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TOXICITY OF INDUSTRIAL ORGANIC SOLVENTS

Revised in consultation with the Toxicology Committee

By **ETHEL BROWNING**

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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.

MISCELLANEOUS

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