AN APPROACH TO QUANTITATE AND CONTROL THE MUTAGENIC HAZARDS OF ENVIRONMENTAL CHEMICAL AND RADIOACTIVE POLLUTANTS

by

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The genetic material in all living organisms, with the exception of some viruses, is deoxyribonucleic acid (DNA). Genetic information contained in the DNA is organised into units which can be broadly called genes. Mutation consists of abrupt heritable changes in the composition or arrangement of genes. Eventhough mutation and selection are known to be two important forces responsible for the evolutionary process, it is generally believed that any further increase in the mutation rate in man is deleterious to his health. Hence many geneticists are of the opinion that Man's genes constitute his most precious heritage and that deterioration in gene quality should be prevented at all costs. It is estimated that about 6-9% of all the children born have some kind of a genetic defect or the other with varying degrees of seriousness[1]. There are nearly 2000 genetic diseases known to-day[2]. Further increase in the mutation rate will only boost this statistics.

In the earlier generations, the so-called spontaneous mutations were caused by factors such as natural background radiation, naturally occuring chemical mutagenes and probably some other unknown agents. The natural background radiation constitutes cosmic radiation, radiation from radioactive substances in earth crust (uranium, thorium, radium etc.) and those present in human body (carbon-14, potassium-40 etc.) The naturally occuring mutagenes constitute mycotoxins such as aflatoxin produced by moulds growing on fermented food; alkaloids present in plants used as food

cooking ingredients or as folk medicine; Cycasin, a water-soluble toxic component of the nuts of cycad plants which are also used as food and in medicinal preparation and a number of miscellaneous products such as oils like Safrol[3].

Gene mutations can also be induced by a number of man-made chemical substances and radiation. With the advent of Science and Technology man has introduced a number of artificial radiation sources such as X-ray generators, radioactive isotopes, nuclear reactors and nuclear weapons, and an even larger number of chemical compounds into the environment. It is estimated that nearly 4 million chemical substances are in use to-day and another 700 new chemicals are being introduced every year. These constitute industrial chemicals, by products, solvents, agricultural chemicals such as pesticides, herbicides, other processed consumer goods such as drugs, pharmaceuticals, cosmetics, food additives and preservatives etc. Many of these are produced in millions of tons every year, are widely distributed and used. During the course of their manufacture, distribution and use, pollution of food, water and air takes place resulting in the exposure of human population both at the occupational and non-occupational levels. While the mutagenic and carcinogenic effects of radiation are well established, many of the chemicals tested are also known to cause similar effects in a variety of biological test systems. Table 1 gives a list of some of the environmental mutagenic agents. Because of the dreadful experiences of the Japanese in Hiroshima and Nagasaki, radiation is the most extensively studied and controlled environmental pollutant.

In order to quantitate the mutogenic hazard of any agent, a number of parameters must be known. A few of these are 1) the spectrum of the genetic effect induced, 2) the heritable properties of the observed damage, 3) the dose-effect relationship at low doses of interest, 4) effect of single and repeated exposures, 5) differences between acute and chronic exposures, 6) dependence of the effect on dose rate, age and sex, 7) influence of repair mechanisms. Information on all these parameters relevant to man must be obtained in order to quantitate and control the hazards. Since it is unethical to conduct experiments on man himself, one has to depend on epidemiological data and animal experiments. As far as radiation is concerned, the present day knowledge on the hazards is based on epidemiological survey of early radiologists and radium dial painters, observations made on the uranium mine workers and patients exposed to radiation for medical purposes, the studies of the Atomic Bomb Casualty Commission on the survivors in Hiroshima and Nagasaki, and on carefully controlled laboratory experiments on animals.

On the basis of these information, we now know that a) the dose required to double the human mutation rate (doubling dose) is about 100 rads[1] and (b) the rate of induction of cancer in human beings is in the range of 100-200 per year in one million population exposed to a dose of 1 rad[5]. Even though there are several uncertainities in the data-base used in generating these quantitative figures, they nevertheless form the corner-stone of an effective program of radiation hazard control all over the world. On the basis of these data, maximum permissible levels for occupational and population exposure to radiation have been recommended at 5 rem/year and 5 rem/generation respectively[6]. The most important aspect of this control program is to emphasise that radiation exposure be kept "as low as readily achievable economic and social considerations being taken into account"[6]. Consequently

the actual exposures experienced by the occupational workers and population are in the range of 1/10 to 1/40[2] of the recommended limits respectively.

One can estimate the risk involved at the permissible exposure level in the application of radiation to human welfare. For the occupational workers, this would mean an additional number of 500-1,000 cases of cancer incidence per year in one million workers. This should be compared with the rate of the so-called spontaneous cancer incidence in the control population which is about 3000 per year per million. For the general population, the limit of 5 rem/generation is about close to the natural background radiation level (3-4 rem/generation). This would mean an increase in the spontaneous mutation rate by about 5% per generation or less than 1% increase in the incidence of genetic disorders. This, coupled with the observation that the actual exposure levels experienced are much less than the permissible ones, constitutes an acceptable risk, in view of the enormous benefits mankind accrues from harnessing radiation.

Let us take a look at the chemicals. Many of these chemicals have been evaluated from general toxicity point of view and acceptable daily intakes (ADI) have been established. However, the mutagenic potentialities of these chemicals are only being realised recently. Hence, the mutagenic significance of the exposures at the levels of ADI is not known.

In order to quantitate the hazard and control human exposure to chemical mutagens we require information on all the parameters listed earlier for each chemical or at least for groups of chemicals. Considering the astronomical number of chemical substances, the task of establishing a data-base is almost impossible both from the economic as well as temporal

point of view. Hence, a short-cut approach is required to quantitate the mutagenic hazards of these chemicals. One of the simplest approaches suggested is to express the mutagenic hazards of chemicals in terms of equivalent radiation units. With the vast experience gained in the control of radiation hazards, such an approach can be easily adopted for risk-benefit analysis in the case of chemicals. In order to promote such an approach, the Committee 17 of the Environmental Mutagen Society of the USA has suggested that a common unit of mutagenicity be adopted[2]. The unit is called rem-equivalent-chemical (or preferably rad-equivalent-chemical)-REC. The "REC is that dose or product of concentration multiplied by time which produces an amount of genetic damage equal to that produced by one rem of chronic irradiation'[2]. The most important advantage of this approach is that the mutagenic hazards of all man-made agents in the environment can be expressed in a single unit. For example, on this scale 1 rem = 1 REC. This will facilitate the control of the total mutagenic burden to the society from all man-made sources. The committee felt that the total mutagenic burden to the society should not exceed the limits set for radiation alone. Hence it recommended that "the total mutagenic exposure from man-made chemicals as well as radiation" be limited to 5 REC/generation[2].

In order to appreciate the usefulness of this approach and estimate the relative hazards of different chemicals at the current rate of exposure, the Committee evaluated the REC values for a few substances[2]. For example, one human therapeutic dose of lycanthone corresponds to about 1.3 REC and approximately 1.2 mg/kg of ethyl methanesulfonate corresponds to 1 REC. Similarly the consumption of nitrite by the average North American man during

the reproductive life time corresponds to as much as 8 RECS. Similar equivalent values, on a slightly different basis, have also been evaluated for a few other chemicals[7]. These are shown in Table 2. Even though the real significance of these estimates are not clear, they still point out the high degree of mutagenic and carcinogenic risk of chemicals in our environment.

There are a number of limitations for the REC approach. The most important is that the mutagenic spectrum caused by chemicals and radiation in a given test system must be similar for a meaningful comparison. This may not always be the case[6]. Further, there may be differences in the mechanism of action, age and sex dependence between radiation and chemicals. Efficiency of a chemical in a test system is also dependent upon other factors such as cell wall penetration, metabolism etc. It is also not clear whether diverse test systems generate similar REC values for a given compound. The question of extrapolating the REC data from test systems to human beings always exists. Notwithstanding these problems, it has been shown by Abrahamson et al[9] and Heddle and Athensiou[10] that the mutagenic efficiency of radiation and the chemical EMS, respectively, can be expressed on a common basis, ie; the haploid genome size, for a number of different species ranging from virus to humans. On the basis of this, it can be expected that a constant REC value can be obtained for a given chemical, irrespective of the test system employed[10]. We have also shown recently that REC values obtained for different end points are also comparable, emphasising the generality of the concept[11]. Thus, eventhough the REC approach is not the final solution to the problem of

quantitating the mutagenic hazards of chemicals in the environment, it will provide, at least, a rough basis for their control which is urgently needed.

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REFERENCES

1) Sankaranarayanan, K. Evaluation and re-evaluation of genetic radiation hazards in man. III. Other relevant data and risk assessment, Mutation Research. 35, 387-414, 1976.

2) Environmental mutagenic hazards - Science 187, 503 - 514, 1975.

3) Clark, A.M. Naturally occuring mutagenes, Mutation Research 32, 361-374, 1976.

4) Fishbein, L. Industrial mutagenes and potential mutagenes. 1. Halogenated aliphatic derivatives. Mutation Research 32, 267-308, 1976.

5) Report of the United Nations Scientific Committee on effects of atomic radiation. U.N. General Assembly Official Records Seventeenth Session, Supplement No. 16 (A/5216) 1962.

6) Annals of ICRP 1977

7) Murthy M.S.S., Radiation Safety Standards : An environmentalists' view. Paper presented at the 4 Annual Meeting of the Indian Association for Radiation Protection. Madras-Kalpakam, 1979.

8) Auerbach, C. The effects of six years of mutagens testing on our attitude to the problems posed by it, Mutation Research 33, 3-10, 1975.

9) Abrahamson, S; Bender, M.A.; Conger, A.D. and Wolff, S. Uniformity of radiation induced mutation rates among different species, Nature 245 460-462, 1973.

10) Heddle J.A. and Athanasiou, A. Mutation rate, genome size and their relation to the rec concept, Nature 258, 359-361, 1975.

11) Murthy, M.S.S. and Sankaranarayanan, K. Determination of radiation equivalence of ethyl methanesulphonate (EMS) for induction of gene conversion in diploid yeast - Manuscript under preparation.

TABLE-1

SOME ENVIRONMENTAL MAN-MADE MUTAGENS

INDUSTRIAL CHEMICALS.

HALOGENATED HYDROCARBONS AND EPOXIDES:

TRICHLOROETHYLENE, VINYL CHLORIDE, 1,1, DICHLOROETHYLENE, CHLOROPRENE, 2 CHLORODUTADINE.

OLEFINIC AND AROMATICHYDROCARBONS:

BUTADINE, STYRENE, STYRENE OXIDE, BENZENE, BENZO (a) PYRENE

AMINES AND NITROSAMINES:

2-NAPHTHYLAMINE, BENZIDINE, 4-AMINOBIPHENYL, 2-ACETYLAMINO-FLUORENE.

AGRICULTURAL CHEMICALS

PESTICIDES AND HERBICIDES:

CAPTAFOL, DAPA, NBT, CAPTAN, DICHLOROVUS, FOLPET, 2-HYDRAZINOETHANOL (HEH), 5-NITRO-1-NAPTHONITRILE (NNN), VAMIDIOTHIN, ETHYLENE DIOXIDE, ETHYLEN DIBROMIDE, HEPTACHLOR, CHLORDANE.

OTHER CONSUMABLE ITEMS:

HAIR DYES; DRUGS (HYCANTHONE, CYCLOPHOSPHAMIDE, ICR 170, SQ 1506 ETC); FOOD ADDITIVES (AF2, NITRITES, SODIUMBISULFITE, SACCHARIN, ETC.)

RADIATIONS

UV, IONISING RADIATIONS (X-RAYS, GAMMA RAYS, NEUTRONS, ETC.)

TABLE-2 : SOME ESTIMATES OF HAZARDS OF EXPOSURE TO CHEMICALS IN TERMS OF "EQUIVALENT RADIATION DOSES"

CHEMICAL COMPOUND	EQUIVALENT RADIATION DOSE
ONE THERAPEUTIC DOSE OF HYCANTHONE	1·3 REC
$NaNO_2$ (CURRENT CONSUMPTION RATE)	8 REC / GENERATION
ETHYLENE OXIDE (5 ppm / 40 hours)	4 Rem
OVERALL EFFECT OF CHEMICAL POLLUTANTS FOR CANCER INCIDENCE	4 - 18 REM