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TOXIC EFFECTS OF PESTICIDES: A REVIEW ON CYTOGENETIC BIOMONITORING STUDIES

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Summary. *Pesticides constitute a heterogeneous category of chemicals specifically designed for the control of pests, weeds or plant diseases. Biological monitoring provides a useful tool to estimate the genetic risk deriving from an integrated exposure to a complex mixture of chemicals. Studies available in scientific literature have essentially focused on cytogenetic end-points to evaluate the potential genotoxicity of pesticides in occupationally exposed populations. A positive association between occupational exposure to complex pesticide mixtures and the presence of chromosomal aberrations (CA), sister-chromatid exchanges (SCE) and micronuclei (MN) has been detected in the majority of the studies. Genetic damage associated with pesticides occurs in human populations subject to high exposure levels due to intensive use, misuse or failure of control measures.*

Key words: *Genotoxicity, Pesticides, Chromosomal aberrations, Sister-chromatid exchanges, Micronuclei.*

Introduction

Pesticides constitute a heterogeneous category of chemicals specifically designed for the control of pests, weeds or plant diseases. Their application is still the most effective and accepted means for the protection of plants from pests and has contributed significantly to enhanced agricultural productivity and crop yields. A total of about 890 active ingredients are registered as pesticides in the USA and currently marketed in some 20,700 pesticide products (1,2). Many of these compounds, because of their environmental persistence, will linger in our environment for many years to come. All people are inevitably exposed to pesticides, through environmental contamination or occupational use. The general population is exposed to the residues of pesticides, including physical and biological degradation products in air, water and food. Pesticides act selectively against certain organisms without adversely affecting others. Absolute selectivity, however, is difficult to achieve and most pesticides are a toxic risk also to humans. Pesticides are the most important method in self-poisoning in the developing world. Three million cases of pesticide poisoning, nearly 220,000 fatal, occur world-wide every year (2).

The International Agency for Cancer Research (IARC) has reviewed the potential carcinogenicity of a wide range of insecticides, fungicides, herbicides and other similar compounds. Fifty-six pesticides have been classified as carcinogenic to laboratory animals. Associations with cancer have been reported in human studies for chemicals such as phenoxy acid herbicides, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), lindane, methoxychlor, toxaphene and several organophosphates (3). Epidemiological data on cancer risk in farmers are conflicting. Meta-analyses showed that farmers were at risk for specific tumors including leukaemia (4–6) and multiple myeloma (7). For most other cancer sites, farmers were found to have lower rates than other people, probably due to healthy worker effect. Exposure to pesticides has also been the subject of great concern in view of its possible role in the induction of congenital malformations. The incidence of congenital malformations and parent's exposure to pesticides have been covered by a number of studies, the results of which have been conflicting and sometimes in conclusive (8–10). Recent findings suggest that female workers in flower greenhouses may have reduced fertility, and that exposure to pesticides may be part of the causal chain (11).

Pesticides have been considered potential chemical mutagens: experimental data revealed that various agrochemical ingredients possess mutagenic properties. The genotoxic potential for agrochemical ingredients is generally low, as they yield positive results in few genotoxicity tests. The lowest effective dose in single test is generally very high. As most occupational and environmental exposures to pesticides are to mixtures, the genotoxic potential evaluated on single compounds could not be extrapolated to humans.

Toxic effect, mainly genotoxic potential is a primary risk factor for long-term effects such as carcinogenic and reproductive toxicology. The cytogenetic biomonitoring in human populations is a useful tool to estimate the genetic risk from an integrated exposure to complex mixtures of chemicals. Although a number of biomarkers are available to assess transient and permanent genotoxic responses, biomonitoring studies on human populations exposed to pesticides have essentially fo-

cused on cytogenetic end-points, namely chromosomal aberrations (CA), micronuclei (MN) frequency and sister-chromatid exchanges (SCE).

Cytogenetic biomonitoring studies

Genetic damage at the chromosomal level entails an alteration in either chromosome number or chromosome structure, and such alterations can be measured as CA or MN frequency. Conventional techniques for measuring chromosomal changes require proliferating cells so that chromosomes can be seen at mitosis. Micronuclei are acentric chromosomal fragments or whole chromosomes left behind during mitotic cellular division and appear in the cytoplasm of interphase cells as small additional nuclei. In contrast to the CA, evaluating the scoring of micronuclei in lymphocytes is simple and fast.

The SCE analysis was also adopted as an indicator of genotoxicity, although the exact mechanism that leads to an increased exchange of segments between sister chromatids is not known in detail at present. Recent studies revealed the nucleotide pool imbalance can have severe consequences on DNA metabolism and it is critical in SCE formation. The modulation of SCE by DNA precursors raises the possibility that DNA changes are responsible for the induction of SCE and mutations in mammalian cells (12,13). While increased levels of CA have been associated with increased cancer risk (14,15) a similar conclusion has not been reached for SCE or MN. However, high levels of SCE and MN frequency have been observed in persons at higher cancer risk due to occupational or environmental exposure to a wide variety of carcinogens (16–20). A review of the literature dealing with genotoxicity in human groups exposed to pesticides showed a large number of studies employing CA test, SCE analysis, or MNassay (2).

Evidence of CA increases, mainly as structural chromosomal aberrations in occupationally exposed populations, was demonstrated in the vast majority of available studies. The sensitivity of SCE is lower than that of the CA test in detecting genotoxic effects related to pesticide exposure and fewer data are therefore, available for MN than for the other cytogenetic endpoints. The negative studies out number the positive ones (21–26). Cytogenetic studies in the scientific literature, refer to different typology of exposure and provide different information about the genetic risk associated with pesticide exposure.

Pesticide users

The large majority of cytogenetic monitoring studies in human populations exposed to pesticides concerns the genotoxic effects of chronic low doses of a single compound or of a complex mixture of chemicals. A number of studies have reported a significant incidence of cytogenetic damage such as CA, SCE and MN frequency in agricultural workers, forestry workers, floriculturists, vineyard cultivators, cotton field workers and others. However, these positive findings have not been substantiated by all investigators. The inconsistent responses among studies could reflect different exposure conditions, such as the exposure magnitude, the use of protective measures and the specific genotoxic potential of the pesticides used. In addition, the crop type and the environmental factors can influence the kind of pesticide formulations used as well as the chemical absorption. A number of factors have been used to describe pesticide exposure in cytogenetic studies: pesticide consumption (kg per year), amount of genotoxic chemicals used, total number of pesticide formulations used, extension of the areas of pesticide application, and working conditions.

Agricultural tasks greatly influence the extent of exposure independently from the grown crops. People involving in preparing and spraying pesticide mixture could be identified as the most exposed groups of farmers. Pesticide sprayers represent the most exposed group of agricultural workers. The pesticides most often used were chlororganics and, more recently, carbamates, organophosphates and pyrethroids which have been reported to be positive for genotoxic effects in experimental studies in bacterial and in mammalian systems (27–31). The occupational exposure to pesticide mixtures in sprayers is associated with a genetic risk, as it has been demonstrated by the use of cytogenetic biomarkers.

Effects of genotypes on cytogenetic damage

Genotypes responsible for inter individual differences in the ability to activate or detoxify genotoxic substances are recognized as biomarkers of susceptibility to mutations, cancer and other diseases. Many enzymatic isoforms have been suggested to contribute to individual cancer susceptibility as genetic modifiers of cancer risk after exposure to genotoxic agent (32,33). Unfavourable versions of the different polymorphic genes have been associated with an increased activation and decreased detoxification of hazardous compounds, and could entail an increased genetic susceptibility to pesticides. Positive effects on indicator genotype interaction are reported for cytogenetic biomarkers, such as SCE, CA or MN, although the large majority of studies in the scientific literature failed to reveal any clear indication (34,35).

Despite the limited number of subjects Scarpato *et al*. (36) observed a higher chromatid type CA frequency in smokers, exposed and controls with the GSTM1 and also with GSTT null genotypes. In a further study (37), slight and not significative associations were observed between baseline SCE and GSTT1 positive genotype and between CA frequency and GSTM1 genotypes in smokers. Falck et al. (22) neither found any genotype effect exclusively in the pesticide-exposed subjects. The GSTM1 positive genotype was associated with an increased MN frequency irrespective of exposure. The

NAT2 fast acetylator genotype was associated with an increased MN frequency in all smokers including exposed and controls.

Dose-dependence of cytogenetic damage

A dose–effect relationship was observed for cytogenetic damage in pesticide-exposed populations. The increase seen in cytogenetic damage was related to the extent of exposure, with cytogenetic parameters increasing as a result of heavy pesticide exposure. Positive findings were even reported when blood samples were obtained from people suffering from severe pesticide intoxication resulting from violation of occupational safety measures or attempted suicides (38,39). Significant differences in cytogenetic damage were detected in individuals with symptoms of chronic intoxication with respect to those without (40,41). In agricultural workers an increase in chromosomal damage was observed during the spraying season when pesticides were used intensively, mainly in workers who had not used protecting clothing and gloves (22,42-45). The condition of exposure was also associated with an increase of cytogenetic damage. It was observed that individuals working exclusively in greenhouses showed higher levels of chromosomal damage as CA (46) or MN (21,47) than subjects working in open-fields. A significant increase of cytogenetic effects was observed regarding individual protection. The use of mask and gloves seems to protect the workers by reducing incidence of cytogenetic outcomes (40,48,49). Finally, smoking may potentiate the genotoxic effects of pesticides due to an increase of oral exposure during the agricultural practices. A high frequency of chromosomal damage was detected in smoking greenhouse workers who had not used protective gloves (44). A significant increase in CA (50,51) and SCE (52,53) was observed in smokers compared with non-smokers from pesticide-exposed groups.

Time-dependence of cytogenetic damage

Duration of employment was used as a surrogate of exposure in a number of studies where a quantitative evaluation of the exposure is usually difficult. The incidence of CA, MN and SCE positively correlated with duration of exposure in many of these investigations (21,23,24,40,41,54,55,56). The reversion of chromosomal damage fit with the information about the normal turnover of lymphocyte populations. Lymphocyte survival cannot be considered a passive phenomenon, but it is rather a continuous and active process in which each lymphocyte must compete with other lymphocytes (57). The majority of lymphocytes in peripheral blood has an half-life of less than 2 weeks: new lymphocytes are continuously produced. However a subset of around 10% of all circulating lymphocytes may live for almost 9 months or more (58,59). The clastogenic effects seem to be cumulative for continuous exposure to pesticide mixtures. People chronically exposed are more susceptible to the clastogenic action of pesticides.

Conclusions

Occupational exposure to mixtures of pesticides has been associated with an increase in genotoxic damage. The cytogenetic damage induced by pesticides appears to depend on the degree of exposure. A dose–response relationship can be hypothesized. A dose–effect increase of cytogenetic damage was also revealed in a number of field studies where the extent of exposure was described as quantity of pesticide used, extension of area of pesticide application and inadequate working conditions.

Genotoxic damage by chemical compounds could also be influenced by the individual inheritance of variant polymorphic genes involved in the metabolism of chemical compounds and in DNA repair mechanisms. Although the available data on farmer populations suggest that subjects with unfavourable metabolizing alleles are more susceptible to genotoxic effects than those with favorable alleles, there are no conclusive findings on whether metabolic polymorphisms affect the chromosomal damage induced by pesticides. Since workers are frequently exposed to complex mixtures of pesticides, it is difficult to attribute the genotoxic damage to any particular chemical class or compound. The organochlorine compounds used in the past have been replaced by organophosphates and carbamates, and more recently by pyrethroids, which represent the chemical classes of pesticides most often used nowadays. Although the significance of increased genotoxic effects is difficult to predict for individual subjects the positive findings ensuing from biomonitoring studies suggest a genotoxic hazard at the group level. The evidence of a genetic hazard related to exposure resulting from the intensive use of pesticides stresses the needs for educational programmes for farmers in order to reduce the use of chemicals in agriculture and to implement protection measure.

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TOKSIČNA DEJSTVA PESTICIDA: PREGLED STUDIJA O CITOGENTSKOM BIOMONITORINGU

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Kratak sadržaj: *Pesticidi čine heterogenu kategoriju hemikalija specijalno napravljenih u cilju kontrole štetočina, korova ili bolesti biljaka. Biološki monitoring je korisno sredstvo procene genetskog rizika koji čini sastavni deo izlaganja složenoj mešavini hemikalija. Dostupna naučna literatura se generalno bavi izučavanjem citogenetskih krajnjih tačaka u cilju procene potencijalne genotoksičnosti pesticida u populaciji koja je izložena na radnom mestu. U većini studija otkivena je pozitivna povezanost izmedju izloženosti složenim mešavinama pesticida na radnom mestu i prisustva hromozomskih aberacija (CA), izmena sestrinskih hromatida (SCE) i mikronukleusa (MN). Genetska oštećenja izazvana pesticidima javljaju se u ljudskoj populaciji koja je izložena visokim nivoima, što je rezultat intenzivne upotrebe, zloupotrebe ili neadekvatnih kontolnih mera..*

Ključne reči: *genotoksičnost, pesticidi, hromozomske aberacije, izmene sestrinskih hromatida, mikronukleus*