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TOXICOLOGY OF SOME CHLORINATED AROMATIC HYDROCARBONS

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SUMMARY

1. Chlorinated aromatic hydrocarbons, like chlorobiphenyl and trichlorobenzene, exert a well-defined toxic action. Inhalation of their vapors at industrial concentrations of the order of 0.2-0.3 mg/liter when continued for a long time causes pathological changes in the organs of the experimental animals.

2. Poisoning by chlorobiphenyl causes pathological changes in the parenchymatous organs, primarily in the liver, in which phenomena of the type of acute yellow atrophy develop.

3. The toxic effect of trichlorobenzene is more marked than that of chlorobiphenyl, in which connection the nervous and vascular systems are mainly affected by the application of the poison.

4. Both of the test substances when given to animals cause serious pathological changes in the blood-producing organ - the ~~XXXX~~ spleen, which clinically in the first stage of poisoning ~~XXXXXXXXXXXXXXXXXXXX~~ should be accompanied by leucocytosis, and in the subsequent stage by leucopenia.

5. In the picture of the pathological changes that are observed when poisoning is with a mixture of chlorobiphenyl and trichlorobenzene (Soxtol I) predominate the phenomena that are caused by the action of the trichlorobenzene.

6. In the manufacture of chlorinated aromatic hydrocarbons it is necessary to take the following principal prophylactic measures in order to protect the workers from the toxic action of the compounds:

a) a medical selection of the workers with rejection of all people who have ailments of the liver, kidneys, nervous system and blood-producing organs;

b) taking every possible measure to keep the technological process airtight;

c) obligatory installation of local ventilation hoods over all of the processes where hermetic sealing is not possible;

d) taking measures to provide the workers with individual protection (special clothing and footwear) and requiring the workers to take a hot shower after work.

In conclusion I consider it my duty to express my gratitude to Candidate of Medical Sciences A. G. Varshavskii, consultant of the toxicological laboratory, for the friendly assistance shown to me when running the histological tests.

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In recent years some chlorinated aromatic hydrocarbons have widely been used as electro-insulating fluids in the industries building capacitors and transformers. The question is of chlorinated benzene derivatives and particularly of chlorinated biphenyl.

In that respect, the important ones among the chlorinated biphenyl derivatives are tetrachlorobiphenyl (boiling point 220-245⁰), pentachlorobiphenyl (boiling point 242-260⁰) and their mixture, known under the name "Sovol", used for filling capacitors.

Sovol, as well as its components, is a translucent, colorless, oily, and very viscous fluid. For lowering the viscosity of Sovol, one adds to it trichlorobenzene - a fluid consisting of two isomers, i.e. 1,2,3- and 1,2,4-trichlorobenzene. The new Sovol mixture with trichlorobenzene thus obtained is known under name of "Sovtol" and is used in the construction of transformers in two modifications: "Sovtol I" containing 75% Sovol and 25% trichlorobenzene, and "Sovtol II" containing 64% Sovol and 36% trichlorobenzene. The boiling temperature of Sovtol is lower, the higher is its contents of trichlorobenzene. Consequently, the volatility of Sovtol rises as its dilution with trichlorobenzene increases, while trichlorobenzene volatilizes in the first place.

Thus, under the conditions of utilization of capacitors and transformers filled by the named fluids, it is necessary to take into consideration the possibility of polluting the air with the vapors of Sovol, tetra- and penta-

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chlorobiphenyl, respectively, and with the vapors of trichlorobenzene. Actually, numerous determinations of the air pollution in the experimental plant for the manufacture of Sovol capacitors carried out by the chemical laboratory of the Institute of Obuch (by chemist S. L. Ginzburg) showed that in a series of operations in the event of failing of hermetic sealing of the production process, the contents of chlorinated aromatic hydrocarbons in the air reaches 0.1-0.2 mg/l. It is true that such a concentration remained shortly, so that after a half hour the air proved to be practically free of these pollutants.

However, this actually does not remove the rising question on the degree of hazard of the indicated product to the organism, the more so that the perspectives of their introduction in the industry is not limited to the manufacture of capacitors and transformers: they are also used as plastisizers for nitrocellulose and benzylcellulose lacquers; moreover, investigations are carried out on the application of chlorobiphenyl in the manufacture of chemically stable plastics, heat transfer agents, etc.

The literature data on the toxicity of chlorobiphenyls is very limited. In 1936, in one of the American Bakelite factories, three cases of fatal poisoning by chloronaphthalene with admixture of 10% chlorobiphenyl were reported. For this reason, Drinker, Warren, and Bennett investigated, on rats, the toxicity of chloronaphthalene and incidentally of chlorobiphenyl by various ways of introduction (inhalation, subcutaneous, gastro-intestinal) and established that both substances caused injury to the liver, having the character of yellow atrophy. Regarding trichlorobenzene, we were not able to find any literature data on its toxicity.

Our study of the toxicity of chlorobiphenyl (in the form of commercial Sovol), of commercial trichlorobenzene, and of a mixture of these substances (in

the form of Sovtol I) was carried out on white rats which received these substances subcutaneously as well as by inhalation in the vapor state.

The first tests on 28 rats by subcutaneous introduction of the substances (once 7.5 mg/1 g body weight) were carried out for obtaining preliminary data on the character of their activity and on the degree of toxicity of the investigated substances. Since the results of these tests essentially do not differ from the results of the subsequent tests where the substances were introduced in the vapor state by inhalation, for the sake of brevity we omit their description and proceed directly to the tests on the intoxication by inhalation.

The inoculation of the rats was carried out in a small chamber of 22 L capacity, through which a stream of air was continuously passed at a rate of 1-1.5 L per minute, which was previously passed through a glass gooseneck containing the investigated fluid. From time to time, air samples were taken from the chamber, and the concentration of the investigated substances was determined.

The tests were carried out by two methods. In the first method the animals were subjected to a single acute exposure to the vapors of the investigated substance at relatively high concentrations, with the average concentration of 10 mg/L. In the second method, the animals were subjected to a repeated action of significantly lower concentrations of the investigated substances, in conformity with the conditions of a chronic intoxication. Consequently, we have several test series.

Series A. A single intoxication with the chlorobiphenyl vapors (Sovol) of a high concentration: Four rats were placed in the chamber; exposure time, three hours. At the beginning of the test the animals were somewhat excited, but shortly after they quieted down and sat motionlessly. The respiration was

accelerated. A disordered motion coordination (unsteady gait) was observed. After 2.5 hours, one of the rats lied in the lateral position. After finishing the test and removing them from the chamber, the animals moved with difficulty. All the animals died within 24 hours.

An autopsy showed a clayey yellow color of the liver and stasis in the lungs.

Histological studies of the internal organs showed the following: necrotic foci of the hepatic parenchyma, infiltrates in the vicinity of hepatic vessels and adiposis of hepatic cells spreading from the center of the lobules to the periphery; in the kidneys - thick swelling of the protoplasm, of the epithelium cells in the canalicules, here and there with focal necroses; in the heart - a stasis; in the lungs - drastic alterations in the bronchi with destruction and exfoliation of their epithelium and the appearance of interstitial pneumonia; in the spleen - a stasis, necrobiotic and necrotic phenomena.

For illustration, we present the results of a study of rat No. 62.

Liver: Numerous necrotic foci of the parenchyma, located mainly in the center of the lobules; around some foci accumulation of neutrophiles; the nuclei of many remaining hepatic cells are pycnotic, the protoplasm is homogeneous. Around the vessels and bile ducts there is proliferation of cells with a stretched, elongated nucleus and accumulation of lymphocytic cells. The endothelium of the veinal walls, especially of small veins, swollen and exfoliated in the lumen of the veins; the diapedesis phenomena are observed; in larger veins the walls are homogenized. Around some vessels the proliferation of adventitious elements is observed. Almost all remaining hepatic cells are in a state of a fatty degeneration.

Kidneys: The epithelium of the convoluted canalicules in large sections is necrotized and disquamated; the lumen of the canalicules contains granular masses of protein and exfoliated epithelium cells. The endothelial nuclei of the glomerules for the most part are pycnotic. The epithelium of the Henle loops is in the state of necrosis.

Lungs: The epithelium of the bronchi is flattened and is preserved only in small sections; around the bronchi and greater part of the vessels there are round-cellular foci; the alveolar partitions are wide, their capillaries are dilated and filled with leucocytes. The walls of the vessels have a coarse homogeneous shape; in many places parietal blood clots are visible.

Spleen: Has a variegated appearance due to the presence of numerous necrotic foci in the pulp; the follicles are hardly distinguishable; the sinuses are dilated and filled with lymphocytes; the vessel walls are homogenized; megacaryocytes are encountered in the pulp.

Heart Muscles: The transversostriated pattern of the fibers is poorly expressed; the capillaries contain numerous leucocytes.

Epicrisis: Most of the organs show drastic necrotic alterations: the liver shows conditions approaching an "acute yellow atrophy"; the kidneys show focal necrotic nephrosis. Also, the lungs and the heart muscles are injured. In the spleen, along with a rapid maturing of the lymphocytes, a destruction of the pulp cells is observed.

Series B. A single intoxication with trichlorobenzene vapors of a high concentration: 4 rats intoxicated in a 3-hour exposure. At the very beginning of the test, the rats are restless, and rub the snouts with their paws. The ears, snouts and paws are colored bright pink. After 15 minutes tetanic spasms set in

which toss them high from the floor of the chamber; the spasms last about 10 minutes and then become weaker and less frequent. After a half hour the rats still move in the chamber, dragging the rear part of the torso. During that time the spasms still continue. Of the four intoxicated rats, one assumed a lateral position one hour from the start of the test, the second one after 1.5 hours and the remaining 2 after 2.5 hours. A mild convulsive twitching of the muscles in the torso and paws continues all the time. After 2.5 hours one rat died. After stopping the 3-hour intoxication, the remaining rats were removed from the chamber in a comatose state with mild fibrilar twitchings of the muscles in the torso and extremities. A half hour after termination of the experiment, two more rats died and after one hour and fifteen minutes the last rat died, too.

The autopsies of all rats revealed a spotty coloration of the liver, a stagnant hyperemia of the vessels in the soft cerebreal membrane with areas of fine internal hemorrhages. In a histological study of the internal organs, one notices: in the liver a pronounced adema and stasis, necrotic foci, infiltrate in the vicinity of the vessels, a scattered fine granular adiposis of the protoplasm cells; in the kidneys - a pronounced adema, stasis, and necrotic changes in the epithelial cells of the canalicules. In the lungs, heart, and spleen - a pronounced stasis; in the brain - adema, stasis, and necrobiotic alterations in the nerve cells.

As an example, we present the results of a histological study of the organs of rat No. 33.

Liver: Hyperemia around some veins, round cellular foci; the veinal endothelium has a wrinkled pycnotic nucleus; a leucocyte diapedesis is observed; capillaries contain numerous leucocytes. Some hepatic cells with a pycnotic

nucleus and homogeneous protoplasm, a part of them in a necrotic state; the necrotic areas permeated with leucocytes.

Kidneys: Necrobiosis and desquamation of the epithelium of the convoluted canalicules and Henle loops, in their lumen exfoliation of the epithelial cells and proteinaceous cellular masses; the vascular walls are thickened, their endothelium is pycnotic and some areas are desquamated.

Lungs: The blood vessels are hyperemiated, the capillaries are dilated and contain many elements of the red and white blood; the alveolar membranes are attenuated and the alveolar lumen is dilated; around the bronchi round-cellular infiltrates; the epithelium of the bronchi is partly desquamated.

Spleen: The number of the malpighian bodies is in a normal range; they almost all consist of mature lymphocytes; the sinuses are dilated, their endothelium is desquamating into the lumen of the sinuses, and the pulp contains numerous splenocytes; some cells with pycnotic nucleus are encountered.

Heart muscles: Hyperemia of the vessels.

Cerebrum: In the cortex area, round-cellular foci; hyperemiated vessels; a majority of the pyramidal cells is altered: a part of them is colored dark, wrinkled, the nucleus indistinguishable, lack of processes; in contrast, the other part has a very pale color, with hardly noticeable outlines of the nucleus; in the stem part of the brain, the nerve cells of the ganglions lose their spurs; their nuclei are pale and in some of them there remained only faintly noticeable outlines.

Epicrisis: The most severely injured are the nerve cells in the brain cortex and in the nuclei of the stem part. As for the internal organs, there is

noticed a disturbance in the blood circulation with a stasis in a small circle, a damage to the vessel walls and incipient necrobiotic processes in the hepatic cells and renal epithelium. On the part of the spleen, there is a rapid maturing of lymphocytes.

Series C. A single intoxication with the vapors of a mixture of chlorobiphenyl 75% and trichlorobenzene 25% (Sovtol I) at a high concentration.

In the intoxication of rats by higher concentrations of the Sovtol vapors the symptoms of the intoxication fully repeat the phenomena of the intoxication by trichlorobenzene: irritation of the nose mucosa, cramps, necrosis, bright pink coloration of the ears, snouts, and paws. Of four rats, one died in the course of the test, another died two hours after the exposure, and the remaining two died the following day. The substance remaining in the gooseneck flask toward the end of the experiment thickened to the consistency of chlorobiphenyl, indicating that during the experiment mainly the trichlorobenzene vapors entered into the chamber. Histological findings revealed the symptoms observed in the intoxication with trichlorobenzene but in more drastic forms. Particularly in the spleen of the rats that died during a longer time following the test, a drastic disintegration of the pulp cells is observed reaching a complete destruction of the spleen tissue. Here also in the first place the alterations are in the nerve cells of the nuclei in the stem section and cortex of the brain, vascular disorders in the internal organs, and necrotic processes in the parenchyma cells of the liver, kidney, and spleen. The lungs revealed the symptoms of acute bronchitis.

Series a and a'. Repeated intoxications with chlorobiphenyl vapors at low concentrations: an intoxication with chlorobiphenyl vapors at low concentrations were carried out in two series - at the concentrations of 0.5 and 0.25 mg/L. In

the first series, one rat died after 8 exposures and two were killed after 11 exposures. In the second series one rat was killed after 16 exposures and the remaining 4 after 69 exposures, while they all were found to be entirely in a satisfactory condition.

In a histological examination of the internal organs we observed alterations analogous to those observed in the acute intoxication tests with higher concentrations of chlorobiphenyl (Series A). For example, in the liver one observes adiposis, granular and thick swelling of the cells, adema and stasis, infiltrates in the vicinity of the vessels and hyperplasia of Kupffer's cells; in the kidneys - a moderate swelling of the protoplasm in the epithelial cells of the canalicules.

Series b. Repeated intoxication with trichlorobenzene vapors at low concentrations: the intoxication with trichlorobenzene vapors was carried out at an average concentration of 0.3 mg/L. The intoxication symptoms remind the results of an acute test but in a more moderate degree; the same bright pink coloration of the ears, snouts, and paws, mild convulsive twitchings of the torso muscles, extremely slow and limp behavior of the animals. The rats started to die after the second 4-hour exposure: of 10 rats, 4 died after 3-9 exposures, 2 after 10 and 17 exposures, and the others were killed: 2 after 40 and 2 after 57 exposures. An autopsy shows the same changes in the color of the liver and hyperemia of the vessels in the soft brain membrane. A histological examination of the internal organs revealed changes similar to those observed in the animals which died from the subcutaneous injection or inhalation of larger quantities of trichlorobenzene; particularly, on the part of the brain, small hemorrhages in the soft brain membranes and changes of the nerve cells in the nuclei of the remaining part of the brain are also observed.

Series c and c'. Repeated exposures to the Sovtol I vapors at low concentrations. The intoxication by the Sovtol I vapors were also carried out in two series: at the concentration of 1 and 0.2 mg/L. The first three rats of the first series died after 3 exposures; the fourth - after 4 exposures, the fifth - after 5 exposures. The sixth rat was killed after 10 exposures. The rats of the second series, except for one, were killed after 30 exposures. One died after 7 exposures. The intoxication symptoms and also the histological examinations of the organs of the rats from the first series were analogous to the observations in the intoxications by trichlorobenzene. In the rats of the second series almost no changes in the organs were found, except for some diffuse adiposis of the hepatic cells and infiltrates around the liver vessels.

Consequently, in the tests of the rat intoxication by subcutaneous injection of the investigated substances as well as in the inhalation of their vapors, the same type of changes in the internal organs are observed. Regarding the separately investigated substances, one notices a quantitative difference as well as some qualitative differences in the alterations caused by the substances, especially on the part of the central nervous system.

Even the observations of the clinical results of the acute intoxication permit to notice some differences in the intoxication symptoms. While during intoxications with larger doses of trichlorobenzene, shortly after admitting its vapors into the chamber, the animals experience cramps, comatose state, and drastic dilation of the blood vessels, similar phenomena are not observed in the intoxication with chlorobiphenyl. Histological examinations of the organs of the animals intoxicated with trichlorobenzene reveal drastic alterations in the nerve cells of the brain. Therefore, one can assume that trichlorobenzene in the first place affects the nervous system. In the acute intoxication with chlorobiphenyl

such drastic effects on the part of the nervous system are not observed. In an acute intoxication with a mixture of trichlorobenzene and chlorobiphenyl, along with the changes with the nervous tissue, one observes more drastically expressed effects of the toxic action on the internal organs, particularly on the spleen.

Such differences can be noticed in a chronic intoxication of the animals with the investigated substances.

The bronchitis and peribronchitis symptoms observed in all tests by the inhalation of the vapors indicated a local irritating action of the vapors of the investigated substances.

The changes in the spleen - a rapid maturing of lymphocytes and filling of the capillaries with the elements of white blood during the first stages of the intoxication - indicate a development of leucocytosis. A subsequent increase in necrobiotic and necrotic changes of the pulp in the spleen apparently leads to the transition of leucocytosis, in the following intoxication stage, to leucopenia, which most strikingly appears during intoxication with chlorobiphenyl.

Conclusions

1. Chlorinated aromatic hydrocarbons - chlorobiphenyl and trichlorobenzene - have strikingly expressed toxic activity. Inhalation of their vapors in the industrial concentrations at the level of 0.2-0.3 mg/L in repeated exposures causes pathological changes in the organs of the test animals.

2. The intoxication by chlorobiphenyl causes pathological changes in the parenchymatose organs, in the first place in the liver, where acute yellow atrophy type symptoms occur.

3. The toxic effect of trichlorobenzene is stronger than that of chlorobiphenyl, while the main point of stress of the toxic effect is the nervous and vascular system.

4. Both investigated substances, in the intoxication of animals, cause serious pathological changes in the hematogenesis organs - spleen, which, clinically, in the first stage of intoxication is supposed to be accompanied by leucocytosis and in the following stages by leucopenia

5. The symptoms of the pathological alterations taking place during intoxication by a mixture of chlorobiphenyl and trichlorobenzene (Sovtol I), are dominated by the phenomena caused by the action of the latter.

6. With the industrial introduction of chlorinated aromatic hydrocarbons, the following basic prophylactic measures are necessary for preventing the toxic effects of the substances on the organism of the workers.

a) A medical selection of workers, with exclusion of all persons having diseased liver, kidney, nervous system, and hematogenetic organs.

b) All possible hermetic sealing of the technological process.

c) Obligatory installation of local ventilators in all processes where a hermetic sealing is not feasible;

d) Provision of the workers with individual protection measures (special clothing and footwear) and taking hot shower after work.

The last paragraph of the article is an acknowledgment which is not translated.

References

1. Drinker, Warren a. Bennett, The Journ. of ind. Hyg. and Toxicol., v. XIX, Nr. 7, 1937.— 2. Bennett, Drinker a. Warren, Ibidem, v. XX, Nr. 2, 1938.— 3. Greenburg a. Mayers, Ibidem, v. II, Nr. 2, 1939.— 4. Drinker, Ibidem, v. XXI, Nr. 5, 1939.—

5. Sovol i Sovtol. Tr. Vsesoyuz. Elektrochem. Inst., Vol. 58, K. A. Andrianov, 1941.