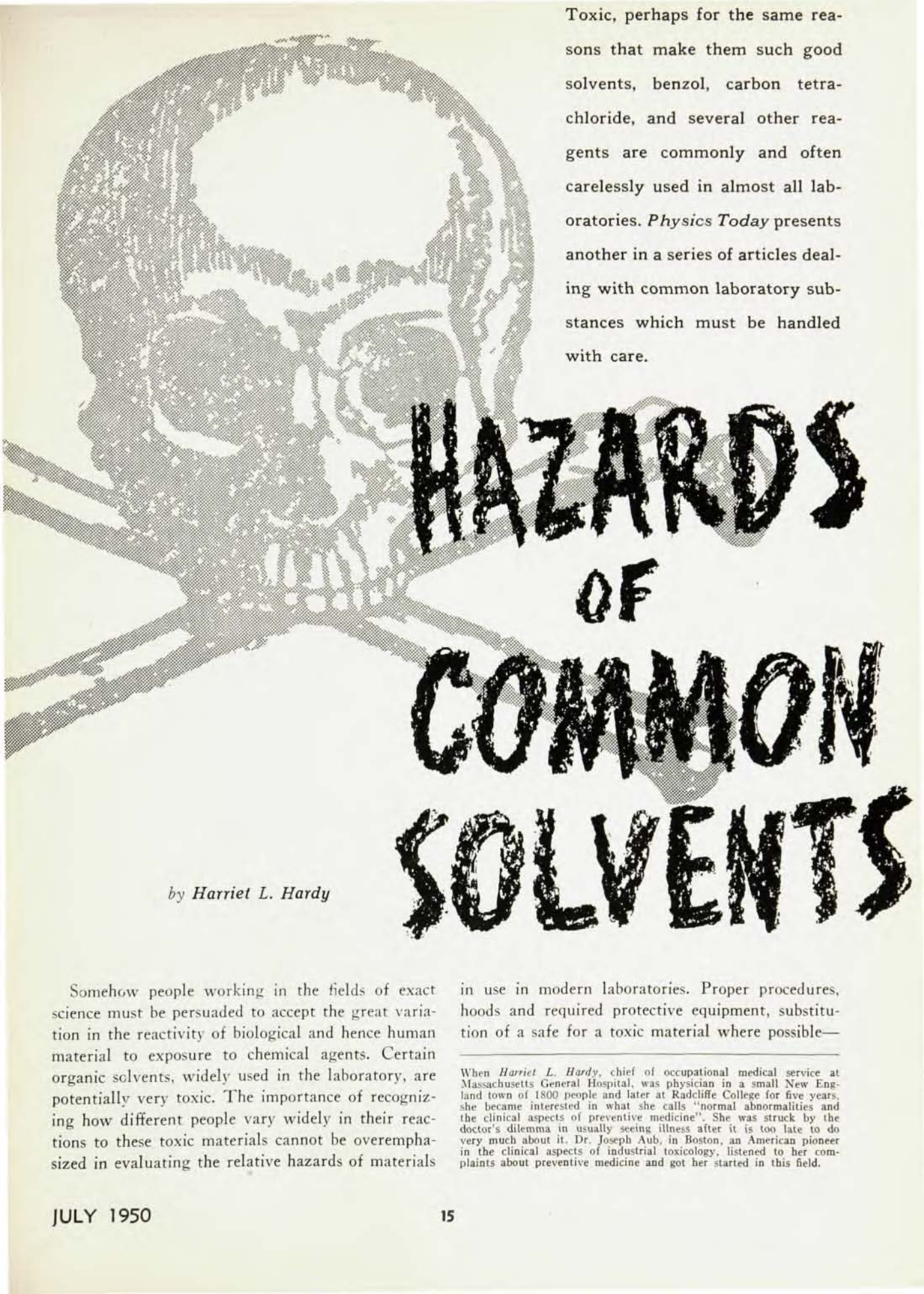


Toxic, perhaps for the same reasons that make them such good solvents, benzol, carbon tetrachloride, and several other reagents are commonly and often carelessly used in almost all laboratories. *Physics Today* presents another in a series of articles dealing with common laboratory substances which must be handled with care.



HAZARDS OF COMMON SOLVENTS

by *Harriet L. Hardy*

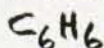
Somehow people working in the fields of exact science must be persuaded to accept the great variation in the reactivity of biological and hence human material to exposure to chemical agents. Certain organic solvents, widely used in the laboratory, are potentially very toxic. The importance of recognizing how different people vary widely in their reactions to these toxic materials cannot be overemphasized in evaluating the relative hazards of materials

in use in modern laboratories. Proper procedures, hoods and required protective equipment, substitution of a safe for a toxic material where possible—

When *Harriet L. Hardy*, chief of occupational medical service at Massachusetts General Hospital, was physician in a small New England town of 1800 people and later at Radcliffe College for five years, she became interested in what she calls "normal abnormalities and the clinical aspects of preventive medicine". She was struck by the doctor's dilemma in usually seeing illness after it is too late to do very much about it. Dr. Joseph Aub, in Boston, an American pioneer in the clinical aspects of industrial toxicology, listened to her complaints about preventive medicine and got her started in this field.

all provide means for safe work. Scientists working with these materials must, however, know the dangers. Familiarity should breed caution.

Benzene (Benzol)



Benzene (C_6H_6), an aromatic hydrocarbon, is better named benzol to distinguish it from benzine, a paraffin hydrocarbon of low toxicity. Benzol is a very toxic material, widely used because it is an excellent solvent of high volatility, of low cost, and is easy to get. Because of its properties as a solvent it is highly prized by industry in the manufacture of rubber cement, artificial leather, and paint remover. Certain gasolines for internal combustion engines contain a high percentage of benzol. Many research laboratories at times use benzol in relatively large amounts for cleaning, and for the recovery of certain organic materials. This writer cannot recall ever being in a laboratory—industrial, basic research, student, or hospital—where benzol could not be found. Because most paint removers contain from five to fifty percent benzol, this toxic hydrocarbon is found in homes in connection with interior decorating or redoing antique furniture, in adult education classes, and in art museum workshops.

In this country medical knowledge of ill effects due to benzol dates back to World War I when the German supply of coal tar solvents was cut off. American coal by-products plants were then built to supply phenol and toluol for explosives and as a consequence benzol was produced. From the experience of the early days of benzol manufacture when very heavy exposures (up to as high as 1 part per 1,000 of air) were allowed because of ignorance, it is known that acute benzol effect is a narcotic one accompanied by confusion and unconsciousness which may lead to death. Such exposures have not occurred except by rare accident for years. The more recent use of benzol in industry, involving lower level exposure, has been more apt to produce chronic benzol poisoning which is characterized by less immediately acute illness but still too frequent fatalities.

From human experience and animal experimentation we know that about half of the benzol absorbed in the blood (about 30 percent of that inhaled) is excreted and the other half is fixed in the bone

marrow, fatty tissue, and liver. The toxic effect of the benzol comes from its action on the bone marrow where blood cells of all varieties are formed. The resultant clinical picture of repeated benzol exposure of sufficient quantity over a sufficient period of time is anemia of varying character and severity. Here must be emphasized the great variation in individual reaction to the toxic effect of benzol and the frequent delay in onset of illness after leaving benzol exposure.

A famous case, presented by Dr. F. T. Hunter, shows how insidious benzol poisoning may be. A woman telephone operator used a small amount of paint remover to clean her switchboard daily for six years. After her death, caused by an anemia which did not respond to treatment, it was discovered that the paint remover which this woman used contained 50 percent benzol. I was recently consulted in the case of an artist who had used paint remover to clean and renew old canvasses bought abroad. Here death followed acute leukemia, a form of malignancy of the white blood cells believed to be caused in a few cases by benzol. The experience of a small artificial leather plant where a benzol containing dope has been used off and on for years also provides another illustration of the delayed and unpredictable toxic effect of benzol. Of seventeen men studied after exposure from four to twelve years in length, one man died, one gave evidence of benzol effect by symptoms and changes in his blood count, four had blood count changes with no symptoms, and the others were free of abnormal findings.

The clinical picture and abnormal postmortem findings in fatal cases of benzol intoxication are similar to the findings following harmful doses of radiation. The variations in severity of benzol effect may depend on such factors as chronic hemorrhage which calls for bone marrow activity, intake of drugs affecting the blood-forming organ, or excessive radiation. These points are brought up to urge the necessity for absolutely minimum exposure to benzol since the bone marrow with its blood-forming function is a vital organ.

There are many ways of controlling the benzol hazard, especially for laboratory workers. First, it may be possible to use a material of lower toxicity such as methylene chloride or naphtha. Parenthetically, householders working with paint removers should know that they can obtain these agents benzol-free on demand. In operations where benzol

must be used, proper ventilation can be planned if air analysis shows there to be more than 35–50 parts of benzol per million of air in the worker's breathing zone. If an operation is under scrutiny as potentially toxic, the urine sulfate test designed by Shrenk and his co-workers may be used to evaluate the danger. (See *Journal of Industrial Hygiene and Toxicology*, 18, 69, 1936.) This test takes advantage of the fact that benzene is oxidized in the body to phenolic derivatives which are found in the urine conjugated with sulfate radicles. The percentage of inorganic sulfates decreases, and that of the organic sulfates increases, if benzol has been absorbed to any degree. The test is useful if done immediately following benzol exposure but like all tests cannot be relied on completely.

Finally, if laboratory workers are to have definite benzol exposures of measurable amounts or have had indefinite past exposures, medical examinations with complete blood study at appropriate intervals are wise preventive steps. These measures are similar to current procedure in health protection of workers exposed to low level radiation—benzol air analysis being comparable to physical monitoring. If the benzol exposure ceases short of an unknown damaging dose, all blood count changes reverse and the patient never develops symptoms. Should the margin of safety be passed, there is unfortunately no treatment available for the bone marrow depression and destruction caused by benzol. Fatal anemias and leukemias have been far too common in those workers exposed to small as well as large amounts of benzol to regard lightly even slight or intermittent contact with this useful and dangerous hydrocarbon.

Carbon Tetrachloride CCl_4

This very familiar chlorinated hydrocarbon is, like benzol, in wide use because of its properties as a good solvent with high volatility, low cost, and noninflammability. The public knows carbon tetrachloride (CCl_4) as a household cleansing agent although often the material bought in a mixture under a trade name bears no label warning the user of its presence and toxicity. The United States Public Health Service lists thirty-five such products. Fire extinguishers for home, automobile, and modern fire fighting equipment are usually filled with

carbon tetrachloride. In small and large industries carbon tetrachloride is used as a dry cleaner, grease remover, type cleaner, spotting agent, and rubber solvent. Hospital and biological research laboratories use carbon tetrachloride in recovering certain organic materials such as steroids. Miscellaneous uses that have been studied are cleaning photographic film, jewelry, gas masks, motors, nozzles, as well as the operations of gasoline tank cementing, balloon cementing, carburetor jet testing, multi-graphing, cement mixing. Because fires are so feared in atomic energy development laboratories, carbon tetrachloride is often used for cleaning metal parts and glassware. In fact, in my experience, every scientific laboratory contains some carbon tetrachloride. These laboratory users of carbon tetrachloride vary greatly in knowledge of its toxic properties with resultant caution or casualness in labelling, pipetting by mouth, pouring, and heating under hoods or in the open laboratory. Stock room personnel are for the most part informed and respectful of the hazards of handling this solvent.

Knowledge of the biological effects of carbon tetrachloride arose in large part from its medical use for hookworm and other intestinal parasitic infestation. As little as one teaspoonful by mouth has been fatal to an adult so that carbon tetrachloride is no longer used as a drug. Mistaking cleaning fluid in medicine closets for safe mixtures, using fire extinguishers in a closed space such as a clothes closet or automobile, cleaning clothes in small, poorly ventilated basement rooms have caused sudden deaths. Coroners have been so often involved in such cases that most public health officials have become keenly aware of the hazards of using carbon tetrachloride and only recently the *New York Herald Tribune* reported that cleaning fluid killed two people in twenty-four hours in Westchester County, bringing to four the number of local victims from that cause in six weeks! Dr. David M. Spain, Westchester County Medical Examiner, issued a warning, cautioning that cleaning fluid be used only in well-ventilated areas, that spilling on skin or inhaling the fumes be avoided, and that susceptibility to such poisoning varies greatly, being especially marked for obese persons and those suffering from diabetes or alcoholism.

One of the victims, a garage worker, died after using the fluid to clean automobile upholstery; another, a maid, was cleaning curtains. From such

evidence, as well as experimental study, it is clear that the chemical may enter the blood stream by inhalation or through the intestinal tract and that short intense exposures, often of apparently small doses, are treacherous. Short, continuous exposures may produce serious irreversible pathology with vague early symptoms followed by later fatality.

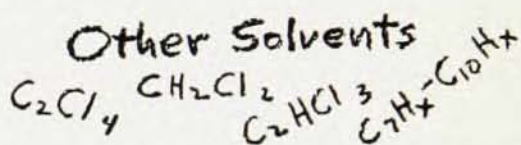
Carbon tetrachloride can produce damage in the eyes, intestinal tract, lung, liver, and kidney. As a result the symptoms the victim complains of vary with the system affected. Most frequently headache, nausea, and dizziness precede by hours or days the more serious jaundice, hemorrhage from lung or intestinal tract, and kidney shutdown indicating serious damage in the particular organs involved. The size of the dose of carbon tetrachloride is obviously a decisive factor, and if exposure ceases with the warning subjective reaction of headache and nausea the pathologic changes set up by the toxic material are reversible.

Clinical experience and animal study have shown that a high intake of alcohol coincident with carbon tetrachloride exposure or a low protein diet will greatly increase the toxic potential of the material. A good example was cited by W. J. Perry who, in reporting on eighty-eight cases of carbon tetrachloride poisoning in the *Army Medical Bulletin No. 64, p. 71, 1942*, told of five men severely poisoned by the solvent with which they had cleaned their rifles in a closed barracks-room. The two men who died were heavy periodical drinkers. This emphasizes again the variation in reaction of individuals to identical insult and in most instances the explanation is not so clear as it is in the case of the synergistic action of carbon tetrachloride and alcohol. Such data are further clear reason for the urgency of not depending on the use of small amounts of carbon tetrachloride since the fatal dose or that required to produce symptoms and perhaps permanent damage is low and unpredictable from worker to worker.

Carbon tetrachloride poisoning can be prevented readily with the facts at hand. First, it is often possible to substitute trichloroethylene or perchloroethylene. Stoddard solvent can be used if rapid evaporation is not necessary and complete noninflammability essential. Warning labels of arresting size and design should certainly be on all carbon tetrachloride containers in the laboratory and in the home. Because of the high volatility of carbon tetrachloride, air analysis in the worker's breathing zone is very

useful in determining the hazard of any operation. Experience has shown that at about and below 40 parts of carbon tetrachloride per million of air, workers experience no discomfort and hence probably no damage during continuous operations. If higher working concentrations must be developed, operations need to be completely enclosed. There is no routine biological test in current use to determine undue absorption of carbon tetrachloride. If symptoms do arise, however slight, medical study of visual status, liver, gastro-intestinal tract, and kidney function are in order since individuals vary so in their reporting of subjective symptoms and may show evidence of damage with few complaints.

Physicians, public health officers, industrial toxicologists view the use of carbon tetrachloride in any quantity with alarm. Wherever possible another material should be used. When this is impossible, all those potentially exposed should be thoroughly warned as to the danger involved in the use of carbon tetrachloride and protected by proper engineering devices.



Methylene chloride (CH_2Cl_2) has been mentioned as a substitute in certain operations for benzol. At high air concentrations methylene chloride may be expected to act as a narcotic like an anesthetic such as ether. There have been no reports of harmful effect from human exposure or animal study. Since this material has as yet been little used, the recommendation at present is that a safe level of air concentration is 200 parts of methylene chloride per million parts of air. This figure, probably lower than necessary, means that it is about five times as safe to handle as benzol, the safe breathing figure for which is 35-50 parts per million of air.

Trichloroethylene (C_2HCl_3) and tetrachloroethylene (C_2Cl_4), commonly called perchloroethylene, are similarly recommended as substitutes for carbon tetrachloride. At high levels these organic materials can cause headache, dizziness, nausea, confusion, staggering gait, and, if exposure continues, unconsciousness and even death. The action is, again, anesthetic-like. Occasionally in large industrial degreasing operations accidental over-exposures result

in fatalities. However, in laboratory scale usage these materials have proven entirely safe and useful substitutes for carbon tetrachloride. The allowable continuous worker's breathing concentration is considered 150–200 parts of the solvent per million parts of air which gives a large margin of safety over the safe average level of 50 parts per million of carbon tetrachloride in air. Mild subjective symptoms due to trichloroethylene or perchloroethylene are believed transient without any damage to the individual and merely serve as a warning that engineering steps must be taken to make a comfortable working environment.

The naphtha (C_7H_x – $C_{10}H_x$) here referred to is one of the paraffin hydrocarbons which is often called varnish makers' or painters' naphtha. With benzene and petroleum ether it is obtained from natural gas and petroleum. The hazard of fire limits the usefulness of this material, but it is often used where solvents are needed. In high concentrations naphtha is irritating to nose and throat and, in concentrations of 1,500–3,000 parts per million of air, dizziness, faintness, and other symptoms of anesthetic action are reported. Breathing zone levels of 500–1,000 parts of naphtha per million of air are considered safe and comfortable working concentrations. This gives a safe margin of ten times over benzol in situations where naphtha's

inflammability can be managed.

You can see that there is a considerable body of knowledge available through industrial and medical experience of the toxic effects of certain commonly used organic materials. Because of the unpredictability of human reactivity within a wide spectrum, relatively safe materials should be substituted for the more toxic solvents whenever possible.

When this cannot be done, engineering devices can be planned to keep air concentration in the worker's breathing zone at safe levels. Medical examinations are often necessary to detect early changes due to toxic exposures or to make a correct diagnosis if unusual symptoms arise coincident with even remarkably slight exposures to such materials as benzol and carbon tetrachloride.

Certainly atomic energy development laboratories, with their excellent worker health record, are proof that any operation with any material, however dangerous, may be undertaken with safety if those concerned are willing to take the steps necessary to insure protection. In this day of expanding laboratory activity it is relevant to urge that those in charge provide the same scrupulous attention to toxic chemical exposures as is currently lavished on all radiation exposures. This is especially so in view of the fact that knowledge is available with which one can prevent illness and fatalities following such exposure.

Material	Maximum allowable concentration	Evidence of acute effect	Evidence of chronic effect	Available methods of exposure detection
benzol or benzene C_6H_6	35 parts per million of air	headache dizziness narcosis	various types of anemia, leukemia	air analysis urine sulfate test (ratio of inorganic to total sulfates) (normal range 80–95% minimum allowable value 70%) medical examination
carbon tetrachloride CCl_4	40 ppm	same and visual disturbances, intestinal symptoms and renal symptoms indicating liver or kidney failure	intestinal symptoms especially nausea and loss of appetite failure of liver may result	air analysis medical examination including liver and kidney function tests
methylene chloride	200 ppm	headache dizziness narcosis	no knowledge of ill effects from chronic exposure available	air analysis
trichloroethylene or perchloroethylene	200 ppm	irritation of nose and throat anesthesia	no knowledge of ill effects from chronic exposure available	air analysis urine analysis for volatile organic chloride (results of test often not dependable, seldom used)
naphtha, petroleum	1000 ppm	irritation of nose and throat anesthesia	no knowledge of ill effects from chronic exposure available	air analysis

Dr. Hardy cautions that compressing information in a summary such as this has the disadvantage of possible over or under interpretation. The text treats all these points more fully and the interested reader is referred to a recent book by H. B. Elkins, The Chemistry of Industrial Toxicology, John Wiley and Sons, New York, 1950.