TOXICITY AND METABOLISM OF INDUSTRIAL SOLVENTS

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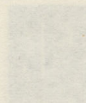
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Preface

It was with some trepidation, following notification that the 2nd Edition of my book 'The Toxicity of Industrial Organic Solvents' published by H.M.S.O. in 1953 was now out of print, that I embarked on the present publication. This does not represent a 3rd Edition of the former book; it is a completely new appraisal, though including some references to the work of earlier authors, of the present position of the principal industrial solvents now in use.

An entirely new feature is, wherever it has been possible, an account of the metabolism in the body of the individual solvents, a process which in the opinion of many authorities forms the real basis of their toxic effects.

It is with gratitude that I wish to express my thanks and indebtedness especially to the authors of two publications – those of Dr. F. A. Patty in his revised 2nd Edition of the second volume of 'Industrial Hygiene and Toxicology', published by Interscience Publishers, New York, and Dr. R. Tecwyn Williams, 'Detoxication Mechanisms', published by Chapman and Hall, London. Their innumerable references not only to published articles but also to their personal researches, have been invaluable in providing me with at least a starting point in my own researches into this vast subject.

Ethel Browning

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Chapter 1

AROMATIC HYDROCARBONS

The term 'Aromatic Hydrocarbons' was originally applied to a group of vegetable products, such as balsams, resins and essential oils, distinguished by a characteristic pleasant aromatic perfume. It was many years before they were differentiated from the 'fatty compounds', now known as aliphatic hydrocarbons, by the fact, postulated by Kekulé in 1865, that the simplest aromatic substances contain at least 6 carbon atoms. Kekulé's formula for the structure of benzene, now generally represented by a hexagon with alternating double bounds

$$\hexagon \quad (C_6H_6)$$
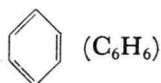
is the foundation of the nomenclature and classification of the aromatic hydrocarbons.

Their present widespread use as solvents in industry can be traced back to 1784, when Lavoisier first demonstrated the true composition of organic substances, though it was not until 1817 that Berzelius postulated that organic compounds were subject to the ordinary laws of chemical combination. For the next twenty years new theories were constantly introduced and almost constantly disputed and rejected, but during these years "the foundation of the great edifice of aromatic chemistry was being laid" (Cohen, 1909).

Between 1830 and 1840 Mitscherlich had obtained benzene from benzoic acid by distillation with lime, and had formed nitrobenzene, chlorobenzene and other derivatives. The benzene so obtained was found to be identical with a hydrocarbon obtained by Faraday in 1825 from an 'Oil Gas' which was being manufactured and compressed into metal vessels for distribution to customers.

The real industrial use of the aromatic hydrocarbons, however, began about 1823, when coal tar naphtha made in the London gas plants was found to be an excellent solvent for rubber (Gerarde, 1960), and the demand for these substances has increased enormously both before and after the two World Wars. In 1957 the production in the U.S.A. of the principal industrial hydrocarbons (benzene, toluene, xylene, ethyl benzene, styrene and naphthalene) had reached a total of over 7500 million pounds (Katzen, 1958).

The chief sources of aromatic hydrocarbons are coal and petroleum. During the heating of coal at temperatures of 1000–3000 °F, without access to air, coke, coal gas and coal tar are produced. From the light oil fraction of coal gas are obtained benzene, toluene, xylene, crude coal tar naphtha and heavy solvent naphtha; from coke oven gas crude 'motor benzol' consisting chiefly of benzene

and toluene; from coal tar, diphenyl, naphthalene, methylated naphthalenes, indene, acenaphthene, fluourene, chrysene and phenanthrene.

From petroleum, by various methods of fractional distillation or catalytic reforming, a wide variety of hydrocarbons are obtained. These include not only benzene, isolated from catalytically reformed light naphthas by distillation or solvent extraction, xylene, toluene and ethyl benzene, but also many other aromatic compounds less frequently encountered in industry. (For a detailed account see Gerarde, 1960.) They will be further described under their separate headings.

These aromatic hydrocarbons and their derivatives obtained from petroleum are known as 'petrochemicals', and the petrochemical industry is a rapidly growing source of the ever increasing demand of industry for aromatic hydrocarbons, with full knowledge of how to take full advantage of their enormous advantages with adequate precautions against their potential toxicity.

1. Benzene

Synonyms: ben : , phenyl hydride, coal naphtha, phene benzole, cyclohexatriene

1a. Pure benzene

Molecular weight : 78.11

Benzene, a coal tar product and petrochemical, has been until recently in Great Britain, and still is in many parts of the world, among the most widely used of all industrial solvents, partly on account of its excellent solvent capacity, partly because of its relatively low cost.

Of recent years the recognition of its great potential hazard of chronic poisoning from comparatively slight repeated exposure has led to considerable effort to substitute less toxic compounds.

The unfortunate similarity of the words 'benzene' and 'benzine' is also at last becoming generally recognised and the difference in chemical constitution and toxicity of these two solvents understood.

Benzine is not an aromatic hydrocarbon, nor even a chemical entity, but a volatile mixture of aliphatic hydrocarbons or 'petroleum ethers' derived from petroleum distillation, with a varying content of paraffins and cycloparaffins. Its chronic systemic toxicity is devoid of the haemopoietic effect characteristic of chronic benzene poisoning.

The danger of confusion between benzene and benzine has been exemplified by Heim de Balzac and Agasse Lafont (1933) in their report on a series of 36 cases of benzene poisoning, eight of them fatal, following the accidental substitution of crystallisable benzene for the benzine previously used as a rubber solvent.

Properties: a colourless liquid with a characteristic not unpleasant aromatic odour.
　boiling point: 80.1 °C at 760 mm Hg
　melting point: 5.4–5.5 °C
　vapour pressure: 74.6 at 20 °C
　vapour density (air = 1): 2.77
　specific gravity (liquid density): 0.884 at 15 °C
　flash point: 12 °F *autoignition temperature:* 1000 °F
　conversion factors: 1 p.p.m. = 3.19 mg/m³
　　　　　　　　　　　1 mg/l = 313 p.p.m. at 25 °C, 760 mm Hg
　solubility: in water, 1430 v/v; miscible with alcohol, chloroform, ether, CS_2, acetone, glacial acetic acid, CCl_4.
　maximum allowable concentration: 25 p.p.m. (see also p. 7)

1b. Commercial benzene

(sometimes called 'benzol')

(a) Commercial crystallisable – said to contain 99–100% benzene:
  boiling range: 80–81 °C
  specific gravity: 0.879 at 20 °C

(b) 'Benzol 90' (90% benzene) – contains toluene (13–15%), xylene (2–3%) and sometimes traces of olefins, paraffins, H_2S and other substances.

(c) 50% Benzol – a mixed product, 50% of whose constituents distil below 100 °C and 90% below 120 °C.

The term 'benzols' (plural) is sometimes applied to mixtures of benzene, toluene and xylene. That benzene may contain appreciable amounts of polycyclic aromatic hydrocarbons, some of them carcinogenic, has recently been demonstrated by Lynski and Raha (1961). Their analyses were made by adsorption and partition chromatography (Lynski, 1960), followed by spectroscopic analysis of the fraction.

The benzene samples were found to contain very low but identifiable concentrations of anthracene, benzanthracene, benzopyrene, pyridine, and other compounds, too low for identification.

ECONOMY, SOURCES AND USES

Production

As already mentioned, benzene is produced chiefly from the coal gas arising from the heating of coal at temperatures of from 1000 to 1300 °F. The coal gas is passed through tar and ammonia scrubbers and oil absorption tanks, with a resultant light oil fraction containing benzene, toluene, xylene, crude coal tar naphtha and heavy solvent naphtha. Crude 'motor benzol', consisting mainly of benzene and toluene, is obtained by scrubbing of coke oven gas (Gerarde, 1960).

Benzene is also produced from petroleum by the catalytic reforming (*i.e.* in the presence of molybdenum, chromium or precious metal oxide supported on alumina) of light naphthas from which it is isolated by distillation or solvent extraction.

Industrial uses

The applications of benzene are manifold and ubiquitous. In 1957 its production in Western Europe and the U.S.A. amounted to 2430 million pounds (U.S. Tariff Commission Report, 1958).

It is used not only as a solvent, a constituent of aviation and motor fuel and a degreasing agent, but also as the starting material for a wide variety of materials in the chemical industry. From this last application it makes its entry into a vast and sometimes unsuspected number of industrial processes. It is concerned in the manufacture of rubber, plastics, paints, lacquers, linoleum, artificial manure, glue and adhesives, rotogravure printing, extraction of oils and fats, floor waxes and polishes, etc. The rubber industry itself includes many aspects where the use of benzene might not at first sight appear prominent, *e.g.* the sealing of cans with rubber cement dissolved in benzene, the manufacture of straw hats, shoes, cameras, cardboard boxes, and even in the watchmaking industry for cleaning the separate parts. (In Sweden, according to Larssen and Thrysen, 1951, there have been many cases of benzene poisoning from this particular application.)

In addition to these processes, where benzene is used mainly as a solvent, there are also the 'closed systems', where it is handled in large quantities, as during its production from coal gas and in the blending of motorfuels.

SUBSTITUTES FOR BENZENE

It is becoming more and more widely realised that the individual susceptibility to a variation of exposure to benzene is so great that merely reducing its content in the working atmosphere is not the complete answer to the problem of reducing the incidence of benzene poisoning.

It is by no means an unusual experience when making blood examinations of a group of workers on an exactly similar benzene process to find a few showing relatively severe disturbance, while others show a normal blood picture. This inequality of reaction has been observed also with regard to the actual content of benzene in the blood. In 1949, Bernard, Braier and co-workers pointed out that some workers handling products with a high benzene content showed a low level of benzene in the blood, while others exposed to low concentrations had a high benzenemia. They attributed this variation to the differing capacity of individuals to eliminate benzene from the blood stream, normally a rapid process due primarily to exhalation of unchanged benzene from the lungs (Gerarde, 1960). Benzene has in fact in some cases of poisoning been detected in the blood several years after cessation of exposure (Fabre, 1946).

It is therefore of great importance to replace benzene wherever possible by a solvent which will be technically acceptable and at the same time, if not entirely innocuous, at least devoid of the specific haemopoietic effect.

Suggested substitutes

Among the solvents suggested as suitable replacements for benzene are toluene, xylene, isopropyl benzene, solvent naphtha, benzine, trichloroethylene, cyclohexane and heptane. None of them has been found completely ideal from either the toxicological or the technical aspect, and it has been emphasized (Fabre *et al.*,

1955) that caution must be exercised in extrapolating to man the results of animal experiments on the relative innocuousness of the proposed substitutes; also that recommendation of any of these substitutes does not mean that they are entirely devoid of toxic effects, merely that they are less injurious to the health of workers than benzene itself.

Toluene, xylene and solvent naphtha, though devoid of the specific effect of benzene on the blood forming organs, have the disadvantage that the widely used commercial form contains a significant percentage of benzene.

Isopropyl benzene (Cumene) has been found to cause no significant variation of the blood picture in animals exposed to 500 p.p.m. 8 h a day, for 150 days (Fabre *et al.*, 1955), nor was the femoral marrow cell population diminished in rats given subcutaneous injections of 1 ml/kg body weight daily for two weeks (Gerarde, 1956). Hyperaemia of the lungs, liver and kidneys were, however, observed in Fabre's animals.

Cyclohexane has been chiefly recommended in France, where it is regarded as significantly less toxic than benzene. This view is supported by the experiments on animals of Treon *et al.* (1943) who found no symptoms of ill-effects or tissue damage from repeated exposure to 434 p.p.m., but minor degenerative changes in the liver and kidneys of rabbits exposed to 786 p.p.m.

Heptane. The most recent search for an acceptable substitute by Cirla (1960) had led him to recommend heptane, which in addition to presenting very slight systemic or haematological hazard to workers exposed to it, is also, according to the technologists, an adequate substitute from the point of view of solvent capacity. Earlier investigations on animals by Fuhner (1921) had shown it to be a narcotic in acute exposure (lethal in concentrations of 1.5–2%), but in human beings Baldi and Ricciardi-Polloni (1954) stated that it carried only a slight risk to workers using it and considered 300 p.p.m. as the maximum tolerable concentration. Slight variations of the blood picture were described by Nunziante and Granata in 1955.

In Cirla's investigation of 382 men and 149 women who had used heptane for 1–5 years in a rubber tyre process where the concentrations ranged from 0.75 up to 1000 p.p.m., the principal haematological variation was anaemia, which though slight, was present in fairly high percentage especially of the women; slight leucopenia (not less than 4100 /μl) was present in only 2%, and slight neutropenia in 9% of the men and 12% of the women. Clinical symptoms – headache, fatigue and dyspepsia – and positive liver function tests were also found but were not considered toxicologically significant. It was concluded that heptane does show a slight toxic effect similar to that of benzene, but in comparison it presents very little systemic or haematological hazard.

MAXIMUM ALLOWABLE CONCENTRATION

The 'Maximum Allowable Concentration' or 'Threshold Limit' for repeated exposure to benzene has been reduced from the original 100 p.p.m. postulated in 1939 by American Standards Association, to 35 p.p.m. from 1951 to 1957, to the level of 25 p.p.m. (0.08 mg/l) at the present time.

It has to be remembered that these threshold limit values are not intended as unalterable minimal levels. They are based on "various criteria of toxic effects or on marked discomfort; thus they should not be used as a common denominate of toxicity, nor should they be considered as the sole criterion in proving or disproving diagnoses of suspected occupation diseases" (Threshold Limit Values for 1962).

In Russia the limits proposed (Novikoff, 1957) are approximately 60 p.p.m. for a single exposure and 20 p.p.m. for 24-h level. They base these recommendations on the effects on the conditioned reflex activity of rats subjected to daily inhalations of benzene, and on the olfactory concentration in human beings; this was found to be about 75 p.p.m. for a sensitive person, and the imperceptible concentration about 60 p.p.m. (It may be noted that Gerarde, 1960, gives the olfactory threshold for benzene as 1500 parts per billion).

It may yet be found that a 'benzene effect' may be caused by concentrations even lower than 25 p.p.m. It has not always been possible to evaluate the concentrations in the air of workrooms where relatively slight, though definite signs of haematological disturbance characteristic of exposure to benzene have been detected by routine blood examination. It is always possible, as pointed out by Hamilton-Paterson and Browning (1944) that the general atmospheric concentration of benzene is not an entirely reliable criterion of benzene expousre, since workers may at some time be exposed to localised 'pockets' of high exposure. This was clearly brought out also by Graham (1958) in an investigation of a can-making process which was apparently very adequately enclosed and under good exhaust ventilation. Estimations of the air concentrations showed, however, considerable variation; even when they were generally low they showed 'surges' up to much higher levels. For example, while the general atmosphere away from the tanks showed usually a concentration of 28 to 42 p.p.m., there were surges of 55 p.p.m., and in the pump room during pumping the concentrations varied from 22 to 100 p.p.m.

BIOCHEMISTRY

Estimation

(1) In the atmosphere

The rapid method using formaldehyde and concentrated H_2SO_4, described in Leaflet no. 4 of the Department of Scientific and Industrial Research, (1939)

has the disadvantage that the brown-violet reaction is interfered with by all homologues of benzene.

A reaction which is virtually specific for benzene in the presence of toluene, xylene and other homologues was described by Dolin in 1943. In this (the Butanone) method, a nitrating mixture (equal parts of concentrated H_2SO_4, and fuming nitric acid) is used as the absorption fluid. Butanone is added to the ether extract, diluted with ethyl alcohol, and the reading from a colorimeter compared with a calibration curve made by treating 50–500 g of benzene in the same way.

A modification of this method suggested by Zurlo and Metrico (1960) is the use of carbontetrachloride as the absorption fluid instead of the nitrating mixture.

Elkins (1959) describes an ultraviolet spectroscopic method for both benzene and toluene, using silica-gel apparatus with the addition of iso-octane. This method is based on that of Maffet et al. (1956).

(2) In blood and tissues

Several methods of estimating the amount of benzene in blood and tissues have been described, generally on the basis of colorimetric procedures (Yant et al., 1935; Pearce et al., 1936), or on ultraviolet spectroscopy (Mayer, 1938). The latter method has been used by Guertin and Gerarde (1959) for the blood content of benzene in a form modified to obviate the necessity for large samples of blood and of time consumed in two distillations. It depends on extraction of the benzene from the blood with cyclohexane. The blood is first haemolysed with 0.1 N HCl and the lower (aqueous) layer after shaking with cyclohexane removed. The cyclohexane layer is then centrifuged and its ultraviolet absorption spectrum compared with a previously prepared calibration curve.

(3) In urine

Since some of the metabolites of benzene (see p. 11) are excreted in the urine in conjugation with sulphuric acid as ethereal or organic sulphates, it follows that absorption of benzene is associated with an increase of these in proportion of the excretion of inorganic sulphates.

It was suggested by Yant et al. (1936) that determination of the ratio between them might serve as a method of diagnosis of early benzene poisoning. Owing to discrepancies in the results of many investigators of the relation between this proportional excretion and haematological evidence of benzene poisoning, it is now generally agreed that while the test may be accepted as a measure of the amount of exposure to benzene it is not to be regarded as an estimation of toxic effects.

The normal ratio of inorganic/organic urinary sulphates varies, according to several authorities, from 80/20 (Yant et al., 1936; Kammer et al., 1938) to 92.5/7.5 (Teisinger and Fiserova-Bergerova, 1955).

Discrepancies in the ratio in workers exposed to benzene are ascribed to the