Mutagenicity, Carcinogenicity, and Teratogenicity of Industrial Pollutants

Edited by
Micheline Kirsch-Volders

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This book is dedicated to our colleague and friend,

Prof. Dr. Fernand Poncelet,

President of the Belgian Environmental Mutagen Society,
who died in an accident in October 1982

Preface

This book is intended for anyone who cares about the health of people exposed to industrial pollutants. Attention is given to those pollutants which present a possible risk to the genetic material of exposed workers. Chapters are devoted to heavy metals such as arsenic, beryllium, cadmium, chromium, lead, mercury, nickel, etc.; insecticides (chlorinated, organophosphorus, and carbonate insecticides); monomers such as vinyl-chloride, acrylonitrile, styrene, vinylidene chloride, butadiene, chlorobutadiene, hexachlorobutadiene, etc.; and halogenated hydrocarbon solvents such as chloroform, carbon tetrachloride, trichloroethylene, 1,2-dichloroethane, tetrachloroethylene, dichloromethane, and 1,1,1-trichloroethane.

The main aim of this work is to provide the physician, the biologist, the pharmacologist, or anyone involved in genetic toxicology with a useful compendium of up-to-date information and references.

Efforts are made to open the field to nonspecialists. An introductory chapter deals with the mechanisms whereby a given compound, reaching genetic material, either directly or indirectly, may increase the risk of a cancer developing in the exposed individual and of abnormalities being passed on to his or her progeny.

Efforts are also made to allow easy and efficient reading for those who are not interested in detailed results. Comparative tables provide the following data on the compounds studied: chemical properties, production, occurrence, accepted standards in the industry, and positive or negative results with different test systems.

Finally, senior research workers might find good descriptions in this book of the most recent results from mutagenesis and carcinogenesis testing in plant, nonmammalian, and mammalian systems.

I hope that this book will contribute to a better link between university research workers and industrial teams who have to reconcile the necessity of production with the health of workers. This is not only our wish, but also the

well-defined proposal of the International Environmental Mutagen Society and our local section, the Belgian Environmental Mutagen Society.

M. Kirsch-Volders
Brussels

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F. Poncelet, M. Duverger-van Bogaert, M. Lambotte-Vandepaer, and C. de Meester

Introduction

Mutagenesis as a Health Problem

C. Susanne

Man has been able to make tools for at least 5 million years, to make fire for at least a half-million years, and practice farming and agriculture for at-least 10,000 years. In a sense, it is a long time ago that man developed control over ecological factors. Even pollution is not a new problem, since agriculture itself cannot avoid altering the naturally balanced ecosystems. Pollution is certainly not limited to advanced civilization (Brothwell, 1972). Since the neolithicum, forests have been permanently destroyed by fire and the ground has been degraded (North Africa, the Middle East). Irrigation of fields has been known for 5000 years in Egypt and Mesopotamia, and resulted in an increase of schistosomiasis. Growth of populations resulted in new urban environments and air pollution. Since chimneys were absent in primitive houses, evidence of anthracosis has been found in some Egyptian mummies. Lead poisoning was already known during the Roman period.

However, the problems created by pollution are surely more serious in our industrial societies, where energy and efforts are needed to control its effects. One aspect of pollution is difficult to study because the effects are not observed directly, but sometimes appear years later in terms of cancer or congenital diseases. Mutagens are introduced in our environment and could potentially increase the frequency of mutations. These mutations are modifications of the DNA at gene level (point-mutations: classical recessive, dominant, sex-linked mutations), at chromosome level (modification of structure such as deletions, translocations, dicentrics, ringchromosomes), or at genome level (modification of the number of chromosomes). These different types of mutations occur in somatic cells and might, for example, lead to cancer or alterations in germinal cells which, in turn, may give rise to congenital diseases. Moreover, they have a definitive and additive character.

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The potential increase in the frequency of mutations is today an important problem, not only in relation to the amount of potential mutagens, but also because better protection against infectious diseases has led to the relative increase of congenital diseases.

Mutagenesis is a health problem also, due to the fact that some similar mechanisms are involved in carcinogenesis and teratogenesis. Many authors correlate somatic mutations with the mechanisms for carcinogenesis (Cairns, 1975; Magnee, 1977). Since the work of Boveri (1914), we know that chromosomal aberrations are frequent in tumors.

The promotor–inductor hypothesis for carcinogenesis illustrates this idea. Moreover, the breakage syndromes (Bloom, Fanconi, etc.) are shown to present higher risk for cancer. Also, most carcinogens are mutagens (Ames *et al.*, 1973). Finally, one cannot exclude the possibility that interactions with RNA or proteins might result in epigenetic mechanisms of aberrant differentiation (Weinstein *et al.*, 1975).

Teratogenic agents may be exogenous factors inducing abnormal embryogenesis, but may also be endogenous, such as point mutations or chromosomal aberrations. Radiation, some chemicals, and certain viral infections are teratogenic, but are also carcinogenic and mutagenic as well. However, for many agents, the mechanisms of teratogenesis are not related to those of mutagenesis or of carcinogenesis (Kalter, 1975; Poswillo, 1976).

Mutagenic mechanisms involve anything that damages DNA or interferes with the structure of the DNA, or with cell-division. They involve not only the replication of DNA but also transcription and repair. Mutagenic conditions include, for instance, modifications of nucleotides resulting in mispairing and base pair substitutions, local misalignments in base pairing (Frameshift mutations), modifications of bases leading to aborted DNA synthesis, and different factors influencing DNA metabolism (for instance, deprivation of some bases, analogues of amino acids, alkylation of enzymes of DNA metabolism).

Cells are, however, able *to protect themselves against* defective replications and DNA damage by DNA repair processes. In human cells, the two processes of excision repair and post-replication repair are considered important. Other processes perhaps also occur such as photoreactivation and SOS repair. In excision repair, which is an error-free repair system, a damaged single-strand region is replaced by a new strand of bases (Lindhal, 1976). It involves various enzymatic mechanisms needed for recognition of damaged sites, for nuclease action, and also for dissociation of DNA from the histones of nucleosomes (Cleaver, 1977). The molecular mechanisms of the post-replication repair are less well understood. Perturbations of DNA replication are observed in damaged cells, and *de novo* replication fills the gaps produced by the abnormal replication. Post-replication repair might be partially error-free, but is sometimes error-prone (SOS repair). These repair systems are

generally error-free, but when confronted with excessive doses of mutagenic factors they may saturate, resulting in mutations.

In spite of the existence of repair systems, ionizing radiation has been shown to be mutagenic. It induces single or double breaks in the phosphodiester strands. The mutagenic nature of ionizing radiation is not discussed by geneticists or biologists, at least at the qualitative level. The interpretation of the quantitative effects of radiation is, however, far more difficult, and estimations of these genetic effects have been published by international commissions (Unscear, 1972).

Our knowledge of the effects of irradiation is certainly not complete, but it is much more comprehensive than our knowledge of chemical mutagens. International associations have been formed to coordinate the studies of these factors (Environmental Mutagen Society, European Environmental Mutagen Society), but intensive work is still needed.

Mutagenic chemicals can themselves be intrinsically mutagenic, or can become mutagenic after activation by enzymatic reactions of the tissues or of the intestinal flora of the host. Thus, when methods are used to detect mutagenic effects, the use of microorganisms which lack the requisite enzymes for activation will give misleading results, and, in this cell, the use of an activation system is desirable.

Many tests have been developed to give rather rapid and *accurate results.* Chromosomal aberrations can be studied in animals exposed *in vivo.* This type of experiment allows comparison of genetic risks in somatic (bone-marrow), and germinal cells (spermatocytes). Other tests on animals for dominant lethals or numerical sex chromosome anomalies are useful too. As far as extrapolation to man is concerned, the use of experimental animals phylogenetically closer to man must be recommended. Of course, man himself can be used when accidentally exposed.

In vitro tests can be performed on bacteria or mammalian cells. The Ames test, for instance, uses a histidine mutation in *Salmonella typhimurium.* Different mammalian cell lines, such as Chinese hamster CHO or V79, human lymphocytes, or HELA cells are also routinely used. However, as already discussed, the addition of an activation system is necessary.

The choice of a test system is important, but no less important is the choice between the different cytological techniques recently developed to reveal the genetic changes.

One of these techniques reveals genetic exchange between sister double-stranded DNA molecules at the chromosomal level (sister chromatid exchange) (Perry *et al.*, 1974). These changes occur spontaneously, but higher frequencies are induced by numerous chemical mutagens, even when the cells are exposed to low concentrations. Sister chromatid exchanges develop as a consequence of DNA lesions, but only a minority of exchanges will result in the development of aberrations.

These different techniques help lead to a better knowledge of mutagenicity and to a better definition of norms. But many problems are not yet solved. These include the problems of extrapolation from *in vitro* results to *in vivo* situations, from results on experimental animals to human beings, and from somatic to germinal mutations. It is also clear that, until now, most energy has been directed towards solving the problems of acute or subacute exposure. In the future, much effort will be needed to study the effects of chronic exposure, which has a direct bearing on national health. Moreover, most studies are designed to analyze the effect of only one factor or agent, and not the global influence of two (or more) different mutagenic agents. The global influence of two chemicals is not necessarily equal to the sum of the two independent influences; a former or simultaneous exposure may inhibit, modify, or stimulate the influence of the other chemical.

Society must realize that this health problem is important. Yearly, about 250,000 new chemical agents are produced and, of these, about 300 are biologically active, and are introduced into our environment without a precise knowledge of their mutagenic (or carcinogenic) effects. It is no longer possible to hide behind our ignorance.

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