TOXICITY OF
INDUSTRIAL ORGANIC SOLVENTS

Revised in consultation with the Toxicology Committee

By ETHEL BROWNING

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Corrigendum

On pp. 71, 73, for " bitumastic " read " bitume-mastic " (from the original French of des Essarts). It is understood that " Bitumastic " is a proprietary name and registered Trade Mark throughout the world and should therefore not be confused with " bitume-mastic " nor used in any sense as a generic term.

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PREFACE TO THE SECOND EDITION

IN response to a request from the Home Office in 1935, the Council undertook to investigate the possibility that various volatile substances, used industrially as solvents and often in enormous quantities, might injure the health of the workers handling them. A special Committee on the Toxicity of Industrial Solvents, under the chairmanship of Sir Joseph Barcroft, was appointed to advise on this matter.

At the time when the Committee was formed, there was, to quote the Preface to the First Edition of this Report, "a clear need for research into the possible effect of substances that seem open to suspicion, either through having a chemical constitution closely allied to that of compounds already proved to be dangerous or through complaints of ill-health among those who constantly use them. As a first step, however, it was plainly desirable to take stock of existing knowledge of the subject."

The Committee therefore asked Dr. Ethel Browning to compile a summary of the available information on such solvents as were then in general use. Issued in 1937 as No. 80 in the Council's Series of Industrial Health Research Board Reports, it was almost the only publication of its kind in existence and, although not exhaustive, was for practical purposes sufficiently detailed to show the extent of the problem and to indicate the most suitable points of attack. Requests for copies came from all parts of the world, and the demand continued for some years after the edition had gone out of print. Consequently, in 1946 it was decided that the Report should be re-issued, having first been revised and also enlarged to include those solvents which had come into use since the first edition was prepared. Fortunately, Dr. Browning was willing to undertake the formidable task of revision, and the Council would like to take the opportunity of expressing their thanks to her for the care with which she has completed it.

The original Committee had not met during the War, and the responsibility for supervising the new edition, on which Dr. Browning was already working, fell to the Toxicology Committee, appointed in 1947 under the chairmanship of Professor G. R. Cameron. In discussing what additions or changes might be made, the Committee decided that the new edition, like the old, should be limited to substances used primarily as solvents, and that the Report should retain its original form as a compendium of information rather than attempt a critical review of the published literature.

In recent years a number of new books dealing with industrial toxicology have been published. Most of them cover a wider field than this Report, but do not deal so comprehensively with the industrial solvents. This new edition, with its extensive bibliography covering the years up to 1948, should be a valuable source of references for medical officers and others responsible for the health of workers concerned with the manufacture, transport and use of organic solvents.

MEDICAL RESEARCH COUNCIL,
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TOXICITY OF INDUSTRIAL ORGANIC SOLVENTS

INTRODUCTION

THE following Report summarizes the existing available information about the effects on animals and man of the various solvents used in industry. The literature from which the Report has been compiled is widely scattered in various books and scientific periodicals, and although much trouble has gone towards its composition, completeness of the references cannot be vouched for. Moreover, new work is being published at frequent intervals, and the bibliography must rapidly cease to be up to date.

The main object in the collection and publication of these data is the avoidance of poisoning from the use of these solvents, some of which are used on a vast scale in industry. To suggest the ease with which intoxication could occur, and to emphasize the importance of finding appropriate measures for its prevention, the following figures are quoted from statistical records. The Annual Abstracts of Statistics shows that in the United Kingdom in 1950 the consumption of ethyl alcohol as 68 O.P. spirit was 36·8 million gallons; that of methyl alcohol was 72,000 tons. The Ministry of Fuel and Power's Statistical Digest records that, in 1951, the total production of different fractions of benzol, excluding motor and aviation spirits, was 15·2 million gallons, of which 9·2 million gallons were the 'pure' solvent; the total production of toluol was 8·7 million gallons, of which 4·9 million gallons were 'pure'. Similar figures for other solvents are not readily available, but these few are surely impressive enough to indicate the need for investigation.

It is often difficult to determine, should illness occur in a worker or group of workers, whether or not this is due to the toxic action of chemical agents, and, if so, which particular agent is responsible. This difficulty is often increased by the slow development of symptoms which may occur after prolonged or intermittent exposure to low concentrations. The direct method of determining the possible and relative toxicity of a substance to man is by experiments with that substance on man himself, under conditions as nearly as possible parallel to those under which a worker is exposed. Experiments on man, however, are not justified, and the indirect method using experiments on animals in the laboratory must therefore be adopted.

Owing to the expense and difficulties of housing large animals, preliminary investigations are nearly always made on large numbers of small animals, although no general rules can be laid down which relate the sensitivities to poisons of small rodents and of man. There are many poisons which produce completely different effects in different species of animals, but it is very exceptional for a substance which is toxic to various species of rodents to be innocuous to man, and vice versa. It is to be anticipated that there will exist qualitative and quantitative differences in response to any poison between man and the lower animals, just as they are known to exist between different species of lower animals themselves. Nevertheless, there can be no doubt that experiments on small animals are of value in giving an indication of the type of toxic action as well as the relative toxicity of the substance under investigation. Thus the fact that butyl cellosolve (ethylene glycol mono-*n*-butyl ether) is five times as toxic to mice as ethylene glycol at least gives a warning that the former compound may have greater potential dangers for man than the latter.

In attempting to relate experimentally determined effects on small animals to probable or suspected effects on man, certain factors have to be taken into consideration. The first of these is the size of the animal. As regards the systemic actions of poisons, depending as they do mainly upon the concentration of the poison which occurs in the blood and tissues, it is generally true that a given amount of poison will produce greater effects in a small than in a large animal. No entirely satisfactory method is known for correlating accurately dosage and body weight, but a useful approximation is obtained by the usual method of stating the dosage as per kilogramme of body weight; however, it will be readily understood that if the minimum lethal dose of a solvent for a rat weighing 0·2 kg. is 1 ml., it does not follow that the corresponding dose for a man weighing 70 kg. will be 350 ml. Even such an approximate relation does not hold good for the local effects of poisons, before they are absorbed. For example, a given concentration of a volatile solvent in air may produce local effects on the lungs, the intensity of which bears no relation to the weight of the animal.

It is now known that individual variation is found in response to all drugs and in all populations of animals. Measurements of toxic effects on animals usually express the average or median toxic dose or concentration, i.e., the quantity that produces the observed effect in half the population studied. Unfortunately the range over which individual variation is scattered differs widely in the case of different drugs. Some individuals will be less, some more, sensitive to a toxic action than the majority. This is of especial importance in human beings when it is necessary to avoid producing toxic effects on any particular individual. There is also the important question of exceptional sensitivity or idiosyncrasy to poisons. It has been found that certain drugs, which have been widely used for many years without apparent danger, can nevertheless produce very serious toxic effects in certain exceptional individuals. It is possible that cases of personal idiosyncrasy would occur with all drugs though they may be only recognized with those that are widely used. Similar cases of idiosyncrasy will no doubt arise from the use of substances in industry, and slight signs of intoxication occurring with any new solvent should consequently be regarded seriously, even if other individuals have sustained greater exposure without any apparent injury.

Consideration of the available literature on the actions of solvents has shown that many experiments have been made with little direct relation to the conditions that may possibly occur in industry. For example, the effect of the subcutaneous injection of a large dose of substance may be entirely different from, and have little bearing upon, the effects which may be produced by prolonged inhalation of small quantities. The Committee had some hesitation in including an account of such experiments, but for some substances they were the only ones available. The results have therefore been included partly for completeness and partly for such evidence as they afford.

One other difficulty should be mentioned. The number of chemical compounds used as solvents is large, but unfortunately the number of proprietary names is much larger, and a toxic substance may be concealed under such a name. It has not been possible to give a glossary of proprietary names, and although many are mentioned in the text and appear in the index, this report will, in general, only be of service in judging the safety of a solvent in those cases where the chemical composition of the solvent is known.

CHAPTER I

HYDROCARBONS

1. Benzene

(Benzol)

C_6H_6, i.e. 

PROPERTIES

BENZENE, or benzol, a hydrocarbon of the aromatic series, and a coal tar product, is to be carefully distinguished from benzine, a mixture of varying and uncertain proportions of hydrocarbons, chiefly hexane and heptane, which is a distillate of petroleum.

A certain amount of confusion has arisen from time to time in reports of cases of toxic injury due to benzine, e.g. the case of fatal aplastic anaemia in a cellulose sprayer in 1934 (Special Article, *Lancet*), in which the toxic agent was referred to as benzine, when benzol was meant. Simonin (1934) points out that the distinction between benzene and benzine is not merely one of theoretical importance. He quotes as an instance the occurrence of a severe collective intoxication in a boot factory in 1932, involving forty-four workers, eight of whom died, caused by the misinterpretation of an order for benzine, benzene being delivered instead (Merklen and Israël, 1934).

The effects of chronic poisoning by these two substances, especially with regard to the blood picture, are clearly distinguishable, while the acute narcotic effect of benzine on animals has been shown to be less than half that of benzol (Bamesreiter, 1932).

It has been suggested by some French workers, notably Duvoir (1922), that benzine should be called *petrol essence* and that the word *benzinism* should be replaced by *petrolism*.

Benzol is graded commercially as crude or refined, according to the percentage which distils below 100° C. *Pure benzol* should be the pure substance strictly designated as *benzene* (C_6H_6), B.P. 80° C., Sp. Gr. 0·884 at 15° C., M.P. 5° C., soluble in water to the extent of 0·082 g. per 100 ml. at 22° C. It is an excellent solvent for rubber, gums, resins, and fats of all kinds. *Commercial benzol* is practically never pure; it contains traces of xylene, toluene, phenol, thiophene, carbon disulphide, acetonitrile, and, according to Ellis and Meigs (1921), probably pyridine, and many other substances. (For method of analysis see Gooderham, 1935). A process for removing thiophene by the action of acidified hypochlorite solution with only a small attendant loss of benzene has been described by Ardagh and Bowman (1935). There are three usual commercial types.

(*a*) *Commercial crystallizable.* 100 per cent benzene, B.R. 80–81° C., Sp. Gr. 0·879 at 20° C. This variety appears to produce very severe toxic effects, many cases of poisoning having been reported from its use. A typical example is the series recorded by Heim de Balsac and Agasse-Lafont (1933), of which eight cases were fatal, and by Merklen and Israël (1934) who describe their cases as "haemorrhagic aleukaemia" from the use of crystallizable benzene. These investigators urge that the use of crystallizable benzene should be prohibited.

(*b*) *Commercial 90 per cent benzol.* 90 per cent by volume distils below 100° C. It contains 13–15 per cent toluene, 2·3 per cent xylene, and sometimes, traces of olefins, paraffins, sulphuretted hydrogen, and other bodies.

(*c*) 50 *per cent benzol.* 50 per cent of constituents distil below 100° C. and 90 per cent below 120° C.—a highly mixed product.

The usual *commercial* 90 *per cent benzol* is a colourless, mobile, refractive liquid, with a not unpleasant odour. It burns with a luminous but smoky flame; it is extremely volatile, especially if slightly heated. Its relative time of volatilization compared with that of ethyl ether is 3 : 1 (I. G. Farbenindustrie, 1930). It is a good solvent for a number of cellulose esters and ethers, especially ethyl cellulose, for most oils, ester gums, benzyl abietate, copal ester, coumarone, benzyl resin, and many other resins. It does not dissolve cellulose acetate or nitrate, copal, or shellac.

MANUFACTURE

Benzol is given off during the distillation of coal in a closed vessel, part remaining in the tar and part occurring in the gas. The chief means of recovery is by "stripping" the benzol from the coke oven gas, a method which has of recent years largely superseded distillation of the tar from gas works and coke ovens. During 1934, of the total production of crude benzol at coke ovens, gas works, low temperature carbonization works and tar distilleries, about 80 per cent was obtained from the gas, and 20 per cent from distillation of tar (Secretary for Mines, 1934).

A full description of the distillation method was given by Lehmann (1910) and of the "stripping" process in the Final Report on Benzol of the National Safety Council (1926).

USES AND APPLICATIONS

The use of benzol received a great impetus during the 1914–18 war, and since that time its extension has been wide and rapid. While in 1922, 68 million gallons were used in America, by 1928 the figure had reached 115 million gallons (McCord, 1929). During the 1939–45 war, benzol was again increasingly used owing to the scarcity of other solvents.

Benzol may be regarded as having two more or less distinct fields of application in industrial processes:

(*a*) Where it is handled in large quantities in closed mechanical systems.

(1) The distillation of coal and coal tar in the production of benzol.

(2) The blending of motor fuels.

(3) The chemical industries, including oil extraction, the manufacture of dyes and dye intermediates, paints, varnishes and stains, and paint and varnish removers.

(*b*) Where it is used as a solvent or diluent.

(1) The rubber industry, in solutions for rubber cement in the manufacture of straw hats, cardboard boxes, waterproof goods, shoes, cameras, and the sealing of cans; in the manufacture of rubber tyres, the metal case on which the tyre is built being usually coated with rubber cement in which considerable quantities of benzol are used.

(2) The manufacture of artificial leather; textiles are spread with a coating of a viscous liquid consisting essentially of a solution of nitrocellulose, benzol in amounts up to 60 per cent being added as a diluent.

(3) In the dyeing and cleaning industry for degreasing, mordanting and removing grime from clothing and other articles; also generally for cleaning

purposes in workshops. In many dyeing and cleaning establishments, however, other solvents have largely replaced benzol.

(4) In the paint and varnish industry as a diluent for lacquers, a constituent of quick-drying paints, in bronzing and gilding pottery, in varnishing reservoir vats, ships, motor cars, etc., and in floor and woodwork stains and floor waxes.

(5) In the aviation industry as a constituent of the dope solution, to the extent of about 20 per cent.

(6) In the linoleum and celluloid industries.

(7) In artificial manure and glue manufacture.

(8) In electrical fitting and accumulator works.

(9) In chemical laboratories as a solvent.

(10) In the alkaloid industry for the extraction of atropine, hyoscine, codeine, etc.

(11) In the photogravure printing process.

BENZOL VAPOUR

Concentration in Air of Factories

The actual concentrations of benzol in air to which workers have been exposed have been found to vary greatly. The earliest figures, given by Lehmann (1910), ranged from 25 to 106 p.p.m. of the air in benzol washing and distillation plants. Legge (1919–20) found the quantities in the atmosphere of a balloon fabric spreading room to range from 210 to 1,050 p.p.m. in different parts of the room, and in a pneumatic tyre manufacturing room from 800 p.p.m. with an exhaust fan in operation to 2,800 p.p.m. with the windows open. In a Milan raincoat factory, where three fatal cases occurred, Pugliese (1922) found 1,000 p.p.m.; in the printing works referred to by Saita and Dompé (1947) they found the concentration of benzol varied from 188 to 908 p.p.m. In the National Safety Council Report of 1926, examination of the air of 18 different workrooms, representative of the various processes in which benzol is used in rubber, artificial leather, wire insulating, dry cleaning, and sanitary can manufacture, revealed a very wide variation of its benzol content, 0 to 4,140 p.p.m., the latter in a dry cleaning process during the summer when no other solvent than benzol was used. It should be noted that the method used for the estimation of benzol in the survey failed to distinguish between benzol and other solvent vapours such as alcohol, methyl acetone, etc., but the figures for solvent vapours were all computed in terms of benzol. These studies brought out the importance of local exhaust ventilation in reducing the atmospheric content of benzol. The Report concludes that "rooms in which benzol is evaporated into the air without local exhaust ventilation will in most cases show high concentration of the fumes in the air of the rooms. With ideal local exhaust ventilation on the other hand even large quantities of benzol can be used without heavy atmospheric contamination". After the occurrence of two fatal cases in Edinburgh in 1918, it was found that without ventilation the concentration of benzol in the room reached 16,800 p.p.m., and with 30 changes of air per hour was reduced to 550 p.p.m.

Risk of Explosions

The vapour of benzol, which has a flash point (Fl.P.) of 10° F. (−12° C.), forms an explosive mixture with air in proportions from 5 to 8 per cent. Escape of the vapour or liquid may occur through faulty design of the plant or faulty ventilation, and ignition may be produced by the presence of naked lights, the

production of sparks by the use of tools or appliances, such as electric fans and motors, and by iron-shod boots on stone floors, trolley wheels, etc. Precautions to avoid these dangers are described in the Chemical Works Regulations Reg. 4 b (1922), also in *Safety Circulars* Nos. 29, 43, and 51 of the Association of British Chemical Manufacturers (1929, 1931) and in *Quarterly Safety Summary* (1930, 1931, 1932).

Concentration in relation to Toxic Effects

The maximum allowable concentration above which toxic symptoms may be expected to occur was estimated by the National Safety Council (1926) as 100 p.p.m., and this figure was again taken by the American Standards Association in 1941. It has been suggested by Greenburg and Moskowitz (1945) with regard to the war-time use of benzene as a solvent for synthetic rubber that 50 p.p.m. is a safer desirable maximum, since, they state, "death may occur with exposures to only 25 p.p.m., and at least one such case has been observed". The concentration which produces fatal results in a very short time appears to be 19,000 to 20,000 p.p.m. In a report made by McNair to the Home Office* on a fatal case of benzol poisoning occurring in 1930, he states that to form a mixture which would be fatal would require 2 volumes in 100 of air, representing 7 oz. of benzol per 100 cubic feet. He also states that 1 volume in 100 of air can be recognized by smell, while *Safety Circular* No. 51 states that more than 1 mg. per l. (0·029 per cent) is necessary before the smell is distinctly perceived.

The concentrations of benzol and their effects and time of exposure (Table 1) are taken from the table drawn up by Sayers and Dallavalle (1935).

TABLE 1

Effects from different concentrations of benzol vapour

Concentration in air (p.p.m.)	Effects
19,000	Fatal in very short time
3,000	Dangerous with exposures of ½ to 1 hour
3,130–4,700	Maximum concentration for exposures of ½ to 1 hour
1,570–3,130	Slight symptoms with exposures of several hours
100	Maximum concentration allowable

More recently (1949) the standard limit suggested has been lowered to 35 p.p.m. (Congress of American Hygienists).

Estimation in Air

Numerous methods for the determination of the amount of benzol in air have been described. The majority of the earlier ones are reviewed by Tausz (1924) and include the nitration method, introduced by Harbeck and Lunge (1898), used by Lehmann (1910) and adapted by Smyth (1931) for concentrations as low as 30 p.p.m., and the method of activated charcoal considered superior to all others by Tausz himself, and used by the National Safety Council in 1926. More recent methods include those of Ficklen and Cook (1933) and of

* References to cases reported to the Home Office are taken from confidential records, to which the author had access, of the Factory Department, Home Office, later transferred to the Ministry of Labour and National Service.

Cook and Ficklen (1935); the former, the pernitric method, has since been found not applicable because of the interference of toluene; the latter, the oxidation method with peroxide in presence of iron salts, is described below. A simple test, involving the absorption of the benzene vapour in formaldehyde–sulphuric acid, has been devised by the Department of Scientific and Industrial Research (1939).

(1) *The nitration method.* The method described by Smyth (1929) consisted in catching the benzene vapours in a mixture of sulphuric and nitric acids, neutralizing, separating the dinitrobenzene formed in the acids by steam distillation from a buffered solution when toluene was present in the air, and then titrating the nitro compound with titanous chloride. This method was shown to be 93·1 per cent correct for pure benzene vapour at 11,000 p.p.m., and 99·2 per cent correct at 200 p.p.m. In order to adapt the method for concentrations as low as 30 p.p.m., Smyth (1931) took larger samples of air for analysis than formerly, so as to obtain enough dinitrobenzene for titration. He found the method 99–100 per cent correct with pure benzene vapours at concentrations of from 30 to 585 p.p.m., even in the presence of various aliphatic alcohols and acetates. In the presence of not more than three times as much toluene as benzene, the accuracy was over 85 per cent down to a concentration of 30 p.p.m. of benzene.

It is pointed out by Cook and Ficklen (1935) that the method requires transportation of air samples to a central laboratory for determination of the amounts of benzene present. A modification of it is, however, described by Schrenk, Pearce and Yant (1935) by which small samples of air can be used and as little as 0·001 mg. of benzene can be determined, and further modifications by Dolin (1943), and by Duvoir and Fabre (1946). The latter claimed that a variation in the technique serves to distinguish benzene from toluene with an error of less than 10 per cent. The titrating reagent used is methyl ethyl ketone in a 40 per cent solution which gives a violet colour not given by the higher homologues of benzene. Dolin's technique has been still further elaborated by Milton (1945), making the reaction still more specific for benzene in the presence of xylene and toluene.

(2) *The activated charcoal method* (National Safety Council 1926). Special precautions to render the sampled air moisture-free before passing it into the charcoal absorption tube consisted in the provision of a first tube filled with soda-lime for the absorption of acid vapours and a second with calcium chloride for absorption of water vapour. The charcoal tube itself contained approximately 7 g. of 8–14 mesh activated charcoal. The charcoal was also dried overnight in a constant temperature oven at 105° C. The charcoal tubes were equilibrated before use by the passage of compressed air, flowing at the rate of approximately 6 l. per minute, through a chain composed of the following elements: cotton-wool tube, soda-lime tube, calcium chloride tube, glass tubing manifold and six charcoal tubes. A sample of the air of the workroom, usually 20 l. in amount, was aspirated through the prepared charcoal, and the increase in weight of the charcoal was taken to represent the approximate amount of solvent vapours in the atmosphere sampled. Where benzol is the only solvent used, this increase in weight represents that due to benzol vapours only, but since the charcoal absorbs other solvent vapours also the method is not specific for benzol.

(3) *The oxidation method with hydrogen peroxide in presence of iron salts* (Cook and Ficklen, 1935). In this method the air to be sampled is streamed at the rate of 2 l. per minute on to the surface of glass beads in a U-tube packed round with solid carbon dioxide; the tube is later removed and immersed in hot water when the collected benzene is volatilized, passed through a bubbler unit containing 25 ml. of water for the removal of the more water-soluble vapours, and thence into a trap immersed in a solid carbon dioxide and acetone cooling bath, the benzene and a small portion of less water-miscible solvents being frozen out in the trap. For the estimation of the benzene, 5 ml. of 0·5 per cent ferrous sulphate followed by 2 ml. of 1 per cent hydrogen peroxide is directed down the inlet tube of the trap, the contents of which are then shaken and transferred to a test-tube. If benzene is present in an amount of 0·005 ml., a characteristic brown coloration is produced in 2 to 5 minutes; if in amounts of 0·010 ml. to 0·050 ml., a black amorphous precipitate also appears. Upon the addition of 1 ml. of 2*N* nitric acid the black amorphous precipitate will dissolve and the solution may then be diluted with water and compared with standards in a colorimeter.

A number of other solvents, having boiling points relatively near that of benzene (toluene, xylene, methanol, ethyl acetate, trichloroethylene, carbon tetrachloride, cellosolve, acetone) were tested, and did not give the reaction when no benzene was present. Carbon disulphide gave a greenish amorphous sulphur precipitate, which, if benzene is being simultaneously estimated, must be filtered from the solution after the addition of nitric acid, the benzene being then estimated from the coloration of the filtrate.

Ficklen and Cook (1933) observe that, owing to the complicated nature of the reaction, the method is only approximately quantitative, but sufficiently so to permit estimation of the concentration of benzene in air within the limits required in an industrial hygiene investigation.

(4) *The formaldehyde-sulphuric acid test* (Department of Scientific and Industrial Research, 1939). A sample of the air to be tested is drawn through a tube containing the reagent —concentrated sulphuric acid containing a trace of formaldehyde—by means of a hand pump of definite capacity. From the number of strokes of the pump required to produce the standard orange-brown colour, the concentration of benzene vapour present is obtained by reference to a given table. The colour with the formaldehyde–sulphuric reagent is also given by the vapours of toluene and of coal-tar naphthas. Crude benzols, which may contain compounds such as thiophene and unsaturated hydrocarbons, might give a slightly different, yellow or red shade of colour, but the quantities of such substances usually present in commercial grades of benzenes should not interfere with the comparision of the depth of colour of the reagent and standard.

(5) *The interferometer.* Data on the use and value of this instrument are supplied by the United States Bureau of Standards, and by the catalogue of the Arthur H. Thomas Co. It is stated (Answer to a letter, *J. Amer. med. Ass.*, 1935) that the instrument is of restricted value under many industrial circumstances, owing to the fact that benzene, benzine, naphtha, toluene, and xylene are rarely used as single entities, but as mixtures with various esters, acetates alcohols and glycols. This fact precludes any ready standardization of the apparatus to meet the diversity of vapour conditions likely to be encountered.

ESTIMATION IN BLOOD AND IN TISSUES

The chief methods of estimating the amount of benzol in the blood and tissues of animals or human beings subjected to exposure to benzol vapour have been described by Peronnet (1934).

(1) *Method of Lazarew, Brussilowskaja and Lawrow* (1931a, b). The benzol is extracted by a current of air flowing over a sample of blood, and the amount present in the air measured by the method described by Matveev, Pronin and Frost (1930), which consists in combustion of the air in an electric oven and titration of the CO_2 formed by conductivity.

(2) *Method of Gadaskin* (1928). The oxalated blood is nitrated by means of sulphuric and nitric acid and the *meta*dinitrobenzene formed is reduced to *meta*phenylenediamine, which by oxidation with dimethyl*para*phenylenediamine gives a violet colour.

(3) *Method of Peronnet* (1934). The benzol extracted from a slightly heated sample of blood is nitrated to *meta*dinitrobenzene, which is then diluted with distilled water, neutralized and rendered alkaline. Alcohol is added, followed by a solution of laevulose in 70 per cent alcohol and soda. The violet colour formed is compared in a colorimeter with that produced by a benzene solution of known concentration. This method is not applicable in the presence of xylene or toluene.

A modification of this method has been used by Koppenhöfer (1935) in estimating the benzol content of the blood and tissues in a fatal human case of benzol poisoning, and by Duvoir and Fabre (1946) in estimating separately benzene and toluene in the blood.

TOXICITY

As an acute poison benzene is a narcotic, producing severe, or even fatal, depression of the central nervous system. Its chronic toxic effect is that of injury to the bone-marrow, producing great variety in the blood picture, with the salient feature of aplastic anaemia.

It is clearly apparent, both from the study of cases of benzol poisoning in human beings, and from experimental work on animals, that acute and chronic benzol poisoning are two entirely distinct phenomena.

"In acute benzol poisoning the symptoms are due to a severely irritant and destructive effect upon the central nervous system, whereas in chronic benzol poisoning the relatively slight effects on the central nervous system are not at all comparable with the severity of the degenerative changes occurring

in the haematopoietic system. In acute poisoning benzol thus acts as a convulsive neurotoxin and later as an asphyxiant narcotic." (Batchelor, 1927.)

Chronic poisoning presents a wide variety of subjective symptoms, both in number and in degree of severity, and although the classical picture of anaemia of aplastic type is still the most widely recognized example of benzene poisoning, extensive investigations of recent years have tended to bring out the salient fact that this is by no means the invariable one. This concept of expected variation tends to alter the value of the criteria of benzene poisoning, or benzene absorption, such as those laid down in the Report of the National Safety Council on Benzol, 1926.

Toxicity in Industrial Processes

In the earlier literature, cases were reported with some frequency of acute, sometimes fatal, poisoning from swallowing benzol. Such were the two cases recorded in St. George's Hospital Reports for 1877–78, and those of Averill (1889), Simonin (1903) (in this case the patient survived, but developed swelling and oedema of the skin), Hetzer (1922), in which the poisoning was followed by intense toxic gastritis and later pyloric stenosis, and Nick (1922), in which recovery followed the injection of 5 ml. of a 10 per cent lecithin emulsion.

Although it has been stated by Hamilton and Johnstone (1945) that "acute benzol poisoning is of little importance under modern industrial management", owing to unforeseen imperfections of plant, or neglect of the precautions provided, severe and even fatal cases do occur. During the last seven years thirty-one cases, nine of them fatal, have been reported to the Factory Department. Most of the total number of fatalities recorded in the literature have been caused by the entry of workmen into tanks containing benzol, or having contained it at some time.

With regard to the possibility of reducing the incidence of acute benzol poisoning from this cause, Marian-Wolfen (1925) suggests certain measures for the cleaning of benzol containers. He states that removal of benzol residues from tanks is not possible by means of water alone, that in fact such a method increases the danger, since the benzol, being of comparatively low specific gravity and scarcely soluble in water, forms a layer on the walls of the vessel which is later vaporized. The passage of steam through the container, however, with the provision of several openings for the escape of the steam and volatilized benzol, and of an exit at the lowest level of the container for the escape of the benzol-containing water of condensation will, he claims, constitute an entirely successful procedure for cleaning out vessels containing benzol and removing the residue; this method should, if carried out universally, much reduce the danger of severe and fatal cases of benzol poisoning.

It may be mentioned, however, that though the number of acute fatalities has certainly decreased since the need for adequate protection has been realized and acted upon, one of the nine cases reported to the Factory Department occurred in 1945 during the steam-cleaning of a condenser, the procedure advocated by Marian-Wolfen.

According to Pfeil (1932), cases of poisoning reported from the exhaust gases of machines in which benzol is used as a motor fuel are not actually due to the benzol but to carbon monoxide, since exhaust gases contain no benzol.

In the rubber industry four cases of poisoning, two of which were fatal, from the use of shoe cements containing a large proportion of benzol were reported by Hunter and Hanflig in 1927. With regard to the sealing of cans, Hamilton

(1931) remarks that since the introduction in 1926 of rubber latex as a substitute for rubber dissolved in benzol, many works have substituted latex for the benzol rubber sealing mixture, but that no less than one third of all food cans are still sealed with benzol. In tyre-building, five cases (three fatal) of poisoning with aplastic anaemia and haemorrhages occurred (Harrington, 1917). Six deaths and twelve severe and several slighter cases of poisoning occurred in a rubber factory in Vienna in 1932, although all the apparatus used was of the closed type. The trouble arose apparently from the transportation of goods moist with benzol from one room to another (Fischer, 1932). An Austrian Government Order of May 1, 1934, prohibited workers in processes using benzol, toluol, xylol, or trichloroethylene from working more than 4 hours a day, and, when large quantities are used, not more than 2 hours a day. The processes covered by the more stringent restrictions include the cold vulcanization of rubber and the production of rubber substitutes.

Two of six cases of benzol poisoning reported by Hunter and Hanflig (1927) and a fatal case mentioned by Hamilton (1928a) occurred in the manufacture of patent leather.

In connexion with quick-drying paints, it is emphasized by Flury and Zernik (1931) that the use of benzol is attended with special danger from the fact that it volatilizes quickly from the painted surface, especially when the surface is warm, as in metal parts of machines, or when the paint is sprayed on. Details of the conditions and risks of this process are given by Smyth and Smyth (1928) summarizing the findings of the Pennsylvania Department of Labor and Industry (1926) and of the National Safety Council Committee on Spray Coating (1927). It was finally recommended by the Committee that no lacquers be used for spraying which contain over 0·5 per cent of benzol.

An investigation by Kranenberg and Peeters (1928) of workers in an aeroplane factory showed great and characteristic changes of the blood picture in a large number. In one case, after six years' exposure, there was a relative lymphocytosis of 62 per cent and a reduction of haemoglobin to 65 per cent.

Attention has been drawn by Bloomfield (1928) to the possibility of poisoning in laboratories where tests are conducted with rubber, paint, varnish and oil products, and involve centrifuging the material to be tested with benzol. He found a considerable amount of benzol in the air of such laboratories, 28 to 223 p.p.m., and examination of workers revealed in three cases a change in the ratio of polymorphonuclear leucocytes to lymphocytes.

Nine cases of chronic benzol poisoning in workers in the alkaloid industry were reported by Mitnik and Genkin (1931).

In England benzol is rarely used in high concentration in printing inks, but an investigation made by Saita and Dompé (1947) in Italy revealed that the percentage of benzol in the ink solvents and diluents varied from 66 to 93 per cent. Of the fifty-five operatives examined, 67·3 per cent showed some abnormality of the blood picture, and at one of the factories there had been two serious cases of benzene poisoning, one of which was fatal. In England also a series of cases of severe intoxication has occurred during recent years (p. 42).

TOXIC EFFECTS IN ANIMALS

Absorption and Excretion

Absorption

(*a*) *Through the lungs.* Rabbits, according to the investigations of Lehmann (1910), have a smaller capacity for absorption of benzol through the lungs than

human beings. Whereas men absorbed 80 per cent of the benzol vapour inhaled, rabbits absorbed only 63 per cent. No definite ratio between the relative amount absorbed and the total amount present in the air was found, but Robinson and Climenko (1941) have since observed that rabbits exposed to about 1,000 p.p.m. for 2 hours show a blood concentration of 25 to 30 mg. per 100 ml.

(*b*) *Through the skin.* The investigations of Lazarew, Brussilowskaja, Lawrow and Lifschitz (1931c) have shown that benzol in the form of vapour, as well as in liquid form, can be absorbed through the skin of animals. In liquid form, benzol produced great irritation. Immersion of the ears of rabbits for 2½ to 3 hours was followed by inflammation and oedema, then pus formation, and finally by mummification of the ear, while immersion of the whole body of a mouse was followed by death after about 3 hours.

When animals were kept in a chamber filled with benzol vapour, their heads being passed outward through an opening so that inhalation of the vapour was impossible, no general symptoms of intoxication were observed. Evidence of absorption through the skin, however, was obtained in three ways:

(1) The hydrocarbon content of the air expired by tracheotomized rabbits with one foot immersed in benzol was estimated. The estimation was carried out by the method of Matveev, Pronin and Frost (1930). The benzol appeared in the expired air after 3 or 4 minutes in amounts of 1·2 to 1·5 mg. per l., the total amount expired in the course of 115 minutes' immersion of the foot being 138 mg. The speed of absorption of benzol through 1 sq. cm. of skin was therefore calculated as more than 0·016 mg. per minute (0·013 to 0·76 mg. in a later investigation by Lazarew *et al.*, 1931c).

(2) Phenol, an oxidation product of benzol in the urine, was estimated. The urine of animals kept as described above in a chamber filled with benzol vapour showed a strong phenol reaction (Millon's reagent).

(3) The amount of benzol in the blood of rabbits after immersion of the ear in benzol was estimated by Lazarew *et al.* (1931a, b), and the average amount during 30 minutes' immersion plotted as a curve, which rose to between 50 and 100 mg. per kg. of blood taken from the external jugular vein.

Lazarew and co-workers correlate the absorption of benzol through the skin with its water solubility as well as its fat solubility. They estimate its water solubility as 0·033 to 0·040 g. per l. and explain its greater speed of absorption as compared with that of benzine by the lower water solubility of the latter (0·007 to 0·015 g. per l.).

(*c*) *Distribution in the body tissues and fluids after absorption.* The experiments of Yant, Schrenk, Sayers, Horvath and Reinhard (1936), and Schrenk, Yant, Pearce, Patty and Sayers (1941) have shed much light on the biochemical action of benzene. Of special importance is the partial explanation they afford of the injurious effect of benzene on the haematopoietic system—the predilection of benzene for fat, of which the bone-marrow essentially consists. The concentration of benzene in the fat, bone-marrow and urine of the exposed animals was approximately twenty times that in the blood.

Other conclusions reached were:

(1) The initial rate of absorption of benzene by the blood was extremely rapid, a matter of minutes.

(2) The final equilibrium value was attained very gradually, after several hours of exposure.

(3) The final elimination took place very slowly, the time increasing as the length of exposure increased. In some cases complete elimination had not

taken place until about 13 hours after termination of exposure. The fat, acting as a reservoir, is saturated slowly, and also loses its benzene slowly.

(4) The red blood cells contained approximately twice the concentration of benzene found in the plasma, and the muscles and vital organs about one to three times that in the blood.

(5) Benzene absorbed into the body by inhalation was apparently excreted into the stomach, and the high benzene concentration in the urine indicated that the benzene is concentrated by the kidneys.

Excretion

While the greatest amount of benzene is excreted unchanged by the lungs, a certain amount is oxidized in the body and excreted in the urine in the form of phenol, catechol, hydroquinone, and muconic acid (Jost, 1932). In animals the excretion of benzene in the urine has usually been estimated by the amount of phenol excreted. The phenol excretion of rabbits after 2 hours' daily inhalation of benzene in a concentration of 13·6 mg. per l. has been estimated by Sartorius and Sudhues (1933). The average phenol excretion rose almost immediately from a normal level of 2 mg. per day to 50 mg., and later to nearly 100 mg. When inhalation was stopped the phenol excretion sank to the normal level only after 4 or 5 days. This finding appears to indicate, according to Sartorius and Sudhues, that many cell systems must constitute special storage centres for benzene, or its ethereal sulphates.

Change in sulphates in urine. Some investigations by Yant *et al.* (1936) show that a change in the normal ratio of inorganic to organic sulphates, i.e. a decrease in inorganic sulphates, in the urine is a constant and early sign of benzene poisoning in animals. The analysis of urine specimens from 79 dogs exposed to concentrations of from 100 to 800 p.p.m. of benzene vapour for periods of 100 to as long as 1,000 days in one instance showed that a rapid and marked decrease occurred in the percentage of inorganic sulphates in the total sulphates in the urine. Single examples of their figures will suffice to show the quantitative aspect of this decrease (Table 2).

TABLE 2

Decrease in urinary inorganic sulphates after exposure to benzene

Concentration (p.p.m.)	Daily exposure (hours)	Exposure period (days)	Percentage of inorganic sulphates	
			Before exposure (average)	After exposure (average)
100	8	42	89·4	57·0
500	8	317	94·7	28·8
800	1	17	86·7	62·5
800	8	192	96·5	6·3

A distinct decrease in the percentage of inorganic to total sulphates occurred even with conditions of exposure which did not produce anaemia or leucopenia. With conditions which produced benzene poisoning a great decrease occurred weeks and months in advance of anaemia, leucopenia, and the common signs and symptoms of benzene poisoning. The mechanism of the response is believed to be due to oxidation of the benzene to phenol or phenolic derivatives, which in

turn are conjugated in the liver with sulphate ions to form ethereal sulphates, thereby causing a shift to the right in the system: inorganic sulphates ⇆ conjugated sulphates. The shift or decrease in inorganic sulphates is related quantitatively to the severity of the exposure to the point of complete elimination of the inorganic sulphates (p. 26).

Acute Poisoning

It has long been known that benzene in large doses produces in animals a severe narcosis, often accompanied by symptoms of irritation of the central nervous system, tremor, muscular twitching, etc., and, above the minimum lethal dose, followed by death. It was believed that the cause of death was invariably respiratory paralysis, but some investigations by Nahum and Hoff (1934) suggest that, although death may occur from respiratory failure during the stage of narcosis, it may also occur suddenly from myocardial failure produced by the action of benzol, both by causing the liberation of adrenaline and at the same time sensitizing the myocardium to its toxic action.

The acute effects of benzene upon animals have been studied from results of intraperitoneal injections and of inhalation. The symptoms arising from irritation of the central nervous system are essentially similar in both modes of administration, but the intense effect is most apparent when benzene is administered intraperitoneally, owing to its rapid absorption.

Effect of Intraperitoneal Injection

Lethal dose. For guinea-pigs, 0·73 ml. per kg. body weight (Chassevant and Garnier, 1903); for rats, 1·5 to 1·75 ml. per kg. (Batchelor, 1927).

Symptoms. Profound tremor and muscular convulsive twitchings were produced by doses as low as 0·25 ml. per kg. body weight, and in addition, a definite narcotic effect, with drowsiness, instability of gait, impaired equilibrium, weakness, paresis, decreased susceptibility to pain stimuli, and cessation of voluntary movement; as the spinal cord was affected, loss of reflexes resulted.

Post-mortem findings. Batchelor observed intense acute congestion of the peritoneum and abdominal viscera, with much fibrin deposit on these surfaces, considerable sero-sanguinous intraperitoneal exudate, injection of the gastric mucosa with small haemorrhages and ulceration, and acute congestion of the lungs. No appreciable effect was noted on the blood cell count.

Effect of Inhalation

In large doses, the effect of inhalation of benzol vapour upon animals is that of a nerve poison, with a characteristic neuro-irritant effect, as evidenced by muscle twitching, convulsions, general tremor (compared by Bénech (1897) to that of paralysis agitans), and a state of hypertonicity of the body and musculature (Batchelor, 1927), shown in many cases by a peculiar rigid S-shaped formation of the tail (Lazarew, 1929a).

A toxic action upon the heart is also postulated by Nahum and Hoff (1934), i.e. progressive anoxaemia of the myocardium, and a sensitization of the myocardium to the effects of adrenaline, so that death may occur from ventricular fibrillation.

Different species of animals vary in their susceptibility to acute benzol poisoning, the rabbit being more resistant than the mouse (Lehmann, 1912), while the cat appears to have a special sensitivity (Lederer, 1932; Engelhardt, 1931). A sinus arrhythmia, with ventricular asystoles, due to the action of benzene, either on the myocardium itself or on the vegetative nervous system has been observed by Caccuri (1940).

According to Lehmann and others, animals of the same species, especially cats, also show a great variation in individual susceptibility, death occurring sometimes with relatively small dosage and short exposure, while on the other hand, feeble animals receiving large doses may show only slight weakness and others may recover from severe narcosis. It appears from the work of Nahum and Hoff (1934), and also that of Caccuri (1940) that some of these individual susceptibilities may be explained by variations in adrenaline response; periods of hyperexcitability being accompanied by increased liberation of adrenaline, to the action of which the myocardium is already sensitized by the action of benzol.

Lethal and narcotic concentrations

These are given in Table 3.

TABLE 3

Lethal and narcotic concentrations of benzene by inhalation

Animals	Lethal concentration (mg./l.)	Lethal concentration (p.p.m.)	Narcotic concentration (mg./l.)	Narcotic concentration (p.p.m.)	Author
Mice ..	45	14,000	—	—	Lazarew (1929a)
,, ..	—	—	38	12,000	Führer (1921b)
Cats ..	170	53,000	60	19,000	Lehmann (1912)
,, ..	—	—	30	9,500	Bamesreiter (1932)
Dogs ..	146	46,000	—	—	Luig (1913)
Rabbits ..	46 (after 3 hours)	14,500	—	—	Lehmann (1912)
Guinea-pigs	—	—	40	12,600	Peronnet (1934)

Symptoms

The onset of acute symptoms is apparent at concentrations ranging from 15 mg. per l. (4,700 p.p.m.) for mice to 22 mg. per l. (7,000 p.p.m.) for cats (Bamesreiter, 1932).

Table 4 taken from Lehmann (1912) shows the progress of effects with different concentrations in rabbits.

TABLE 4

Effect of inhalation of benzene on rabbits

Concentration (mg./l.)	Concentration (p.p.m.)	Time of exposure	Time before apparent effects: Convulsions	Lateral position	Light narcosis	Deep narcosis	Further progress
37	12,000	5 hr.	2¼ hr.	35 min.	—	5 hr.	Slow recovery.
46	14,500	3 hr.	80 min.	—	—	2 hr.	Death after 3 hr.
92	29,000	70 min.	9 min.	9 min.	40 min.	50 min.	Slow recovery.

(It should be noted here that the results obtained by Bamesreiter (1932) with regard to the narcotic symptoms produced by inhalation of benzol vapour by cats give a toxicity greater than that found by Lehmann. Lehmann, in a note appended to Bamesreiter's article, observes that the discrepancy is due to the fact that Bamesreiter has used a modification of the original *Würzburger* apparatus, the new *Ludwigshafen* apparatus, described by Gross and Kuss (1931).)

Bamesreiter's results are summarized as follows:

Lateral posture	..	above 22 mg. per l. after 6 hours' exposure
Light narcosis	..	above 28 mg. per l. after 6 hours' exposure.
Deep narcosis	..	above 30 mg. per l. after 6 hours' exposure.

Post-mortem findings. The organs of animals dying from inhalation of lethal concentrations of benzol vapour have not shown any specially characteristic changes; haemorrhage of the lungs has been observed in a few cases. The most outstanding feature was the fact that the blood remained fluid for a long time after death (Beinhauer, 1896; Lehmann, 1912; Heffter, 1915). No microscopic changes in the blood were found in Lehmann's animals; an odour of benzene could be detected in the lung cavity if opened promptly after death.

Local irritant effect

Mucous membranes. In rats, irritation was caused by concentrations of 1,000 to 2,400 p.p.m. or even less (Batchelor, 1927).

Cornea. In rabbits, irritation with turbidity and a blister-like appearance after repeated exposure to 38·6 mg. per l.

Lungs. Histamine may be liberated (Garan, 1938).

Effect on the blood

The effect of a single exposure to 7,500 to 12,000 p.p.m. for 2 hours was found by Climenko and Macleod (1942) and Robinson and Climenko (1941) to be an immediate temporary leucopenia followed within 22 hours by a leucocytosis. There was no evidence of neutropenia, but on the contrary, varying degrees of neutrophilia, with a shift to the right. There was also a fall in the number of circulating erythrocytes. These investigators assume from the reaction of the white cells that the bone-marrow under benzol exposure is refractory to the normal endogenous stimuli which maintain the equilibrium of juvenile to senile cells; it proved, however, responsive to the more potent exogenous stimulus of sodium nucleinate.

Effect on the Body Temperature

According to Gaede (1944), the effect of administration of benzene to animals, orally, rectally, or intravenously, in doses of 5 to 20 drops, is an immediate rise of temperature. This, it is suggested, is due to stimulation of the temperature-regulating centre of the brain. With narcotic doses, the temperature falls, this being due to paralysis of the centre. Inhalation of 100 p.p.m. causes a rise of temperature during the first half hour, followed by a rapid fall.

Effect of Mixtures of Benzene and other Solvents

An investigation by Svirbely, Dunn and von Oettingen (1943), on the acute toxic effect of certain mixtures of solvents containing benzene, toluene and xylene, has shown that so far as the lethal effect is concerned, benzene is less toxic than either toluene alone, or the blends of benzene, toluene and xylene. Pulmonary irritation was more predominant with benzene alone, but pathological changes were not prominent owing to the short exposure and resulting early death of the animals.

Chronic Poisoning

Both by subcutaneous injection and by inhalation experiments on animals, the toxic effects of benzol have been investigated and described by a large number of workers beginning with Santesson (1897), Langlois and Desbouis

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