RISK ASSESSMENT OF EXPOSURE TO CHEMICALS

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I INTRODUCTION

A FAIRLY large number of the synthetic organic chemicals in common use today are potentially toxic to man and other living organisms. Many of them are alien to our environment and consequently are capable of disturbing ecological equilibrium. Some chemicals are almost indispensable for the life styles prevailing today. The question that arises, therefore, is what is the basis on which we accept the risk inherent to the use of chemicals? As corollaries to this basic question, we have to ask ourselves what is the risk involved in the continuous and often life-long exposure of man to low doses of a chemical which when given in a large enough dose, at a time, produces serious health injury and often death? Does the state of our present knowledge of human health effects of chemicals give us the confidence to calculate risk factors and thus clear them as safe for human use? Do we have the capability to predict the environmental impact or injury to ecosystems of our biosphere likely to arise by the continuous diffusion of a relatively non-degradable chemical compound? Taking an example of immediate relevance to us in the less developed countries, has the decision to permit the continued use of DDT as an insecticide without the backing of an adequately conducted risk-benefit analysis?

This paper is an attempt to project some aspects of the management of the risk of exposure to chemicals. Broadly, risk management is made up of the following components: identification of hazard, estimation of the risk, assessment of risk to a community in a given set of circumstances, estimation of the willingness of the community to accept or propensity of the ecosystem to adjust itself to the risk, analysis of benefits and harm and alternatives[1]. It is worthwhile to question whether decisions taken in the management of the risk of exposure to some chemicals are determined by the above components or by the pressure exerted by vested interests or public opinion based on fear. All these aspects cannot be obviously dealt within this brief overview. It is hoped, however, that the problems posed will lead to a wider and deeper discussion of the many issues involved.

II NATURE AND MAGNITUDE OF THE PROBLEM

By the end of 1930 *Chemical Abstracts* had already covered over five million chemical species which give an idea of the number of chemicals known to man and produced by him for one use or the other. Currently, there is substantial world trade in about 45,000 chemical substances. One hundred and fifty chemicals are produced in quantities exceeding 50,000 tons per annum. About one hundred and fifty million tons of synthetic organics are manufactured annually. These figures indicate the magnitude of the global impact of the spread of chemicals. The list of chemical entities used for producing synthetic polymers and plastics enumerates about five thousand items of which more than a hundred are recognized as "highly toxic" or "highly hazardous". This example is enough to realise the nature of the problem of exposure to man-made chemicals[2,3]

All chemicals known to man can be divided into two broad groups: (i) natural products, and (ii) xenobiotics. All chemicals formed by the activity of living organisms in the biosphere or by natural processes involving cosmic and ter-

restrial chemical reactions constitute natural products. Xenobiotics, on the other hand, are those compounds produced by man, normally absent in the environment, and contain often structural features incompatible with the metabolic capabilities of living organisms or the resilience of eco-systems. Thus, in his relentless search for unique properties such as thermal stability, durability or a given biological activity, man has exploited functional groups like long chain silicones, nitro or trifluoromethyl substituted aromatic rings or multiple halogen substitution—groups rarely found in living organisms. Again to confer durability man has used polymerization reactions with cross linking of chains in the recalcitrant chemical substances of today.

It is rather difficult to draw a sharp line between natural products and xenobiotics in regard to their/compatibility with the environment or their toxicity to living organisms. Thus, all natural products are not unexceptionally safe or compatible with the environment and all xenobiotics are not unsafe to living organisms or incompatible with the environment. Furthermore, the recent discovery of persistent aromatics including dioxin in the fly ash of thermal power stations or polychlorinated organics in some marine organisms has challenged the very basis of differentiation between natural products and man-made chemicals[4-6]

III CHEMICAL POLLUTION

Our deep concern today with the pollution potential of chemicals owes its origin to one or more of the following:

i) increasing industrial activity associated with development and dependent on modern chemical technology,
ii) growing needs for energy,
iii) updating of agro-techniques,
iv) disturbing revealations by sophisticated analytical instruments with capabilities of estimating chemicals at picogram levels that many more chemicals are persistent in the environment than were thought to be a few years back,
v) ability of some chemicals to bio-accumulate because of their lipophilic characteristics,
vi) emergence of newer concepts of injury caused by chemicals including their eco-toxic effects,
vii) limitations of currently available experimental methods to demonstrate biological effects of chemicals at levels detected by modern physical techniques, and
viii) global spread of chemicals and variation in regulatory controls from country to country.

Chemical pollution itself is made up of two ominous sides:

a) health effects on man and his ecological partners in the biosphere, and b) injury to ecosystems.

Health effects of chemicals are related to their toxicity. Injury caused by chemicals to ecosystems results from both their biotic and abiotic effects.

The terms risk, injury and exposure commonly used while discussing the effects of chemicals on man or ecosystems need some definition. *Risk* can be considered as the product obtained by multiplying chance by injury. *Injury* can be defined as the product obtained by multiplying toxicity by exposure. *Exposure* can be taken to represent the product obtained by multiplying concentration with time. It is evident from the above over-simplified definitions that whereas injury and exposure can be quantitated with some confidence, the involvement of the factor chance makes it difficult to quantify risk with any reliability. Another dilemma that faces us today is the realisation that risk assessment cannot be dissociated from risk benefit considerations. However, the latter envisages many imponderables and are often subject to socio-political value judgements which are obviously beyond any mathematical conceptualization.

IV ASSESSMENT OF HEALTH EFFECTS OF CHEMICALS

The two approaches used currently to evaluate health effects of chemical pollutants on man are—

i) epidemiological studies, and
ii) laboratory studies.

Two binary types of variables have to be taken into consideration in epidemiological studies, *e.g.* loss of function/no loss of function, cancer/no cancer, exposure to a chemcical/no such exposure[7-9]. The occurrence of disease, signs, symptoms, etc., has to be measured. Diverse types of questionnaire based protocols are used and subjective data is supplemented with objective tests. Prevalence and incidence rates are commonly used indicators of health effects which lead to reasonable estimates of population at risk. The standard morbidity ratio is another indicator. Exposure indicators, and the other useful parameters are more difficult to be standardized. The reliability of the inferences depends much upon the quality of the data collected and the manner in which they are assembled for analysis. Registries maintained by hospitals can give useful information. Registries of births and deaths maintained by civil authorities can be valuable sources. In many countries such as India, registries are either totally non-functional or inadequate to undertake retrospective studies. *Cohort* studies in selected population at risk can generate some data but extrapolation of the same to the general population is not possible under all situations.

The main justification for retrospective and prospective epidemiological studies is the likelihood of gaining access to data which with suitable mathematical modelling can be used for predictive purposes.

Mathematical models for exposure—effect relationships have relied on multivariate linear and logistic types such as —

$$\ln (pD/1 - pD) = \sum_{i=1}^{k} b_i x_i \qquad (1)$$

where pD = probability of disease in a given period.

b_i = linear set of coefficients in the function $\Sigma b_i x_i$ estimated and coefficients of discriminate functions.

x_i = set of exposure indicators and/or effect modifiers.

From (1) we get

$$pD = \frac{1}{1 + \exp(-\Sigma b_i x_i)}$$

which gives the probability of D as a weighted multiple logistic function of the k "predictors". If the x's are binary, the estimated $\exp(b_i)$ gives the estimate of the risk ratio.

Laboratory studies on health effects use animal models to simulate the expected effects on humans or *in vitro* test systems consisting of whole perfused organs kept physiologically alive for short periods or selected animal or human cell lines in culture. Limitations of laboratory experiments on animals have wide fluctuations, lack of reproducibility and as yet undiscovered mechanism of interaction of factors of homeostatic control in test animals with exogenous factors[10]

Quantitative evaluation of the biological changes elicited by chemicals is carried out in animal models in order to establish dose-effect and dose-response relationships. Such studies conducted both under acute and chronic conditions of exposure by diverse routes help in the computation of LD_{50}'s or LC_{50}'s which give quantitative estimates of concentration of the chemcial required to cause 50% mortality from which chemicals are broadly classified as "extremely toxic", "relatively toxic", "relatively non-toxic" and "non-toxic". Many protocols for testing chemicals on selected species of animals, birds and fish are available. In order to render

the data derived from animal tests of relevance to the human situation, it is of utmost importance to incorporate different internal and external variables[11].

Quantitation of biological effects elicited by chemicals is based on differentiating the nature of effects between adverse and non-adverse or reversible and irreversible. Absence of changes in the gross morphology of cells of vital tissues such as liver, brain, heart, kidneys, reproductive organs, or no perceptible effects on growth, development and life span is taken as non-adverse effects. Such effects, if any, are assumed not to lead to the impairment of the capacity of the organism to compensate for auditional stress. Such effects, if any, are assumed not to lead to the impairment of the capacity of the organism to compensate for additional stress. Such effects, furthermore, are reversible on the cessation of exposure to the incriminated chemical. In contrast, adverse effects refer to those changes that lead to the impairment of functional capacity determined by anatomical, physiological, biochemical or behavioural parameters. They also lead to the depression of the ability of the organism to compensate for additional stress. Adverse effects are generally irreversible and enhance the susceptibility of the organism to the deleterious effects of other environmental influences.

Adverse effects have been brought within the purview of statistical definitions which in turn have permitted the derivation of the "confidence limits" or "tolerance limits". In general, chronic toxicity studies aim to establish the "maximal no-observed-adverse effect level" and to determine the signs of chronic intoxication and the organ and physiological systems affected by exposure to the chemical. Effects produced have to be related to the toxicokinetics of the chemical in order that the rate of absorption, distribution, metabolism and elimination of the chemical lead to an understanding of the mechanism of toxicity and to identify target organs. In quantifying biological effects, one has to account for the subtle departures from "normal" physiology of the intact organism as well as the morphology of the target organ.

V EXTRAPOLATION OF LABORATORY DATA TO MAN

Animal studies provide basic information on the toxicity of chemicals, including toxic doses and types of injury and mechanism of toxic action. The data can be used, within certain constraints, to establish new or correct existing environmental exposure limits for humans. Although qualitative effects in humans can usually be inferred from animal studies with a high degree of certainty, the reliability of quantitative prediction is influenced by the choice of animal species, design of the experiment and the assumptions made in the extrapolation.

Quantitative differences in toxic response exist between humans and animal species. Man is generally more sensitive to lethal doses than most of the animals commonly used in experimental work. Thus, the human is 100–350 times more sensitive to atropine, morphine and nicotine than are laboratory animals. Even among animal species, there are wide differences, *e.g.* the mouse is more sensitive to the carcinogenic action of vinyl chloride than the rat whereas reverse is the case in regard to the carcinogenicity of aflatoxin. Species differences in sensitivity to toxic chemicals are related to routes of exposure and rates of their absorption, biotransformation, excretion or the toxicokinetic parameters[13-15]

In the extrapolation of interspecies data, a species conversion factor is used. This factor can vary from one to ten. One can also calculate the dose of a chemcial per unit surface area approximately equivalent to the weight raised to the power two thirds. The alternative approach, the "body weight rule" is based on an established relationship between the indices of acute toxicity and body weight for different animal species. For 80–85% of the total number of 700 substances tested, the logarithm of toxicity indices in the laboratory animals show a linear regression to the logarithm of body weight. The regression coefficients for individual ranges from 0.1 to 5.5. For most substances the values lie between

0.9 and 0.5 suggesting that the sensitivity of the animals to those chemcials increases as a linear function of body weight. It is possible to construct monograms from data obtained from experiments with four animal species and derive "maximum allowance concentrations" or "threshold limit values"

Laboratory experiments are conducted with genetically homogeneous inbred strains of animals and extrapolation has to be made to a widely heterogeneous genetically "outbred" human population. Epidemiological studies are also usually conducted on specified groups such as those occupationally exposed to a chemical. The data thus generated have to be extrapolated often to a population which includes genetically predisposed individuals with increased susceptibility to the chemical. In animal experiments, it is possible to control the influence of environmental factors such as ambient temperature, hygiene, diet, light, etc. In epidemiological studies, it is not possible to distinguish between individual and synergistic effects of chemicals or their modulation by environmental factors. Besides, there is a great variation in human health and individual resistance to the deleterious effects of xenobiotics and infections. The socio-economic factors determining the living conditions of the majority of human beings likely to be exposed to toxic chemicals have to be taken into consideration while assessing the safety of chemicals. As at present there are no conceptual approaches to quantitate the influences of these factors.

A safety factor has been introduced to obviate differences of species, response, etc. and is calculated from the relationship:

$$K = A \cdot Z_{CH} \cdot \frac{W}{Z_{AC}}$$

where K is safety factor

A = a coefficient characteristic of the chemical.

Z_{CH} = coefficient of chronic effects.

$$= \frac{\text{Threshold of acute effects}}{\text{Threshold of chronic effects}}$$

Z_{AC} = coefficient of acute effects

$$= \frac{LC_{50} \text{ or } LD_{50}}{\text{Threshold of acute effects}}$$

W = Coefficient of hazard of inhalation

$$= \frac{\text{Maximum conc. at } 20^\circ C}{\text{Threshold of chronic effect}}$$

$$= \frac{\text{Maximum conc. at } 20^\circ C}{\text{Threshold of chronic effect}}$$

Safety factors have been calculated for many industrial chemicals on the basis of experimental data.

An *alternative method* is to relate the size of the safety factor to parameters of the concentration time dependence curves constructed from experimental studies. According to the size of the safety factors, chemicals can be divided into "extremely hazardous", "highly hazardous", "moderately hazardous" and "mildly hazardous". The value of safety factors depends on the nature of the toxic effects, the type of dose-response curves, the size and type of population to be protected and above all the quality of the toxicological data. In industrial hygiene practice, safety factors range from 2 to 10 whereas for carcinogenic chemicals safety factors ranging from 10 to 5000 have been proposed.

Low dose extrapolation is based currently on mathematical models employed to predict the response at a given low dose or to predict that dose which gives a predetermined low response. Several extrapolation procedures have been proposed which will give an upper limit to the dose corresponding to a low response. Two of the most commonly used procedures are: one hit model, and the probit model. The one-hit model assumes that an effect can be induced after a simple susceptible target has been reached by a single biologically effective unit or dose. In their

simplest form, and on the assumption that a true response at zero dose is zero, the following procedures are used:

i) the upper 99% confidence limit (*UCL*) is estimated for the observed response at a dose *d*,
ii) a desired limit is set for a low response (R), *e.g.* 1 in 100000, and
iii) the dose (dc) that would produce a response which is with 99% probability.

R is then calculated from the equation.

$$dc = \frac{d \cdot R}{UCL}$$

The probit model gives a dose-response curve that is concave at low levels; it is less conservative than the linear model based on one-hit hypothesis. The procedure involves—

i) the choice of a desired limit of response R (1 in 1000000)
ii) the estimation of the upper 99% confidence limit for the observed effect at dose *d*
iii) imposing a probit-log dose straight line through UCL with a slope equal to 1.

Low-dose extrapolations made by the above procedures still suffer from a certain degree of arbitrariness. Indeed the same degree of arbitrariness is part of "decision taking" while fixing "maximum allowable concentrations", "threshold limit values" and "admissible intakes", etc.

It is accepted today that the intensity of the effect or the biological response to a chemical, decreases with the reduction in the dose and the effect often reaches zero before the dose level is reduced to zero. Below a certain limiting exposure level, called a *threshold level*, a chemical may not generally elicit a toxic effect. However, the existence of a threshold for all adverse effects is a matter for debate. Thus, it is believed today, thanks to the advances made in our knowledge of biochemical mechanism of tumour induction, that a single molecule of a carcinogen can trigger the process that leads to the end effect. Similarly, a single hit on one adenine base, of the nucleotide sequence of DNA is capable of producing mutation of genetic activity. Is it justifiable, therefore, to fix "threshold values" or "admissible intakes" for suspected carcinogens or mutagens[16-22]?

VI ASSESSMENT OF CHEMICAL INJURY TO ECOSYSTEMS

The response of organisms to xenobiotics in the laboratory as in the classical model, fish in a tank, differs from the response of the same organisms to the same concentration of the chemical in its natural habitat. Hence, there is a need to develop methodologies to assess the toxicity of chemicals under field conditions in specified ecosystems. In order to reduce the complexities of field experiments, microcosms have been employed in ecotoxicological studies.

The initial step in risk assessment to ecosystems is to arrive at estimates of exposure to the pollutant. The concentration of a chemical in an environmental subcompartment depends on the rate of input (loading), the size of the reservoir and the rate of removal. The flow rate in or out is referred to as fluxϕ. The residence time (trs) is defined as the ratio of the amount of material in the reservoir at a given time to the instantaneous rate of addition or substration of material. The fundamental relationship used is

$$\frac{-\,\mathrm{d\ tres}}{dt} = \frac{\phi}{V} \cdot C$$

where C is concentration, V is volume of reservoir and when $t = 0$ and $C = Co$

$$C = Co \exp(-\phi / V)t$$

The amount of a chemical found in any particular environmental sub-compartment is modulated by—

i) the rate and place of release
ii) equilibrium distribution process and
iii) loss, degradation, disappearance.

Dynamics of a xenobiotic in the environment can be taken as the integration of many contributing processes. It is evident from the above that if the contributing processes and the physico-chemical properties of the chemicals are known one can get a fairly accurate estimates of the pollutant load. There are, however, some problems when one evaluates the current procedures for monitoring the pollutant loads. Computerised, exposure analysis modelling systems (EXAMS) have been used in U.S.A. for predicting environmental concentrations.

Effects on ecosystems have to be measured in terms of loss of productivity, biomass, disturbances in food web etc., or erosion into aesthetic values. A number of indicator models have led to International Programme such as the Mussel watch or the Global Environmental Monitoring (GEM) Programme initiated by UNEP. There are also attempts to conceptualize the health of an ecosystem analogous to health of a human being. On the whole, the currently available methods for the assessment of risk to ecosystems need considerable refinement to permit quantitation[23-27]

VII CONCLUSION

As evident from the above discussion risk assessment of exposure to chemicals is at the moment based on statistical probabilities. Extrapolation of data collected from the laboratory or the field to the human makes many assumptions. Risk ratios, risk factors, threshold limits, maximum allowable concentrations, all need constant updating. And yet, important legislation is evolved on these factors, to take care of the safety of workers or the common man consuming a chemical product.

The ability to take risks varies from individual to individual and from communities to communities depending on a variety of complex psychological and socio-political factors. The risk of a patient suffering from side effects of a toxic drug administered for a specific therapeutic purpose is decided by the ethical relationship between the physician and the patient. However, when a person becomes a victim of self-medication or abuse as in the case of narcotics, society steps in to evaluate the risk and counter it. It is argued from one end that development leads inevitably to pollution and society must learn to manage the risk of exposure to a diverse variety of chemicals in view of the progress to be attained by development. From the other end, the rejoinder is: risk at whose cost? Scientists concerned with the multidisciplinary area of safety evaluation of chemicals are caught between these two extreme views. Since decision-taking will ultimately depend on the information provided by scientists, it is their social responsibility to fill existing gaps in the knowledge of the mechanism of toxicity, environmental behaviour of chemicals and to devise appropriate predictive models based on data of unquestionable integrity and validity[28,30]

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