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EXPERIMENTAL STUDIES ON THE CHRONIC TOXIC EFFECTS OF VINYL CHLORIDE IN RATS

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INTRODUCTION

It is now recognized that vinyl chloride (VC) causes neoplastic and non-neoplastic diseases in man as well as in animals. Animal studies have been concentrated mainly on the carcinogenic and mutagenic action of VC (1, 5, 10, 16, 19, 23, 27). Less is known about chronic systemic effects of VC, their dose-response relationship and pathomechanism.

The main objective of the present study was to document the time course of chronic toxic effects of VC in rats at different concentrations of VC ranging from 50 to 20 000 ppm.

MATERIAL AND METHODS

Animals

340 two-month-old male Wistar rats weighing 180—220 g were divided into 4 equal groups: 3 experimental and one control. The rats were caged in groups with free access to food (Laboratory chow Murigran) and tap water except during exposure in inhalation chambers.

Conditions of exposure

Vinyl chloride of 99.7 % purity (kindly supplied by Chemical Plant, Tarnów, Poland) was used throughout the study. Rats were exposed to VC in dynamic inhalation chambers (1 m^3 volume) at concentartions of 50 ppm, 500 ppm, and 20 000 ppm for 10 months (mo), 5 hours daily, 5 days a week. Control animals were maintained under the same conditions but exposed to ambient air only. VC concentration in inhalation chmbers was checked daily by gas chromatography (9).

Scope of investigations

Individual body weight, general appearance and behavior were recorded weekly. Before the onset and then after 1, 3, 6 and 10 mo of exposure the following determinations were performed: hematological indices (hemoglobin concentration, packed cell volume, counts of erythrocytes, reticulocytes and blod platelets, total and differential leucocytes) and urine examination including appearance, specific gravity, pH, glucose, protein, occult blood, ketones, bilirubin, and microscopic constituents.

After 1, 3, 6 and 10 mo of exposure, total plasma protein, plasma concentrations of urea, inorganic phosphates, citrates, and calcium, plasma activity of alanine aminotransferase (ALAT), aspartate aminotransferase (AspAT), lactate dehydrogenase (LDH) and serum activity of alkaline phosphatase (AP) were determined in blood samples from 7—10 rats of each group.

Acid mucopolysaccharides and hydroxyproline content in 24-hour urine samples from 14—20 rats of each group were determined before the onset and after 1, 3 and 6 mo of exposure (4, 6, 21).

Five control rats and five rats exposed to VC at concentrations of 500 ppm and 20 000 ppm were subjected to X-ray analysis in order to control the state of the skeletal bones.

The histopathological examinations of tissues were carried out in 114 rats exposed to VC and 42 control rats. The rats were sacrificed after 1.5, 3, 6 and 10 mo of VC exposure. Brain, cerebellum, medulla oblongata, spinal cord, lungs, heart, lymph nodes, bone marrow, spleen, liver, stomach, intestines, kidneys, urinary bladder, testes, epididymis, seminal vesicles, hypophysis, adrenal glands, thyroid gland, pancreas, lacrimal glands, salivary glands, skin, muscles, bones, and blood vessels of the distal parts of the extremities were fixed in Baker's formol calcium. Additional blocks of liver, kidney, spleen and heart were fixed in Carnoy's fluid. Tissue specimens were embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin. Frozen sections of formalin-fixed liver and kidney were stained with Fat Red 7B for neutral lipids.

The ultrastructure examinations of the liver were carried out in 36 rats exposed to VC for 3, 6 and 10 mo, and in 18 controls. Sections of the liver were fixed in 3,6 % glutaraldehyde buffered with sodium cacodylate, postfixed in 1 % osmium tetroxide, dehydrated in ethanol and embedded in Epon epoxy resin. Thin sections were double-stained with uranyl acetate and lead tartrate and then examined with the use of a JEOL JEM — 100 C electron microscope.

Statistical analysis

Statistical significance of the differece between the means was assessed by Student's t-test or Cox-Cohran's C-test depending upon the ratio of population variances (F-test). The frequency data were analysed by the chi-square test.

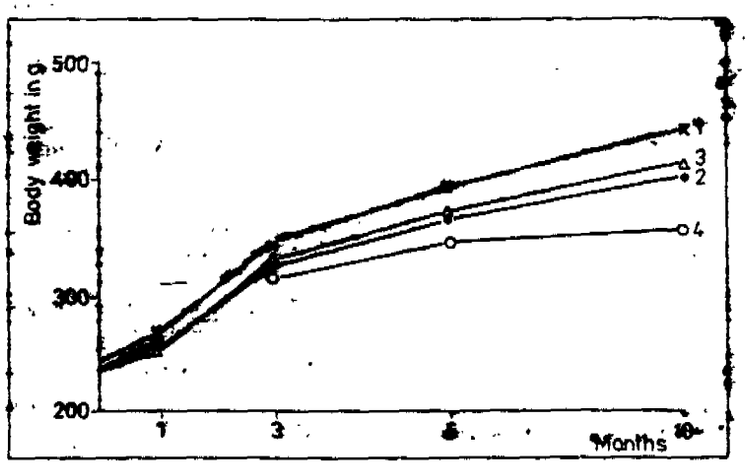

Fig. 1. Changes in mean body weight of rats exposed for 10 months to VC at concentrations: 1 — 0 ppm, 2 — 50 ppm, 3 — 500 ppm, 4 — 20 000 ppm. Each point represents the mean of 42—80 individual body weights.

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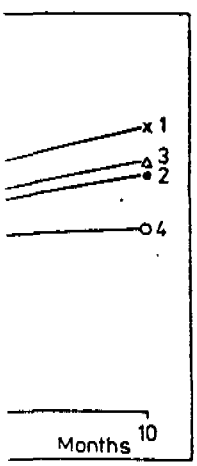

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RESULTS

General condition of animals and gross observations

During the total period of experiment the VC-exposed rats did not show any evident changes in general appearance or behaviour but their body weight did not increase at the same rate as in non-exposed animals (Fig. 1). After 10 mo of treatment, the difference from the controls was statistically significant ($p<0.05$) at all levels of VC-exposure. At that time, the relative weights of spleen, liver, kidneys, heart and testes were significantly elevated in some groups of the exposed animals, the difference being most pronounced for the spleen and dose-related for the liver and kidneys (Table 1). The VC-exposed rats subjected to X-ray analysis did not exhibit any alteration in the skeletal bones.

Histological and ultrastructural data[*]

No histological changes of internal organs were observed in rats exposed to VC for 1.5 and 3 mo. In the later period of exposure, the histological changes related to the treatment developed only in the liver and testes. Scanty histological changes in the liver, seen as increased nucleus polymorphism of hepatocytes and proliferation of reticulo-endothelial cells lining the sinusoids, occurred in rats exposed to 500 and 20 000 ppm of VC for 6 mo but not at the 50 ppm level and in parallel controls. After 10 mo of exposure, diffuse changes of that type (Fig. 2) were observed at all levels of exposure. In addition, fatty degeneration of hepatocytes developed, and necrotic foci of the spermatogenic epithelius and disorders of spermatogenesis were noticed in the testes. The lesion of the testicular epithelium was most marked at the 500 ppm exposure level and only at this concentration it was accompanied by large multinuclear syncytial cells in the testicular tubules (Fig. 3). The histological alterations of the liver and testicular epithelium, were also detected in some of the 10 mo control rats.

Incidence rates of such effects as increased nucleus polymorphism of hepatocytes, proliferation of RE-cells in the liver and disorders of spermatogenesis were significantly higher in animals exposed at the 20 000 and/or 500 ppm level than in the controls but they were not clearly dose-related (Table 2).

Two rats exposed to VC for 10 mo developed adenomatous nodular hyperplasia of the liver. (Fig. 4). This tumor was found in one animal at 500 ppm and in another at the 20 000 ppm level, none was observed in control animals.

In the 10th mo of experiment, some rats showed pathomorphological features of interstitial pneumonia. The incidence of these findings in exposed animals did not differ significantly from the controls.

The ultrastructural changes in the hepatocytes noticed for the first time after 3 mo were progressing with the duration of exposure. Proliferation and dilatation of the cisternae of smooth endoplasmic reticulum (Fig. 5) and small droplets of lipids were seen at all concentrations of VC. At the 500 and 20 000 ppm levels a number of swollen mitochondria and invaginations of the nuclear membrane were also observed. After 6 mo of exposure, nuclear membrane invaginations were still observed (Fig. 6a) and giant mitochondria with broken cris-

[*]) Details of histopathological and ultrastructural findings will be published elsewhere.

Table 2. Incidence of histopathological lesions in the liver and the testes of male

Concentration in ppm	N	Organ weights	
		Heart	Spleen
0	7	1413±156 325±18	998±111 226±126
50	7	1466±216 358±25[b]	1094±257 264±28[b]
500	7	1431±315 338±58	1309±349 308±70[b]
20 000	7	1375±97 358±31[b]	1127±143 295±49[c]

a — male Wistar rats. The data are expressed as the mean ± SD
b — $p < 0.05$ significantly different from control

tae (Fig. 6b) were seen for the first time at all exposure levels. The areas of focal cytoplasmic degradation developed at 20 000 ppm (Fig. 6c). After 10 mo, ultrastructural changes were more marked and observed in a higher number of hepatocytes at all exposure levels. No ultrastructural changes were noticed in the hepatocytes of control rats.

Blood and urine analysis

Plasma protein content and plasma or serum activities of alkaline phosphatase, alanine aminotransferase and lactate dehydrogenase were slightly elevated in VC-exposed rats, the difference from parallel controls being statistically significant only in some groups of animals (Fig. 7). The activity of lactate dehydrogenase was related, to some extent, to the duration of exposure and concentration of VC.

The number of red blood cells was slightly increased after 10 mo at the 50 and 500 ppm exposure levels and some fluctuations in coagulation time were observed in the last period of exposure.

Table 1. Absolute and relative organ weights of rats after rats exposed to vinyl chloride for 10 months

	Vinyl chloride concentration (ppm)			
	0	50	500	20 000
Nuclear polymorphism of hepatocytes	2/28	5/21	18/34[c]	10/17[c]
Proliferation of hepatic reticuloendothelial cells	3/28	3.21	13/34[a]	8/17[b]
Damage of spermatogenic epithelium	3/28	3/21	13/34[a]	5/17

a — $p < 0.05$ significantly different from control
b — $p < 0.01$ significantly different from control
c — $p < 0.001$ significantly different from control

10 months of inhal

absolute (g)
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kidneys

3163±327
716±72
3062±418
749±61
3441±661
807±65[b]
3279±376
849±40[c]

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Table 3. Excretion

Vinyl chloride concentration in ppm

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Table 4. Excretion

Vinyl chloride concentrations in ppm

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10 months of inhalation exposure to vinyl chloride[a]

absolute (g)
relative (mg/100 g of body weight)

kidneys	adrenals	testes	liver
3163±327	65±16	300±505	9944±1234
716±72	15±3	677±99	2233±146
3062±418	60±12	2853±573	9776±1164
749±61	15±4	692±89	2393±202
3441±661	59±9	3006±485	10753±1600
807±65[b]	14±1	700±111	2531±109[d]
3279±376	70±15	3173±549	12020±1216[c]
849±40[c]	18±4	821±106[b]	3116±213[d]

c — $p < 0.01$ significantly different from control
d — $p < 0.001$ significantly different from control

Table 3. Excretion of acid mucopolysaccharides in urine (in μ/24 h) of control rats and rats exposed to vinyl chloride [a]

Vinyl chloride concentration in ppm	Before inhalation exposure	Time from the onset of inhalation exposure		
		1 month	3 months	6 months
0	99±26	106±47	130±43	156±41
50	96±19	107±37	131±33	152±49
500	101±23	104±25	127±38	153±34
20 000	95±21	100±35	110±36	152±47

[a] The 24-hour urine samples were collected twice with the 24 h interval from 2 rats kept together in a Simax metabolic cage. Two separate determinations were made and the results were averaged. The data are expressed as the mean ± SD of 7—10 averages.

Table 4. Excretion of hydroxyproline in urine (in μg/24 h) of control rats and rats exposed to vinyl chloride [a]

Vinyl chloride concentrations in ppm	Before inhalation exposure	Time from the onset of inhalation exposure		
		1 month	3 months	6 months
0	300±155	398±204	375±121	368±131
50	287± 68	367±273	354±104	328± 92
500	341±127	309±115	339±140	339± 80
20 000	230± 91	307± 17	332±127	331±137

[a] The 24-hour urine samples were collected twice with the 24-h interval from 2 rats kept together in a Simax metabolic cage. Two separate determinations were made and the results were averaged. The data are expressed as the mean ± SD of 7—10 averages.

The excretion of acid mucopolysaccharides and hydroxyproline in the urine of exposed animals did not differ significantly from the controls during the 6 mo observation time (Tables 3 and 4).

There were no differences in the other hematological or biochemical indices studied and no alterations were observed in the microscopic constituents of the urine.

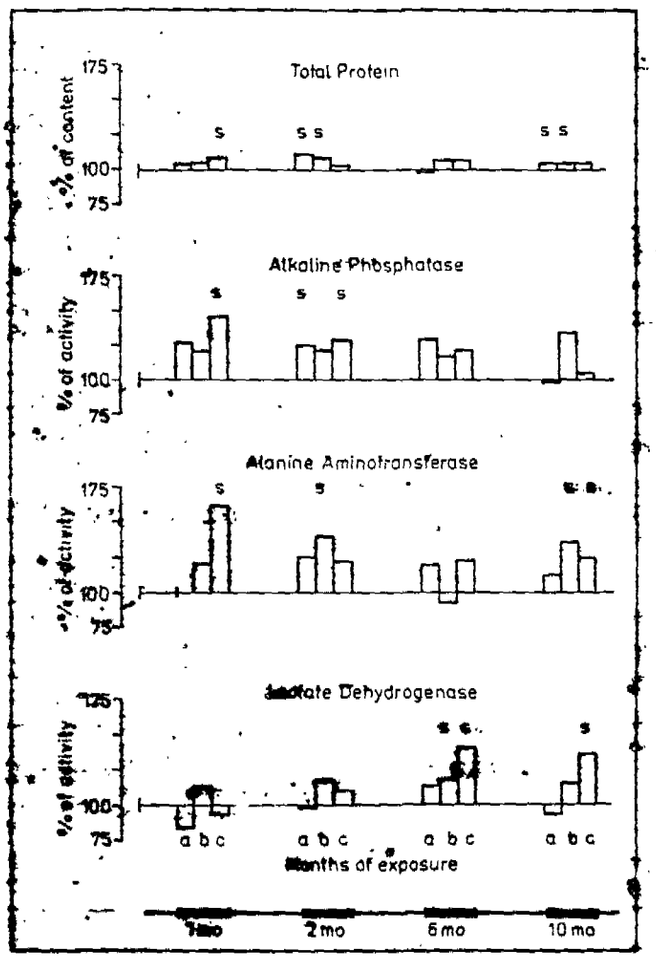

Fig. 7. Serum activity of alkaline phosphatase, plasma activity of alanine aminotransferase and lactate dehydrogenase, plasma total protein in rats exposed to VC at concentrations: a — 50 ppm, b — 500 ppm, c — 20 000 ppm. Results are shown as percentages of parallel control assumed as 100 %. All results represent the means of 7—10 separate determinations. S — statistically significant difference from control.

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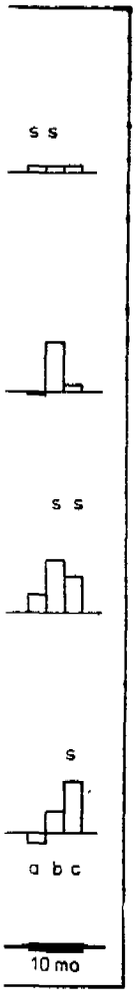

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DISCUSSION

Chronic inhalation exposure to VC has been reported to induce degenerative changes in the liver, kidneys, spleen, brain, lungs, skin and bones of experimental animals [2, 17, 24, 26].

In our study on rats exposed to 50—20 000 ppm of VC for 10 mo, apparent treatment-related pathomorphological changes developed in the liver and testes. The liver changes were observed much earlier and at lower concentrations of VC than those in the testes.

The increased organ/body weight rations of spleen and kidneys were not accompanied by any histological changes in these organs and the indices of kidney function disorders were negative. No biochemical evidence of disturbances of the connective tissue and mineral metabolism could be provided. Thus we did not confirm the results of the study of Viola [26] who, using the same strain of rats and similar conditions of massive exposure to VC, described histopathological alteration in the brain, kidneys, skin and bones. Whether it was due to the 2 mo longer exposure time in Viola's experiment, remains unanswered till now. It appeared from our toxicity study that the liver was the critical organ in the rat, this conclusion being in agreement with Torkelson's data [24].

The lesions in the testes observed in our study indicated the possibility of VC-exposure resulting in reduced reproductive ability of the males. The scope of our study did not permit a more specific interpretation. Epidemiological studies suggested that VC produced germinal mutations as manifested by increased fetal mortality observed in the wives of men who were occupationally exposed to VC [8]. Short et al. [19] found no evidence of either preimplantation or postimplantation loss in pregnant untreated females mated with male rats exposed to VC for 11 weeks, however, reduced fertility was observed in male rats exposed to 250 and 1000 ppm of VC.

The incidence of histopathological changes in the liver and testes of VC-exposed rats did not correlate well with the exposure level. The incidence was considerably higher at the 500 ppm level than at the 50 ppm level, and only a small difference (if any) was observed between the 500 ppm and the 20 000 ppm exposure levels. This phenomenon can be explained in the light of the general concept developed by Gehring et al. [7] stating that the toxic effects resulting from biotransformation products of a chemical should be related not to the degree of exposure but rather to the amount of the biotransformed compound. Since the toxic action of VC is attributed to its metabolites and the amount of VC metabolized increases very slowly above 2500 ppm [7], one could expect that the biological effects of VC-exposure will be increasing only slightly with the concentration of VC at high exposure levels. In addition, depression of the rate of VC metabolism could be inferred from the reduced rate of excretion of thioglycolic acid after long-term exposure to high concentrations (20 000 ppm) of VC [25]. These toxicokinetic features of VC were probably underlying the dose-response character of our pathological findings in the liver and testes, and the results further suggest that VC requires biotransformation to an active metabolite (s) for nonmalignant liver injury.

Two cases of adenomatous nodular hyperplasia were considered to be induced by VC-exposure since it is known from literature (12, 18, 20) and from our own observations that this tumor is extremely rare in Wistar rats. So far, this type of tumor has not been reported to develop in animals and humans exposed to VC.

Laboratory liver function tests have been reported to be frequently abnormal in VC workers (13, 14, 22) but their usefulness in the detection or diagnosis of VC-induced liver damage is controversial (3, 11, 15). The elevations we observed in the activities of plasma enzymes in rats exposed to VC were very small. The estimations of AspAT, ALAT and AP seemed to be of doubtful diagnostic significance, also with respect to the lack of any relation to morphological injury of the liver and the degree of exposure. The estimation of LDH may be of some diagnostic value since its activity is related better to the degree of exposure and the pathological changes in the liver.

From our toxicity study, the no-toxic-effect level of VC could not be established. The lowest concentration of VC (50 ppm) still caused some toxic effects in rats: depression of the body weight increase, increased relative weights of some internal organs, slight hematological and biochemical changes and fluctuations and, what is more important, ultrastructural changes in hepatocytes and the tendency for an increased incidence of histological liver alterations. Considering our results from the health safety aspects, the 50 ppm could be regarded as the threshold concentration of VC in rat, and the safety factor of 10 would be resonable in view of the structural alterations present in the liver, the character of the dose-effect curve, and only one animals species studied. On the basis of these assumptions it could be suggested that the safe exposure limit in industry in relation to systemic effects of vinyl chloride would be in the region of 5 ppm.

SUMMARY

Male rats were exposed to vinyl chloride at the concentrations of 50, 500, and 20 000 ppm, 5 hours daily, 5 days a week for 10 months. Morphological lesions in the liver and the testes detected by light and electron microscope and depression in body weight increase intensified with the duration of exposure. Increased relative weights of some organs and slight hematological and biochemical changes in blood during the course of the experiment were also observed. Some toxic effects including morphological liver injuries arose at the smallest exposure level, i. e., 50 ppm. Assuming 50 ppm as the threshold concentration for rats, the 5 ppm level has been estimated as the safe exposure limit in industry in relation to systemic effects of vinyl chloride.

RÉSUMÉ

J. A. Sokal, B. Barański, J. Majka, R. Rolecki, J. Stetkiewicz, J. Kołakowski, S. Szendzikowski, K. Wróblewska: **L'étude expérimentale des effets toxiques chroniques de chlorure de vinyle sur les rats**

Les mâles de rat étaient exposés à du chlorure de vinyle dans les concentartions de 50, 500 et 20 000 ppm pendant 5 heures par jour et 5 jours par semaine au cours de la période de 10 mois. Des lésions morphologiques sur le foie et sur les testicules constatées à l'aide du microscope lumineux et éléctronique ainsi que la réduction de

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l'augmentation de poids devenaient plus intensives au fur et à mesure de la durée de l'exposition. Au cours de l'expériment on pouvait aussi observer de petits changements hématologiques dans le sang et l'augmentation du poids rélatif de quelques organes. Quelques effets toxiques y compris des lésions de foie se produisaient pendant les niveaux les plus bas de l'exposition, à savoir à 50 ppm. Sous la condition que 50 ppm réprésentent la concentration de seuil pour les rats, on a fixé la limite de sécurité de l'exposition pour l'industrie par rapport aux effets de système de chlorure de vinyle, à savoir au taux de 5 ppm.

ZUSAMMENFASSUNG

J. A. Sokal, B. Barański, J. Majka, R. Rolecki, J. Stetkiewicz, J. Kołakowski, S. Szendzikowski, K. Wróblewska: **Eine experimentelle Studie der chronischen, toxischen Wirkungen des Vinylchlorids an den Ratten**

Die Rattenmännchen wurden zu Vinylchlorid bei Konzentrationen 50, 500 und 20 000 ppm fünf Stunden und fünf Tage wöchentlich, insgesamt 10 Monate exponiert. Die morphologischen Läsionen an der Leber und den Hoden die mit Hilfe eines Licht- und eines Elektronmikroskop bestimmt wurden, sowie auch die Senkung des Gewichtszuwachses haben mit der Länge der Exposition an der Intensität zugenommen. Während des Experiments wurden auch kleine hämatologische und biochemische Veränderungen im Blut beobachtet und eine relative Gewichtszunahme einiger Organe eruiert. Einige toxische Wirkungen einschliesslich der morphologischen Beschädigung der Leber, entstanden bei dem niedrigsten Expositionsniveau d. h. bei 50 ppm. Unter der Voraussetzung , dass 50 ppm die Schwellenkonzentration für die Ratten ist, wurde eine Sicherheitsgrenze für die Industrie in Bezug auf Systemwirkung des Vinylchlorids in einer Höhe von 5 ppm bestimmt.

RESUMEN

J. A. Sokal, B. Barański, J. Majka, R. Rolecki, J. Stetkiewicz, J. Kołakowski, S. Szendzikowski, K. Wróblewska: **El estudio experimental de los efectos tóxicos crónicos del vinilcloruro en ratas**

Los machos de las ratas se les exponían al vinilcloruro en concentraciones de 50, 500 y 20 000 ppm todas las 5 horas al día y los 5 días por la semana, en total durante meses. La lesión morfológica en el hígado y los testículos detectados por los microscopios luminos y electrónico así que la disminución del aumento de peso han obtenido más de intensidadconladuración de la exposición. Durante el experimento se les observaban también pequeñas modificaciones hematológicas y bioquímicas en la sangre y el aumento de peso relativo de algunos órganos. Algunos efectos tóxicos, incluso las lesiones morfológicas del hígado, originaban a los niveles más bajos, de la exposición, o sea, a la de 50 ppm. Suponiendo que 50 ppm esté una concentración de umbral para las ratas, el límite seguro de la exposición se fijó al nivel de 5 ppm en relación con los efectos de sistema del vinilcloruro.

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