Methods for Estimating Risk of Chemical Injury: Human and Non-human Biota and Ecosystems
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Chemicals: A Possible Cause of Genetic Disorders

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ABSTRACT

It is likely that chemical mutagenesis occurs and that it contributes to different types of mutations observed in various organisms. However, as regards human hereditary disorders, this is only a hypothesis since there are no valid criteria for extrapolating animal experimental data to human populations. The best approach to estimating how much chemical exposures may add to the incidence of human genetic disorders seems to be to monitor the frequency of chromosome aberrations and sister-chromatid exchanges in lymphocytes of human subjects exposed to chemicals, particularly in relation to various types of pregnancy outcomes (stillbirths, spontaneous abortions, normal births). Another useful approach would be systematically to record hereditary pathology in the progeny of human individuals exposed to chemicals.

There is a considerable amount of data concerning the mutagenic properties of different chemicals that occur in the human environment: in agriculture, industry, in ambient air, as food additives, household products and drugs. According to various authors, about 5–10% of such chemicals are mutagenic. Experimental data are being collected concerning the combined mutagenic activity of mixtures of pollutants isolated from the ambient air, water and the air in the workplace. In addition, an enhancement of mutagenic activity has been shown to result from an increase in the total air and water pollution.

It is likely that chemical mutagenesis occurs commonly and universally and that it is manifested in different types of mutations in a variety of organisms. Available experimental data indicate that both the number of subjects exposed to chemical mutagens and the intensity of mutagenic activity may increase, and this may result in a higher incidence of hereditary disease. However, at the present time this is only a hypothesis.

As sufficiently valid criteria for extrapolating experimental animal data to man, particularly as regards mutations in gametes, are lacking; the answer to the question of the possible induction of genetic disorders by chemicals can only be

obtained by the analysis of data on the relationship between exposure to chemicals and the frequency of disturbances of a genetic nature that may occur in the outcome of pregnancy or in the health of the offspring.

Disorders such as spontaneous abortion, congenital malformations, and chromosomal and genetic diseases are considered to be of primary importance. From the available information it appears that no less than 50 % of spontaneous abortions, and 50–60 % of congenital malformations are due to hereditary factors (chromosome and gene mutations), and that chromosomal diseases are entirely of genetic origin, no less than 95 % resulting from mutations in parental gametes.

Studies in which the exposure (concentration and time) to certain chemicals or their combinations are strictly recorded should be considered methodologically correct. It is essential to know which of the parents has been exposed. Using this information, it would be possible to evaluate embryotoxic effects (exposure of the mother) and purely mutagenic effects (exposure of the father).

Though the effects of chemicals on progeny have been examined in many studies, few of these studies have fulfilled the necessary methodological requirements. Furthermore, it has been noted that authors prefer to publish studies showing positive correlations between exposure to chemicals and genetic consequences than those with negative results.

Stillbirths in women whose husbands worked with chemicals have been reported in several studies. Workers exposed to chemicals in the vinyl chloride industry (Infante *et al.*, 1976), a lead smelter (Nordström *et al.*, 1978), as well as anaesthesiologists (Cohen *et al.*, 1980) were examined. As none of the groups was tested repeatedly, it is difficult to draw any conclusions concerning the mutagenicity for human gametes of the substances under study. Both the demographic data and the living conditions of the families of subjects examined should be considered with utmost care in these kind of investigations. Questioning of both parents appear to be obligatory from the methodological viewpoint. The 'blind method' should be applied where possible, so that the observer recording the medical history of the outcome of a pregnancy is not aware of the level of exposure of the woman under study. Some data have been reported in the literature, which indicate that the incidence of stillbirths is not influenced by vulcanization accelerators, substances which are apparently mutagenic (Aleksandrov, 1976).

Data concerning increased incidence of hereditary disease among subjects exposed to certain chemicals could provide the best possible evidence for genetic effects of chemicals. However, such data are still not available since retrospective studies involve a large number of methodological errors and prospective studies have not yet been carried out. As far as methods are concerned, studies in which chromosomal diseases, most of which are due to new mutations, are recorded would be the easiest to carry out. The size of samples for estimating the degree of a given alteration in a mutagenic process have been calculated from data on

spontaneous levels of chromosomal diseases. Thus, for cytogenetic investigations of all types of pregnancy outcomes (spontaneous abortions, stillbirths, normal births) examination of as many as 400 pregnancies is considered sufficient for a mutation process of an intensity of about 50‰, and 2000 for an intensity of about 20‰. So far, such studies have not been carried out. Although these studies are not time-consuming from the cytogenetic point of view, prospective supervision of the group under observation is necessary after pregnancy registration.

Estimation of gene mutations (dominant phenotype, biochemical markers) for the detection of possible effects of chemicals on human heredity is such a laborious method involving studies of millions of offspring, that it does not seem to be a real possibility at the present time. Although knowledge concerning the mutation-inducing effects of chemicals on human gametes is lacking, this does not exclude the urgent need to record the frequency of hereditary pathology in the progeny of human subjects exposed to chemicals. Indirect data relevant to this problem exist in addition to the three reports already mentioned, showing some preliminary evidence of genetic effects.

First, examination of the frequency of chromosomal aberrations and sister-chromatid exchanges in lymphocyte cultures of human subjects exposed to chemicals has indicated mutagenic effects in somatic cells in many cases and for various compounds. There can be no doubt about the correctness of this conclusion, since it has been verified for several different types of chemicals.

Second, numerous *in vivo* and *in vitro* studies have shown that compounds which induce chromosome aberrations in human subjects as well as many other compounds that occur in the human environment, also have mutagenic properties. Studies of mutagenic activity of compounds *in vivo* and *in vitro* usually give comparable results, as is the case with results of experimental estimation of mutagenic activity in different test systems, the cytogenetic examination of peripheral blood lymphocytes, and the epidemiological examination of progeny of human subjects exposed to chemicals. Some examples are shown in Table 1.

Thus, on the basis of data from cytogenetic and epidemiological studies of workers engaged in the chemical industry, it may be concluded that chemicals may be associated with the incidence of genetic disorders, if the environmental exposure is sufficiently high. The current level of chemical pollution in industrialized countries is high, but it is unlikely to increase in the future. A general evaluation of the frequency of hereditary disorders currently observed seems to indicate that a chemically induced component is involved. However, its value is hardly significant, since temporal changes have not been seen in the frequency of spontaneous abortions or in the number of children with congenital malformations and Down's syndrome. Thus an integrated approach to genetic monitoring appears to be necessary, taking the environmental conditions into consideration.

Table 1 Qualitative comparison of mutagenicity, cytogenetic effects and lethal outcomes of pregnancy associated with some chemicals

Chemical exposure	Results of experimental test for mutagenicity	Cytogenetic effects in peripheral blood	Lethal outcomes of pregnancy
Vinyl chloride	+	+	+
Lead	+	+/−	+
Inhalation of anaesthetics	+	+	+

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