II Health Hazards to Workers from Industrial Chemicals

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Our affluent society could not have evolved had we not been an industrial society. Chemistry and the chemical industry have made a substantial contribution to our economic progress, with its constant efforts not merely to develop entirely new products, but also to find improved methods of making existing products better and more cheaply. The blessings thus conferred upon mankind, however, require, by the very nature of the industry, that workmen continue to work with materials that may be toxic, foul-smelling, corrosive, dermatitic, carcinogenic, powerfully staining, allergenic, and offensive in every conceivable way.

Increasing public awareness of the problems of toxic chemicals is thus reflected not merely by interest in ecological considerations, but also by changing social attitudes in respect of health hazards to workers. Unfortunately, this desirable trend is not always based upon proper understanding, and the purpose of my remarks this morning is to throw some light upon what is commonly described as 'industrial toxicology'.

Toxicology is the study of poisons and poisoning. It has several facets, each of which involves different criteria. Thus, the toxicology of drugs and medicines involves different considerations from forensic toxicology, which again involves different considerations from the toxicology of chemical additives to food, or to food-packaging materials. Industrial toxicology is different yet again. It may be defined as 'the study of chemicals used in industrial processes with regard to their liability to produce adverse effects upon the health or efficiency of workers from industrial conditions of exposure'. Experimental toxicology is the tool which is common to all of these different aspects of toxicology, but it should be noted that industrial toxicology is primarily about people who work in factories and not about animals in experimental laboratories. The latter are simply a means to an end; they do not constitute an end in themselves. The artificial laboratory situation, where measured quantities of chemicals are fed to experimental animals, or deliberately introduced into their bodies by injection, does not, in any way, replicate industrial conditions to which workmen are exposed. The fundamental concept of all toxicology is that any chemical will exert toxic effects if it enters the body in sufficient quantity, even salt or sodium bicarbonate, and the art of industrial toxicology is concerned not only with the nature of the toxic effects that a specific chemical will induce, and the quantity of it that is required to induce them, but also with those factors which influence the extent to which that chemical will enter the workman's body. If one excludes

local effects on skin and eye, it must be self-evident that no toxic chemical can exert its toxic effects upon a workman unless and until it has been absorbed into his body. There are three routes by which chemicals may enter a workman's body from industrial exposure:

(1) they may be ingested, *i.e.* taken into the mouth and swallowed. This route is of little importance in industrial toxicology. Workmen do not customarily eat the chemicals with which they work, and the requirements of the Factories Acts prevent the workmen from eating where noxious dust or fumes are given off, so there is little opportunity for their food to become inadvertently contaminated.

(2) they may be absorbed through the skin. This is a far more important route than generally realized, and many important industrial chemicals are readily absorbed through the skin, *e.g.* aniline, nitrobenzene, other nitro- and amido-derivatives of benzene, phenol, nicotine, stilbestrol, parathion, HCN, *etc.* It is mainly a question of high lipid solubility associated with some water solubility, but not all the factors are fully understood. Compounds of high molecular weight are seldom absorbed through the skin.

(3) they may be absorbed by inhalation. This is the commonest route by which industrial chemicals gain access to the body. It implies that they must be airborne, as a dust, fume, mist, or vapour. When inhaled, they may have a local effect on the respiratory tract, *e.g.* sulphur dioxide or phosgene, but they may also be readily absorbed and exert a systemic effect, *i.e.* they may pass into the blood-stream and be distributed throughout the body, *e.g.* HCN, carbon monoxide, H_2S, or lead dust or fume.

There are three separate though related matters which are commonly confused—sometimes even by toxicologists, regrettably—and I would like to ensure that you all understand the difference between them. They are:

(*a*) The toxicity of a compound.
(*b*) The toxic hazard of that compound.
(*c*) The toxic hazard of an industrial process in which that compound is used.

The *toxicity* of a compound is something that is capable of being measured by animal experiment. There is frequently, of course, considerable variation in species response, both qualitatively and quantitatively, but this is not the place to enlarge on that problem. The purpose of the experiment is not to determine whether a compound is toxic or non-toxic, but to determine what is the nature of the toxic effect, and what dose has to be absorbed to induce the toxic effect. Both acute and chronic toxicity studies may be necessary, *i.e.* investigations into the short-term effects of large doses and the long-term effects of small doses.

The *toxic hazard* of a compound is only partly a function of its toxicity (as measured by experiment), but also a function of the ease with which it is absorbed into a workman's body—*i.e.* with compounds of similar toxicity, a compound readily absorbed through the skin will be more hazardous than one which is not, a volatile compound (*i.e.* one that is readily inhaled) will be more hazardous than one which is not volatile. Sodium cyanide and hydrogen

cyanide provide an excellent example. They are of virtually the same toxicity, the toxic effect resulting from the circulation of the cyanide ion within the body. However, although of similar toxicity, they present very different degrees of toxic hazard. Hydrogen cyanide is a volatile liquid, readily absorbed through the skin, and wherever it is used it presents a most serious toxic hazard. Spillage will result in volatilization, and when a workman inhales the vapour, if it is there at more than a very low atmospheric concentration he will die. Similarly, quite a small splash on the skin will be absorbed very quickly, and, again, the workman will die. Sodium cyanide, on the other hand, is commonly used in a variety of industries with very much less care than is necessary for HCN. It is a crystalline solid, usually compressed into 'eggs'. It is not volatile, and there is little, if any, airborne dust. It is not absorbed through the skin to a significant extent, and although it has a very high degree of acute toxicity it cannot exert its toxic effects if it has not been absorbed into the workman's body.

The toxic hazard of an *industrial process* in which a specific compound is used depends not merely upon the toxic hazard presented by the compound itself, but also upon the circumstances of its use, as it is the latter which determines the extent to which the noxious agent — if indeed it is noxious — contaminates the environment of the workplace. The most toxic chemical in the world will not poison a process operator if it remains totally enclosed within a sealed reaction vessel. Thus, before commenting on the toxic hazard of a particular industrial operation, it is essential to know — and to understand — the nature of that operation. It is essential to know what is involved in filtration procedures, in stove-drying, in spray-drying, in grinding, milling, and blending, and in discharging a product into drums or sacks. Regrettably this obvious and simple rule is not always observed, and profound statements of gloom — and impending doom — are from time to time made by individuals unprepared to take the trouble to go and see what actually happens in the factory. The lead hazard provides a simple and obvious example. Should a workman spend his entire day handling lead ingots, he is unlikely to develop any adverse effects on his health (unless he drops one on his toe or strains his back). However, if he puts these lead ingots into an open furnace, heats them until they melt, and maintains the molten lead at an elevated temperature, unless adequate arrangements are made to deal with the lead fume which is given off in such circumstances, he will inhale the lead fume, and if this is repeated day after day will undoubtedly be at risk of developing lead poisoning.

I mentioned that the toxicity of a compound can be measured by animal experiment. The customary yardstick of *acute* toxicity is the LD_{50}, *i.e.* the dose level (administered as a single dose, and expressed in terms of weight of compound per unit body weight of the animal, *e.g.* mg kg^{-1}), which kills 50% of the experimental population thus treated. An LD_{50} of less than 1 mg kg^{-1} represents an extremely toxic substance, and anything with an LD_{50} of less than 50 mg kg^{-1} is generally considered to be highly toxic — though not necessarily highly hazardous. Such measurements are of only limited value. They do give an indication of the order of magnitude of the acute toxic effect, and in respect of highly

toxic compounds this is sometimes important. It must be borne in mind, however, that acute industrial poisoning is very rare. Most industrial poisoning results from repeated exposures to a toxic agent, with repeated absorption of very small quantities, leading to chronic poisoning. For example, by far the commonest industrial poisoning in this country is lead intoxication. The relevance of the LD_{50} to chronic toxic hazards, and therefore to most industrial toxic hazards, is virtually non-existent, but unfortunately this easily understood term has become a piece of fashionable jargon, and is being used for a variety of purposes, usually legislative, where it is simply not meaningful. More of that later, when I come to the Robens' Report.

One of the important pieces of information derived from the LD_{50} experiment, apart from the determination of the actual figure, is that it provides useful information regarding the nature of the toxic effect. This can be a valuable piece of evidence with regard to deciding the need to carry out subacute or chronic toxicity studies, but too much weight must not be placed upon the qualitative effect, however unpleasant, without taking quantitative considerations into account. It can sound quite frightening to discover that, in poisoning by such and such a compound, the liver simply shrivels up or the testicles drop off, but if it takes dose levels of 10 gm kg^{-1} day^{-1} for several weeks to bring this effect about, it is of no consequence as far as industrial toxicology is concerned. From time to time I find it necessary to take issue with Government departments over the transport of so-called 'toxic substances', and on more than one occasion it has been my pleasure to point out that although 'ringing in the ears, with some loss of hearing, nausea and vomiting, accompanied by profuse perspiration and severe thirst, dizziness and drowsiness progressing to delirium, hallucinations, convulsions, and coma, with death the inevitable outcome in severe cases', may sound very frightening, it is simply a description of aspirin poisoning, and that there is not a single recorded case of occupational poisoning in dockers, or indeed in any transport worker, from the handling, in transit, of packages of aspirin tablets.

Another piece of toxicological jargon that has crept into everyday parlance is the term 'Threshold Limit Value'. This is a level of atmospheric concentration of potentially hazardous gases, vapours, or dusts, to which it is believed that workers may be exposed eight hours a day, 5 days a week, 50 weeks a year, without adverse effects on health or efficiency. The figures are not generally exactly the same as Maximum Allowable Concentrations, except in a few instances designated as Ceiling Values, insofar as they represent a time-weighted average, and small swings above the T.L.V. are permitted for limited periods provided they are compensated by equivalent swings below the level. They represent informed opinion on safe conditions, but they have no statutory significance (although they are intended as guidelines of good practice). They do not constitute scientific fact in the way that boiling points or vapour pressures constitute scientific fact, and as they are based on limited evidence, it is not surprising that from time to time they are altered — usually in a downward direction. It should be noted that T.L.V. figures do not represent a yardstick

of hazard. For example, phenol has a T.L.V. of 5 p.p.m., whereas benzene has a T.L.V. of 25 p.p.m. This does not in any way indicate that phenol is more toxic or more hazardous than benzene — on the contrary. In fact, most of you will know that where benzene is used on an industrial scale it requires considerable effort to maintain the atmospheric concentration below the T.L.V., whereas with phenol, a much less volatile compound, there is really no problem.

There are few aspects of chemical toxicity which have aroused more emotion or led to more muddled thinking than carcinogenicity. In recent years there has been greater awareness of the problem (though little increase in the general understanding of it), not merely because the epidemiologists have demonstrated a number of new occupational cancer hazards, not merely because of the publicity arising from litigation, but also because increasing animal experimentation has shown that many common industrial chemicals are 'carcinogenic', and because modern sophisticated analytical techniques have shown the presence of carcinogenic impurities in other industrial products not themselves generally believed to be carcinogenic. The two latter points are worth elaborating in a little more detail.

Firstly, experimental evidence of carcinogenicity. It is frequently assumed that substances that induce tumours when deliberately introduced into the bodies of experimental animals by a variety of routes, often at very high dose levels, will necessarily do so in workmen exposed in industrial conditions. It is scarcely necessary to point out that this is a *non-sequitur*. Carbon tetrachloride is carcinogenic to the mouse, the hamster, and the rat; chloroform produces liver tumours in the mouse, but despite widespread exposure there is no evidence at all to suggest that either carbon tetrachloride or chloroform has caused cancer in man. Tannic acid also induces liver tumours in the rat, whereas the drug Isoniazid induces lung tumours in the mouse. Does anyone seriously believe that these compounds present a carcinogenic hazard to man? The only assumption that should be made on the basis of such experimental evidence is that it might represent a hazard, and therefore all available evidence ought to be critically evaluated both qualitatively and quantitatively. You may not all appreciate quite the number of chemicals involved. In the 1972 List of Toxic Substances published by NIOSH,* 645 different industrial chemicals were listed as either 'carcinogenic' or 'neoplastic', though these terms were not clearly defined. The figure 645 indicated that a large number of chemicals is involved, but the magnitude of the problem becomes more apparent when careful inspection (of the NIOSH list) reveals that α-naphthylamine is not described as either carcinogenic or neoplastic. This suggests that a detailed survey might well reveal other known carcinogens to be missing.

The second point mentioned earlier as requiring some elaboration is concerned with trace impurities of known carcinogens in products not themselves carcinogenic. There is a widespread, though by no means universal, view that there is no such thing as a safe dose of any carcinogen. This is not a school of thought

*U.S. National Institute for Occupational Safety and Health.

to which I myself subscribe. It is a speculative view, unsupported by either experimental or epidemiological evidence, derived from statistical considerations unrelated to reality, and furthermore it is a view which most of us reject in our normal lives. For example, the first recognized carcinogen was soot, the cause of chimney sweep's cancer of the scrotum, first described by Percival Pott in 1775. Few of us would hesitate to clean out a fireplace each morning at home simply because a small amount of soot is present. Those of us who do not clean out the fireplace ourselves do not feel it necessary to give our wives warnings of the dangers of scrotal cancer — or indeed of any cancer which might be caused by soot. Similarly, although many doctors prescribe coal-tar ointments to be used by their patients with skin disease, I have never known any doctor so prescribing to warn his patient that the medicament might cause cancer — for coal tar was one of the first experimental carcinogens. I can only conclude that most doctors share my view that for this carcinogen also there *is* a safe dose. Similar considerations apply to sunlight. It is well known that exposure to sunlight is responsible for many cases of skin cancer on the exposed areas of the body. Yet this undoubted fact does not inhibit those of us who can afford it from dashing off to the Mediterannean to expose ourselves to the maximum amount of sunshine which we find tolerable.

On a more scientific note, it can be stated that not a single carcinogen has been described in respect of which it is experimentally impossible to find a dose which will not cause tumours in a finite experimental population. In practical terms, for workmen exposed to small quantities of carcinogens, a 'safe' dose can be defined as one which does not bring about a statistically significant increase in tumours, beyond the normal incidence in a population not so exposed.

Consider the rubber antioxidant phenyl-β-naphthylamine (PBN). This is not itself carcinogenic, but analysis by gas–liquid chromatography revealed that until about two years ago, commercial PBN generally contained a β-naphthylamine impurity in the range 20—50 p.p.m. Despite the widespread use of PBN in the rubber industry throughout the world for many years, no excess tumour incidence has been attributed to it. Three recent epidemiological surveys (Veys, 1973; Parkes, 1972; Department of Employment, 1972) in the U.K. all indicate that in workmen who joined the rubber industry only after Nonox S was abandoned in 1949 (Nonox S was the antioxidant whose extensive use in the rubber industry led to an occupational bladder tumour hazard in workers who joined the industry prior to 1950), the incidence of bladder tumours is not greater than in the population at large. Indeed, an expert committee (whose members included the Senior Medical Inspector of Factories and the Medical Adviser to the T.U.C.) recommended two years ago that rubber workers exposed to such products with carcinogenic impurities should not be subjected to urinary screening, as opposed to workers known to be at risk of chemically-induced bladder tumours. This apparent absence of hazard with PBN (containing up to 50 p.p.m. of β-naphthylamine) enables important inferences to be drawn in respect of other compounds with carcinogenic impurities. Its importance cannot be over-emphasized.

The real question which has to be considered is not whether such and such a compound is carcinogenic, but whether its manufacture and use presents a carcinogenic hazard to workmen; and, if so, whether adequate precautions can be introduced to obviate that hazard. This involves making a judgement in respect of each single carcinogen, indeed in repect of each single process involving a carcinogen. Making such judgements is not easy, but it is certainly not impossible. Indeed it is essential, because without them there can be no justification for continuing to manufacture or use on an industrial scale any of the hundreds of experimental carcinogens.

The basis of the judgement can be made under four headings:

(1) Critical evaluation of the experimental evidence, both qualitative and quantitative.
(2) Epidemiological evidence — when available. Epidemiology is the study of the incidence of disease, and is an essential tool in identifying cancer risks — or non-risks.
(3) Physico-chemical properties, insofar as they influence absorption in conditions of industrial exposure.
(4) Chemical relationship to other compounds of known hazard, *e.g.* methylene bis-(*o*-chloroaniline) (MOCA) is related to aromatic amine carcinogens.

The second part of the question concerns whether adequate precautions can be introduced to obviate the hazard. This is primarily a question of chemical and engineering techniques, associated with biological and environmental monitoring, which need not be discussed here. Nevertheless, by the application of appropriate measures, it has been found possible to wipe out the incidence of lung and nasal cancer associated with the Mond process for refining nickel, and the cancers associated with isopropyl alcohol manufacture: it has been found possible to use carcinogenic *X*-rays for purposes of medical diagnosis; and to use, for industrial purposes, highly hazardous radio-isotopes of undoubted carcinogenicity.

The Robens' Committee made far-reaching recommendations for the control of toxic substances, and the Department of Employment has recently published consultative proposals regarding the implementation of these recommendations. Many of the proposals require discussion at length, but I intend to mention only one this morning. It is concerned with the notification of new substances, or those coming into commercial use for the first time, to the proposed Advisory Committee on Toxic Substances. The criteria which have been suggested are that notification should be required only where the oral LD_{50} in the rat is less than 200 mg kg^{-1}*, or where the percutaneous LD_{50} in the rat (*i.e.* the LD_{50} by absorption through the skin) is less than 4000 mg kg^{-1}. Now most industrial poisoning, as I told you earlier, has nothing to do with acute toxicity. Most industrial poisoning arises from chronic exposure, from the repeated absorption of small quantities of a toxic agent over a period of weeks, or months, or years.

*The figure of 200 mg kg^{-1} in the Consultative Document was a misprint. It has subsequently been corrected to 2000 mg kg^{-1}. The comment in the penultimate paragraph is, therefore, perhaps less relevant than was the case when it was made in October 1973.

The criteria suggested would permit substances as hazardous as β-naphthylamine, or toluene di-isocyanate, to be introduced without any reference to the Advisory Committee, thus defeating the whole object of the exercise. In my view, the only way in which the Robens recommendations can be properly implemented is by notification of all new substances, together with essential chemical, physical, and basic toxicological data about them. The basic toxicological data would simply be an oral LD_{50} figure, together with data regarding irritant effects on skin and eye. Armed with this information, the expert committee can then decide whether any further testing is necessary, *e.g.* percutaneous toxicity, inhalation toxicity, sensitizing potential, carcinogenicity studies, and the like. One may or may not believe the Robens recommendations to be sensible, but this is the only way of implementing them. Anything short of this is simply window-dressing. If it is worth doing at all, it is worth doing properly.

Mr. Chairman, that is all I wish to say. We all have a duty to pay a great deal of attention to health hazards to workers, and I am grateful for the opportunity to express my views.