 5.1%

Right

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Observation of the development of the offspring of the young animals that had been exposed to benzene at the $\sim Lim_{ch}$ level revealed increased postnatal mortality (44/115 = 38.3% in the experimental group vs. 24/118 = 16.2% in the controls; $P < 0.001$) and reduced erythrocyte counts in the females (4.87 $\pm$ 0.16 million in the experimental group vs. 5.39 $\pm$ 0.17 million in the controls; $P < 0.05$). If exposure had been at the MAC level, the young rats had increased body weights at the ages of 1 and 2 weeks.

The body weight of the offspring decreased during the first month of life in the group of adult rats exposed to the higher concentration (52.7 $\pm$ 1.4 g in the experimental group vs. 67.4 $\pm$ 2.2 g in the controls; $P < 0.05$), and the male offspring showed increased excitability of the nervous system (3.8 $\pm$ 0.1 in the experimental group vs. 4.5 $\pm$ 0.3 in the controls; $P < 0.05$). When the adult mothers were exposed to the lower concentration, the offspring showed a weight loss at the age of one month (58.9 $\pm$ 8 g in the experimental group vs. 67.4 $\pm$ 1.2 in the controls; $P < 0.01$).

The above findings indicate that benzene affected the reproductive function of animals which had had their first contact with this substance as adults or as young animals during their sexual maturation. The changes observed in the animals which had first been exposed to benzene during sexual maturation were no more serious than those found in those animals which were first exposed to this substance when they were already adults. This could be assumed to be due to the fact that the young animals were at a physiologically more adequate age (the age of the young animals at mating was 5.5 months, vs. 8 months in the case of the adult animals). However, comparison of the parameters obtained for the adult and young control animals failed to reveal any differences between these control groups.

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This experiment does not allow the action of benzene to be considered as purely gonadotropic because benzene is deposited in the organism, and it circulates in the organism, especially under the conditions of chronic poisoning (E. S. Mironos). Thus it could have both affected the fertilized ovum and penetrated through the placenta.

The embryotropic action of benzene was demonstrated by V. A. Gofmekler. Benzene is detectable in the milk, it influences the lactation (D. I. Khoroshanskaia; V. A. Kaianovich; N. P. Mikhailova), which may be responsible for the weight loss of the offspring and of the increased postnatal mortality. This effect of benzene is probably nonspecific, because increased vascular permeability, reduced ability to perform physical work, and changes in the functions of the nervous system and in the blood, etc., were observed in the animals exposed to the given concentrations, which are all in agreement with the observations made by K. A. Kormilitsin and M. V. Vashakidze, V. A. Kaianovich, et al., and by N. P. Mikhailova, although these investigators did not observe any specific changes or diseases of the female reproductive tract which could be related to the effects of benzene.

Conclusions. 1. At low concentrations, benzene influences the reproductive functions of both adult and young animals.

2. This effect manifests itself against the background of general changes in the organism, i.e., it is nonspecific.

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