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EFFECT OF VINYL CHLORIDE ON EMBRYOGENESIS IN THE RAT

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The fact that there are widely scattered throughout the U.S.S.R. many plants involved in the production of vinyl chloride (VC), polyvinyl chloride (PVC) and in the manufacturing of them into finished articles and that there is a significant quantity of workers who are women makes it necessary to study the embryotropic effect of the said compound. Vinyl chloride in high concentrations together with ethanol produces an embryotoxic and teratogenic effect (Zohn et al.). The purpose of our investigation was to study the embryotropic effect of VC in an experiment in concentrations on the level of those existing in the present MAC and those on the order below the MAC.

METHOD. The embryotropic effect of VC was studied in rats of the Wistar population. The animals were subjected to the inhalation effect of the toxin for the full course of pregnancy for four hours per day in conditions of dynamic inoculation. The gas content in the inoculation chambers was $35.5 \pm 3.5 \text{ mg/m}^3$ (MAC level) and $4.8 \pm 0.5 \text{ mg/m}^3$ (on the level below the MAC).

Beginning with the sixteenth day of pregnancy the rats were monitored for a series of integral and special indicators.

In order to clarify the harmful effect of VC on the fetus, a

portion of the rats was sacrificed on the twentieth day of pregnancy. The pre and post implantation death rate and also the general embryo death rate were calculated. The pathology of the internal organs of the fetuses was studied in a series of microscopic sections (Wilson method modified by A. P. Dyban et al.).

In connection with the fact that the development of defects frequently appears in the postnatal period, a portion of the rats was allowed to go on and give natural birth. As this occurred, a calculation was made of the survival and lactation coefficient. Beginning with the age of 3 days a test was made of the induced motor activity in the offspring, and when they were 2 months old a test was made of the food conduct reaction. As indicators which characterize the induced motor activity of the offspring of the rats of differing age, we used the time the animals spent on a horizontal cord, the time they spent on a vertical cord of 3 diameters (11, 17 and 25 mm), various elements of motor reaction on the vertical cord (Altman and Subarashan). In all, 230 analyses were conducted. Specialized forms of appetite, general appetite and thirst were used as "food behavior" indicators. At the age of 6 months the offspring were investigated (with respect to gender of the animals) for a series of indicators which reflected the function of the nervous system, liver, kidneys, a study was made of the morphological composition of the peripheral blood, a calculation was made of the weight of the internal organs.

In the experiment a total of 130 pregnant rats were used, an analysis was conducted on 230 of the offspring, produced and

found during observation of 700 specimens of offspring.

INVESTIGATION RESULTS. The results of studying the general toxicity of VC are presented in the table. It was established that VC in concentrations on the level of those existing in the MAC in the pregnant animals causes a decrease in erythrocyte content in the blood and a lowering of the hippuric acid in the urine. In reactions of the toxin at concentrations one order of magnitude less than the MAC, with respect to all of the indicators selected, no deviation could be shown in comparison to the controls.

At the above-indicated concentrations VC had no negative effect on the pre and post implantation and general embryonic death rate. Tests on the fetuses conducted by the microanatomical method showed an increase in the relative number of them with hemorrhages ($51.2 \pm 6.3\%$; $P < 0.001$ under the effect of the greatest concentration; $49.3 \pm 8.7\%$; $P < 0.001$ under the effect of the average concentration; $12.3 \pm 3.2\%$ in the control). Under the effect of VC at a concentration of 35.5 mg/m^3 there was also noted an increase in fetuses with intumescence ($62.0 \pm 7.9\%$ with $4.2 \pm 3.2\%$ in the control; $P < 0.001$).

The effect of VC on pregnant rats at concentrations of 35.3 and 4.8 mg/m^3 did not lead to a change in such indicators as lactation coefficient and offspring survival coefficient.

An analysis of the reactions conducted in the offspring which during the antenatal period were subjected to the effect of VC in the larger concentration showed an increase in the retention time of the 9-11 day old rats on the vertical cord ($98.3 \pm 8.49 \text{ s}$ with $23.8 \pm 3.88 \text{ s}$ in the control; $P < 0.001$). In this very same group a

larger number of those which remained on the vertical cord for 1 minute was noted (62.5% with 10.4% in the control) and there were practically no cases of them jumping off of it (54.2% in the control). The 9-11 day old offspring subjected to the effect of VC in the antenatal period at the lesser concentration were able to stay on the horizontal cord for a more prolonged period of time (24.2 ± 2.7 s with 16.9 ± 1.47 s in the control; $P < 0.05$) there were no cases of retention on the vertical cord for 2 minutes. Investigations of the specialized form of appetite, general appetite and thirst in the 3 month old offspring in the test groups did not show any reliable changes.

Investigations in the 6 month old offspring showed changes in the function of the nervous system, liver and of the composition of the blood. Thus, for example in the offspring of the male gender of the first test group a lowering of the orientation reaction was noted (2.1 ± 0.41 arbitrary units with 4.1 ± 0.5 arbitrary units in the control; $P < 0.01$), total subthreshold impulse (4.7 ± 0.3 arbitrary units with 5.6 ± 0.31 arbitrary units in the control; $P < 0.05$), a lowering of the hemoglobin in the blood (13.1 ± 8 g/l at 169 ± 7.6 g/l in the control; $P < 0.01$), a lowering of the weight coefficients of the heart, liver, kidneys and spleen. In the female offspring of this very same group a lowering was noted of the leucocyte content in the blood, an increase in quantity of hippuric acid in the urine, an increase in hexenal sleep time, a lowering of the weight coefficient of the heart.

THE RESULTS OF THE INVESTIGATION OF PREGNANT RATS SUBJECTED TO THE EFFECT OF VC AT CONCENTRATIONS OF 35.5 AND 4.8 mg/m³

а Показатель	б Группа		
	с контрольная (n=11)	д 4.8 мг/м ³ (n=10)	д 35.5 мг/м ³ (n=10)
еСПП, усл. ед.	4.9±0.14	4.1±0.12	4.7±0.1
фКорковый рефлекс, усл. ед.	5.8±0.57	7.5±1.54	7.6±0.92
гОриентировочная реакция, усл. ед.	7.9±0.86	11.2±1.03	10.2±1.04
нРектальная температура, °C	36.4±0.12	36.8±0.09	36.7±0.1
иСДА, усл. ед.	66.6±9.9	53.5±12.9	84.6±12.4
жСодержание Нб, г/л	125±5.4	132±8.2	128±5.2
кЭритроциты, 10 ¹² л	4.9±0.15	4.8±0.22	3.9±0.33 P<0.02
лЛейкоциты 10 ⁹ л	12.8±1.4	11.0±0.1	11.4±0.84
мГиппуровая кислота, мг/мл	145.2±15.0	139.6±10.8	96.2±12.9 P<0.05
пДиурез, мл	5.7±0.76	4.5±0.53	6.7±0.55
оБелок в моче, мг/л	5750±760	5590±1040	4450±430
рХлориды в моче, ммоль	0.05±0.004	0.05±0.006	0.04±0.003
qМасса тела, г	342±6.7	347±10.3	313±13.4
рКоэффициент массы внутренних органов:			
сМозг	0.50±0.02	0.49±0.02	0.57±0.03
тСердце	0.29±0.008	0.28±0.006	0.33±0.01
иЛегкие	0.55±0.01	0.56±0.01	0.62±0.03
уПечень	4.70±0.2	4.97±0.25	5.06±0.12
вПочки	0.54±0.01	0.57±0.01	0.60±0.02
хСелезенка	0.40±0.02	0.41±0.03	0.51±0.05

- а - Indicator
 б - Group
 с - Control
 д - mg/m³
 е - Total subthreshold impulse, arbitrary units
 ф - Cortical reflex, arbitrary units
 г - Orientation reaction, arbitrary units
 н - Rectal temperature, °C
 и - "SDA", arbitrary units
 ж - Content of Hb, g/l
 к - Erythrocytes, 10¹² l
 л - Leucocytes, 10⁹ l
 м - Hippuric acid, mg/ml
 п - Diuresis, ml
 о - Albumin in the urine, mg/l
 р - Chlorides in the urine, mmole
 q - Body weight, g
 р - Weight coefficient of the internal organs:
 с - Brain
 т - Heart
 и - Lungs
 у - Liver
 в - Kidneys
 х - Spleen

In the investigation of the offspring of the second test group (4.8 mg/m^3) a whole series of changes also showed up. In the males a lowering of the hemoglobin was noted ($146 \pm 8 \text{ g/l}$ with $169 \pm 7.6 \text{ g/l}$ in the control; $P = 0.05$) and a lowering was noted of the content of leucocytes in the blood, an increase in the content of hippuric acid in the urine ($141 \pm 14.8 \text{ mg/ml}$ with $88.3 \pm 9.4 \text{ mg/ml}$ in the control; $P < 0.01$), a change in the weight coefficients of the liver, kidneys, and spleen. In the males of this group a drop was noted in the erythrocyte and leucocyte content in the blood, an increase in the hippuric acid content of the urine and a drop of weight coefficients of the lungs and liver.

CONCLUSION. VC at concentrations at the level of the existing MAC (35.3 mg/m^3) in a reaction during the course of the total pregnancy of Wistar rats caused in them the signs of a general toxic effect which were manifested in the form of disorders of the liver function and of the morphological composition of the peripheral blood. With the indicated changes in the organism of the pregnant animals as a background, the harmful effect of VC was established on the development of the fetus and offspring. An embryotropic effect was detected just as in the microanatomical investigations of the offspring at various periods of postnatal development.

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Under the effect of vinyl chloride in concentrations on the order of magnitude lower than the MAC (4.8 mg/m^3) in the pregnant animals, according to all of the tests selected by us, no changes were found (compare table). Still, VC produced an embryotropic effect which took the form of permeability disorders of the vessels

of the fetus and of the functional deviations from the normal with respect to the nervous system, liver, morphology of the blood, changes in the weight coefficient of a few internal organs in the offspring.

The experimental materials which were presented attest to the fact that concentrations of vinyl chloride at the level of those existing in the present MAC indicate a general toxic effect on the organism of pregnant animals and produce a pronounced embryotropic effect. Concentrations on the order of magnitude less than that of the MAC do not indicate a general harmful effect on the organism of pregnant rats, nevertheless they do cause a significant disruption in the embryogenesis which confirms the presence of a select effect of the toxin on the development of the fetus. The resulting materials indicate that we should reexamine the MAC for vinyl chloride in the area of the work place with respect to the identified embryotropic effect.

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