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Dichloroethane

25

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Dichloroethane

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The series is intended for toxicologists, hygienists and all those responsible for evaluation and control of harmful effects of chemicals to human health and the environment.

DICHLOROETHANE

Dichloroethane, a colorless liquid [1]
Molecular formula: $C_2H_4Cl_2$ [1, 2]
Structural formula
1,2-dichloroethane $CH_2Cl=CH_2Cl$
1,2-dichloroethane $CHCl_2=CH_3$
Molecular weight — 98.945 [1, 2]
Synonyms — for 1,2-dichloroethane — symmetrical dichloroethane, ethylene chloride, chlorous [1] ethyleneà
— for 1,1-dichloroethane — unsymmetrical dichloroethane, chlorous ethyledine, ethylene chloride.
Melting point — 35.87° C [1, 2]
Flash point — 14.4° C [2]
Density — 1.28082 at t=0° C [1, 2]
1.2569 at t=20° C
Boiling point — 83.7° C [1, 2]
Flammable limit — 449—449° C
Relative vapor density:
21 mm Hg at 0° C
61 mm Hg at 20° C
1231 mm Hg at 100° C [1, 2]
Practically, dichloroethane is insoluble in water [1, 2]: 100 parts of water dissolve corresponding dichloroethane proportions of:
0.869 parts at 0° C
0.885 parts at 20° C
0.984 parts at 30° C

PRODUCTION PROCESS(ES)

Dichloroethane is obtained by the reaction of chlorine with ethylene. Two methods for dichloroethane production currently in use are injection and bubbling. Both methods are suitable for operation on pure ethylene as well as ethylene-containing gases. Under the former method, technical ethylene passes through the stage of pretreatment with sulfuric acid or, better still, with chlorine. The latter's quantity must be sufficient to bind all propylene and butylenes. Treated ethylene is fed into the injec-

tor. Chlorine quantities corresponding to the quantities of ethylene are delivered into a second injector. Dichloroethane comes into the injectors from a pressure tank; it gets saturated with chlorine in the second injector while the reaction of chlorine with ethylene occurs in the first one. The dichloroethane dripping from the pressure tank joints the dichloroethane that forms in the injectors and then enters the cooler and on into the collector. Raw dichloroethane contains 3% of higher chlorides at the maximum [3].

Under the second method, chlorine and ethylene are driven down the tower with an iron capping until it becomes half-filled with dichloroethane. The tower has a jacket with circulating water and the temperature inside maintained within the range of 18 to 25° C all through the process. The bubbling method has the advantages of needing less sophisticated hardware, greater ease of servicing, and a higher yield of the product.

Flue gases (the nonreacted components, impurities and noncondensed dichloroethane vapors enter the condenser where water and alkali make them give out hydrogen chloride before the gas is supplied into scrubbers. Here the previously non-condensed dichloroethane vapors are absorbed by kerosene and the waste gas discharged into the atmosphere.

Raw dichloroethane is likely to contain impurities of other dichloroalkyls, trichloroethane and a variety of unsaturated compounds. Water content makes yet another quality characteristic of dichloroethane. Water present in quantities at or below 0.08% keeps dichloroethane transparent even in winter-time. Given higher humidity and low temperature, water may separate out as a phase immiscible with dichloroethane [1, 3].

USE

As a solvent, dichloroethane finds numerous applications in e. g. the butter and fate industry; to recover asphaltites from bituminous rocks and montainwax from brown coals; in the petroleum industry, as a selective solvent in deoiling and deparaffination; for sulfur extraction from sulfur-containing ores; for regeneration of wiping material and degreasing shavings in the metal-working industry; to produce nitrocellulose and cellulose-acetate lacquers; to degrease metal surfaces; to dissolve man-made and natural resins; to clean woolen, silk and cotton cloths.

Applications for dichloroethane as a starting product abound in the production of ethylene glycol, glycol esters, vinyl chloride, ethylene diamide, thirubber and a host of other products.

The pharmaceutical industry employes dichloroethane to obtain synthomycin and other medicines; the flour-milling and grain-elevator industries use it as an anticeptic agent and fumigant [1, 4].

PATHWAYS INTO THE ENVIRONMENT

Wide-ranging use of dichloroethane — as a solvent, an intermediate product for the synthesis of polymeric materials etc. — raises the possibility of its arrival into the environment with the waste waters of numerous industries. Dichloroethane-polluted water constitutes poor target for biological treatment, thus poising heavy risks of its getting into open water reservoirs.

The production facilities either producing or consuming dichloroethane constitute sources of atmospheric air pollution with dichloroethane vapors [6].

In the process of quaiacol production [7] — during its extraction with dichloroethane — the latter was detected in the air of production departments in concentrations that were 1.5 to 4 times the maximum allowable level. Steady levels of dichloroethane in the air may be due perhaps to its desonation from the walls of working rooms and the equipment involved.

Dichloroethane — related atmospheric pollution [4, 6] is a likely occurrence in the production of synthetic synthomycin. Dichloroethane vapors in amounts close to 1,100 kg per day are ejected into the atmosphere in the waste gas flues and exhaust emanating from all plants on all stages of synthomycin production, beginning with the apparatus to obtain acid chloride and ending with the sites of dichloroethane distillation from the ketone soution inherent in dichloroethane.

The air may become polluted with dichloroethane vapors during the production process of quality lubricating oils. The rate of dichloroethane emission approximates 1,500 kg/day for all of the process stages [4, 6].

CONCENTRATIONS

Dichloroethane concentrations at varying distances from synthomycin-producing plants amount to 12.2 mg/m^3 as an average concentration and 33.1 mg/m^3 as a maximum one-time concentration at 100 m 8.7 and 20.9 mg/m^3 at 250 m; 8.4 and 33.0 mg/m^3 at 500 m; 5.5 and 21.9 mg/m^3 at 1000 m; and 3.7 and 28.5 mg/m^3 at 1500 m away from the facility.

Dichloroethane vapor contents in the air around a selective oil refinery were 19.4 mg/m^3 (average) and 38.6 mg/m^3 (maximum one-time) 100 m away from the source; 8.2 and 20.0 mg/m^3, respectively, 1000 m away, and 3.5 and 17.6 mg/m^3 2000 m away [4, 6].

ENIRONMENTAL FATE TESTS

The effect of light and atmospheric oxygen on pure dichloroethane is relatively minor and fails to cause its major changes. Technical grades of dichloroethane include impurities which res-

pond to a combined impact of light and oxygen yielding phosgene and polymeric compounds. The impurities, by virtue of their presence, control the value of «resistance», the parameter governed by the ability of a test sample of dichloroethane to split off a particular quantity of hydrogen chloride when boiled with water for an hour with reflux condenser. To some or other extent, the stability of dichloroethane is subject to the adverse effects of light and presence of moisture and oxygen, the latter always acting in combination with light.

ENVIRONMENTAL FATE

On exposure to moisture coupled with elevated temperature and heightened pressure, the stability of dichloroethane falls abruptly, especially at temperatures above 110° C e. g. 0.66% acidity results in dichloroethane at 90° C, 0.4% acidity at 110° C, and 7 to 12% acidity at 140° C.

Major quantities of dichloroethane vapors are sorpted by the covering of walls in production departments and clothing fabrics; furthermore, greasy loths bind 28 times as much vapors as do clean cloths. This sorption capacity comes to its heighest in woolen cloth and the lowest in chintz (of cotton fabrics) [1].

The method of gas-liquid chromatography has been able to establish that maximum dichloroethane absorption by the coal grade SKT-6a from blood occurs within the first 3 to 5 minutes — 87.7 to 89,8%, and then diclines but still persists on an impressive 85.9% level after prolonged, 45 minutes perfusion (the blood sample is passed through a column with coal at a rate of 40—50 ml/min). The sorptive activity of the coal grade AR-3 is somewhat lower and maximum absorption, within the first 20 minutes of perfusion, somes to 18.4% and then 12.7% by the 45th minute [9].

Stability of dichloroethane was examined at a temperature of 20 °C in model 20 l aquaria by pouring fresh river water samples and adding dichloroethane in concentrations roughly similar with its contents in treated industrial effluents. To clear up the principal mechanism of dichloroethane transformation, a paralleled study focused on its decomposition in distilled water [5].

The dichloroethane concentrations of 35 and 125 mg/l were instilled into river water with pH=7 and 9, and those of 55 and 150 mg/l into the distilled water. In natural and sterile conditions dichloroethane takes a relatively short time to get removed from water. Though by the end of the first 24 hours dichloroethane concentrations in the river water still had amounted to 8 and 30 mg/l, there was nothing left of the initial 35 mg/l concentration by the 3 rd day and of the initial concentration of 125 mg/l by the 6 th day. From the distilled water, the lower dichloroethane concent-

ration had been fully banished by the 7th day — when a mere 2,4 mg/l was lingering of the greater concentration.

No chemical conversion products, like ethylene glycol or formaldegyde, had been identified and it was inferred that the mechanism of dichloroethane removal from water must apprently be controlled by evaporation. In support of the inference were also the findings of research into the behaviour of dichloroethane in closed vessels. There, the losses of dichloroethane ranged from 12 to 20% during 30 days. No decomposition products had been spotted in this case either [5].

BIOCONCENTRATION/CLEARANCE TIME/ MAMMALIAN METABOLITES

The method of gas-liquid chromatography led to to identifying one hour's time as being sufficient for complete dissolution (distribution of dichloroethane in blood [9].

When a rabbit body (but not the head) was exposed to contact with dichloroethane vapors in a concentration of 10 mg/l a short 15 minutes had been enough to establish the presence of 0.15 mg/100 ml dichloroethane in the blood. Towards the end of two-hour exposure the blood contained 2.05 mg/100 ml — revealing the capacity of dichloroethane for fast penetration through unaffected skin and significant build-up in the blood.

In a few days post-intoxication the dichloroethane that had been entered into the rabits' organism became detectable in the parenchymatous organs, gastro-intenstinal tract and brain [10].

It has been found that dichloroethane, as it comes into contact with the arm skin of nursing women, tends to push up concentrations of the poison in the milk with an extended time of contact from 5 to 60 minutes. Dichloroethane contents in exhaled air were modest immediately after the contact and progressively smaller in subsequent samples [11].

After a breast-feeding woman stayed for one hour in a room with a 0.063 mg/l dichloroethane concentration, her milk exhibited 0.54 to 0.63 and the exhaled air 0.058 mg/l of dichloroethane. In some of the cases dichloroethane was detected in the milk some 18 hours after the workday ended: there was 0.195 to 0.63 mg% dichloroethane found in the milk [11].

Dichloroethane production employees were found to have higher dichloroethane concentrations in the air they exhaled than those present in the air or the production repartments. The inflow of dichloroethane into the blood through contaminated skin lasts persists as long as the product has been wiped away from the skin [12].

After ten-minute immersion of a rabbit helix into dichloroethane, there was 6 mg% of dichloroethane in the blood sample taken from the external jugular vein, 1.6 mg% in the arterial

blood (the carotid artery), and 0.28 mg/l in exhaled air. In the human hand, that had been dipped into liquid dichloroethane for 10 minutes 4.8 mg% of dichloroethane was discovered in the blood taken from the anconal flexion vein of the same arm and 0.09 mg/l in exhaled air.

Human arm, if kept in liquid dichloroethane for a brief 2—3 minutes, absorbs on average 0.021 mg per one cm^2. The dichloroethane exposure through human skin occurs by degrees so that an arm taken out from a dichloroethane vessel has on its surface 0.015 mg of dichloroethane, or 60% of the initial amount one hour later, and 0.009 mag or 43%, and 0.006 mg or 26% respectively two and three hours later. The curves illustrating the decline of dichloroethane concentrations, following the end of contact with it, in skin washing, blood, and exhaled air run approximately parallel; two hours after withdrawing the arm from the dichloroethane vessel the washings contained 43% blood 38,5%, and exhaled air 32% of the initial quantity [13].

Upon single administration of a 500 mg/kg dichloroethane dose it surfaced up in the blood one hour later in a concentration of 12.1 ± 1.6 mg%. The determination of blood dichloroethane buildup in the blood to 140 ± 3.0 mg% was observed four hours after its arrival. Further on, its quantity diminished until no longer detectable in the blood one and three days later. Some correlation was traced between the 1,2-dichloroethane buildup level in the blood of affected humans [14].

With entry by inhalation into the rat organism in concentrations equel to 870 and 3,200 mg/m^3, there was a noted increase of dichloroethane blood content with the greater length of exposure, reaching 20 and 56 mg/l respectively after 3-hour exposure. With intragastric and intraperitoneal administration of dichloroethane at a dose of 250 mg/kg, the observed dependency of the poison's blood content upon time was also exponential. In addition, the intraperitoneal administration resulted in a maximum dichloroethane level in the blood two times as high (86 mg/l), and the time to achieve it half as short (45 min) is with the intragastric exposure to the same dose. This points to a far greater speed of dichloroethane absorption if given into the stomach. Likewise, the contents found in the organs and tissues were also higher for the intraperitoneal than the intragastric route of entry [15].

The blood-tissue relationship of dichloroethane is a constant value specific to any particular organ, regardless of the dose and route of administration. Assuming dichloroethane content in blood and tissue equal to unity, its corresponding concentrations will be 0.8 in the liver, 0.44 in the kidneys, 0.36 in the heart, 0.34 in the adrenals, 0.27 in the spleen and pancreas, 0.05 to 0.1 in the lungs, 0.7 in the spinal cord, 0.57 in the afterbrain, and 0.15 to 0.2 in the cerebellum, cortex and subcortical centers of the

brain. The differences of dichloroethane distribution through the central nervous system spring apparently from the dissimilar contents of fats and lipids in the tissues and high dichloroethane solubility in the latter [15].

Based on dichloroethane contents in the urine (0.24 to 4.2 mg%) and its relatively low daily quantities (up to 10 ml), it was concluded that the kidneys were unable to provide the primary route of dichloroethane elimination from the organism.

Subsequent to intraperitoneal administration of a 250 mg/kg dichloroethane dose, 30% of the total substance instilled into the organism of albino rats was eliminated within 4-5 hours in exhaled air. The same time was needed for half that much dichloroethane to be cleared off after intragastric administration of the same dose and for twice that amount to be removed after intravenous injection.

The half-existence time of dichloroethane in the blood takes up 88 minutes and the time of half-clearance with exhaled air 76 minutes.

For the intravenous injection of 25 mg/kg of dichloroethane its declining contents in the blood followed a bi-exponential curve with the half-existence times of 17.5 and 72 minutes; for the dose of 50 mg/kg, the curve traced a tri-exponential pattern and the corresponding half-existence times were 16.5 and 90 minutes. Similar findings resulted from analysis of the exhaled air [15].

Chloroethanol, one of the principal metabilités of 1,2-dichloroethane in warm-blooded organisms, metabolizes, in its turn, into monochloroacetic acid. Following a single dichloroethane injection into the stomach of albino male rats at a dose of 750 mg/kg (LD_{50}) and in the form of a 10% oil solution, chloroethanol was identified in the blood and liver with a method of gas-liquid chromatography. Chloroethanol quantities in the blood and liver of the rats having been poisoned with 1,2-dichloroethane became detectable within the first two hours of intoxication. Specifically, its blood contents reached maximum in four hours (67.8 g/ml) and liver conterts by the end of the first 24 hours (15.5 μg/g) [16].

The pattern of change in the morphological constitution of the peripheral blood had very much in common for the case of poisoning with dichloroethane, and its most toxic metabolite, chloroethanol, the only difference being a more distinct character and earlier dates of the pathological process caused by the chloroethanol intoxication [17].

Chloroethanol constitutes a highly toxic substance: when introduced to the stomach of albino rats, its LD_{50} is equal to 87 ± 11.3 mg/kg and the corresponding maximums are reached after 30 minutes in the blood and after four hours in the liver. By the end of the first 24 hours chloroethanol is to be detected

neither in the liver, nor in the blood on account of its having been metabolized to monochloroacetic acid in both. Due to the ability of 1,2-dichloroethane to store up in the fatty depots, the poison may be getting into the blood for another two days to form chloroethanol. Since dichloroethane metabolites — chloroethanol and monochloroacetic acid — prove more toxic than dichloroethane, the latter's metabolism in the warm-blooded organisms progresses with «lethal synthesis» [16].

Chloroacetic aldehyde is an intermediate metabolite between chloroethane and monochloroacetic acid [18].

In response to poisoning with monochloroacetic acid (280± ±10 mg/kg), the liver and kidneys of albino rats exhibit more drastic changes than in chloroethanol poisoning. There are reasons to assume that the histostructural changes in the parenchymatous organs brought about by acute dichloroethane intoxication emanate, to a large extent, from the toxic effect of exactly this metabolite — monochloroacetic acid [18].

MAMMALIAN TOXICITY ARRAY

Given two-hour inhalation exposure to dichloroethane the lateral position in albino rats was observed at the concentration of 15 to 20 mg/l and death at 35 mg/l. About 24 hours post-exposure the animals died that had been poisoned with dichloroethane vapors concentrated to 5 to 10 mg/l (two-hour exposure) [1].

With respect to dichloroethane lethality for albino rats, 12.1 mg/l proved 100% lethal after 3—6-hour exposure and 4 mg/l were 25 to 60% lethal after 7—8-hour exposure; all animals survived exposure to 1.2 mg/l [1].

The effect of eight-hour exposure of guinea pigs to 8 mg/l and more caused their death sometime during or after the experiment. In dogs exposed to 20 mg/l, death came within four to seven hours later.

Monkeys inhaling 18 mg/l of dichloroethane during 10 minutes displayed light lacrymation and impaired equilibrium.

By the intragastric route of administration, 0.5 to 0.7 ml/kg was discovered to be the median lethal dose for guinea pigs, 0.7 to 0.9 ml/kg for rabbits, and 1.3 ml/kg for dogs. The respective absolutely lethal doses were 1.1 to 1.3; 1.5 to 1.7; and 1.9 ml/kg [19].

On data available in different authors, 850 and 500 mg/kg constitute the LD_{50} for rats by intragastric administration [17, 20]. Otherwise, the median lethal dose for albino rats has been estimated at 30,000 mg/m^3 [21].

Dichloroethane given intragastrically to rabbits (0.5 ml/kg) and rats (1.0 ml/kg) iriduced, after as short time as 24 hours, pronounced morphological disturbances of the liver — plethora, discomplexation of liver partitions, abrupt vascular plethora, adi-

pose infiltration into liver cells and necrotic foci along the perimeter of hepatic lobules. During the next 24 hours, however, the antitoxic liver function was the only one to be disturbed, with maximum changes of all liver functions not observed until the third day post-intoxication. Oral administration to rabbits of a dichloroethane dose from 0.75 to 1.5 ml/kg resulted two hours later in an increased activity of the succinate-dehydrogenase and cytochrome oxidase of the myocardium as detected with a histochemical method [23].

An interdependence was identified between the severity of dichloroethane intoxication and the extent of increasing activity of the cytoplasmatic fraction of the aspartate-aminotransferase resident in the peripherial blood. Determination of the aspartate-aminotransferase isoenzymes in dichloroethane intoxication cases permits the depth and extension of cell lesions to be assessed in a more objective way than one can hope to achieve with investigation of the enzyme's general activity [26].

Dichloroethane alters markedly the content of nicotine-amide co-enzymes in the liver and myocardium. 24 hours after poisoning albino rats with dichloroethane at 0.5 ml/kg into the stomach the NAD+NADE concentrations in the liver and myocardium were, respectively, 277 ± 15.3 and 290 ± 19.2 mkg/g of humid tissue, down from the control 342 ± 7.0 and 362 ± 9.2 mkg/g. The downward trend applied also to the $NAD\cdot H_2+NADE\cdot H_2$ contents of 223 ± 12.5 and 200 ± 20.5 μg/g respectively, as compared with 261 ± 10 and 213 ± 6.3 mkg/g in control.

The drop-off in the content of nicotine-amide co-enzymes came apparently in the wake of damage to the cell membranes. In the myocardium, the content of nicotine-amide co-enzymes went down primarily at the expence of the oxidized forms, lowering the ratio of the oxidized and reduced forms [27].

With the dichloroethane oral doses of 0.1—0,3 and 0.5—1 ml given to albino rats, there followed a clear-cut rise of carboanhydrase activity in the myocardium and liver. The enzymes' activity was arrived-at, using Houssler's modification of the Kurat method and a change in the distribution of carboanhydrase activity in the test animals' myocardium and liver was detected with a histochemical method [28].

In a rabbit body (but the head) kept for two hours in a chamber with a 10 mg/l dichloroethane concentration in the air the blood carboanhydrase activity reached 0.79 Krebs units — way above the control 0.56 units [10].

The anhydrase index, relating the enzyme's activity to erythrocyte number in blood likewise became larger — to the extent raising the carboanhydrase activity, on average, from 0.22 to 0.31 in each erythrocyte. In the final leg of the experiment there came a 32% decrease of cholinesterase activity in erythrocytes — to 396 mm^3 CO_2 per one ml of erythrocytes from the initial value of

573 mm^3 CO_2. By way of partial contrast, cholinesterase activity in the blood serum was reduced by a bare 8% [10].

Acute (10,000 mg/m^3) and subacute (20,000 mg/m^3) dichloroethane intoxication increase the blood acetylcholine concentration and modifies cholinesterase activity in the blood serum [29].

While exposed to a dichloroethane concentration of 100 mg/m^3 for 8.5 months three hours daily, rabbits exhibited a somewhat higher acetyl-cholinesterase activity in the initial phase of intoxication and its diminution 4 and 7—8 months post-intoxication. The activity of butyryl-cholinesterase remained unchanged.

Thus, dichloroethane produces similar biochemical changes as it enters the body, by whatever route.

The enhancement of aminotransferase activity, chiefly of alanine aminotransferase, brought about by dichloroethane poisoning occurs in parallel with the rise of dictrophic changes in the liver parenchyme, and varies directly with their severity [24, 25].

Following single intragastric exposure of rate to a dichloroethane dose of 0.7 ml/kg in 20% sunflower-oil solution a typical picture of acute intoxication was seen to have developed and killed out 22 of the 46 rats comprising the study sample, with most of the animals dead within the first three days. Subsequent examination of the blood serum from the poisoned rats discovered to the activity of alanine-transferase to have grown remarkably — 3.2 times that of the control animals after one day, 4.5 times after three days, and two times after six days. By the same token, blood sugar content had increased by the third day to $180\pm12{,}8$ mg% from 89 ± 7.6 mg% in the control rats. A sweeping dislocation of oxidative phosphoryllation was observed that a maximum at the end of the third days. By that time, the phosphoryllation coefficient (P/O) had become 2.5 times as less and reached 0.71 ± 0.09 against 1.77 ± 0.12 in control; oxygen content (in mc-atom per one mg protein) stood at 2.05 ± 0.31 (against 2.64 ± 0.12 in control) and that of phosphorus (in mc-atom per one mg protein) at 1.41 ± 0.28, compared with the control $4.69\pm$ ±0.23 [30].

Intragastric administration of dichloroethane at 500 mg/kg to rats led to an observable reduction in the number of sulfhydrylic groups in the protein-free liver centrifugate, clearly suggesting the blocking of the sulfhydrylic groups of low-molecular compounds. By the fourth hour of poisoning the centrifugate of the test rats eas containing. 0.358 M/100 mg of SH-groups, in contrast with the control amount of 0.711 M/100 mg. No adverse effect of dichloroethane was identified in regard to amine and carboxylic groups [20].

In albino rats exposed to a single dichloroethane dose of 850 mg/kg into the stomach, changes of the erythropoietic function came into evidence four hours later and became allpervading towards the end of the first 24 h post-exposure. They involved di-

minishing quantities of erythrocytes and hemoglobin, reduction of the hematocritic number, and enlargement of the erythrocyte diameter, volume, thickness and sphericity index — Solitary Heinz-Erlich bodies were detected and hemolysis identified as a development accompanying hemoglobin destruction. In support of this was the observation of excessive reticulocyte ejection into the blood, polychromasia and expansion of indirect bilirubin in the blood serum. Further study of the leukocytic constitution of the peripheral blood identified moderate neutrophilic leukocytosis, eosinopenia and monocytopenia, together with substantial numbers of plasmatic cells. With respect to the structure of cell elements, the findings included pyknosis of hymphocyte nuclei, vacuolization of monocyte cytoplasm and decay of nuclear chromatin [17].

Oral administration of 1.2 ml/kg of dichloroethane to rabbits was noted to have caused inhibition of fibrinolytic blood activity. On the third day post-exposure, the prothrombin index went up while thromboplastic activity subsided. On the fifth day the prothrombin and thrombin time was changed towards hypocoagulation. Subacute dichloroethane poisoning was stated to increase the tolerance of plasma to heparin, reduce blood coagulation time and shorten the time required for plasma recalcification [31].

Under the acute intoxication induced by dichloroethane intragastric exposure at doses 2.0, 1.5 and 1.0 mg/kg, albino rats were found to have had changes in the functional stato of the heart, consisting of steady bradycardia and deceleration of atrial-ventricular conduction (an extended P-Q interval to 0.06—0.08 s), that correlated with the value of the dichloroethane dose applied. For a 2 ml/kg dose, respiratory standstill was followed by less frequent heart contractions, total atrioventricular blockade of the heart, and an alteration of the ECG amplitude and shape of the R-wave. Synchronized ECG-respiration recording has led to the conclusion that the respiratory standstill had preceded the cardio arrest, apparently indicating the preponderant effect of dichloroethane on the central nervous system in general and the respiratory centre in particular [34].

Similar ECG changes were identified in dichloroethane-poisoned rabbits subjected to 0.5 ml/kg intragastric exposure. Beyond these, morphological changes were also observed as comprising the dilatation of veins of the cardiac muscle, the latter's overfilling with blood, edema of the intersitial tissue, massive sub-epicardium hemorrhages, and turbid swelling and fragmentation of muscular fibres. The lesion of the heart muscle appeared to increase in severity with the activity of aspartate aminotransferase in the blood serum — the peak values occured on the first and third days post — exposure at 2.33 ± 0.29 and 1.95 ± 0.12 respectively, against 0.41 ± 0.06 in control [35].

In acute dichloroethane intoxication the route of administra-

tion notwithstanding, all of the dogs exposed were selectively seen to have their cornea opasified keratoleukoma some 12 to 14 hours after the dichloroethane exposure. By the end of the first 24 h the nebula was maximized in intensity and vein loops began to grow into the transparent part of the cornea somewhat later [38].

The impact of dichloroethane exposure at 10 mg/m³ for four successive months (five times a week by four hours daily) on albino rats was responsible for the induction of enahnced cholesterol, bilirubin, total protein, hypoalbuminemia and hyper-gammaglobulineamia, together with a build-up of alanine, and reduction of asparagin transaminase. A morphological examination of the stomach uncovered mild gastritis [39].

At a concentration of 2 mg/m³, dichloroethane given to rabbits in protracted 8- to 10-month administration of six 3-hour exposures per week brought no letdown of antibody production in the animals pre-immunized with a subcutaneous injection of one ml of 1.5-billionth suspension of heated typhoid vaccine. The vaccinations were schedulated, on average, the first at 1.5 month, second at 4.5-5 months, and third 7.5-8 months after the start of intoxication. Exposure to 10 mg/m³ of the poison — the maximum allowable concentration — caused some lowering of the antibodies' summary titres, though a measure of adaptation had been observed by the third immunization date. By way of partial contrast, a 100 mg/m³ concentration induced a drastic reduction of antibodies production to one fifth the initial amount after the third immunization. The associated occurrences involved increasing titres of the FS-antibodies and decreasing levels of «normal hemolysins» [32].

Even at the early stages of chronic poisoning dichloroethane brought on severe inhibition of agglutinin formation (2 mg/l dichloroethane concentration, 2-hour daily exposure), thus pushing down immunobiological reactivity in rabbits [33].

Protracted 7-to 11-month inhalation exposure to a concentration of 10 mg/m³ inhibited heavily phagocytic activity and increased the daily excretion of neutral 17-ketosteroids in the rabbits. At 100 mg/m³, dichloroethane brought up the level of total protein in the blood serum at the expense of coarse dispersed globulin fractions (α and β). Of the three concentrations, 10 mg/m³ is near-threshold, 100 mg/m³ effective and 2 mg/m³ ineffective [21].

In humans, dichloroethane doses in the 5—200 ml range induce acute intoxication (106 cases) [1], those in the 20-50 ml range are lethal by the interal routes of admission [36, 41] and 3 ml/kg constitutes the absolutely lethal dose [37].

There are four distinct severity classes relative to liver damages in acute poisoning cases [40].

With the first, light damage the only way to identify the pic-

ture of toxic hepatite is by laboratory investigations (increased bilirubin and enhanced transaminase activity). It comes back to normal within two or three days. Toxic hepatite IInd degree (medium -severe) shows itself as pains in the right hypochondrium, vomit, growth of bilirubin to 3-4 mg% and transaminases to 300-500 units, and diminution of the prothrombin index to 60—70%; it returns to normal in three or four days. Toxic hepatite IIIrd degree is characterized by acute pains in the right hypochondrium, recurrent vomits, distinct jaundice, liver enlargement by 4-6 cm, elevation of bilirubin to 7-15 mg%, build-up of transaminase activity from 600-800 to several thousand units, reduction of the prothrombin index to 30-40%, and hypocholesterinemia. The changes gain maximum intensity on the 4th through 6th days and, with favourable outcome, recovery sets off on the 7th or 8th day. Toxic hepatite IVth degree is extremely severe as highlighted by signs of hepatargy. Bilirubin swings up to 20 mg% or higher, transaminase to 10-12 thousand, and the prothrombin index slides down to 10-20% and even to zero in some cases [40].

The hepatoxicity of dichloroethane stems from its direct impact on the liver cells which destroys their elements, interferes with the biochemistry and thereby leads ultimately to adipose degeneration and distrophy, with the subsequent development of necroses [41, 42, 46].

In the clinical picture of acute peroral dichloroethane intoxication one would generally identify four leading syndromes. They are: toxic encephalopathy, the syndrome of acute gastritis and gastroenteritis; the syndrome of acute cardiovascular insufficiency; and the syndrome of toxic hepatite with symptome of hepatic-renal insufficiency. It is commonly emphasozed that there is a latent period in the clinical picture of acute dichloroethane intoxication [41, 42, 46].

The patients suffering light and medium-severe intoxication complain of headache, somnolence, sweet taste in the mouth, nausea and sometimes vomit, irritation of mucous membranes, a sense of burning hot on the facial skin, weakness heartbeat, dizziness, and aches in the epigastral area and the right hypochondrium. Noted also in reddening of the face and sometimes pallor.

In severe cases the patients complein of strong headache, acute pains in the epigastric area, sharp pain in the eyes, sometimes impaired vision, vomit, diarrhea, and unsteady gait. In some of the cases consciousness is lost, the pulse no longer felt and Cheyne-Stokes respiration detected sometimes [41—46].

An early warning of intoxication comes with acute gastritis (in 77,3% of the patients); toxic encephalopathy was observed in 81,1%, acute cardio-vascular insufficiency with significant depression of the arterial pressure below 80 mm developed in 56.6%, and toxic hepatite was diagnosed in 56.6% of the cases.

The clinical symptoms of dichloroethane poisoning are observed even with minimum dichloroethane concentrations in the blood (0.5 mg%) and the advent of a comatose state is noted for dichloroethane blood levels of the order of 5-7 mg% and greater [36, 37, 47].

The basic clue to understanding the lesions of the liver and kidneys attributed to dichloroethane intoxication lies in the latter's ready solubility in cellular lipids and the associated blockade of cell enzymatic systems, particularly their sulfhydrylic groups which combine readily with dichloroethane. The poison is generally recognized as having an effect on increasing permeability of capillary walls and data are available to support its inhibiting action upon the glomerular filtration of the plasmatic current in the kidneys [48].

The dates of origination and the degree of severity of the hepatic-renal insufficiency caused by dichloroethane poisoning depend on the poison's pathway into the body and on the dose taken-in. Of the eight individuals with inhalations intoxication, all have survived; of the fifty people who suffered internal exposure, 20 died. In twelve of these individuals, who had taken 100 ml or more, death occurred within the first 24 h of intoxication as contributed-to by disorders of the contral nervous system and cardio-vascular insufficiency. The autopsy revealed a plethoric and edematous brain and plethora of the internal organs. The eight patients who died 18 through 22 hours later were found to have developed a pronounced pulmonary edema.

Another eight patients who had received into the organism from 40 to 80 ml of dichloroethane died between the 2nd and 11th days post-intoxication. They were seen to have been victims of hepatic insufficiency after the first 24 hours, compounded by an increase of blood bilirubin to 10 mg% in some of the cases, and glucose to 600 mg%. Activity advantage of asparagin over alanine transaminase was explained in terms of the ability of dichloroethane to induce not only hepatic lesions, but also changes in those other organs rich in asparagin transaminase — like the cardiac muscle, brain, and kidneys.

Renal insufficiency lags the development of hepatic insufficiency. Urinal excretion becomes acutely reduced and anuria development in some individuals, with the protein quantity as high as 6.6%. Microscopy of the urinary sediment brought to light, numerous erythrocytes, leukocytes, and cylinders. In some instances, acute renal insufficiency was rapidly progressing to get uremic coma to develop some four to six days later [49].

On microscopic evidence, the morphological changes disclosed in the kidneys of those who had died of dichloroethane poisoning were essentially no different than all other varieties of the «shock kidney». Early deaths were associated with complete stenosis of the cortical vessels, including the glomeruli and