SUMMARY OF THE NATIONAL SAFETY COUSCIL STUDY OF BENZOL POISONING*

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INTRODUCTION

THE Committee on Benzol[1] was organized as a result of a discussion of the hazard involved in the use of the solvent in question which was presented 3t the 1922 National Safety Congress held in Detroit. The work of the Committee was made possible through the appropriation of $5,000 by the National Bureau of Casualty and Surety Underwriters; through the assignment by the Surgeon-General of the United States Public Health Service of Dr. Leonard Greenburg to work on the problem for almost a whole year; through the Iosning of professional personnel for shorter periods by the Massachusetts State Board of Labor and Industries (Mr. John R. Dexter) and by the Hood Rubber Company (Dr. J. N. Shirley); and through assistance or materials furnished by the Aetna Life Insurance Company, by Dr. N. B. Herman of Johns Hopkins University, by the Yale School of Medicine, and by the Weirton Steel Company.

Progress reports of the Committee were presented 3t the Buffalo Safety Congress in 1923, the Louisville Safety Congress in 1924, snd the Cleveland Safety Congress in 1925. The final report of the Committee was published in May, 1926, as a pamphlet of 128 pages for the Chemical and Rubber Sections of the National Safety Council by the National Bureau of Casualty and Surety Underwriters.

Before considering in detail the conclusions of the Committee it seems desirable to bring out two points in regard to its activities which seem to the miter to be of somewhat more than passing significance.

The first point which may be noted is that we have here a somewhat exhaustive study of an industrial poisonous hazard which has been conducted primarily by and for an organization representing industry itself. It is true that the United States Public Health Service, the Massachusetts State Board of Labor and Industries, and the universities have generously co-operated in the task. Yet the initiative for the whole study has come from the National Safety Council, a group of industridists federated for the safety of the worker on the ground that the human element is a primary factor in production; and the fact that this body

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with its long and splendid record of achievement in accident prevention should have now definitely entered the allied field of industrid poisoning is cause for profound satisfaction. In Europe the whole program of industrial hygiene is essentially a governmental one. In the United States, on the other hand, a major part of what has been accomplished for industrial safety and sanitation has been accomplished by the initiative of broad-minded employers of labor. This benzol study is a new demonstration of the readiness of industrial leaders to learn the facts and then to apply all available knowledge to the promotion of health and efficiency.

Nest, I would call your attention to what I believe to be a second somewhat notable fact about this investigation—the method by which it was conducted. Nearly all previous work on industrial poisons has been of what may be termed a qualitative type. It has dealt with a relatively small number of instances of poisoning which have come, one by one, to the notice of physicians, and such cases, from the nature of the situation) have been as a rule of a more or less aggravated type. In this benzol study there has been for the first time a conscious and definite effort to pick out a representative group of apparently normal workers in a given industry and to make a quantitative study of:

a. Mechanical conditions affecting a possible poison hazard;

b. Analytic data indicating the degree of atmospheric pollution by the poison in question; and

c. Physical findings including delicate chemical, microscopic, and physiologic tests suitable for the detection of latent and incipient damage to the human body such as threatens the subsequent development of active clinical disease.

Since this benzol study was made, two other investigations in this country have been conducted along essentially similar lines—the work of the United States Public Health Service on tetraethyl lead, and the work on spray coating by the Pennsylvania State Bureau of Labor and by the Committee on Spray Coating of the National Safety Council. These three studies, all involving the principles outlined above, seem to the writer to embody a relatively new and highly promising contribution to the technic of industrial hygiene.

With these preliminary remarks we may proceed to a summary of the main conclusions reached by the Committee on Benzol; the body of supporting evidence must be sought in the full report of the Committee itself.

Chemistry of Benzol

Benzol or benzene (C_6H_6) is a colorless liquid, boiling at about 80°C.,[2] obtained from the distillation of coal tar and from the strippings of coke oven gas. It is highly insoluble in water, slightly soluble in alcohol, and completely miscible with ether, acetic acid, carbon disulphide, and a large number of organic substances.

[2] The usual figure given in the textbooks is 80.2°; but it may be noted that a sample of very pure benzol analyzed for the Committee showed that 70 per cent. of the material came off between 79.5 and 79.9°. The International Critical Tables prepared by the Xational Research Council give 79.6°, which is undoubtedly correct.

There are many substances commercially known as "benzol," some of which contain benzene, while others do not. All of them are, of course, to be shnrply distinguished from benzine which is a petroleum product (a mixture of C_6H_{14} and C_7H_{16}).

Benzol was discovered by Faraday in 1825 in the liquid produced by the compression of illuminating gas obtained from certain oils. In 1865 Kekulé announced its structural formula. hfansfield studied its commercial production from coal tar in 1849, and twenty years later Caro Clemen and Engelhorn patented a process for its recovery from illuminating gas. Only, however, with the work of Carves, of von Hiissener, and of Brunck on the production of benzol from coke oven gas, between 1884 and 1887, did this substance come to play a really important part in industry.

Industrial Uses of Benzol

The commercial uses of benzol grew gradually and steadily from 1890 to 1915; but the development of benzol production during the war in connection with the manufacture of explosives led to an increase in the manufacture of benzol which has in turn opened the way for a rapid broadening of the field for the commercial uses of this substance.

In considering the practical problem of the use of benzol in industry it is important to remember that two very distinct types of processes are involved. In such industries as *(a)* the distillation of coal and coal tar in the production of benzol, *(b)* the blending of motor fuels, and *(c)* the chemical industries, including oil extraction, dye and dye intermediates, manufacture of paints, varnishes, and stains, and of paint and varnish removers, benzol is used in large quantities, but the very nature of the industry demands that it be kept in a closed pipe line system, any openings representing a loss of valuable vapors, and making the system an inefficient one with a correspondingly large financial loss.

In a second group of processes represented by the use of benzol *(a)* in the rubber industry, *(b)* in artificial leather manufacture, *(c)* in sanitary can manufacture, *(d)* in dry cleaning, and (e) in connection Kith the handling of paints, varnishes, and stains, benzol is employed chiefly as a solvent or a vehicle, and as a part of the process it must be removed so as to leave the originally dissolved substances in place. The method of removal of the benzol is usually to permit it to evaporate; in most cases this is done in the cold, in some cases, however, the compound may be warmed—a procedure which naturally removes the benzol with greater rapidity.

Benzol *Poisoning*

As in the case of many other toxic substances used in industry, benzol poisoning exhibits itself in two quite distinct forms, acute and chronic, according as esposure is brief and intense on the one hand or moderate and prolonged on the other.

Acute.—Occasional instances of acute benzol poisoning may be found in medical literature extending back to 1862. In our review of the literature for both Europe and America we have obtained a record of over 100 cases of acute benzol poisoning, of which about one-half were fatal (excluding a series of Russian cases complicated by hysteria).

Acute benzol poisoning generally occurs in one of two ways: either (*a*) by the sudden discharge of vapors through the failure to regulate a condensing apparatus or through the occurrence of a leak in piping in the vicinity of stills and other forms of chemical apparatus; or (*b*) by the entrance of workmen into tanks or other confined spaces in which benzol has been stored or used.

The common symptoms of acute benzol poisoning are: (*a*) dizziness, faintness, and drowsiness, culminating in unconsciousness and coma; (*b*) pallor of the face and cyanosis (blueness) of the lips and finger tips; (*c*) feeble and rapid pulse; (*d*) breathlessness and a feeling of tightness in the chest, sometimes culminating in immediate death from respiratory paralysis; (*e*) visual disturbances, with nervous excitation, tremors, and convulsions, and more rarely mania or delirium; (*f*) reddish spots on the skin and internal surfaces due to small hemorrhages in the tissues; and (*g*) where the substance has been taken in by the mouth, symptoms of acute gastro-intestinal irritation.

Death may occur within five minutes after exposure or the patient may epparently recover and succumb several days later. There appear to be marked individual variations in susceptibility to benzol; and the effects of a given atmospheric condition may probably be increased by vigorous muscular exertion, as suggested by the fact that a mnn first rendered unconscious by the inhalation of benzol vapors may often recover while those overcome while engaged in rescuing him may die.

The treatment of acute benzol poisoning involves, first of all, prompt restoration of the respiratory function by artificial respiration.

Chronic.—Chronic benzol poisoning, resulting from continuous or repeated exposure to benzol fumes in concentrations too low to produce marked narcotic effects is, of course, a condition much more obscure, and much more likely to be overlooked, than is acute poisoning. It is particularly likely to occur in the second group of industries alluded to above, in which benzol is used as a solvent and to a greater or less estent evaporated into the sir of the workroom. Chronic benzol poisoning was first described by Santesson, in 1897, in workers in a rubber factory in Uppsala, and was first reported in the United States by Selling in 1910, as occurring in the coating room of a tin can plant.

The more commonly observed symptoms of chronic benzol poisoning may be summarized as follows: (*a*) general systemic disturbance as evidenced by headache, dizziness, mealiness, loss of appetite, and loss of weight; (*b*) pallor, shown by blood esamination to be due to true anemia; (*c*) marked reduction in white blood cells (revealed of course only by microscopic examination); (*d*) bleeding from nose, gums, vagina, and bowels, with the development of purplish spots caused by small hemorrhages within the tissues; (*e*) sore and spongy gums, and burning of eyes and throat; (*f*) shortness of breath and tightness of chest; (*g*) sometimes, abdominal pains, nausea, and vomiting; (*h*) sometimes, slight tremors, visual disturbances, and abnormal sensitiveness to touch; rarely, convulsions and delirium; (*i*) rarely, rashes and skin eruptions.

Detection of chronic benzol poisoning in its early stages, with prompt removal from esposure, generally leads to complete recovery. If the case of chronic poisoning be a severe one, however, certain of these symptoms may persist for a long time after exposure has ceased; and nearly one in five of the cases reported in the literature has ended fatally.

Toxic Action of Benzol

Benzol introduced into the body (which in practice ordinarily occurs as a result of the inhalation of its fumes) exerts three more or less distinct major effects on the body. It plays the part of an anesthetic or narcotic leading to dizziness. faint- and coma. It is at the same time, however, a nerve irritant producing characteristic spasmodic movements, and actual damage to nerve Coma and death may also result from this neurotoxic action as well as from the narcotic action of benzol. Above all, however, this substance possesses a definite and specific destructive power for the blood cells and for those organs which produce these cells. Herein lies its most universal and most characteristic effect.

Effect on Blood Cells.—At first there may be a slight increase in white blood cells but this is really due to a destruction of the white cells in the circulating blood, overbalanced by the compensatory production of more white cells by the blood forming organs (the lymph nodes, spleen, and bone marrow). This condition is exceedingly transient, however. Very shortly the blood forming organs themselves are injured, particularly in respect to their power to produce the special kinds of white cells known as polymorphonuclear leukocytes and lymphocytes. The total white cell count falls rapidly, producing the condition known as leukopenia. The tissues which produce the red cells of the blood are less readily affected and a normal or increased red cell count may persist for some time, parallel with a great decrease in white cells. Ultimately, however, the blood forming organs are so seriously damaged that the number of red cells, too, falls off, producing a pronounced anemia.

A decrease in the white cells of the blood is therefore the first indication of early chronic benzol poisoning, and the effect is so familiar that benzol has been used therapeutically for the treatment of diseases characterized by an excessive concentration of white blood cells. Our studies indicate that a fall from a normal value of 7,500 to 9,000 white cells per cubic millimeter of blood to 5,600 or less may be taken as a fair index of the presence of this disease. Of course, conditions other than benzol poisoning may cause leukopenia, but with a history of exposure to benzol and in the absence of symptoms of certain acute communicable diseases or of certain other industrial intoxications which may be associated with leukopenia, the diagnosis may be made on this basis with reasonable accuracy. This reduction in white cell count generally precedes any other symptoms of benzol poisoning and may therefore exist in persons mho mould be considered normal by the ordinary clinical tests.

The seriousness of benzol leukopenia is emphasized by the observations msde by a number of investigators that resistance to pneumonia and other bacterial infections is greatly reduced by such a condition.

EXTENT OF BENZOL POISONING IN AMERICAN ISDCSTRY

In order to gain some ides of the estent of the benzol hazard in American industry we sent out a questionnaire in 1923 to a group of 324 industrial establishments which, from the nature of their products, might be expected to use benzol. Of these establishments, 140 replied; and, of the 140, eighty-four were found to be making use of this substance in greater or less amount. The largest amounts of benzol mere apparently used in the chemical industries, in the can seal industry, in the rubber industries, and in the manufacture of artificial leather, but in the chemical trades the material is generally used in enclosed processes and the number of employees esposed is small.

From the results of this questionnaire and from our subsequent field studies made in 1924 we collected a list of fifteen fatal and eighty-three nonfatal cases of benzol poisoning occurring during the years immediately preceding. Out of twenty-three establishments in which ten or more persons were esposed to benzol, eleven, or nearly half, reported cases of poisoning, while of *six* plants in which Mty or more employees were exposed, all but one had had cases of poisoning.

During the last year of our work we made no attempt to estend this survey of the extent of the benzol hazard; but at least seven fatalities from this cause were brought to our attention during the first nine months of 1925; and during the five years ending June, 1923, there were in the state of Ohio, alone, twenty-nine cases of benzol poisoning, so obvious as to receive the benefits of industrial compensation.

It is therefore clear that the hazard of benzol poisoning in American industry is a serious one and constitutes one of the major problems of industrial hygiene.

FIELD STUDY

Conditions in Industries Employing Benzol.—In order to determine the actual extent of the benzol hazard under various industrial conditions, we selected, after a preliminary survey of industrial establishments, eighteen workrooms in twelve different plants for further intensive study. Most of these were rubber factories of various sorts, but *dry* cleaning, sanitary can manufacture, and artificial leather manufacture were also included.

The workrooms mere studied from an engineering standpoint, with regard to the conditions under which the benzol mas used and particularly the type of exhaust ventilation provided; analyses of the air were made under both summer and winter conditions, in order to determine the cstent of the resulting contamination of the atmosphere. For air analysis, we used the charcoal absorption method which gave us, not benzol nlonc, but the total content of solvent vapors. For convenience, however, the results have been espressed in terms of benzol. Whether other solvent vapors were actually present or not is of course indicated in each instance.

With small amounts of benzol in use and with no ventilation, or with general ventilation only (which our studies indicate is wholly inadequate to cope with the benzol problem), we found average concentrations of 100 to 1,360 parts of benzol per million parts of air. With large amounts of benzol in use, under similar conditions, we found average values from 340 to 1,800 parts per million. On the other hand, in plants using large amounts of benzol but with enclosed systems of local exhaust ventilation, me found averages only between 70 and 500 parts per million. The plant which had the most efficient systems of local exhaust gave us average values lying between 70 parts in summer and 90 parts in winter.

It appears from this study that some of the workrooms investigated at times approached the concentrations of benzol which have been found to cause acute poisoning (Lehmann states that 0.015 gm. per liter, or 4,700 parts per million,[3] may produce confusion in half an hour, and we found 2,640 parts in one individual analysis in a compound mising room and 4,140 parts in a dry cleaning establishment). Five of the eighteen rooms gave average figures above the value of 550 parts which Legge found associated with clinical poisoning. On the other hand, with efficient local eshaust ventilation, nnd careful management of all details of the processes involved, it seems sometimes possible to use benzol in coating and mising rooms, and in sanitary can manufacture, with an atmospheric pollution amounting to less than 100 parts of solvent vapors per million parts of air. Our nest step was to determine whether this degree of protection was sufficient to avoid danger to health.

Extent of Early Benzol Poisoning

Results of Clinical Tests and Blood Examinations.—The crux of our problem was the esamination of workers esposed to benzol under various industrial conditions, using the white blood cell count as our index of early benzol poisoning. We were ultimately able to make tests of this kind on eighty-one workers in the eighteen workrooms discussed above (see Table 1): and we found that twenty-six of the persons examined, or 32 per cent., showed clear evidence of blood cell destruction, as indicated by a white count below 5,500 (or in one instance a borderline white count of 5,800 with a very low red cell count). In seventeen instances the white count was below 5,000, in ten instances below 4,000, and in three instances below 3,000. In only ten instances, however, was the red cell count below 4,000,000. Control ex-

[3] The factor (313) for converting milligrams per liter of benzene into parts per million is taken from U. S. Bur. Mines, Tech. Paper 248, Table 8, p. 52.

amination of some fifty workers not exposed to benzol failed to show any such abnormal blood pictures.

The results of these blood examinations are distinctly disconcerting. Not only did about one-third of the

TABLE 1.—SUMMARY OF BLOOD FINDINGS IN EIGHTY-ONE WORKERS POTESTIALLY EXPOSED TO BENZOL

GROUP		ROOM	LOCAL VENTILATION	AVERAGE BESZOL IN AIR		BLOOD FINDINGS	
				Summer	Winter	Number Examined (81)	Number Positive (26)
				p.p.m.	*p.p.m.*		
Small amount of benzol used	I-A	150 B	–	100	...	9	2
No local ventilation		60	–	150	...	1	0
Low benzol content in air		27 A	–	110	...	2	1
Small amount of benzol used	I-B	27 B	–	700	...	2	0
No local ventilation		59	–	150	210	9	1
High benzol content in air		61 A	–	130	210	12	6
		61 B	–	1,360	580	1	1
Large amount of benzol used	II-A	78 A	+	70	90	0	0
Local ventilation		150 A	+	90	...	1	1
Low benzol content in air		75 B	+	100	...	3	1
Large amount of benzol used	II-B	91	+	180	400	5	0[1]
Local ventilation		50 B	+	.....	430	3	1
High benzol content in air		50 A	+	.....	500	4	1
		75 A	+	130	330	10	1
Large amount of benzol used	III	78 B	–	340	...	1	0
No local ventilation		23	–	.....	...	6	2
High benzol content in air		53	–	620	...	9	0
		95	–	1,800	...	3	2

[1] Three clinical cases, one fatal since tests mere made.

In only nine cases out of the twenty-six was it possible to obtain a fairly complete medical examination; and of these nine, five gave a history more or less clearly suggestive of chronic benzol poisoning (including two or more of such symptoms as headache, dizziness, pallor, loss of appetite, digestive disturbance, spongy gums, and nosebleed).

eighty-one workers eshibit clear evidence of early benzol poisoning, but, what is still more serious, the evidence of poisoning was clear even with good exhaust ventilation and low atmospheric contamination. In the group of workrooms using large amounts of benzol without local ventilation, ten out of nineteen workers gave a positive picture; in the group of rooms where only small amounts of benzol were used without local ventilation, eleven out of thirty-six workers were positive. In the group using large amounts of benzol but with local exhaust ventilation, only five out of twenty-six workers were positive. Thus, local exhaust ventilation reduced the proportion of workers affected from nearly one-half to less than one-fifth; but even one-fifth remains a pretty high figure. Unfortunately we were unable (after repeated efforts) to make blood examinations in the can factory costing room which gave the best analytic results; but in a coating room with local ventilation, showing only 90 parts of benzol in the air in summer, the single worker exposed proved positive; and in a mixing room in an artificial leather factory, with only 100 parts of benzol in the air in summer, one out of three men proved positive.

We are forced to conclude that the control of the benzol hazard (except where the substance is used in completely closed systems) is exceedingly difficult; that, in practice, systems of exhaust ventilation capable of keeping the concentration of benzol in the atmosphere below 100 parts per million are extremely rare; and that, even when this is accomplished, there remains a decreased, but substantial, hazard of benzol poisoning.

Recommendations in Regard to the Use of Benzol

In Enclosed Systems.— As has already been pointed out, benzol is used in industry under two more or less distinct sets of conditions. In the manufacture of benzol from coal and coal tar, in the blending of motor fuels, and in the chemical industries, the solvent is necessarily handled in closed containers and pipe systems. Here, chronic poisoning is unlikely to occur and the chief hazard arises from acute poisoning due to carelessness in the cleaning of tanks, breaks in the apparatus, and similar accidents.

With regard to this type of process, it seems certain that with proper care in construction, maintenance, and operation the use of benzol can be made sufficiently safe to warrant its employment. It is true that fatal accidents have occurred, and will no doubt continue to occur, in these processes, just as such accidents occur, and will continue to occur, from the use of steam boilers. The danger is, however, in both instances a controllable one to be met by careful attention to safety provisions and not by the abandonment of the use of the substance or of the device in question.

The chief measures of protection which should be enforced in industries of this type are:

a. Regular and systematic inspection of apparatus to insure against breaks or accidental leakage.

b. The greatest possible care in freeing tanks or other receptacles which have contained benzol from all traces of the substance before they are entered for cleansing or repairing.

c. The protection of workers entering enclosed spaces liable to contain benzol fumes by the use of positive pressure air helmets or hose masks; and the conduct of all such work by teams of two or more men who are familiar with the dangers involved.

As a Solvent.—In the rubber industry, in artificial leather manufacture, in sanitary can manufacture, in dry cleaning, and in the use of paints and varnishes, benzol is employed as a solvent or vehicle under conditions which, almost of necessity, permit more or less evaporation of the solvent into the atmosphere. Here, there is relatively little danger of acute benzol poisoning, but very great danger of chronic poisoning, arising from prolonged or repeated exposure to the fumes.

In order to minimize such hazards as far as possible, there are two general types of precautions which should be taken, tending respectively to decrease the degree of esposure and to detect and control incipient poisoning in its earliest possible stages.

1. To diminish esposure, enclosed processes should of course be used wherever possible and, whenever containers are cleaned or apparatus repaired, the special precautions discussed in the preceding section dealiig with enclosed systems and the danger of acute poisoning should be observed. Wherever employees are likely in the course of their work to be exposed to benzol fumes, as in the ordinary solvent and evaporative processes or in handling the products of such processes, they should be protected by the most effective local exhaust ventilation designed according to the following general principles:

a. Where benzol is evaporated at room temperatures, air removal by local exhaust ventilation with down draft is recommended, although in certain enclosed processes direct ventilation (from the enclosure) with upward draft may be indicated.

b. Where locnlized heat is applied in the evaporation of the benzol, hoods or enclosures should be provided with up draft. local exhaust. This draft should be sufficiently intensive and applied so closely to the point of origin of the evaporating benzol as to insure the cotnplete removal of all of the benzol before the heated surface is removed from the hood or enclosure. This recommendation deals with specific processes where sufficient upward air movement is created by the heated surface to overcome the natural density of the benzol vapor.

Masks and respirators should not be relied upon to protect the worker against ordinary routine exposure to benzol fumes, since such devices cannot be made efficient without at the same time making them too uncomfortable to be worn continuously.

2. To detect incipient benzol poisoning at a stage when its effects can be minimized, it seems essential to the' Committee that all workers to be employed in processes where esposure to the fumes of this solvent is involved should be given a thorough medical esamination before employment and should be reexamined, with systematic blood counts, once a month thereafter. In addition to this routine reexamination, absence from work should be promptly followed up by some person conversant with the symptoms of benzol poisoning; and the employees themselves should be made familiar with the symptoms which are most likely to occur.

No worker should be employed

in a benzol process who shows signs of:

a. Organic disease of heart, lungs, or kidneys.

b. Hemorrhagic tendencies.

c. Anemia or any unusual blood picture.

Any worker who, on reexamination, shows any of the following symptoms should be promptly escluded from benzol esposure and transferred to some other department of the industry:

a. Hemorrhages from the mucous membranes of the nose, mouth, or other organs.

b. Decrease of more than the following amount from the employee's normal blood picture (normal conditions will be obtained from previous examinations of the individual employee): *white cells,* decrease of *25* per cent.; but in no case should an employee' with a white cell count of less than 5,000 be continued in benzol processes; *red cells,* decrease of 25 per cent.; *hemoglobin,* below *70* per cent.

LABORATORY STUDY

Relative Toxicity of Benzol and its Higher Homologues

In view of the grave hazards involved in the industrial use of benzol we next proceeded to an experimental study of the relative toxicity of certain of the higher homologues of benzol in the hope that if such substances proved less dangerous they might be substituted in at least certain industrial processes.[5]

The results reported in the literature of the subject are somewhat conflicting, probably because of the uncertain composition of the materials used by certain workers and of the lack of clear discrimination between the various types of toxic action produced. In general, however, the more careful work has suggested that benzol is more dangerous than its higher homologues.

Our own investigation was conducted with adult white rats which were kept on a standard diet and subjected to preliminary study to determine the normal range of variation in the blood count of each animal. The substances used for our tests were four in number: pure benzol (boiling point 80°);[6] toluol (boiling point 111°); xylol (boiling point 139°); and Hiflash naphtha (boiling point chiefly between 165° and 185°). The influence of these solvents was studied in three different ways: by intraperitoneal injection; by subcutaneous injection; and by inhalation in a chamber specially arranged so as to make possible a close control of the proportion of solvent in the atmosphere.

Intraperitoneal Injection. — The method of intraperitoneal injection involves sudden exposure to a relatively intense effect of the injected substance. With benzol, all animals receiving as little as 0.5 c.c. per kilogram of body weight showed marked symptoms of a definite toxic action exerted primarily on the central nervous system, manifested by tremors, twitchings, loss of equilibrium, lack of response to stimulation, and ex-

[4] Reduction in white cells is the most important condition to be noted.

[5] This laboratory study was conducted by Dr. J. J. Batchelor of the Yale School of Medicine, Research Associate to the Committee.

[6] See footnote 2.

treme weakness. With doses in excess of 1 c.c. per kilogram of body weight the temperature of the animal dropped 3° to 8°C. At times paralysis of the extremities was practically complete. The animals always recovered from doses up to 1 c.c., but 2 c.c. per kilogram of body weight always proved fatal. It is of special interest to note that in the animals which recovered neither the white nor the red blood cell counts were materially affected. This is in accord with conclusions from the clinical study of human cases which indicate that acute and chronic benzol poisoning are quite distinct phenomena and that acute benzol poisoning, which is due to violent irritation of the nerve centers and consequent asphyxiation, fails entirely to produce the effect on the cell content of the blood which is characteristic of chronic poisoning.

The other three solvents studied—xylol, toluol, and Hiflash naphtha—when injected intraperitoneally, showed a wholly different picture. Xylol up to 0.75 c.c., and toluol up to 0.75 c.c. per kilogram of body weight, produced no symptoms whatever except slight apathy. Hitlash naphtha in doses of 0.5 c.c. produced some limpness and paresis and a lowering of body temperature. In larger amounts all these three substances produced deranged equilibrium and weakness, culminating in loss of power of movement and ultimately in complete narcosis with fall in temperature, but the effect in the case of toluol and xylol was relatively lacking in the symptoms of toxic stimulation of the nerve centers and was of the nature of a narcosis, rather than of a nerve irritation.

Subcutaneous *Injection.*—In view of the fact that the present study was concerned mainly with chronic poisoning, we have laid chief stress upon our subcutaneous injections. Here, doses of 1 c.c. per kilogram were injected under the skin of the abdomen or back (mixed with equal parts of olive oil to decrease local irritation and delay the mte of absorption). Injections were repeated daily for a period of four to twenty-two days. This mode of treatment leads to a gradual absorption of the injected substance, entirely comparable with what occurs in human cases of chronic industrial poisoning.

In the case of benzol it caused obvious constitutional symptoms, including apathy and weakness, loss of weight, and twitchings and tremors, indicating a toxic effect on the central nervous system and culminating in death when the injections were long continued. The white blood cells were promptly nffected, the red cells more slowly, as in human clinical experience, and ultimately white cells almost disappeared from the blood.

On the other hand, the animals treated by subcutaneous injection with toluol, xylol, and Hiflash naphtha showed no constitutional symptoms whatever, aside from slightly lessened activity and slight loss in weight. The white cells were not permanently nffected at all and the red cells suffered only a slight and transient reduction. The relative effects of the four solvents studied are summarized in Table 2.

Inhalation.—Finally, our inhalation experiments brought out the relative effects of the four solvents with even greater clearness. The results are summarized in Table 3.

We see from this table that, when animals were esposed for eighteen to twenty hours a day for seven days to high concentrations of benzol, toluol, and xylol, toluol and sylol were more toxic than benzol, since 1,600 parts per million of the former solvents proved fatal while 2,440 parts of benzol did not. This is due entirely to the narcotic influence of the solvents in question and is in accord with the general fact that narcotic action often increases with added methyl radicles. On the other hand, toluol

TABLE 2.—EFFECT OF INJECTION OF VARIOUS SOLVENTS

SOLVENT	DAILY SUBCUTANEOUS INJECTION OF 1 C.C. PER KILOGRAM OF BODY WEIGHT[1]				INTRAPERITONEAL INJECTION LETHAL
	Average Number of Injections	Average Loss in Weight	Average Reduction in		
			White Cells	Red Cells	
		%	%	%	*c.c. per* Hg.
Benzol..	13	26	91	28	1.25–2.0
Toluol..	16	6	0	5	1.25–2.0
Xylol.	10	3	0	10	2.00–2.5
Hiflash naphtha..	11	4	0	5	2.5

[1] Five of the animals treated with xylol received 2 c.c. instead of 1 c.c. per day.

TABLE 3.—EFFECT OF INHALATION OF VARIOUS SOLVENTS

SOLVENT	HIGH CONCENTRATION[1]			MODERATE CONCENTRATION[2]			LOW CONCENTRATION[3]		
	Change in Weight	Reduction in White Cells	Symptoms	Change in Weight	Reduction in White Cells	Symptoms	Change in Weight	Reduction in White Cells	Symptoms
	%	%		%	%		%	%	
Benzol	−28	63	marked, neurotoxic	−14	81	moderate	−15	91	practically none
Toluol..	−21	0	narcosis, death	−3	13	slight	+1	15	none
Xylol	−10	9	narcosis, death	−3	8	slight	+3	4	none
Hiflash naphtha	....	...	....	−10	12	slight	−2	9	none

[1] Benzol 2,440 p.p.m.; toluol 1,600 p.p.m.; xylol 1,600 p.p.m.
[2] Benzol 815 and 1,035 p.p.m.; toluol 1,100 and 1,250 p.p.m.; xylol 980 p.p.m.; Hiflash naphtha 567 p.p.m.
[3] Benzol 460 p.p.m.; toluol 620 p.p.m.; xylol 620 p.p.m.; Hiflash naphtha 312 p.p.m.