*Environmental Health Perspectives*
*Vol. 17, pp. 85–93, 1976*

# Aspects of the Toxicology of Chloroprene: Immediate and Long-Term Effects

by I. V. Sanotskii*

**The maximum permissible concentration (MPC) of chloroprene was set at 2 mg/m³ in the USSR in the 1940's. The existing MPC is 4 mg/m³. The threshold of systemic effects as a result of chronic chloroprene exposure is 1.69 mg/m³. However, the threshold for embryotoxic and mutagenic effects is 0.15 mg/m³. In consideration of this information, setting a new MPC for chloroprene at 0.05 mg/m³ is recommended.**

Chloroprene (2-chlorobuta-1,3-diene) is usually obtained by a reaction of vinylacetylene with hydrogen chloride. It is used as a monomer for the production of synthetic rubber and latexes.

Chloroprene may be classified as a polytropic poison since it causes functional and organic disturbances of the nervous system, the cardiovascular system. the liver and the kidneys. In women working with chloroprene (Nairit) latex, pregnancy has been found to take an unfavorable course (1). The maximum permissible concentration (MPC) of chloroprene at 2 mg/m³ was established in the USSR in the 1940's on the basis of calculations and data in the literature.

In connection with the appearance of congenital abnormalities in the children of women employed in the polymerization shop in a chloroprene factory (*2*) women were taken off chloroprene production (*3*). Clinical and safety investigations in factories and a whole range of experimental studies were subsequently undertaken to establish a corrected MPC.

## Clinical and Occupational Safety Investigations

Persons working on chloroprene production, where the concentration of the substance in the air was several times higher than the former MPC, were given medical examinations (*4*). Primary changes in chloroprene production workers were found in the nervous system (5–7). In some workers changes were found in hepatic and renal function (*8*), (*9*), the cardiovascular system (*6, 10*), and the morphological composition of the peripheral blood (*11*).

A special questionnaire was used to study reproductive function in male workers. Altogether, 143 workers from chloroprene shops and 118 controls from factory and office workers in an electrical engineering plant were questioned.

Examinations of chloroprene workers (*12*) revealed functional disturbances in spermatogenesis after 6–10 yr of work in chloroprene production, and morphological disturbances after 11 yr or more. The questionnaire showed that cases of spontaneous abortion in the wives of chloroprene workers occurred more than three times as frequently as in the control group. In persons employed in chloroprene production (analysis of coded preparation), the frequency of cells with chromosome aberrations in a peripheral blood leukocyte culture (Table 1) considerably exceeded the level of aberrations in the control group and the spontaneous level of this indicator in the blood of healthy persons (*4*).

In view of the relatively high concentrations of chloroprene in latex and rubber manufac-

* Department of Toxicology, Institute of Industrial Hygiene and Occupational Diseases, Moscow, U.S.S.R.

Table 1. Frequency and types of chromosomal aberrations in lymphocyte cultures from workers.

| Group | No. of persons examined | No. of cells analyzed | Aberrant cells, % | Aberrations | | Ratio between types of aberration, % | |
|---|---|---|---|---|---|---|---|
| | | | | Total no. | Rate per 100 cells | Chromatid | Chromosome |
| Main group | 18 | 1,666 | 4.77 ± 0.57[a] | 83.0 | 4.9 | 74.4 | 25.6 |
| Control group | 9 | 572 | 0.65 ± 0.56 | 6.0 | 1.0 | 100.0 | 0 |
| Spontaneous level[b] | 181 | 28,386 | 1.19 ± 0.06 | 342 | 1.2 | 50.3 | 49.7 |

[a] $p < 0.001$. All values means ± S.E.

[b] Data of Bochkov et al. (*16*).

turing places and the possibility that the air may contain additional contaminants which makes the interpretation of results difficult, a detailed clinical and safety inspection was made of a factory where chloroprene-based latex was used.

The results showed that the main hazard to workers was chloroprene vapor which varied in concentration from 1 to 7 mg/m³ in the air of the work areas, which is of the order of the previous MPC. The most frequently encountered other volatile substance in latex was ammonia. However, the ammonia concentration (2.0–4.0 mg/m³) in the air of the work areas was not considered a significant health hazard (MPC is 20 mg/m³) (*13*).

Work in these occupations is classified as light labor. Most operations have been mechanized. To determine changes in the state of health of the workers, a thorough medical examination was carried out on 12 men and 53 women (*14*). Two-thirds of the workers in this group had been employed for less than 5 yr in this work.

Examinations of the cardiovascular system showed muffled heart sounds in 30 persons, reduced arterial presure in 14, and tachycardia in 9. A noteworthy feature was a reduction in the red cell count in the peripheral blood which averaged 3,830,000/mm³. In a considerable number of persons there was a reduction in hemoglobin level below 11.5%, i.e., below the lower limit of physiological variation.

Worthy of attention was the predominance of a low reticulocyte count, despite anemia. In half the persons examined, the number of reticulocytes was at the lower limit of the physiological range (3–4%). Together with erythrocytopenia in workers exposed to chloroprene, a tendency towards leukopenia and thrombocytopenia was observed. There was a particularly sharp decrease in the thrombocyte count (less than 175,000/mm³) that was quite frequent in women who had been working with chloroprene for 1–5 yr.

Examination of vestibular function, even in persons with less than 5 yr of work with chloroprene, showed moderate, sluggish nystagmus and a relative shortening of postcaloric nystagmus and inhibition of vestibulo-autonomic and vestibulo-sensory reactions. The systems of disturbances in vestibular functions increased with increased length of employment.

Physiological investigations were carried out (*13*) in a group of women aged 19 to 23 who had worked in this occupation for 2–4 yr and had never worked elsewhere. Women who had had no contact with toxic substances and who were doing light physical labor were used as controls. The results showed that the women workers had an abnormal diurnal variation of arterial presure, with a reduction of its systolic and diastolic components toward the end of the working day. The pulse rate during work (93.1 ± 1.2 beats/min) was considerably higher than in the controls ($p < 0.01$).

An indication of the effect of chloroprene on the central nervous system function was a lengthening of the latent period in the sensorimotor response to a visual cue, as compared with the control group. There was also a reduction in olfactory sensibility, the olfactory threshold being considerably higher among workers with a long employment record than among those who had been in contact with chloroprene for a shorter time.

A cytogenetic examination of the peripheral blood lymphocytes was carried out on 20 female workers (aged 19–23, length of employment 1–4 yrs, and aged 19–50, length of employment 1–30 yr) (*15*). Results are summarized in Table 2. In both groups there was

Table 2. Frequency of chromosomal aberrations in lymphocyte cultures from workers.

| Chloroprene concn in air of work zone, mg/m³ | No. of workers examined | Length of service, yr | Age of persons examined | No. of metphases analyzed | Aberrant cells, % |
|---|---|---|---|---|---|
| 3–7 | 20 | 1–4 | 19–23 | 1,748 | 3.49 ± 0.51[a] |
| 1–4 | 8 | 1–20 | 19–50 | 648 | 2.5 ± 0.49[b] |
| 0[c] | 181 | | | 28,386 | 1.19 ± 0.06 |

[a] $p < 0.001$; all values are means ± S.E.
[b] $p < 0.05$.
[c] Spontaneous level; data of Bachkov et al. (*16*).

an increased number of cells with aberrations, amounting to 3.49 ± 0.51% and 2.5 ± 0.49%, respectively, as against the spontaneous level of 1.19 ± 0.06% (*16*).

To determine the effect of working conditions on specific functions in female workers, a special investigation was carried out on 147 women workers in a chloroprene shop and 100 women in a control group (*17*). The breakdown of noninflammatory morbidity was as follows: the prevalence of tumors among women chloroprene workers was 8.2% and among the controls 1% ($p < 0.05$); primary and secondary sterility in the chloroprene workers was 6.1% and in the controls was 2% (*17*).

## Experimental Studies

The parameters of acute toxicity have been established by a number of investigators, and the results are generally in good agreement in regard to the concentrations typifying the upper levels of chloroprene toxicity (Table 3).

In experiments on two species of laboratory animals (white rats and C57BL/6 mice) a study was made of the systemic, gonadotropic, and mutagenic effects of chloroprene following chronic exposure (4.5 months for rats, 2 months for mice) to low concentrations, i.e., the level of the previous MPC (2 mg/m³) and concentrations 10 to 40 times lower than that. The embryotoxic effect of chloroprene was studied in white rats following exposure during the whole period of pregnancy in concentrations about equal to the previous MPC and 3.0, 10, and 40 times lower. More than 800 rats and 600 mice were used, about 3000 fetuses were analyzed, and 700 offspring were examined. The studies of the embryotoxic, mutagenic, and gonadotropic effects of chloroprene were reproducible.

It was established that following 4.5 months exposure to chloroprene at a concentration close to the former MPC (1.69 ± 0.087 mg/m³) signs of a systemic effect were observed

Table 3. Parameters of acute chloroprene toxicity in various types of exposure.

| Level of exposure | Concentration, mg/m³ (or dose, mg/kg) | Exposure, hr | Animal species | Reference |
|---|---|---|---|---|
| $LC_{50}$ | 2300 | 2 | mice | Zakusov, 1936 |
| $LC_{50}$ | 3000 | 1 | mice | Zakusov, 1936 |
| $LC_{50}$ | 600 | 8 | mice | Zakusov, 1936 |
| $LC_{50}$ | 600 | 8 | mice | Oettingen, 1936 |
| $LC_{50}$ | 3400 | 8 | rabbits | Oettingen, 1936 |
| $LC_{50}$ | 1300 | 8 | cats | Oettingen, 1936 |
| $LC_{50}$ | 2300 | 2 | mice | Volkova, 1969 |
| $LC_{84}$ | 5300 | 2 | mice | Volkova, 1969 |
| $LC_{16}$ | 1500 | 2 | mice | Volkova, 1969 |
| $LD_{50}$ | (3.0, subcutaneous) | | mice | Levina, 1941 |
| $LD_{50}$ | (251, stomach) | | rats | Asmangulyan and Badalyan, 1971 |
| $LD_{50}$ | (260, stomach) | | mice | Asmangulyan and Badalyan, 1971 |

Table 4. Changes in the summation threshold index in animals after chronic exposure to chloroprene.

| Chloroprene, mg/m³ | Summation threshold index after various times [a] | | | |
|---|---|---|---|---|
| | 1.5 months | 2.5 months | 3.5 months | 4.5 months |
| 1.69 | 3.6 ± 0.2 | 4.1 ± 0.2[b] | 3.53 ± 0.22 | 5.5 ± 0.18[c] |
| 0.15 | 3.07 ± 0.12 | 3.55 ± 0.17 | 3.6 ± 0.16 | 3.96 ± 0.16 |
| 0.051 | 3.15 ± 0.14 | 3.5 ± 0.21 | 3.5 ± 0.16 | 3.6 ± 0.15 |
| 0 (control) | 9.09 ± 0.14 | 3.6 ± 0.13 | 3.71 ± 0.13 | 3.75 ± 0.17 |

[a] All values as means ± S.E. in arbitrary units; n = 10.
[b] $p < 0.05$.
[c] $p < 0.001$.

in male rats. There was an increase in the "summation threshold index" after 2.5 months (Table 4), and after 4.5 months a decrease in the synthesis of hippuric acid from sodium benzoate (Quick's test) and an inhibition of gas exchange. Chloroprene had no effect on the selected indicators at concentrations of 0.15 ± 0.0059 mg/m³ and 0.051 ± 0.006 mg/m³.

With the indicators used in the tests, exposure to chloroprene produced no systemic effect in mice at any of the following concentrations: 35 ± 0.7 mg/m³; 1.85 ± 0.18 mg/m³; 0.32 ± 0.06 mg/m³; 0.13 ± 0.01 mg/m³; 0.064 ± 0.01 mg/m³; and 0.054 ± 0.02 mg/m³.

Thus, the threshold for the chronic systemic effect of chloroprene in rats, as established by the indicators used in this study, appears to be 1.69 ± 0.087 mg/m³, which is close to the previous MPC (*18*).

Investigation of the gonadotropic effect of chloroprene showed that a concentration close to the former MPC (1.69 ± 0.087 mg/m³), after 4.5 months exposure in male rats, caused a reduction in the number of normal spermatogonia, an increase in the number of dead spermatozoa, an increased susceptibility of spermatoza to inactivation in an acid medium, and a decrease in their period of motility. Some of the indicators showed values outside the normal physiological range (Tables 5 and 6). A less marked but similar effect was observed after exposure to a chloroprene concentration (0.15 ± 0.0059 mg/m³) one order of magnitude lower than the MPC. A concentration of 0.051 ± 0.006 mg/m³ caused no functional or morphological changes in spermatogenesis. Consequently, a chloroprene concentration of 0.15 ± 0.0059 mg/m³, i.e., one order of magnitude lower than the existing MPC (based on indicators of systemic effect), can be considered to be close to the threshold value for the effect on rat gonads. Study of the gonadotropic effect of chloroprene in C57BL/6 mice has shown that concentrations equal to and one order of magnitude below the MPC caused adverse changes in spermatogenesis (increase in the number of tubules with desquamating germinal epithelium) (Table 1). A concentration of

Table 5. Morphological indicators of the condition of the germinal epithelium in rats after chronic inhalation of chloroprene.[a]

| Indicator | Chloroprene, 1.69 mg/m³ | Chloroprene, 0.15 mg/m³ | Chloroprene, 0.051 mg/m³ | Control |
|---|---|---|---|---|
| Total number of spermatogonia | 7.5 ± 4.2[b,c] | 9.7 ± 3.1[b,d] | 19.8 ± 5.0 | 25.7 ± 5.2 |
| Spermatogenesis index | 1.68 ± 0.62 | 2.18 ± 0.7 | 3.18 ± 0.44 | 3.2 ± 0.46 |
| No. of tubules with desquamating epithelium | 9.7 ± 5.6 | 2.6 ± 0.8 | 2.28 ± 1.5 | 2.28 ± 1.2 |
| No. of tubules in the 12th stage of meiosis | 2.5 ± 1.4 | 2.6 ± 0.54 | 3.28 ± 1.0 | 2.57 ± 0.9 |

[a] All values are means ± S.E., $n = 8$.
[b] Beyond the 2 $\sigma$ limits of mean annual physiological variation in the indicator.
[c] $p < 0.02$.
[d] $p < 0.05$.

Table 6. Functional condition of animal spermatozoa after chronic exposure to chloroprene.[a]

| Indicators | Chloroprene, 1.69 mg/m³ | Chloroprene, 0.15 mg/m³ | Chloroprene, 0.051 mg/m³ | Control |
|---|---|---|---|---|
| Dead spermatozoa, % | 85.8 ± 13.8[b] | 67.7 ± 12.4[c] | 30.3 ± 3.3 | 32.1 ± 3.9 |
| Resistance to acid medium | 5.9 ± 0.46[d] | 5.58 ± 0.45[c] | 3.25 ± 0.53 | 3.8 ± 0.53 |
| Resistance to osmotic pressure | 2.1 ± 0.5 | 2.2 ± 0.17 | 2.6 ± 0.1 | 2.6 ± 0.12 |
| Duration of motility of spermatozoa, min | 91.2 ± 44[e,f] | 126 ± 44.5[d,e] | 296 ± 15.7 | 333 ± 15.4 |

[a] All values are means ± S.E., $n = 8$.
[b] $p < 0.01$.
[c] $p < 0.05$.
[d] $p < 0.02$.
[e] Beyond the 2 $\sigma$ limits of mean annual physiological variation.
[f] $p < 0.001$.

Table 7. Results of qualitative evaluation of the condition of the germinal epithelium in C57BL/6 mice after 2 months exposure to chloroprene.[a]

| Chloroprene concn, mg/m³ | No. of animals | No. of spermatogonia in the tubules | Spermatogenesis index | Tubules with desquamating epithelium, % | Tubules with 12th stage of meiosis, % |
|---|---|---|---|---|---|
| 0 (control) | 8 | 13.2 ± 0.43 | 3.94 ± 0.08 | 2.25 ± 0.49 | 2.0 ± 0.47 |
| 0.06 ± 0.01 (MPC/40) | 7 | 12.1 ± 0.56 | 3.89 ± 0.024 | 3.6 ± 1.19 | 2.3 ± 0.68 |
| 0.32 ± 0.06 (MPC/10) | 8 | 14.2 ± 1.09 | 3.89 ± 0.03 | 9.8 ± 2.96[b] | 4.37 ± 1.13 |
| 3.5 ± 0.74 (≈ MPC) | 8 | 16.6 ± 0.87 | 3.91 ± 0.05 | 16.7 ± 4.24[c] | 3.3 ± 0.86 |

[a] All values are means ± S.E.
[b] $p < 0.05$.
[c] $p < 0.01$.

Table 8. Frequency of dominant lethal mutations in the sex cells of male white rats as a function of chloroprene concentration.[a]

| Chloroprene concn, mg/m³ | No. of animals | | Death before implantation | Death after implantation | Total embryonic death rate |
|---|---|---|---|---|---|
| | M | F | | | |
| 0 (control) | 11 | 11 | 5.7 ± 1.5 | 4.2 ± 1.5 | 9.5 ± 1.8 |
| 0.057 | 10 | 10 | 5.05 ± 1.7 | 5.5 ± 2.6 | 10.4 ± 2.7 |
| 0.14 | 10 | 10 | 7.8 ± 1.8 | 14.4 ± 3.2[b] | 20.9 ± 2.4[b] |

[a] All values are means ± S.E.
[b] $p < 0.02$.

0.064 ± 0.011 mg/m³ had no adverse effect on mouse gonads. A concentration of 0.32 ± 0.06 mg/m³ can thus be considered to be near the threshold for gonadotropic effect in mice (*19*).

The mutagenicity of chloroprene was studied in germ cells (by counting dominant lethal mutations) and in somatic tissue in the bone marrow (metaphase method). It was established that chloroprene, at concentrations close to and one order of magnitude below the previous MPC, increased the frequency of dominant lethal mutations in the germ cells of male rats after 2.5 months of exposure. Chloroprene did not induce such changes in rats in concentrations of 0.057 ± 0.003 mg/m³ (Table 8).

In C57BL/6 mice the frequency of dominant lethal mutations increased in the germ cells after exposure to chloroprene at a concentration close to the MPC (Table 9). An increase in chromosome aberrations in mouse bone marrow cells occurred after exposure to chloroprene for 2 months at concentrations near to (3.5 ± 0.7 and 1.85 ± 0.18 mg/m³) and one order of magnitude below (0.32 ± 0.06 and 0.13 ± 0.01 mg/m³) the previous MPC. A chloroprene concentration 40 times lower than the former MPC (0.054 ± 0.024 and 0.065 ± 0.01 mg/m³) proved inactive in relation to the selected indicators (Table 10).

Thus, the threshold concentration of chloroprene for mutagenicity, as established in chronic experiments on rats and mice, can be considered to be one order of magnitude below the former MPC.

The results of studies of the embryotropic effect showed that a chloroprene concentration of 4 ± 0.7 mg/m³ (the level of the existing MPC) had a systemic effect on pregnant rats (inhibition of spontaneous motor activity, an increase in hippuric acid level in the urine after administration of sodium benzoate, hypoproteinemia, an increase in oxygen consumption, a reduced weight gain, and an increase in the weight coefficients of the brain, lungs, liver, and kidneys). In nonpregnant experimental animals only a reduction in spontaneous motor activity was observed (Table 11). Exposure

**Table 9. Frequency of dominant lethal mutations in the sex cells of male C57BL/6 mice as a function of chloroprene concentration.[a]**

| Series | Chloroprene concn, mg/m³ | No. of animals M | No. of animals F | Fertilizing capacity, % | Death before implantation, % | Death after implantation, % | Total embryonic death rate, % |
|---|---|---|---|---|---|---|---|
| I | 0 (control) | 14 | 31 | 53.5 ± 8.0 | 3.0 ± 1.8 | 26 ± 10.3 | 28.5 ± 10 |
| | 0.064 ± 0.011 | 15 | 35 | 68.8 ± 8.0 | 16 ± 5 | 39 ± 6 | 52 ± 6.8 |
| | 0.32 ± 0.06 | 14 | 31 | 57.1 ± 8.1 | 12 ± 8.6 | 28 ± 8 | 50.3 ± 9.6 |
| | 3.5 ± 0.7 | 15 | 30 | 51.6 ± 8.0 | 32 ± 9.7[b] | 35 ± 3 | 63 ± 9.5[b] |
| II | 0 (control) | 10 | 25 | 79.9 ± 11.0 | 11.4 ± 4 | 10.0 | 19 ± 5.6 |
| | 0.054 ± 0.02 | 8 | 24 | 55.2 ± 12.8 | 23 ± 10 | 12 ± 4 | 33 ± 9.5 |
| | 0.13 ± 0.01 | 11 | 33 | 69.6 ± 10.0 | 21 ± 6.9 | 17.0 ± 5 | 36 ± 7.6 |
| | 1.85 ± 0.18 | 11 | 31 | 80.3 ± 9.7 | 27 ± 4[b] | 27 ± 4 | 42 ± 5.6[c] |

[a] All values are means ± S.E.
[b] $p < 0.05$.
[c] $p < 0.01$.

**Table 10. Metaphase analysis of the bone marrow of mice exposed to chloroprene for 2 months.[a]**

| Series | Chloroprene concen, mg/m³ | No. of animals | No. of cells analyzed | Cells with aberrations, % | Cells with deficiencies, % |
|---|---|---|---|---|---|
| I | 0 (control) | 8 | 750 | 3.05 ± 0.46 | 0.49 ± 0.26 |
| | 0.064 ± 0.01 | 8 | 780 | 2.8 ± 0.33 | 1.4 ± 0.2[b] |
| | 0.32 ± 0.06 | 7 | 567 | 6.07 ± 0.4[c] | 1.44 ± 0.55 |
| | 3.5 ± 0.7 | 8 | 799 | 10.0 ± 0.68[d] | 1.35 ± 0.38[e] |
| II | 0 (control) | 6 | 488 | 2.0 ± 0.58 | 0.94 ± 0.3 |
| | 0.054 ± 0.02 | 6 | 493 | 3.4 ± 0.7 | 0.16 ± 0.16 |
| | 0.13 ± 0.01 | 6 | 344 | 4.65 ± 0.89[e] | 1.6 ± 0.7 |
| | 1.85 ± 0.18 | 10 | 910 | 10.9 ± 1.34[d] | 2.9 ± 0.7[b] |

[a] All values are means ± S.E.
[b] $p < 0.02$.
[c] $p < 0.002$.
[d] $p < 0.001$.
[e] $p < 0.05$.

Table 11. Results of examination of nonpregnant and pregnant rats with chloroprene intoxication.[a]

| | Nonpregnant rats | | | Pregnant rats | | |
|---|---|---|---|---|---|---|
| | Control | Chloroprene, 0.6 mg/m³ | Chloroprene, 4 mg/m³ | Control | Chloroprene, 0.6 mg/m³ | Chloroprene, 4 mg/m³ |
| Nervous system | | | | | | |
| Summation threshold index (arbitrary units) | 3.7 ± 0.13 | 3.4 ± 0.03 | 3.7 ± 0.01 | 3.3 ± 0.2 | 3.0 ± 0 | 3.4 ± 0.3 |
| Spontaneous motor activity (arbitrary units) | 28.2 ± 8.3 | 301.0 ± 24 | 234.0 ± 12 | 100 ± 11 | 121.60 ± 24 | 53.4 ± 9.0[b] |
| Renal function | | | | | | |
| Protein in urine, mg/ml | 1.8 ± 0.3 | 2.2 ± 0.4 | 1.0 ± 0.2 | 2.0 ± 0.8 | 3.3 ± 0.7 | 1.6 ± 0.6 |
| Cl in urine, mg/ml | 0.93 ± 0.2 | 1.2 ± 0.2 | 1.2 ± 0.1 | 2.1 ± 0.4 | 0.7 ± 0.2 | 1.2 ± 0.3 |
| Specific gravity of urine | 1.001 ± 0 | 1.001 ± 0 | 1.001 ± 0 | 1.001 ± 0 | 1.001 ± 0 | 1.001 ± 0 |
| Liver function | | | | | | |
| Hippuric acid in urine, mg | 71.4 ± 9.6 | 60.0 ± 11 | 74.0 ± 5.5 | 68.0 ± 3.6 | 82.0 ± 7.6 | 103.4 ± 11[b] |
| Bromosulfophthalein clearance from blood, % | 82.0 ± 4.5 | 79.4 ± 4.0 | 75.5 ± 3.0 | 82.0 ± 5.1 | 67.0 ± 5.9 | 72.0 ± 6.0 |
| Total serum protein, mg-% | 7.5 ± 0.2 | 7.3 ± 0.2 | 7.4 ± 0.3 | 7.3 ± 0.1 | 6.2 ± 0.2[b] | 6.4 ± 0.2[b] |
| Oxygen consumption, 100 mg/hr | 115 ± 4.6 | 132 ± 17 | 113 ± 21 | 88.5 ± 1.0 | 77.0 ± 9.2 | 118 ± 7.4 |

[a] All values are means ± S.E.

[b] $p < 0.01$.

to a concentration (0.6 ± 0.08 mg/m³) one third the previous MPC produced hypoproteinemia in pregnant animals (6.2 ± 0.02 as against 7.3 ± 0.01 mg% in the controls, $p < 0.01$), but no abnormalities were found in nonpregnant animals. Chloroprene in concentrations one order of magnitude lower (0.13 ± 0.009 mg/m³) and 40 times lower than the previous MPC (0.056 ± 0.006 mg/m³) caused no abnormalities in pregnant animals so far as it could be judged by the selected tests (*20, 21*).

Thus, the threshold concentration of chloroprene based on the indicators of systemic effects in nonpregnant rats is about 4 ± 0.7 mg/m³, i.e., close to the MPC, which coincides with the threshold of chronic effects found in males. The $lim_{ch}$ for pregnant animals was three times lower than the former MPC (0.6 ± 0.08 mg/m³). The results obtained indicate that pregnant rats are highly sensitive to chloroprene.

An analysis of embryonic material obtained from animals exposed to chloroprene during the entire pregnancy showed that in a concentration of 4 ± 0.7 mg/m³ the substance caused an increase in overall embryonic mortality, a decrease in fetal weight (Table 12), and a disturbance in vascular permeability as shown in histological sections. On exposure to the substance in concentration 3, 10, and 40 times lower than the former MPC, no changes of this kind were found, as compared with the controls (*22*).

Exposure to a concentration of 4 mg/m³ at various times during pregnancy (as distinguished from exposure during the whole course of pregnancy) led to teratrogenic effects. Cerebral hernia occurred in fetuses when exposure took place on days 5–6, 9–10, 11–12, or 13–14 days of pregnancy (23.5 ± 17; 13.4 ± 9.8; 13.9 ± 1.0; 1.6 ± 1.5%, respectively). Hydrocephalus occurred as a result of exposure during the same periods, with the exception of days 13–14 (9.1 ± 2.9; 6.0 ± 5.7; and 34.0 ± 13.6%, respectively). No such pathology was found in the controls (*23*).

In offspring whose mothers had been exposed to 4 ± 0.7 mg/m³ of chloroprene during the entire pregnancy, a decrease in the rate

Table 12. Results of examination of embryos from pregnant female rats following exposure to chloroprene.

| Chloroprene concn, mg/m³ | No. of animals | Fetal deaths per female: Before implantation | Fetal deaths per female: After implantation | No. of live fetuses | Weight of fetuses, g | Overall embryonic death rate, % | Microanatomical sections of fetuses: Total no. of fetuses | Hemorrhage into body cavities and tissues: No. of fetuses | Hemorrhage into body cavities and tissues: % |
|---|---|---|---|---|---|---|---|---|---|
| 0 (control) | 20 | 1.0 ± 0.3 | 0.6 ± 0.2 | 11.41 ± 1.1 | 2.3 ± 0.2 | 10.9 ± 2.0 | 165 | 26 | 16.3 ± 5.5 |
| 0.6 | 12 | 1.8 ± 0.6 | 0.4 ± 0.3 | 11 ± 2.3 | 2.2 ± 0.1 | 19.2 ± 0.1 | 71 | 19 | 21.0 ± 4.4 |
| 4 | 17 | 2.7 ± 0.6 | 1.6 ± 0.6 | 9.7 ± 1.1 | 1.8 ± 0.18[b] | 31.9 ± 6.0[c] | 104 | 70 | 70.0 ± 7.8[c] |

[a] All values are means ± S.E.
[b] $p < 0.05$.
[c] $p < 0.001$.

of weight gain and in the urinary content of hippuric acid (Quick's test) were found. At concentrations three times lower than the former MPC (0.6 ± 0.98 mg/m³), chloroprene caused increased numbers of deaths in the first 3 weeks after birth, a reduction in the rate of weight gain, and a disturbance in liver function following administration of a hepatotoxin. After exposure to a concentration of 0.13 ± 0.009 mg/m³, an increase was also noted in postnatal deaths of offspring, together with a decrease in the urinary protein level. Chloroprene failed to produce any abnormalities in the offspring at a concentration of 0.056 ± 0.006 mg/m³, irrespective of the indicators used. Consequently, a chloroprene concentration of 0.13 ± 0.009 mg/m³ is close, under our experimental conditions, to the threshold value for embryotropic effect (*22*).

## Conclusion

The changes found in workers occurred following exposure to chloroprene in the air in concentrations slightly above the MPC established earlier (2 mg/m³).

The threshold for chronic effects of chloroprene on animals (the tests were reproduced many times on males and females) based upon the indicators of general systemic effect, is 1.69 ± 0.087 mg/m³, i.e. about the same as the MPC formerly adopted. The threshold concentration based on specific indicators (embryotropic, gonadotropic, and mutagenic effects) was 0.15 ± 0.0059 mg/m³, i.e., one order of magnitude below the former MPC. The correlation of specific effects was shown previously by Sanotskii et al. (*19*)

The general systemic effect of chloroprene observed at a concentration close to the former MPC, which was based on clinical and epidemiological studies, and its marked specific effect ($Z_{sp} = 12$) on the reproductive function and the development of offspring (in man and animal experiments), provide substantiation for a new MPC for chloroprene of 0.05 mg/m³.

### REFERENCES


1. Vel'kovich, B. G. Clinical observations on persons working with chloroprene latex (in Russian). In: Sbornik Kliniko-Gigienicheskie Issledovaniya po Toksicheskim Veshchestvam, Primenyaemyh v Novykh Proizvodstvakh. Leningrad, Vol. 2 114 (1940).
2. Mirzabekyan, G. I., and Akhverdyan, A. O. The generative cycle of the ovaries and the oestral cycle of white rats exposed to chronic chloroprene intoxication (in Russian). Erevan, 1946: 180. Quoted in N. O. Melik-Alaverdyan, (1967).
3. Sal'nikova, L. S. The specific embryotropic effect of industrial poisons (in Russian). In: Long-Term Sequelae of Human Exposure to Chemicals used in Industry and Agriculture, Moscow, 199, pp. 44–66.
4. Katosova, L. D. Cytogenetic analysis of the peripheral blood of workers employed in chloroprene manufacture (in Russian). Gig. Trud. Profzabolev. 10: 30 (1973).
5. Levina, E. I. Hygienic conditions in the manufacture of synthetic rubber from acetylene (in Russian). In: Kliniko-Gigienicheskie Issledovaniya po Toksicheskam Veshchestvam, Primenyaemym Novykh Proizvodstvakh, Leningrad, Vol. 2, (1940).
6. Drogichina, E. A., et al. The clinical features of chronic intoxication in synthetic (divinylstyrene and chloroprene) rubber production (in Russian). Gig. Trud. Profzabol. 3: 10 (1959).

7. Muradyan, G. T. Clinical forms of damage to the nervous system in chronic exposure to 2-chlorobutadiene (in Russian). Nevropatol. Psikhiatr. im. Korsakova, 58: 10 (1958).
8. Mkhitaryan, V. G. The effect of chloroprene on SH-group levels (in Russian). Izv. Akad. Nauk Arm. SSR, 15: 5 (1962).
9. Gasparyan, E. I. The condition of the kidneys in factory and office workers employed in chloroprene plants (in Russian). In: Tezisyi Dokladov XII Vsesoyuznoi Konferentsii Terapevtov, Erevan, 38-39, 1960.
10. Avakyan, V. M., et al. Dynamics of the study of the cardiovascular system in workers in workshops producing substances in the chloroprene group (in Russian). Trudy Erevanskogo Med. Inst. 11: 237 (1960).
11. Avakjan, V. M., et al. The results of three years' study of changes in the functioning of some organs and systems in workers employed in chloroprene manufacture. Trudy Evanskogo Med. Inst. 11: 241 (1960).
12. Fomenko, V. N., et al. The possibility of extrapolating animal data to man when studying the mutagenic and gonadotropic effect of chemical factors (in Russian). In: Vsesoyuznaya Nauchnaya Konferentsiya Laboratornie Zzivotnie v Medicinskikh Issledovaniyakh Moscow, 1974, pp. 44-46.
13. Bagdinov, Yu. M., et al. Working conditions and the status of a number of the physiological functions in women employed in the manufacture of articles made from chloroprene latex (in Russian). Nauchnye trudy Akushersko-Ginekologicheskaya Profpatologiya, Kazan, 1973, pp. 12–19.
14. Volkova, Z. A., at al. Establishing the value of the MPEL of chloroprene in the air of a work area (in Russian). Gig. Trud. Profzabol. 3: 31 (1976).
15. Fomenko, V. N., and Katosova, L. D. The results of cytogenetic analysis of the peripheral blood in women workers in contact with chloroprene latex (in Russian). In: Nauchnye Trudy Akushersko-Ginekologicheskaya Profpatologiya, Kazan, 1973, 33–37.
16. Bochkov, N. P., Kuleshov, N. V., and Znurkov, V. S. Analysis of spontaneous chromosome aberrations in a human leukocyte culture (in Russian). Citologiya, 14 (10): 1237 (1972).
17. Khaĭrullina, A. Sh. The incidence of gynacological disease among women workers employed in the production of articles made of nairite latex (in Russian). In: Nauchnye Trudy Akushersko-Ginekologicheskaya Profpatologiya, Kazan, 1973, pp. 83–89.
18. Davtiyan, R. M. The toxicological characteristics of the effect of chloroprene on the reproductive function of male rats (in Russian). In: Sbornik Trudov II Vsesoyuznoi Konferentsii Toksikologiya i Gigiena Produktov Neftekhimii i Neftekhimicheskikh proizvodstv, Yaroslavl'. 1972, pp. 95–97.
19. Sanotskiĭ, I. V., et al. Correlations between the gonadotropic, embryotropic and blastomogenic types of effect of chemical compounds (in Russian). Materialy Nauchnoĭ sessii, posvyashchennoĭ 50-letiyu sozdaniya SSSR, Tbilisi, 1972, pp. 117–118.
20. Fomenko, V. N., and Sal'nikova, L. S. Comparative experimental evaluation of the sensitivity of the nonpregnant and pregnant organism to chloroprene (in Russian). Akusherstvo Ginekol., 6: 72 (1973).
21. Sanotskiĭ, I. V., et al. Study of the effect of pregnancy on the sensitivity of animals to chemical agents (in Russian). Gig. Trud. Profzabol. 1: 25 (1976).
22. Sal'nikova, L. S., and Fomenko, V. N. Experimental investigation of the effect of chloroprene on embryogenesis (in Russian). Gig. Trud. Profzabol. 8: 23 (1973).
23. Sal'nikova, L. S., and Fomenko, V. N. Comparative characteristics of the embryotropic effect of chloroprene in relation to exposure conditions in various routes of ingestion (in Rusiian). Gig. Trud. Profzabol. 7: 30 (1975).