THE IMPORTANCE OF TOXICOLOGICAL INFORMATION IN PROCESS DESIGN

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SYNOPSIS

The main hazards to men engaged in processes involving toxic chemicals derive from inhalation of vapour or dust, or from skin absorption. In order to obtain information on the nature and severity of these hazards, it is necessary to have access to an expert assessment of the published literature, or, if this is inadequate, animal experiments must be commissioned and intepreted in the light of the human exposure. This information must be available at an early stage of plant design. Expert advice on the toxicological properties of chemicals is also required to avoid pollution of the environment from effluents discharged into the air or water, or disposed of as waste.

Nature of the Risks Involved

There can be no doubt that the toxicity of the materials used or produced in a chemical process must be given careful consideration during plant design. This contribution to the Symposium will deal with the nature of the information required to assess the toxic risk, how it is obtained, to whom it should be supplied and how it should be implemented.

It should be the aim of a chemical engineer to contain all his product in the plant used in the process. This is rarely possible at an economic cost, and it is necessary, therefore, at some stage to ask " What are the risks involved in the storage of the raw materials and in their transfer to the plant? Will there be any danger from leaks of liquid or vapour from the plant during the process? Can the end product be discharged safely to a container? How can the product be safely shipped to customers and what instructions should be given to the customers on how they should handle the product?" We have, therefore, to consider what are the toxic risks of the chemicals introduced into the plant, of any intermediates which may or may not be isolated and of the end product, or of any materials ancillary to the process, such as heat transfer agents or insulation. In addition, the properties of any residues which must be discharged to waste must not be overlooked as their disposal may present problems.

There is a considerable body of information in the medical literature and in reports such as that issued annually by the Chief Inspector of Factories, that indicates the risks incurred in operations involving chemical substances. Analysis of these statistics suggests that most lost time in industry results from an attack of chemicals on the skin or the eyes, but that most serious and disabling industrial disease is produced by an attack on the lungs by inhalation of a vapour or a dust, or by systemic poisoning from absorption through the lungs or through the skin. Probably the inhalation risk is the most serious, but skin absorption should by no means be neglected.

Collection of Toxicological Information

Information on the toxicological properties of the older materials used by the industry has been obtained the hard way, by careless handling, leading to disease or death in workmen. The more recent products of the major chemical companies have usually been adequately tested in the laboratory, and as a result of an increasing preoccupation with occupational hygiene and the safe handling of chemicals we can in most cases only speculate on their effects on man. Information on these products may be obtained from the scientific literature, from reference works or from the suppliers. It is also necessary to keep a careful and informed eye on the literature to be aware of new evidence of toxic properties hitherto unsuspected. We have seen this with certain aromatic amines, with benzene and more recently with asbestos.*

If a manufacturing process involves a raw material or produces an intermediate or end product that is not adequately described in the literature, it is essential to undertake experimental work in order to ascertain how the substance should be handled. ICI established its Industrial Hygiene Research Laboratories in 1948 to study the toxic properties of the chemicals used in industry, and although in recent years this organisation has rapidly grown, due mainly to an increasing preoccupation with the safety of food additives, occupational toxicology is still an important part of its work. It is not possible to give a figure for the total number of enquiries which are dealt with by the scientific and information staff; this must amount to several thousands a year. The Information Service receives about 750 enquiries a year that require a literature search, and for approaching 100 a year there is insufficient published information and experimental work must be undertaken to assess the toxic hazard. In nearly all cases this involves the use of animals, though there are a few examples where analytical techniques provide adequate information; for example, in the determination of polycyclic hydrocarbons in still residues to assess their carcinogenic properties.

Experience is necessary to interpret published information, which is often incomplete and occasionally conflicting. Experience, too, is required for the design and interpretation

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** The most comprehensive and up-to-date information will be contained in the " Encyclopaedia on Occupational Health and Safety ", shortly to be published by the International Labour Office. Currently available sources are " Industrial Hygiene and Toxicology " Fassett, D. W., and Irish, D. D. (New York: Interscience Publishers Inc.), " Toxicity and Metabolism of Industrial Solvents " and " Toxicity of Industrial Metals ", Browning, E. (Amsterdam: Elsevier Publishing Co.), and " Documentation of Threshold Limit Values ", published by the American Conference of Governmental Industrial Hygienists.*

of the animal experiments, which must bear some relation to the nature and extent of human exposure. It is of little value to dose a group of rats with a compound and then count the bodies. We need to know enough about the qualitative and quantitative aspects of the toxic action, so that we can predict what occupational exposure is likely to be innocuous, and what effects are likely to be produced by prolonged excessive exposure, or by an accident or disaster.

As the most serious risk probably arises from the inhalation of vapours or dusts, any chemical which in some way can be dispersed in the atmosphere must be investigated for its inhalation toxicity. Rats are generally used for such experiments, not because they are thought to resemble man more than any other species, but because they are about the right size, and healthy and standardised strains are available whose characteristics are well known. Other species, such as the guinea-pig, rabbit, cat or dog are used when appropriate, but only rarely are experiments undertaken on man and then only after very careful studies on animals. To study the inhalation toxicity, the animals are first exposed to high concentrations to ascertain the nature of any acute effects, and then the concentrations are progressively lowered until we reach a threshold or no-effect level. In these experiments the animals are exposed daily to the test atmosphere for a period of three weeks, as from our experience this provides us with adequate information, but if the chemical may be handled in large quantities under improper supervision, such as a solvent used in dry-cleaning or degreasing, we may extend the exposure period and use several animal species. The no-effect level is determined by a careful examination of the animals during the exposure period, using any appropriate biochemical tests to assess normality, and at the end of the exposure period a careful haematological examination is made and an autopsy with a histopathological examination of the organs. When the no-effect level is ascertained it is divided by an appropriate safety factor, depending on the nature of the toxic effects produced, in order to obtain a tentative threshold limit value.

The effect of the chemical on the skin is carefully examined by repeated applications to rat skin, in order to ascertain whether the chemical attacks the skin or is absorbed through the skin. The possibility that the chemical may produce an allergic reaction is investigated on the guinea-pig which shows this effect more clearly than the rat. The effect on the eye is studied in the rabbit, which has a large eye capable of revealing any damage. In addition to these experiments which are closely related to occupational exposure, the compound may also be administered in repeated doses to rats by mouth or parenterally in order to study in more detail the nature of the toxic effects produced when the material enters the system.

On the basis of such experiments, which usually take four to five months to complete, a report can be prepared which will provide the chemical engineer, the plant manager, the medical officer, and the occupational hygienist with the information they require. From our experience, experiments of this duration and complexity appear to be adequate, for when our recommendations have been followed we have no record of any incidence of industrial disease.

Communication of Toxicological Information to the Design Engineer

According to our experience, it is possible to supply toxicological information that will enable, with a reasonable degree of certainty, a plant to be designed and operated safely. But such information is only available it if is requested, and it is necessary to consider who should be responsible for such a request at the appropriate stage in the development of a new process. In the case of a process emanating from a research and development department, and which requires the construction of new plant, there is rarely any formal control over toxicological hazards in the laboratory. It is usually considered that the small scale of operation, the short duration of exposure, and the training and experience of graduate staff render a hazard to health unlikely. The subsequent development of the process will no doubt vary from one organisation to another, but in most big chemical firms the practice followed probably is similar to that which exists in most ICI manufacturing divisions. When a process has been developed in the laboratory, it passes to a semi-technical plant in order to manufacture enough of the product for extended user trials, and to gain experience useful for subsequent full-scale production. At this stage the process is still the responsibility of the research and development department, and is usually under the control of the chemist responsible for its early development.

When a decision is reached to enter into full production, the project leaves the research and development department and is taken over by a department responsible for the planning of production. A project group is usually formed which includes representatives from all departments concerned, production, technical service, safety, sales and engineering. The task of this group is to convert the project into chemical engineering terms so that it can be handed over to the engineering department or some outside contractor. There is no doubt that one member of this project group at some early stage should consider what are the toxic hazards of the raw materials, of the end product, and of any effluents, and this individual should be experienced in interpreting toxicological information, or have access to good advice. This system works well in ICI, particularly in those manufacturing divisions which have had a long history of a wide range of toxic products. There are, however, a number of potential loopholes which need careful watching. An organisation which has been accustomed to manufacturing chemicals which are relatively innocuous or which have been handled safely by industry for a long time, may overlook the requirement that some new material may require a different approach. It is necessary to consider the consequences of a process operator opening a valve in error, and how such errors can be prevented. Pipes carrying dangerous liquids should be clearly marked so that maintenance fitters can take appropriate precautions. On occasions the production in a semi-technical plant may be considerable, and the output may be distributed for trials before any assessment of the toxic hazards is undertaken. This also may be the case in changes in formulation initiated by technical service departments or on-plant modifications made by a plant chemist. Even simple variations, such as scaling up a process, or running off a batch before it is cooled down, may introduce new hazards. Another matter which may not be considered at the design stage, is loss of process control. If, through plant malfunction or faulty operation, a process goes out of control, the limits of variation initially prescribed may be exceeded, and byproducts may be formed which were unsuspected at the design stage and whose toxic properties are unknown. It is also necessary to consider at the design stage of a plant handling a very toxic material, what might be the hazard to workmen and the surrounding population in the event of a disaster, and what modifications can be introduced to avoid such risks.

Control of Toxic Hazards

Decisions on how the toxic properties of the materials involved in a chemical process should affect the design of plant, are the province of the chemical engineer, not of the toxicologist. Obviously, these properties will influence the quality of glands and valves which may have to be maintained under reduced pressure, and whether rivetted or welded construction should be used for vessels. A decision must be reached on whether an attempt should be made to maintain a safe environment for workers without protective clothing and equipment, or whether men should be so protected, if necessary, by placing them in space suits. Such a procedure is generally frowned upon by the Factory Inspectorate, and with good reason. With a very toxic material a totally enclosed system may be required, and this would certainly be necessary if known carcinogens were involved. What exactly is meant by a totally enclosed system is not obvious; in the Draft Benzene Regulations this term is used, and as a result of comments on these by the CIA it has been agreed that such a system may include vents if they discharge safely into the air, and sampling outlets may be provided for process control. Moreover, to allow for any minor leaks, there will be a provision in the Regulations to the effect that it shall be a defence to prove that all due diligence had been exercised to prevent a leak.

There is no doubt that with adequate care at the design stage, even the most hazardous chemicals can be produced safely. One of the most dangerous chemicals which is produced in bulk is ethyleneimine; this is corrosive to the skin and lungs and is readily absorbed and severely damages several organs. It is also liable to explode in the presence of traces of acid. One of the few firms manufacturing ethyleneimine is BASF at Ludwigshafen. The care taken in the design of their plant is most impressive; this applies not only to the details of construction, but also all possibility of accidents from human ignorance and folly appear to have been anticipated by control devices.

Hazards from Plant Effluents

The toxicological problems involved in effluents, both gaseous discharges through vents and liquids or suspended solids through drains, and in the disposal of unwanted wastes, are likely to become more important with the increasing preoccupation with the pollution of the environment, and these matters must be given serious consideration in plant design. The products of combustion which are normally discharged through stacks usually present no special problems, though vents used to carry away unwanted vapours may lead to trouble. One has only to think of the role of hydrocarbons in smog production in the Los Angeles area. In some cases, tracking down a disagreeable odour may be a considerable effort in detection to trace the origin, particularly as the discharge may undergo chemical change in the atmosphere. A more pressing problem is the possible effect on the population in the event of plant failure within an urban area. It is generally possible to calculate in advance the range of concentrations likely to be encountered at various distances from the centre of a serious plant failure involving perhaps fire or explosion, and taking into consideration the most adverse climatic conditions. From a knowledge of the properties of the chemicals involved, it is possible to predict the risk to the population in these areas. What are termed emergency exposure limits have been established for the common toxic chemicals; these indicate the concentration and duration of exposure which may lead to distress, reversible damage, chronic disease or death. If such calculations lead to the conclusion that such an accident would have a very serious effect on the population, then the plant must be modified or resited. Our advice was asked concerning a process which could conceivably go out of control and blow its safety valve to discharge the batch into the atmosphere. It was realised that the risk to the community could not be tolerated and a stack was installed with a suitable scrubbing system to reduce the risk to acceptable proportions. In a proposed carbon disulphide factory near Amsterdam it was realised that the risk to the population from sulphur dioxide in the event of a fire could not be permitted, and the factory was sited elsewhere.

The pollution of waterways and estuaries from factory effluents is a different problem. It is likely that restrictions controlling this will become more severe, and not limited to chemicals which make the water unable to support fish. There is an increasing interest in those chemicals which can accumulate in the biological chain and which may reach excessive concentrations in fish and some birds. One can quote the recent investigations into the distribution of methyl mercury and chlorinated hydrocarbons. It is likely that in some cases factory managements will be required to control their effluents at source, and this may present serious problems, particularly in older factories.

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