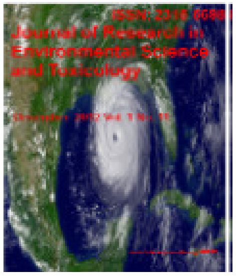

Journal of Research in Environmental Science and Toxicology (ISSN: 2315-5698) Vol. 1(11) pp. 279-293, December 2012
Available online http://www.interesjournals.org/JREST

Review

Pesticides: classification, uses and toxicity. Measures of exposure and genotoxic risks

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Accepted December 03, 2012

The first pesticide synthesized was the dichloro diphenyl trichloroethane in 1874. In 1998, 20,000 commercial products were registered as «pesticides» by the US Environmental Agency of Protection. The classification, according to their toxicity, pesticides can be classified as extremely dangerous, highly dangerous, moderately dangerous and slightly dangerous. According to their median lifetime, they are classified as permanent, persistent, moderately persistent and not persistent. Given their chemical structure, they are classified in several groups, the most utilized of which are organochlorines, organophosphates, carbamates and pyrethrins. Agriculture, public health, structural pest control, industry, green area servicing and the maintenance of reservoirs of water are the main activities in which pesticides are currently employed. The main sources of pesticide exposure to humans are through the food chain, air, water, soil, flora and fauna. While acute poisoning generally affects farmers and industrial workers, chronic poisoning is more common in the general population. Pesticides are mainly absorbed through dermal, respiratory and oral pathways. Although absorption through the skin is prominent in the work environment, the general population are more at risk from ingestion and inhalation. Pesticides are distributed all around the human body through the bloodstream and are eliminated through urine, faces and exhaled air. The main techniques employed in the assessment of pesticides exposure are the history of exposure, the experts evaluation and environmental and biological monitoring.

Keywords: Pesticides, classification, uses, toxicology, exposure assessment.

INTRODUCTION

Synthetic pesticides emerge between 1930 and 1940 as a result of research aimed at developing chemical weapons that were originally tested in insects. One of the first compounds, dichlorodiphenyltrichloroethane (DDT) was synthesized by Zeidler in 1874, and its insecticidal properties were described by Paul Müller in 1939. DDT was first used during World War II to protect American soldiers carried diseases / by vector and was marketed in the U.S. in 1945 (WHO, 1990).

Since 1940 the production, marketing and ongoing use of various pesticides has increased to the present day, exposure to pesticides, either during their development, production or use can have adverse effects on health and the environment. These effects are not always related to immediate and apparent injuries, but can take even years to manifest (Zuniga and Gomez, 2006).

It originated, in turn, a race relentless in finding less toxic analogues to humans and more effective and selective with pests. However, the passages of a few years have become apparent adverse effects of pesticides on human health and on the environment.

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Regardless of its benefits, it is clear that pesticides are toxic chemicals deliberately created to interfere in any particular biological system without actual selectivity. Simultaneously affect, and in varying degrees, both the “target species” as other categories of living beings, particularly humans. Although the general population is exposed to these compounds, pesticide exposure to various pollutants is associated with the occupation, farmers are in a high risk group, thus require biomonitoring studies to assess disease caused by acute and chronic exposure to pesticides (Castro et al., 2004).

The importance of genotoxic hazard biomonitoring is the identification of biomarkers that can define 2enotoxicity of prepatogénesis state and provide guidelines for the prevention of disease. Among the various damage to your genetic material, as a result of adverse environmental conditions, are point mutations and chromosomal, which can lead to cell transformation. Pesticide exposure can cause neuritis, psychiatric manifestations, hepatorenal disorders, neurological and neurodegenerative, immune, metabolic and endocrine. Similarly, it has been linked to increased incidence of leukemia and bladder cancer in farmers, following a genotoxic effect of some pesticides (Larrea et al., 2010).

Genotoxic compounds are those that act directly or indirectly on the DNA or clastogenic event. The genotoxic potential is a primary risk factor for chronic or long-term effects, such as reproductive effects and toxicity. Toxicological evidence of mutagenic and carcinogenic action of several pesticides and occupational or accidental exposure to large human populations to these compounds, have attracted the attention of many cytogenetic studies. A limited number of studies that seek to evaluate the genetic risk of occupational exposure established an association between occupational exposure to pesticides and the presence of chromosomal aberrations, sister chromatid exchanges and / or micronuclei (Au et al., 1999; Antocini et al., 2000; Pastor et al., 2001; Garaj and Zeljezi, 2002; Paz et al., 2002; Bolognesi, 2003; Paramjit, 2003; Ascarrunz et al., 2006).

Pesticide exposure may pose a potential risk to humans, causing neuritis, psychiatric manifestations, hepatorenales disorders, neurological, immunological, metabolic and endocrine. It has also been linked to increased incidence of leukemia and bladder cancer in farmers, following genotoxic effects of some pesticides. Results of this type have led many researchers to evaluate the genetic risk associated with pesticide exposure (Martin et al., 2003; Ascarrunz et al., 2006).

In this paper we review the different uses that have been given to pesticides, sources of exposure in the general population and toxicological characteristics, and review some techniques used to measure human exposure to these chemicals.

Overview of pesticides: Definition

Changes in the global environmental system produced by human activities result in an expenditure of energy and natural resources and growing increasingly untenable. Changes in land use for agriculture and livestock that can cause erosion and desertification, industrialization, urbanization, the expansion of motorized mobility, all of which are activities that produce large amounts of emissions to air, water and soil, and profound environmental degradation that affects society in many important ways. Among these is health that can be affected globally, on a spatial scale greater than in the case of local pollution, but can affect a number of people quite similar (Moreno and Urbina, 2008).

The pollution caused by heavy metals such as lead and mercury or chlorinated organic compounds (pesticides) can have severe health consequences. Both groups are associated with various cancers, especially those of the reproductive system, immune system depression, birth defects, sterility and neurobehavioral problems.

The United Nations Organization for Food and Agriculture (FAO) defines pesticides as any *substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human disease or animal species not unwanted plants or animals that cause damage or otherwise interfere in the production, processing, storage, transport or marketing of food, agricultural products, wood and wood products or animal feeds or which may be administered to animals for the control of insects , arachnids or other pests in or on their bodies* (CICOPLAFEST 1998; Badii and Landeros, 2007, Martinez and Gomez, 2007). Therefore, the purpose of pesticides is to destroy certain living organisms, as well as constituting a particular group of biocides that can reach a wide lethality.

The need to produce a greater quantity and quality of food by pest control resulted in intensive use of pesticides over the last 50 years (Garcia 1997, Chaverri et al., 2000). Pesticides are chemicals used by the very man to control agricultural pests and their correct application is the most accepted and effective for maximum production and quality of crops (Ferrer and Cabral, 1993; Bolognesi, 2003; Mansour , 2004, Martinez and Gomez, 2007). The increasing use and improper handling of these substances have raised concerns about the risks and damage that could result in the economy, the environment and public health (Jiménez 1995). Pesticides poisoning represent problems for handlers, implement or work with these products.

Pesticides are chemical groups more widely used by man, both to protect the production of harmful organisms and quality of crops and for the control of vectors and pests of public health, plus they have livestock use and domestic. These substances have been considered as

Table 1. Classification of pesticides according to toxicity, expressed as LD_{50} (mg/kg)

Class	Toxicity	Examples
Class IA	Extremely dangerous	Parathion, Dieldrin
Class IB	Highly dangerous	Eldrin, Dichlorvos
Class II	Moderately hazardous	DDT, Chlordane
Class III	Slightly hazardous	Malathion

potential mutagens because they contain ingredients to cause changes in deoxyribonucleic acid (DNA).

The World Health Organization (WHO) estimates that each year there are in the world around one million acute poisoning by pesticide exposure, with a fatality rate of 0.4% and 1.9%. Occupational exposure would be behind 70% of these fatalities. Moreover, sustained exposure to low doses of pesticides has been linked to a variety of disorders in the medium and long term, including various cancers, reproductive disorders and nervous system disorders, among other problems. The use of agrochemicals is widely widespread practice worldwide (Benitez et al., 2009).

Also, the WHO proposed classification based on their health risk, based on their toxic behavior in rats or other laboratory animals administered orally and dermally and estimating the median lethal dose (LD50) that produces death in 50 % of the exposed animals (WHO 1990). This ranking order from lowest to highest toxicity in numbers I through IV, being extremely toxic, highly toxic, moderately toxic, slightly toxic, respectively (CICOPLAFEST 1998, WHO 2004). However the most common way to classify them is based on their chemical structure, identifying four main groups: *organochlorines, organophosphates, carbamates, and pyrethroids*.

The former are very persistent in the environment and tend to accumulate in fatty tissues (Waliszewski et al., 2002, 2003a, b, 2004), are used in crops of grapes, lettuce, tomato, alfalfa, corn, rice, sorghum , cotton and wood, for preservation. The second man act on the central nervous system by inhibiting acetyl cholinesterase, an enzyme that modulates the amount and levels of the neurotransmitter acetylcholine, disrupting the nerve impulse by serine phosphorylation of the hydroxyl group in the active site of the enzyme. The third are less persistent than organochlorines and organophosphates and likewise the latter inhibit acetyl cholinesterase. However, in the case of carbamates action is fast and the kinetics of blocking is through the carbamylation of the enzyme by the covalent attachment of electrophilic groups steric carbamoyl sites of the enzyme (Martinez and Gomez, 2007) . The fourth group, also known as pyrethrins, act on the central nervous system causing changes in the dynamics of the Na + channels in the membrane of the nerve cell, causing it to increase its opening time prolonging sodium current through the membrane, in both insects and vertebrates (Perry et al., 1998; Sorgob and Vilanova, 2002).

The main producers and exporters of pesticides worldwide are Germany, USA, England, Switzerland, France, Japan and Italy, which supply all imports of the third world and according to the regulatory agencies, around 30% of the pesticides marketed in developing countries for agriculture and public health, with a value of 900 million U.S. dollars, do not meet internationally accepted quality standards. These pesticides often contain compounds or impurities that are restricted in other countries to be dangerous as they constitute a threat to human health and the environment (WHO 1990).

Classification of pesticides

Due to the large amount of chemicals and pesticides combinations of compounds have been classified for use in insecticides, miticides, herbicides, nematicides, fungicides, molluscicides and rodenticides. The World Health Organization proposed classification based on their health risk, based on their toxic behavior in rats and other laboratory animals by administering oral and dermal and estimating the median lethal dose (LD50) that produces death in 50% of exposed animals (WHO 1990). This ranking order from lowest to highest toxicity in numbers I through IV, being extremely toxic, highly toxic, moderately toxic, slightly toxic, respectively (CICOPLAFEST 1998, WHO 2004). Table 1 gives an idea of this classification.

According to its chemical structure, pesticides are classified into different families, ranging from organochlorine and organophosphorus compounds to inorganic compounds. In this paper, we refer only to some families of pesticides relevant for the damage they cause to human health and high demand for its use. The most common way to classify them based on their chemical structure is split into four main groups:

Organochlorine

Stable compounds are too persistent in the environment and tend to accumulate in fatty tissue (Waliszewski et al., 2002, 2003 a, b, 2004). Its main use is in the eradication of disease vectors such as malaria, dengue and malaria. They are also used in cultivation of grapes, lettuce, tomato, alfalfa, corn, rice, sorghum, cotton and wood, for preservation. His way of exposure is mainly on insects by contact or by ingestion (Ferrer 2003). In humans these substances or their metabolites act primarily at the level of central nervous system altering the electrophysiological properties and enzymatic neuronal membranes, causing alterations in the kinetics of the flow of Na^+ and K^+ through the membrane of the nerve cell (Narahashi et al., 1992), resulting in the spread of multiple action potentials for each stimulus (Kamrin 1997, Ferrer 2003), causing symptoms such as seizures and acute poisoning death from respiratory arrest (Tordoir and Van Sittert 1994).

Organophosphates

They are esters derived from phosphoric acid. In man act on the central nervous system by inhibiting acetyl cholinesterase, an enzyme that modulates the amount and levels of the neurotransmitter acetylcholine, disrupting the nerve impulse by serine phosphorylation of the hydroxyl group in the active site of the enzyme (Fukuto, 1971, 2001 Keith, Sorgob Vilanova and 2002). The symptoms are causing loss of reflexes, headache, dizziness, nausea, convulsions, coma and even death (Sulbatos 1994, Perry et al., 1998). Also described with alkylating properties (Preussman et al., 1969, Fest and Schmidt 1973), which from the point of view of mutagenesis is paramount because they act directly on the deoxyribonucleic acid (DNA) adding alkyl groups methyl and ethyl mainly to the nitrogenous bases with nucleophilic groups capable of reacting with electrophiles (Wild 1975). Organophosphorus compounds are most commonly used in agriculture, most are insecticides and miticides, their way of joining these organizations is by ingestion and contact. They are used in vegetable crops, fruit trees, grains, cotton, sugarcane, among many others.

Carbamates

They are esters derived from acids or dimethyl N-methyl carbamic acid are used as insecticides, herbicides, fungicides and nematicides. Are less persistent than organochlorines and organophosphates and likewise the latter inhibit acetyl cholinesterase. However, in the case of carbamates action is fast and the kinetics of blocking is through the carbamylation of the enzyme by the covalent attachment of electrophilic groups steric carbamoyl sites of the enzyme (Moutchen-Dahmen et al., 1984).

Pyrethroids

They originate from natural insecticide derived from pyrethrum extract derived from chrysanthemum flowers, known as pyrethrins. Subsequently were obtained synthetically and are presently manufactured around 100 different commercial products (Sorgob and Vilanova 2002). Your income is the insects by contact or ingestion. They act on the central nervous system causing changes in the dynamics of the Na + channels in the membrane of the nerve cell, causing it to increase its opening time prolonging sodium current across the membrane in both insects and vertebrates (He, 1994, Perry et al., 1998). These events can lead to neuronal hyperexcitation (Narahashi et al., 1992, He, 1994, Narahashi, 1996, Perry et al., 1998).

Others

In addition other pesticides are as triazine herbicides, ureic, hormonal, amides, nitro compounds, benzimidazoles, ftalamidas, bipyridyl compounds, ethylene dibromide, sulfur containing compounds, copper or mercury, among others.

Use of pesticides

The given to pesticides has been multiple and varied, as shown in Table 2, which explains its ubiquity (Moses, 1993). Agriculture is the largest user of this type of compound used (Al-Saleh, 1994), consuming 85% of world production, to chemically control the various pests that reduce the quantity and quality of food crops and other vegetables. 10% of the total pesticides used in public health activities to control vector-borne diseases such as malaria, Chagas disease and dengue, among others. Also used to control rodents (Goldman, 1998), in water purification and in eradicating crops whose end products are illegal drugs. They are also used to control pests in large structures such as malls, buildings, airplanes, trains and boats. Apply in ornamental landscaping and recreational parks and gardens, to control the proliferation of insects, fungi and growth of grass and weeds. For the same purpose, are scattered along highways, railways and power lines towers with high voltage.

In nature reserves or artificial water pesticides used to prevent weed growth, algae, fungi and bacteria. In industry are widely used in the manufacture of electrical equipment, fridges, paints, carpets, paper, cardboard and food packaging materials, among others, to avoid these products in the growth of bacteria, fungi, algae, yeast or are damage by insect pests and/or rodents.

Table 2. Typical uses of pesticides

Activity	Use
Agriculture	Control of multiple crop pests in any stage
Public health	Control of disease vectors such as malaria, dengue, Chagas disease, onchocerciasis, plague, yellow fever, filariasis, trypanosomiasis, schistosomiasis, leishmaniasis and typhus. Control of pests (rodents) and eradication of plantations whose final product is a prohibited drug
Livestock and domestic care aniales	In the disinfection of sheep and pets like dogs and cats
Treatment of structure	Treatment of public and private buildings, offices, hospitals, hotels, cinemas, theaters, restaurants, schools, supermarkets, department stores, sports facilities, food warehouses and the rail industry and sea and air
Maintenance of green areas	Treatment of parks, gardens, playgrounds, golf courses, highways, railways, platforms, towers, high voltage lines and poles
Maintenance of water reserves	Treatment of large reserves of water, natural or artificial, dams, reservoirs, dams, reservoirs, ponds psicolas, canals, ponds and pools
Industries	In the manufacture of refrigerators, electrical equipment, paints, resins, adhesives, pastes, waxes, liquid limpiamentales, tents, sails for sailing, sports nets, mats, carpets and tapestries, the timber industry, packaging materials food, cardboard and paper multiple products. In the food industry for the preservation of fresh foods such as meat, pesacados, etc .
Home	Incorporated in products such as cosmetics, shampoos, soaps and insect repellents. They are used in the washing and drying of carpets, household disinfectants and care products for pets and plants, and the use of insecticides

Home is an area of particular interest: 90% of U.S. households' pesticide use and 83% of the total used is applied inside the house, the rest in surrounding areas. This practice in the world grows primarily from the specific use of insecticides because, of the 14 most consumed pesticides, 12 are insecticides. Moreover, it is common to use pesticides veiled, because without being cited in the regulatory label of the product and without warning the consumer about the precautions of use, are incorporated into products as cosmetics and shampoos to preserve the growth of fungi and bacteria, insect repellents and also in products for the care of pets and plants to attack or prevent insect infestation.

In Mexico it is used 60% of the 22 pesticides classified as harmful to health and the environment, 42% of which are manufactured in the country. Also used 30 pesticides (INEGI 1998). The regulation of pesticides in Mexico is done through different federal agencies: the transport by the Secretariat of Communications and Transportation, the impact on the environment by the Secretariat of Environment and Natural Resources, biological efficiency for agricultural use by the Secretariat of Agriculture, Livestock and Fisheries and the health aspects by the Ministry of Health (SEMARNAP 1996, Rosales Castillo 2001).

In addition to large amounts of pesticides imported by Mexico, there are plants in Coahuila, Chihuahua, Guanajuato, State of Mexico, Querétaro, Tlaxcala and Veracruz. The products for sale are classified according to their toxicity in 57% slightly toxic, 25% moderately toxic, highly toxic 9%, 9% extremely toxic (Perea, 2006).

In Mexico, the crops that apply the bulk of these products are corn, cotton, potatoes, peppers, tomatoes, beans, corn, avocado, coffee and snuff, in quantities ranging from 395 to 13.163 tons of pesticides to years (AMIPFAC 1995). In addition to the many products that are applied, there is the problem of collection, treatment and disposal of more than 12,000 empty pesticide containers, which are being addressed through the program "us preserve a clean field" trying to create awareness among farmers, regarding the safe handling and proper disposal of waste generated.

This program is being carried out in the State of Mexico through leaflets and radio messages transmitted in Sonora, Sinaloa, Querétaro, Guanajuato and Nayarit (AMIPFAC 2001, INE 2005). According to the Ministry of Health, 80% of cases of pesticide poisoning reported each year worldwide occur in developing countries.

In Mexico, employing 260 brands, of which 24 are prohibited and 13 restricted the main causes of poisoning poor forecasting and control measures. According to the Department of Epidemiology of the Ministry of Health, the number of cases of poisoning by pesticides significantly decreased from eight thousand to 2.532 between 1995 and 2001. However, the record also mentions that the following year the number increased slightly to settle at 2.802 in 2003 to 3.849 again rose cases and in 2005 was 3.898. However, the authorities recognize that there is underreporting or "dark figure" in the number of cases of poisoning by the use of agrochemicals (Perea 2006). The indiscriminate use of pesticides and comprehensive has created serious problems for the environment and for the agencies "not white" as well as for men (CICOPLAFEST 1998).

The states with the highest pesticide use are Sinaloa, Veracruz, Jalisco, Nayarit, Colima, Sonora, Baja California, Tamaulipas, Michoacan, Tabasco, Mexico State and Puebla-Oaxaca, being approximately 80% of total pesticides which applies in these regions (Albert 2005).

Sources and exposure patterns

The environment is a major source of exposure to pesticides from farming. Approximately 47% of the applied product is deposited at or adjacent soil and water is dispersed in the atmosphere. This situation depends on weather conditions such as rain and wind direction and intensity, of geological and soil type and the presence of water currents, and other factors such as the formula and product presentation (liquid, powder, gel, gas, etc.) and application technique (air, land, etc.). Strong winds, high temperatures and unstable terrain favor the drag of the product, and the presentations powder, aerosol or smoke and, of course, aerial applications.

Other phenomena that favor environmental dissemination are photo degradation and volatilization, and leaching and washing soil surface, both related to the flow of water and rain. Work activity is important as a source of pesticide exposure in agricultural workers and their families, in chemical industry workers manufacturer of these products, fumigants, and in general, all those who formulated, manufactured, mixed, transported, loaded, stored or apply pesticides. The level of exposure and the likelihood of acute poisoning in these groups are substantially higher for continuous close contact with the chemicals. Although the period of contact with the agent are relatively short, they are still intense and repeated during the working day, causing toxic effects that vary with the type and amount of pesticide to which he was exposed, being relatively infrequent episodes of such accidental or intentional.

The exposure that affects the general population tends to be ubiquitous and crónica1. There are various types of pesticides for prolonged periods, from multiple sources and low doses penetrate the body using different routes. The main sources of exposure in the population are plant foods (fruits, vegetables, grains, legumes) or animal (beef, pork and its derivatives, fish, dairy products, eggs, etc.), And to a lesser extent water, air, soil, fauna and flora contaminated. So are the everyday industrial products that contain or are pesticides themselves and affecting directly or indirectly to human. It states that there is one segment of the general population free of exposure to these compounds and their potential adverse health effects (Barr et al., 1999).

Pesticides and its effects

According to estimates by the World Health Organization (WHO) each year between 500,000 and 1 million people are poisoned by pesticides and between 5,000 and 20,000 die. At least half of the intoxicated and 75% of those who die are agricultural workers, the rest is due to poisoning by eating contaminated food. In total between the two groups in mortality reached the figure of 220,000 deaths per year (WHO 1990, Eddleston et al., 2002).

Although pesticides have been developed to produce toxic effects in the fighting pests and although these effects may also potentially result in living organisms "nonwhite" of its action, the latter possibility will only occur if exposure these bodies reach sufficient levels to produce the toxic effect.

Therefore, besides knowing the physical, chemical and toxic pesticides, knowledge of each country or estimate potential exposures of humans and other organisms, which may occur in the localities in which they apply or you come to spread in the environment or through the food chain.

According to the type of toxicity, these chemicals affect the growth and survival of reproductive factors, and in the case of acute toxicity may cause death of exposed organisms (Campbell 1987). They have also been associated with long-term carcinogenicity, mutagenicity, reproductive and hormonal effects, among others. Agrochemicals able to induce changes in the genetic material of somatic and germinal tissue are considered mutagenic, contributing to the appearance of congenital malformations and cancer etiology (Wesseling ,1993, 1997). Epidemiological studies have associated with the cancer, gastric, skin, kidney, liver, prostate, testis in individuals exposed; besides sarcomas, leukemia, non-Hodgkin lymphoma, myeloma and others (Wesseling,1997).

Exposure to pesticides, either during development, production or use causing adverse effects on human health. These effects are not always related to immediate and apparent injuries, but can take even years to appear. Although the general population is exposed to these compounds, farmers are in a high risk group and therefore require biomonitoring studies to evaluate acute and chronic diseases caused by exposure to pesticides. Farm workers Irrigation District 03 (DR03) Mezquital Valley, Hidalgo, may be having genotoxic damage type for continuous and systematic use of pesticides. The amount of damage can be indicative of the need for continuous biomonitoring farmers occupationally exposed to various mixtures of pesticides, using a battery of tests of genotoxicity. On the other hand, illustrates the need to implement general guidelines to minimize or prevent exposure.

Toxicological aspects of pesticides

Without ignoring the importance of pesticides in agriculture and in public health activities, are undeniable that generate toxic effects in humans. Its bioavailability in the body depends on its toxicokinetics: absorption, distribution, metabolism and elimination. These processes are influenced by external factors related to exposure patterns and chemicals (employment rate, temperature, type of pesticide, frequency, intensity and duration of exposure, etc..) and by factors inherent to the individual (age, sex, genetic endowment, health, nutritional status, lifestyle, main route of absorption, etc.) (Fait and Colosio, 1998). Diets low or lacking in protein and states of dehydration are factors that influence the severity of damage to health. In laboratory animals undergoing LPDs, the LD_{50} of some pesticides can decrease between 4 and 2100 times, a situation that could be extrapolated to humans. In this regard, a large proportion of the overall workforce and exposed live in underdeveloped or developing countries, where pesticide use is as common as nutritional deficiencies mentioned.

The absorption depends on the properties of the formulation and the route of entry, determining cross product body barriers to reach the blood or other tissue in particular. The pathways may be multiple and simultaneous, the most common being the dermal route, the digestive and respiratory. Pesticides penetrate the skin by passive diffusion across the stratum corneum. In the workplace the dermal route is the most important, because through it and depending on the surface of exposed skin, are absorbed significant amounts of various pesticides that vary in their level of absorption.

Organochlorine (OC) passing through the skin varies widely depending on the type of substance, for example, DDT is poorly absorbed, but others such as endrin, aldrin, dieldrin and heptachlor the largest share and penetrate faster. Can be found in the dermis residues chlordane compounds as parathion or even months after the last exposure. Already absorbed soluble pesticides diffuse through the fatty components of the skin and blood, while they do soluble molecules through the intracellular protein aceous material.

In the general population the most important route of absorption is the digestive system from ingestion of contaminated food and water, as mentioned in the previous section. Deliberate or accidental ingestion is relatively rare. The fineness and thinness of the alveolar epithelium favors gas exchange in the lung, but also allows rapid and efficient absorption of pesticides, which are captured by air quickly into the bloodstream. In the workplace the use of fumigants as gases, dusts, vapors and mists, puts the airway as the second most important. In the general population the airway is another important route of absorption, the widespread use of pesticides in farming areas by air, the wind drift to surrounding areas and the use of common household aerosol products, sprays, smoke bombs, etc.. favor the presence of the product in the environment continuously in small quantities.

Circulation transplacental and breastfeeding are considered transfer mechanisms rather than absorption, as many pesticides or their metabolites pass directly to new being through hematoplacentaria barrier and / or during breastfeeding. Pesticides are distributed in the body through the bloodstream. Liposoluble compounds bind to lipoproteins, whereas they do soluble molecules to proteins in plasma or blood remain dissolved. by affinity, the pesticide shall be specific organs or tissues, such as liver or kidney disease, and those that are lipophilic and accumulate in adipose tissue and nervous, as in the case of DDT and, in general, pesticides OC. Two types of reactions by which the pesticides are metabolized in the body: the first phase reactions (oxidation, reduction and hydrolysis), which are generally catalyzed by liver enzymes, and the second stage, which are the synthesis and conjugation. Metabolites resulting from the first stage are associated with endogenous molecules synthesizing water soluble components and readily removable by bile and urine, as water-soluble metabolites pyrethroids. The biotransformation of pesticides may result in reduced toxicity or substances chemically inactive, as with the final metabolite dimethoato. On the contrary, can be generated more toxically active substances than the parent compound, as is the case carbosulfan, carbofuran transformation into, or of parathion to paraoxon giving rise, metabolites with high affinity for DNA and mutagenic capability important. The human body eliminates pesticides in three main ways: urine, feces and exhaled air.

Some water-based materials, such as lindane and phenoxy type herbicides are easily eliminated through urine without undergoing any change. Bile is the primary means by which some soluble compounds such as DDT and other OC are eliminated in the stool. Fumigants reaching the body as gases or vapors are commonly removed by airway, as in the case of acrylonitrile or methyl bromide.

Risk assessment of pesticides

Risk assessment is a procedure to determine objectively and transparently, how much a pesticide under the conditions of use, as well as in various circumstances, including the worst-(different scenarios), is likely to cause

Tabala 3. Cytogenetic Biomonitoring studies through the use of tests for chromosomal aberrations (CA), micronuclei (MNs), sister chromatid exchange (SCE) and comet assay (C_A) in human populations exposed to pesticides

No. Individuals and Type of Exposure	Biomarker Used	Place of Study	Result	Reference
48 farm workers exposed to mixtures of carbaryl, mancozeb and 50 witnesses	MN ICH	Italy	Positive (MN) Negative (SCE)	Pasquini et al., 1996
23 growers exposed to a mixture of 100 pesticide formulations and 22 witnesses	CA MN SCE	Italy	Positive (SCE, CA) Negative (MN)	Scarpato et al., 1996
27 vineyard workers exposed to mixtures of pesticides mainly 2,4-D and 35 control individuals.	CA MN SCE	Former Yugoslavia	Positive (MN, CA) Negative (ICH)	Joksic et al., 1997
38 exposed to malathion in a pest eradication program and 16 witnesses	MN	Berkeley, U.S.	Negative	Titenko-Holland et al., 1997
80 workers exposed to mixtures of pesticides carbamic, dithiocarbamic, organochlorines, pyrethroids, phenoxyacetic acid, etc.. and 24 witnesses	CA	Hungary	Positive	Paldy et al., 1987
15 vintners exposed to copper sulfate and organochlorine and organophosphorus insecticides and 10 witnesses	CA	India	Positive	Rita et al., 1987
55 greenhouse workers exposed to mixtures of organophosphate and carbamate, pyrethroid acaricides and fungicides and 60 witnesses	CA	Hungary	Positive	Nehéz et al., 1988
25 horticulturists contact organochlorine insecticides, herbicides and organophosphorus ureic and 30 witnesses	CA SCE	India	Positive	Rupa et al., 1988
50 workers exposed in open field to carbamates, organophosphates and pyrethroids and 47 in the control group	CA SCE	India	Positive	Rupa et al., 1989
44 people exposed to the fungicide mancozeb and 30 witnesses	CA SCE	Czech Republic	Positive	Jablonika et al., 1989
27 workers exposed to mixtures of pesticides and 28 witnesses	SCE	Spain	Negative	Carbonell et al., 1990
26 workers exposed to mixtures of organochlorines, organophosphates and pyrethroids and 26 witnesses	CA	India	Positive	Rupa et al., 1991
32 growers exposed to mixtures of organophosphates, organochlorines, pyrethroids and 31 witnesses	CA SCE	Italia	Positive	De Ferrari et al., 1991
12 applicators of 2,4-D and 12 individuals in the control group	MN	Berkeley, U.S.	Positive	Holland et al., 2002
10 workers exposed to mixtures of pesticides atrazine, alachlor, cyanazine, 2,4-dichloro phenoxyacetic acid and malathion in industry and production of these 20 people in the control group	MN CA C_A	Croatia	Positive	Garaj-Vrhovac y Zeljezic 2002
107 growers of greenhouse and open field exposed to mixtures of organophosphates, pyrethroids, carbamates, benzimidazoles, amides and 61 witnesses	MN in peripheral blood lymphocytes	Italy	Positive	Bolognesi et al., 2002
20 workers exposed to mixtures of atrazine, 2-4D and malathion and 20 witnesses	CA C_A	Croatia	Positive	Zeljezic y Garaj-Vrhovac 2001

adverse effects human health and biota in organizations "not white" of its action. Also, by this method can predict the doses or concentrations of pesticides that have no effect on other receptors (PNEC for its acronym in English) and the concentrations that can be found in the environment: water, air and soil (PEC for short in

English), and calculate the Acceptable Daily Intake (ADI) and Total (TDI).

Added to this, and based on the magnitude of the risks identified, you can set priorities for action to prevent, control or remedy the damage caused by handling of pesticides. From these assessments, also, you can set the maximum permissible levels of pesticides in different media and maximum residue limits (MRLs) for agricultural products.

For new pesticides, the assessment of risks to identify if they are excessive, in which case you can be banned trade, or decide to marketing approval and to adopt measures to prevent risks and ensure safe handling . The risk assessment is based on knowledge of the properties that make them dangerous to pesticides and capable of causing damage to the health of humans and other living organisms, depending on exposure.

Genotoxic compounds and their effects

Genotoxic compounds are those that act directly or indirectly on the DNA or clastogenic event. The genotoxic potential is a primary risk factor for chronic or long-term effects, such as reproductive effects and toxicity. As shown in Table 3, a total of 17 studies reviewed, 15 reported positive differences in subjects occupationally exposed to pesticides compared to unexposed groups, based on their statistical significance, which permits the inference that these biomarkers are adequate evidence for this type of population monitoring. For chromosome aberrations (CA) work show positive results represent 100%, for sister chromatids exchange (SCE) and 62.5% for induction of micronuclei (MN) 75%. The comet assay (C_A) shows 100% success, but for being a technique that has recently begun to use in occupational studies, it is difficult to even determine their degree of reliability.

Toxicological evidence of mutagenic and carcinogenic action of several pesticides and occupational or accidental exposure to large human populations to these compounds, have attracted the attention of many cytogenetic studies. A limited number of studies that seek to evaluate the genetic risk of occupational exposure established an association between occupational exposure to pesticides and the presence of CA, SCE and/or MN (Au et al., 1999; Antonicci and Syllos, 2000, Pastor et al., 2001; Paz et al., 2002; Garaj and Zeljezic, 2002; Bolognesi, 2003; Paramjit et al., 2003). If such changes occur in proto-oncogenes or tumor suppressor genes, which are involved in cell growth and differentiation, may promote the development of cancer in the organ involved, contribute to premature aging, producing vascular diseases, autoimmune or degenerative. If they occur in the germ line, can cause reproductive problems (infertility) as increasing off-spring genetic diseases, monogenic and polygenic both (Bolognesi et al., 1997; Holsapple, 2002; Paramjit et al., 2003; Hagmar et al., 2004).

Some studies show that various agrochemical ingredients possess mutagenic properties, ie inducing mutations, chromosomal alterations or DNA damage and a marked correlation between genotoxicity and carcinogenicity testing and indicate that short-term genotoxicity are useful in predicting carcinogenicity (Table 3), since it has been found that most of genotoxic carcinogens are, therefore, genotoxicity could be a biomarker intermediate between onset of effect and early indicators of disease or susceptibility (Albertini et al., 2000; Ramirez and Cuenca, 2002; Poli et al., 2003).

Pesticide exposure may pose a potential risk to humans, causing neuritis, psychiatric manifestations, hepatorenales disorders, neurological, immunological, metabolic and endocrine. It has also been linked to increased incidence of leukemia and bladder cancer in farmers, following genotoxic effects of some pesticides. Results of this type have led many researchers to evaluate the genetic risk associated with pesticide exposure (Márquez et al., 2003; Larrea et al., 2010).

Currently used in various tests in vivo and in vitro in prokaryotic and eukaryotic cell systems with a high degree of sensitivity, to measure various types of DNA damage. These include proof of micronuclei (MN), chromosome aberrations (CA), sister chromatid exchange (SCE) and comet assay adducts by HPLC (Au et al., 1999; Antonicci and Syllos, 2000; Pastor et al., 2001; Paz et al., 2002; Garaj and Zeljezic, 2002; Bolognesi, 2003; Paramjit et al., 2003).

In general, SCE and comet tests are useful in this assessment, by its sensitivity to detect acute and chronic damage respectively, by the rapidity with which they perform and their potential usefulness in evaluating any eukaryotic cell population (Larrea et al., 2010). The test sample SCE high resolution in the evaluation of chronic damage, while the comet assay allows analysis of individual data and the use of extremely small tissue samples, among other advantages (Albertini et al., 2000; Garaj and Zeljezic, 2001; Poli et al., 2003; Marquez et al., 2003; Gabbianelli et al., 2004).

Chromosomal aberrations (CA) can be used as an early warning sign for the development of cancer, as the evidence of genotoxic damage correlated with the early stages of cancer in humans has been consolidated in cohort studies, and confirmed that detecting an increase in the frequency of CA, associated with exposure to genotoxic agents, can be used to estimate the carcinogenic risk. Although several studies have focused on populations occupationally exposed to pesticides, by analyzing different cytogenetic tests, some of the reported data are confusing and inconclusive. These studies require continuous assessment due to differences in the number, concentration and pesticide mixtures, and also the differences in protection measures, crop and weather conditions among others (Garaj and Zeljezic, 2000; Bonassi et al., 2004).

Exposure meter

The measurement of the exposure and the possibility to establish a dose-response gradient are relevant aspects in studies of pesticides. Measuring exposure to pesticides in an individual or in a population is complex because it is influenced by factors such as the diversity of products sold, their indiscriminate use, multiple sources of exposure and variation in the intensity and duration of the an exposure period. All these aspects are beyond the control of the researcher and are generally lacks complete and timely information on them (Meinert et al., 2000). Several epidemiological studies have used a combined some measurement tools, such as exposure history, expert evaluation, environmental and biological monitoring, in order to achieve greater accuracy in measuring exposure.

The collection and analysis of retrospective exhibition is the most widely used measurement tool in epidemiological studies. The history of pesticide exposure is an indirect method that uses a structured individual questionnaire or some specific records, for homogeneous and systematic information on different aspects of exposure to these compounds over a period of time. Collect further data on socio demographic variables, confounding variables and other variables of interest. Both questionnaires as records are designed primarily for labor studies, but as the case is suitable for application in other populations. A common practice to extend or validate information initially obtained from a questionnaire, is the subsequent collection of detailed data on exposure (specific agricultural activity, type of application equipment, personal protective devices, previous damage to health, personal hygiene, etc.) or use of records such as purchase, or the management and use of pesticide products that have been implemented in various companies in the agricultural industry (Olshan and Daniels, 2000). More complete information on the history of exposure will result in a more accurate classification of subjects, reducing the potential effects of recall bias and improve the sensitivity and specificity.

The history of contact with pesticides are important but not sufficient to characterize exposure should be supplemented with information obtained by other techniques such as environmental monitoring and / or biological, to more accurately determine the level of exposure of the study subjects. Depending on the type of study can be contrasted with the current limits.

Biomarkers used for cytogenetic biomonitoring of populations exposed to pesticides

Biological markers or biomarkers are the biochemical, physiological or morphological measurable occurring in a biological system and interpreted marker reflecting or exposure to a toxic agent (Garte and Bonassi 2005). Biomarkers are used as indicators of health status or risk to disease and are used in both in vitro and in vivo that may include humans. Biomarkers are generally classified into three particular types (although some of them may be difficult to classify): exposure, susceptibility and effect and are a useful tool to assess the potential risk of different exposures. At the individual level can be used to support or refute the diagnosis of a particular type of poisoning or other adverse effects induced by chemicals.

Biomonitoring studies in agricultural populations published since the early 70s indicate mixed results, has been used for a wide variety of cytogenetic biomarkers and heterogeneous populations across the studies (Paldy et al., 1987, Rupa et al., 1989 , De Ferrari et al., 1991, Carbonell et al., 1993 Bolognesi et al., 2002). It is also important to consider that studies of pesticide exposure and genotoxic effect must take into account the reliability of injury exposure, the strength of the studies, the similarity of the control group and the protocols used for genotoxicity (Bull *et al .* 2006).

The cytogenetic damage causes changes and alterations in the number or structure of chromosomes, these effects have been evaluated using biomarkers as chromosome aberrations (CA), micronuclei (MN) and sister chromatid exchange (SCE) has also been possible to determine disorders that are manifested by changes in cell proliferation kinetics, which can be observed and evaluated during mitosis (Yakovenko and Zhurkov 1976, Pearson et al., 1981, Rupa et al., 1989, Diaz et al., 1990). Also we used the alkaline single cell electrophoresis or comet assay to assess DNA damage and repair in both in vitro studies and in vivo (Moretti et al., 2000).

One of the most important problems is occupational exposure to these compounds, so many studies have been conducted in order to assess the risk involved, especially for farm workers, through the evidence of chromosomal aberrations (CA), micronuclei (MN), sister chromatid exchange (SCE) and comet assay (C_A), the results have been controversial, because there are several factors that can cause differences. These may be the chemical group to which they belong pesticides, technical formulation and the active ingredient which is the product, the type of exposure (acute or chronic), the time that the individual has been exposed, the way it has been the contact (direct or indirect), the amount used, exposure to mixtures, the weather and the time of year that are sprinkled, the age of people, among other factors.

The CA is an error during meiosis the gametes or the first division of the egg and causes an abnormality of the number or structure of chromosomes and can be observed in the metaphase of the cell cycle and that originate in breakage (clastogenic processes) of the unrepaired DNA chains or poorly repaired, among other factors (Nussbaum et al., 2008).

The MN are chromosome fragments or whole chromosomes spontaneously or because of broken chromosomes agents such as radiation (agents that are called clastogens) or damaging the mitotic spindle, such as vinchrystine (aneuploidogens) fall outside the core during mitosis. Are known in the field of hematology as Howell-Jolly bodies and is generally round shape or almond with a diameter ranging from 0.4 to 1.6 microns. Its formation is based on that in the anaphase any chromosomal fragment that does not have centromere can not join a core lacking the essential element bearings in the spindle apparatus. After telophase, normal chromosomes and having centromere fragments, give rise to daughter cells nuclei, but lagging element, which may be fragments or whole chromosomes, are included in the cytoplasm of cells daughters, and a proportion of them is transformed into one or more secondary cores. Such nuclei are much smaller than the core, and hence the name "micronucleus". Then, if the test compound is a clastogen, MN will form small, but it is a aneuploidogen, which will observe the formation of MN. Among the variety of cells can be identified in peripheral blood and buccal mucosa by a smear (Zuniga and Gomez, 2006).

The SCE is a normal cellular event that occurs during the S phase of mitosis. Represents the symmetrical exchange between homologous loci of replication products. These exchanges are produced by breakdown and subsequent repair of DNA, at loci which are exchanged during the synthesis phase of the cell cycle. Occur without loss of DNA or chromosome morphology changes and may detect in metaphase chromosome preparations obtained from cultures spiked with a base analogue of DNA (Perez et al., 1999; Morales et al., 2007).

C_A is a biomarker fast, simple, and sensitive visual known as unicellular alkaline electrophoresis which is used to measure and analyze the DNA breaks. Differences detected intracellular damage repair processes virtually all cells (Speit and Hartmann 2006). The EC kite is to quantify the damage induced in the DNA of cells which are embedded in agarose, lysed and then subjected to electrophoresis in alkaline pH, thus making the chromosome fragments are directed towards the anode and the tail are disclosed as of a comet, which is displayed after staining with a fluorescent dye (Tice et al., 2000; Cossio et al., 2004). The ability of DNA migration depends on the number of breaks produced by the agent in question (Garaj and Zeljezic 2001), so each damaged cell has the appearance of a comet with a head and a tail and bright fluorescent cells not appear to have been damaged intact nuclei without tails (Möller 2006).

It is known that the active ingredients used in the production of commercial pesticides have harmful health effects, both final consumers of food treated as in exposed workers (Ballantyne, 1994) and between effects caused by pesticides, the most relevant genotoxicity. There are numerous studies linking the use of glyphosate with damage to genetic material highlighting the occurrence of birth defects, cancer and abortions. The mechanism is given by the genotoxicity that pesticides have shown, and glyphosate is no exception.

In a recent technical report submitted to the Council of State of Colombia by Mark Chernaik, eminent American toxicologist stated that "glyphosate exposure represents a risk in pregnant women." This statement is based on the study by Arbuckle (2001) which found a higher incidence of spontaneous abortions between 0:19 weeks of pregnancy in women exposed to glyphosate initiated before pregnancy. Similarly found glyphosate genetic effects in vitro cultures of bovine and human lymphocytes. In a study in Ontario, Canada, on the relationship between exposure to various types of pesticides and the occurrence of spontaneous abortions in farm households, 2,110 women were evaluated on the basis of 3.936 pregnancies, and included 395 spontaneous abortions. One of the interesting aspects of this study is that there is more interaction between pesticides to which a person is exposed as time passes. Usually, farmers and their families are exposed to a variety of different chemical families of pesticides (organophosphates, carbamates, etc..) These interactions cause an increased incidence of fetal death. Furthermore the chemical nature of the pesticide, the toxicity of the time depends also on the exposure occurs. There are critical times of fetal development and reproductive system in which pesticides are more toxic (Chernaik, 2003).

Biomonitoring studies

Pesticide exposure interferes with human health, because there are problems of morbidity and quality of family life genotoxic derivatives to generate birth defects, carcinogenic, among others, exposure to pesticides does not exempt any age group or gender, variously affects the exposed (Badii et al., 2007; Yucra et al., 2008).

The check for induction of DNA damage is performed by various tests, but human biomonitoring studies by cytogenetic assays are the most commonly used. The objectives of the biomonitoring as part of the genetic risk assessment are detecting exposure to environmental genotoxins, the determination of genotoxic effects in vivo (Bonassi et al., 2004) and the identification of biomarkers of genotoxicity can define a state of prepatogénesis and provide guidelines for disease prevention. Within genotoxicity biomarkers that have been used widely, are the frequency of sister chromatid exchange (SCE), micronuclei (MNs), chromosome aberrations (CA) and comet assay (C_A) (Bolognesi et al., 1997; Vigreux et al. 1998; Garaj and Zeljezic 2000; Pastor et al., 2001;

Holsapple, 2002).

This study will assess the genotoxic damage and measure the genetic risk in farmworker populations occupationally exposed to a mixture of pesticides, through 4 different methods: sister chromatid exchange (SCE) analysis of chromosomal aberrations (CA), micronuclei (MN) and comet assay (C_A).

CONCLUSIONS

The extensive application of pesticides is a common practice around the world. Although the production and marketing of certain pesticides harmful to humans have been banned, other products continue to be used, without knowing fully the negative impact that these compounds may have on ecosystems and public health. Evidence indicates that pesticides pose a risk to public health, so it is necessary to conduct more studies using different models and indicators to assess the potential risks to health and the ecosystem. Therefore, unintelligent use of pesticides has led to reduced connectivity (trophic interaction between organisms), loss of biodiversity, ecological imbalance and environmental stability decreased. Consequently, man, by the lack of rational use of pesticides, has been and is threatening the sustainability.

This literature review shows that more tests or biomarkers used to evaluate the genotoxic effect of pesticides are MN, CA, SCE and recently the C_A. This is based on studies conducted by researchers from different countries of the world, which provide scientific evidence indicates positive correlations between exposure time, dose and high frequency CA, MN, SCE and C_A. However, it is common to find discrepancies in results across studies, which may be due to the age of people, the use of mixtures of pesticides, genetic polymorphism, forms of application, level of genotoxic compounds , the characteristics of the spray (enclosed or open field) or the interaction of these situations. Considering this, it is important the introduction of agricultural practices that reduce pesticide use in this sense is vital to incorporate measures of biological control and integrated pest management. It is also essential to intensify efforts in training and updating of technical staff, laborers and farmers, and to strengthen prevention and education to the community.

Cytogenetic monitoring should be considered as an integral part of good medical surveillance on people in contact with pesticides, since it allows to evaluate the potential risk of occupational exposures, which would take the necessary measures for early identification of genetic risk. Monitoring of human populations by analysis of chromosomal aberrations and sister chromatid exchanges in peripheral blood culture and micronucleus and comet.

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