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Pesticides and Human Health

Khaled A. Osman
Alexandria University, Department of Pesticide Chemistry & Toxicology, College of Agriculture, El-Chatby, Alexandria, Egypt

1. Introduction

Chemical pesticides when used properly have been of tremendous benefit to man and his environment especially in developing countries, where they are used to eradicate insect-borne, endemic diseases, to produce adequate food and protect forests, plantation and fibers. Presently, more than 2.5 million tons of pesticides valued over US $30 billion are being used in cultivation alone all over the world. The Rachel Carson's "Silent Spring" (Carson, 1962), awakened the public to the potentially "disastrous" effect of chemical pesticides on human and the environment. "Silent Spring" heralded the start of the U.S. environment movement in which a number of biologists and ecologists all echoed the same basic view that planet earth was a finite entity and that man and the whole global biosphere were doomed unless immediate action was taken to reign-in what was considered a runaway technology. When pesticides misused or used carelessly they have caused considerable harm. The risk or hazards of using chemical pesticides have increased in recent years with the sharp rise in their consumption by agriculture, industry, householders, and government. Pesticides lead to over three million poisoning cases annually and up to 220,000 deaths, primarily in developing countries. Pesticides may present immediate danger to the user if applied improperly or without sufficient knowledge of their toxic effects. Some are highly toxic and may cause serious illness and even death if spilled on the skin, inhaled, or otherwise used carelessly. In addition, potential future hazard to human health and wildlife can be created by residues from some long-lived pesticides that may build up in the food chain and cause widespread contamination of the environment. The risk is defined as a measure of the probability that an adverse effect will occur (Wilkinson, 1986). In the case of a chemical, it is a function of the intrinsic capacity of the material to cause an adverse effect (acute toxicity, neurotoxicity, cancer, etc.) and the dose, which is usually determined by the intensity, frequency, or duration of exposure. Risk assessment is the process by which estimates of risk to humans from exposure to potentially toxic agents are extrapolated from existing data, usually generated from laboratory animals (National Research Council [NRC, 1983]). Strauss (1991) divided the risk assessment into 4 components: hazard identification, exposure assessment, dose-response assessment and risk characterization (Fig. 1).

The aim of the assessment of human exposure to pesticides is the identification of dose-effect relationships in man after both single and/or repeated exposures and also the methods for prevention of such adverse effects due to these chemicals. According to the circumstances, size of dose, and methods of assessment, human exposures might be divided

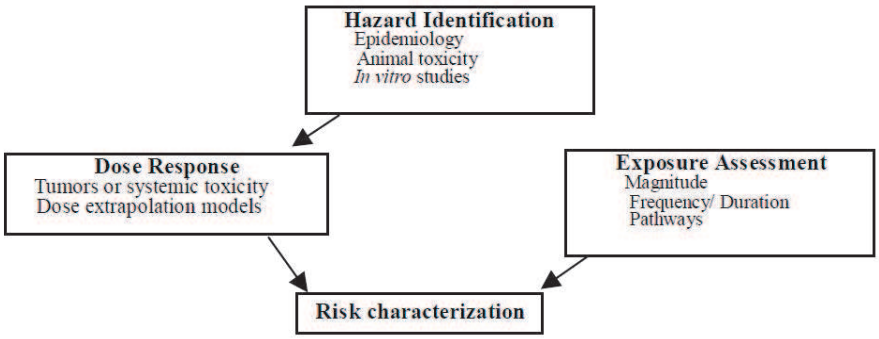

Fig. 1. Risk assessment components, adapted from Strauss, 1991.

as: a) acute/subacute poisoning (intentional, accidental, and occupational), b) long term occupational, and c) environmental exposure (via food, water etc.). The relationship among different exposures is depicted in Fig. 2.

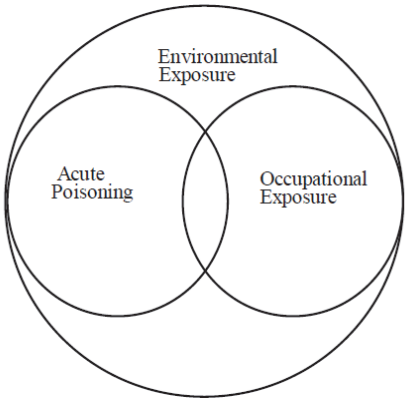

Fig. 2. The relationship among different exposure, adapted from Lotti, 1992.

It is crucial importance to understand the terminologies that describe risk assessment as following:

Risk: The probability of an adverse health effect as a result of exposure to a hazardous substance.

Risk Assessment: The use of available information to evaluate and estimate exposure to a substance and its consequent adverse health effects.

Risk Identification: The qualitative evaluation of the adverse health effects of a substance in animals or in humans.

Exposure Assessment: The evaluation of the types (routes and media), magnitudes, time, and duration of actual or anticipated exposures and of doses, when known, and when appropriate, the number of persons who are likely to be exposed.

Dose-Response Assessment: The process of estimating the relation between the dose of a substance(s) and the incidence of an adverse health effect.

Risk Characterization: The process of estimating the probable incidence of an adverse health effect of humans under various conditions of exposures, including a description of the uncertainties involved.
Risk Management: The regulatory decision that incorporates information of benefits versus risks of exposure to certain situation.
Ecological Risk Assessment: The likelihood of adverse ecological effects caused by any chemical or nonchemical stressor that can exert adverse effects on components such as individuals, population, communities or ecosystem.
No Observed Adverse Effect Level (NOAEL): The highest dose in an appropriate study that is not associated with adverse effect on the test organisms.
No Observed Adverse Effect Concentration (NOAEC): The highest concentration in an exposure media in a study that is not associated with an adverse effect on the test organisms.
Reference Dose (RfD): An estimate of the exposure that can occur continuously, on a day basis, over a prolonged period, with a reasonable expectation that no adverse effect will occur from that exposure (refer to non-cancer hazards associated with the chemical).

$$RfD = NOAL_{\text{critical effect}} / UF_{\text{interspecies}} \times UF_{\text{intraspecies}} \times MF \quad (1)$$

Where, $Uf_{\text{interspecies}}$, $UF_{\text{intraspecies}}$ and MF are safety factor for differences within species, between species and expert-derived modifying factors, respectively.
Benchmark dose (BMD): The lower 95% confidence interval on that dose level (benchmark effect, BME), or the statistical lower bound on a dose corresponding to a specific level of risk (1, 5, or 10% risk level).
Threshold limit value (TLV): The concentration of a hazardous substance to which the majority of industrial works may be repeatedly exposed every day without adverse effects.
Permissible Exposure Limit (PEL): The maximum exposure to a given chemical that an industrial worker is allowed during eight-hour workday and 40 hour workweek.
Acceptable Daily Intake (ADI): An estimate of the daily exposure that is likely to be without deleterious effects even if continued exposure occurs over a lifetime.
Maximum Residue Limit (MRL): The maximum residue level that is expected to occur in a commodity following the application of a pesticide according to good agricultural practice (GAP).
Theoretical maximum daily intake (TMDI): An estimate of dietary intake calculated using the MRL and the average daily per capita consumption of each food commodity for which an MRL has been established. The TMDI is calculated by multiplying the MRL by the average food consumption for each commodity and then summing the product:

$$TMDI = \Sigma F_i \times M_i \quad (2)$$

Because of the lack of vigorous legislation and regulations to control pesticides as well as training programs for personnel to inspect and monitor, use and to initiate training programs for pesticide consumers, the goals of this chapter is to discuss and focus on the risk assessment components and the adverse effects of pesticides.

2. Hazard identification

Hazard identification uses available data on biological end points related to chemical to determine if that chemical is likely to pose a hazard to human health. These data are also used to define the type of potential hazard, that the chemical dose induces: tumor formation, developmental effects, to act as a kidney toxicant, and so forth.

2.1 Epidemic outbreaks due to occupational and non-occupational exposure to insecticides

Toxic outbreaks or collective poisonings have resulted from misuse of almost all types of pesticides: organochlorine insecticides such as DDT, lindane, toxaphene, endrin, aldrin and dieldrin, OPs and carbamate cholinesterase (ChE) inhibitors. Such collective outbreaks may be defined as the effect, in an exposure incident, of a chemical or group of chemicals on a population in which several to many individuals are poisoned. They may occur in the general population from oral or cutaneous exposure or they may be occupational in nature, involving manufacturing workers or formulators, mixers, or applicators in agriculture and public health. While it is clear that such incidents can occur in any country, in recent years they have become less common in developed countries than in developing countries. Recently, public concern over potential adverse health effects has focused on a number of chronic end points carcinogensis, developmental and reproductive effects, immunological effects, and neurotoxicity (Hodgson & Levi, 1996). One of the most severe epidemic poisoning incidents occurred in India when lindane intended for preservation of seed grains was mixed with food grains and was consumed (Khare et al., 1977). The onset of signs of poisoning was sudden with seizures of the mixed type, i.e., grand mal, petit mal, and myoclons, predominating. The highest risk of adverse reproductive effect has been seen among male production workers at the Occidental Chemical plant in Lathrop, California, who had handled the nematicide dibromochloropropane (Babich & Davis, 1981). Also, the continued use of this pesticide in banana plantations in Costa Rica is reported to produce high rates of sterility (Thrupp, 1991). Incident cases of carcinogenic risk associated with pesticide exposure in adults of both sexes in 5 hospitals used by residents of 5 Italian rural areas were reported (Settimi et al.,1990).

2.2 Cytotoxic effects of insecticides

2.2.1 Carcinogenic effects

A number of epidemiological studies have been carried out to evaluate the association between exposure to pesticides and cancer (Settimi et al., 1990, Wolff et al., 1993 and Dewailly et al., 1994). These pesticides can play a role in the cancer process by either nongenotoxic mechanisms such as promotion, peroxisme proliferation, and hormone imbalance (Hodgson & Levi, 1996), or by affecting carcinogenic process in a variety of ways, both by altering the genome and by providing a growth advantage for neoplastic cells (Williams et al., 1992). Therefore, risk assessment model should reflect these differences in cancer mechanism. The US-Environmental Protection Agency ([U.S. EPA], 1986) has generally categorized the carcinogenic potential of a chemical based on the overall weight of evidence. The categories are as follows: Group A (Human Carcinogen), Group B (Probable Human Carcinogen), Group C (Possible Human Carcinogen), Group D (Not Classified as to Human Carcinogenicity), and Group E (Evidence of Non-carcinogenicity for Humans). DDT and its metabolite DDE, *o,p*'-DDT, an isomer of DDT, chlordecone, heptachlor, and other

pesticides which are still persistent in the environment long after being banned are considered carcinogens and involved in the causation of breast cancer as a result of estrogenic activity (xenoestrogenic substances) (McLachan et al., 1993, Stone, 1994). *p,p'*-DDT, methoxychlor and chlordecone affect estrogen production and metabolism and thus function as xenoestrogens (Davis et al., 1993). Epidemiological studies have found that breast fat and serum lipids of women with breast cancer contain significantly elevated levels of some chlorinated hydrocarbons compared with non cancer control. Therefore, tests for estrogenicity could become critical screening tools to assess the potential health consequence of new and existing pesticides. So, cancer risk assessment seeks to measure increases in the frequency of occurrence of an event in a population and to detect the occurrence of low probability events at low doses over long periods of time (Wilkinson, 1986). Also, various compounds of halogenated hydrocarbons inhibit gap junctional intercellular communication (GJIC) in normal human breast epithelial cells (HBEC) when given as a single compound or as mixtures where they can alter the post-translational level, have tumor-promoting potential in human breast tissue and exert some human health effects if they meet all the conditions to inhibit GJIC (Kang et al., 1996).

OPs react with biological molecules by means of phosphorylation of serine hydrolases (acetylcholinesterase, AChE) and of alkylation of macromolecules, DNA (World Health Organization [WHO], 1993b) which are considered to account for the acute cholinergic toxicity and initiation of the carcinogenic process, respectively. When the rate of phosphorylation is substantially higher than the rate of alkylation, *in vivo* genotoxic effects are unlikely to occur because effective doses cannot be achieved due to acute toxicity. Diazinon and dichlorvos meet these criteria, where the rate of phosphorylation of AChE being much faster than that of alkylation. On the other hand, methidathion was categorized as a group C (possible human carcinogen) depending upon evidence of increased incidence of benign and malignant hepatocellular tumors in male Chr-CD-1 mice (Quest et al., 1990).

2.2.2 Reproductive and development effects

Potential non-cancer health outcomes that may be influenced by an agent in the environment, particularly pesticides, include deleterious effects on the nervous, renal, respiratory and reproductive systems of both men and women. The mammalian development toxicity is referred to as the adverse effects initiated or evident during *in utero* development. The development toxicity includes adverse effects on the developing organism that may have resulted from exposure of either parent before conception, of the mother during prenatal development, or postnatally to the time of sexual maturation. Embryo is the most vulnerable to the initiation of major birth defects between 3 weeks and 2 months of gestation, the critical period of organogensis. The exposure to toxic chemicals during the first 2 weeks leads to fetal death, while exposure after organogensis is more likely to cause growth retardation and functional deficits (Hodgson & Levi, 1996). Also, the pesticide used by appliers and exposure of the general population of the crop-growing region of Western Minnesota are associated with increased birth anomalies (Garry et al., 1996). The primary DDT metabolite, *p,p'*-DDE interferes with the action of male sex hormones, or androgens affecting mammalian sex differentiation (Kelce et al., 1995). It is now recognized that numerous endocrine disrupting pesticides from different chemical groups have been released into the environment in large quantity since world war II and exert their action as agonistic and antagonistic receptor binding, and affect hormone synthesis, storage, release, transport, and clearance (Kavlock et al., 1996). As shown in Fig. 3,

the theoretical basis for environmental chemicals to exert hormone-like effects is relatively straight forward (McLachlan, 1993). In the simplest model, chemicals can mimic a hormone by binding to its receptor and eliciting a spectrum of biological effects. Conversely, a foreign chemical does not elicit these effects could bind a hormone receptor as inactive compound and thus block the response to the natural hormone. In both cases, the result would be an alteration in the function of the hormone system.

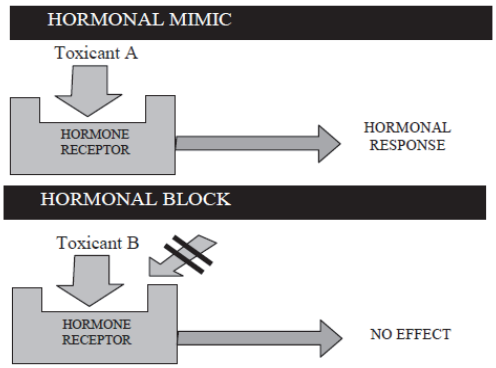

Fig. 3. Exogenous chemicals may act at hormone action site, adapted from McLachlan, 1993.

2.2.3 Neurobehavioral effects

Because of the basic similarities between mammalian and insect nervous system, insecticides (organochlorines, OPs and carbamates) are designed to attack the insect nervous system and capable of producing acute and chronic neurotoxic effects in mammals (Tanner & Longston, 1990). Both acute and chronic alterations in sensory, motor, autonomic, cognitive, and behavioral functions have been observed in people exposed occupationally to relatively high levels of insecticides. These neurobehavioral effects and chemical-induced changes in behavior may be a relatively sensitive indicator of nervous dysfunction (National Academy of Science [NAS], 1975) and can be used in neurotoxicology for neurotoxicity risk assessment (Evangelista de Duffard & Duffard, 1996). Organochlorine insecticides have effects on motor, sensory, or cognitive function that are detectable using functional indicators of neurotoxicity (Evangelista de Duffard & Duffard, 1996) to assess neurotoxicity risk.

A number of OPs cause neurotoxicity, characterized as central- peripheral distal axonopathy (Lotti, 1992 and Osman et al., 1996 and 2001). This syndrome commonly known as organophosphate induced delayed polyneuropathy (OPIDP), is totally independent of inhibition of AChE and is delayed as symptoms appear after 2-3 weeks. The mechanism of initiation of OPIDP involves the phosphorylation of a protein in the nervous system called neuropathy target esterase (NTE) and the aging of the phosphoryl enzyme complex (Johnson, 1982). The inhibition of NTE activity in human lymphocytes has been shown to predict the onset of OPIDP in a patient poisoned with chlorpyrifos (Lotti et al., 1986). Preliminary studies in Central America suggested that mild or subclinical cases of OPIDP after severe cholinergic poisoning with methamidophos may be much more common than previously suspected (WHO, 1993a). In humans, OPIDP also has been reported to occur after poisoning with merphos, mipafox, leptophos,

trichlorphon and trichlornate (Lotti et al., 1984). One of the main tasks of toxicology and risk assessment is to determine, through experiments with animals and documentation of adverse effects following accidental exposure of human, safe limits of exposure to toxic chemicals. Since new pesticides are being released into the environment, it is essential to use rapid and sensitive toxicological screening procedures for these and already existing pesticides. Once behavioral neurotoxic effects have been identified, it is important to improve the understanding of the mechanism of neurotoxicity at the neurochemical, neurophysiological, cellular, and molecular levels of analysis (Evangelista de Duffard & Duffard, 1996). Neurotoxicity risk assessment will be improved by a more complete understanding of the interrelationships between the various levels of nervous system. Neurobehavioral toxicology contributes directly to this issue by systemically assessing the threshold and magnitude of exposure beyond which normal processes are significantly affected.

2.2.4 Immunotoxic effects

The exposure of humans to some insecticides alters immune phenotypes or function and potential disease susceptibility (WHO, 1990). Aplastic anemia has been described as idiosyncratic immunologic response to exposure to organochlorine pesticides (Hayes & Laws, 1991). Also, allergic responses, especially allergic dermatitis, can be seen with many classes of pesticides (Hogan, 1990). Individuals consuming ground water contaminated with low levels of aldicarb in Wisconsin were reported to have abnormalities in T-cell subset in women with otherwise intact immune systems and they are potentially at risk for immunologic damage (Fiore et al., 1986). It has been argued that decrease immune surveillance resulting from inhibition of monocyte esterases by chronic OPs exposure may result in the development of lymphoma (Newcombe, 1992) and the exposure to chlorpyrifos during a development period is known to produce deficits in immune competence (Navarro et al., 2001).

3. Dose-response assessment

3.1 The basic elements of dose- response assessment

In the dose-response assessment, data from human and animal studies are used to estimate the amount of chemical that is expected to produce a given effect in humans. In this step it is generally necessary to apply mathematical models to calculate a quantitive risk estimate usable for low-dose exposure. Dose-response assessment can be viewed as three critical steps identification of the effect (and related exposure level) of most concern, a characterization of the uncertainty present in the database, and an estimate of the exposure level presumed to be free of risk to the human conceptus (Kavlock & Setzer, 1996). In the first step, data from exposed experimental species, as well as any epidemiological information, is examined for the highest dose level that is without a significant adverse effect (the no observed adverse effect level, NOAL). In the second step, the adequacy, relevance, and uncertainties in extrapolating the NOAEL from the experimental species to the target species are estimated. In the final step, the critical NOAEL (The lowest NOAEL in the database on a particular chemical) is divided by the product of uncertainty factors (UF), as well as any expert-derived modifying factors (MF) to obtain the reference dose (RfD) or reference concentration (RfC) for an inhaled chemical. The current methods for estimating human health risks from exposure to threshold-acting toxicant in water or food, such as those established by U.S. EPA, (1980). These methods generally estimate a single, constant

daily intake rate that is low enough to be considered safe or acceptable. This intake rate is termed the acceptable daily intake (ADI, expressed in milligrams per kilogram). Another avenue to improve the dose-response component of the risk assessment process is to better use data generated from standardized testing procedures, independent of knowledge of toxicokinetic or toxicodynamic factors that may be used to adjust the magnitude of the uncertainty factors. This can be done by using benchmark dose (BMD) approach (Crump, 1984). In the BMD approach, a particular effect level is chosen and the dose inducing that response is calculated using a statistical model (Fig. 4). The BMD is then defined as the lower of 95% confidence interval on that dose level (benchmark effect, BME).

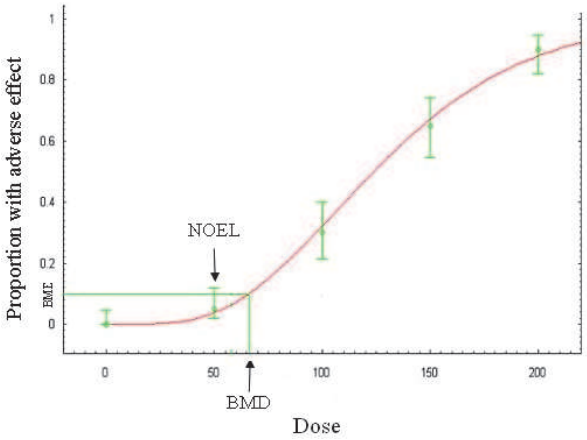

Fig. 4. Benchmark dose calculation, adapted from Crump, 1984.

The dose-response curve (Fig. 5) can take an anomalous form because the effective dose is not directly proportional to administered dose (O'Flaherty, 1986). This is particularly true at the high or maximum tolerated doses that are characteristic of toxicity and carcinogenicity studies. Also, among the many reasons why administered and effective dose may not be directly proportional to each other are capacity limited systemic or first pass elimination, rate limiting availability of cofactors, shifts in tissue distribution caused by saturation of binding sites, especially in plasma and alterations in blood flow rates to critical tissues.

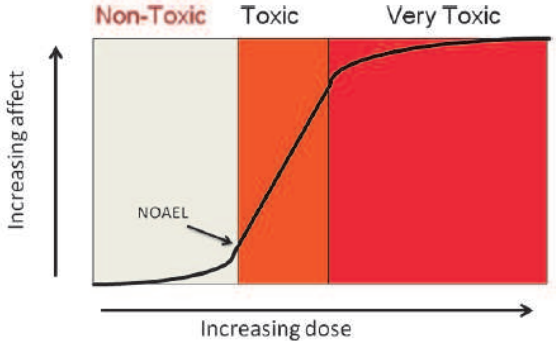

Fig. 5. The dose-response curve, adapted from O'Flaherty, 1986.

3.2 Toxicity test in animals: extrapolating to human risks

The process of assessing risks based on animal experiments involves extrapolations from high doses to low doses, between dose route and exposure scenarios, and between various animal species (Clewell & Anderson, 1985). Risk assessment oriented-research paradigm in toxicology centers on the relationships linking exposure tissue dose, initial tissue interaction, and toxic response, together with the strategies for extrapolating from observed responses in animals to expected response incidence in humans exposed at very much lower concentration as shown in Fig. 6.

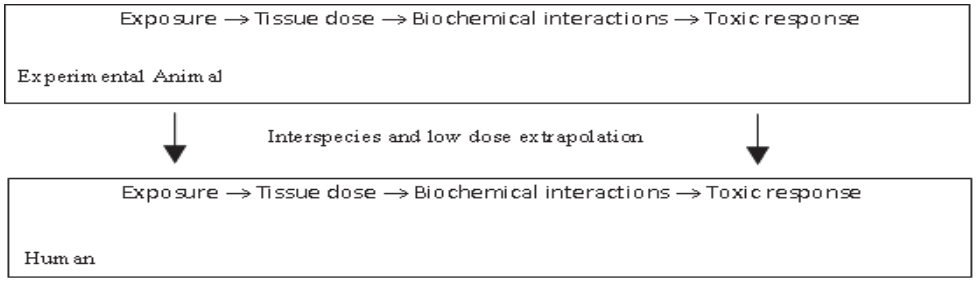

Fig. 6. The individual processes involved in the expression of toxic responses in a risk assessment context. Adapted from Andersen et al., 1995.

The dose-effect and dose-response relationship in occupational neurotoxicology are rarely studied by means of biochemical methods. Some biochemical methods are however available to extrapolate from animal to man and used in monitoring human exposures and can be framed in three categories: exploring the delivery of chemicals to the site of action, the modifications of the molecular target induced by chemicals, and the biochemical consequence of these modifications. The possibility of measuring adducts in hemoglobin will enable an estimation of the dose of electrophiles closer to the target and to extrapolate dose more precisely across species (Lotti et al., 1989). Once the number of adducts and their persistence in man, after exposure to a given chemical are known, it will be possible to compare them with data from animals dosed with a known amount of electrophilic chemicals and therefore to extrapolate toxicity more precisely. There are number of OPs that cause OPIDP when the threshold of inhibition of NTE reach 70-80% (Johnson, 1982). For an OP the use of the therapeutic index (TI) is useful to predict the safety. The TI is defined as the ratio of the median toxic dose (TD_{50}) over the median effective dose (ED_{50}). For maximal safety, the TD_{50} must occur at a dose far as possible above the LD_{50}. That is, the dose-response curve for the toxic effect should be as far to the right of the dose-response curve for effect dose as possible (Klassen, 1986).

4. Exposure assessment

The exposure assessment seeks to determine the extent to which a population is exposed to the material. Exposure assessment uses available data relevant to population exposure, such as emission data, measurement of the material in the environmental media, and biomarker information. Fate and transport of the material in the environment, routes of exposure and

pharmacokinetics of the chemical in the body may be considered in the exposure assessment.

4.1 Dietary exposures to insecticides

The consumption of foods and water containing environmental contaminants is a potentially significant source of human exposure to numerous pesticides. So, it is important to understand the magnitude, sources, and variability of dietary exposures to environmental contaminants experienced by members of the population, the precision of dietary exposure estimates possible from existing data, and the prospect of using dietary exposures in epidemiologic studies designed to characterize the human health effects of specific insecticides or classes of insecticides (Berry, 1992). Total exposure assessment from dietary and other sources is used in evaluating risk and for comparison with recommended allowable daily intake. Food and water-borne residues are the most important sources of exposure to the general population. In many countries including Argentina, Panama, Brazil, Costa Rica, Guatemala, El-Salvador, Mexico and India, nursing infants potentially ingested organohalogens at a ratio many times that of ADI as estimated by Food and Agriculture Organization/World Health Organization [FAO/WHO], 1988). A high proportion of DDE in Indian buffalo's milk that might reflect the presence of ages residues of DDT, whereas that of TDE would indicate contamination of more recent origin (Kapoor & Kalra, 1993). Therefore, animals yielding milk contaminated with high levels of DDE will require fairly long holding period than those are able to yield milk of acceptable quality after the elimination of the potent source of contamination.

Data from toxicological investigations are a substantial part of the assessment of a pesticide. The toxicological studies should identify possible adverse health effects of the compound and establish the dose at which such effects are likely to occur, and particularly identify a dose level where adverse effects are absent. The majority of the toxicological data used in the risk assessment are generated in studies performed according to internationally accepted standards (guidelines), which for each type of study state the minimum requirements for an acceptable performance. In addition, regulatory agencies also require that, to be used in decision making, the investigations are performed according to Good Laboratory Practice (GLP) involving quality control and quality assurance. The different types of toxicological investigations required for the evaluation of a pesticide involve studies on acute effects, including effects on skin and mucous membranes, and more important long-term studies on chronic effects, including carcinogenicity following repeated daily exposure. Studies of effects on reproduction over a minimum of two generations are also required, as well as special studies on teratogenicity and embryo/fetotoxicity, and on effects on the genetic materials. In addition, studies on absorption, biotransformation, distribution, and excretion are also required. In these studies, effects on macromolecules, such as DNA, enzymes, and other biochemical parameters are often included. The toxicological data that are used in risk assessment are usually generated from animal experiments and *in vitro* investigations. When human data are available, for example from occupational or accidental exposure, these of course are considered highly valuable. From the toxicological data a NOEL or NOAEL is identified as the highest daily dose level that does not produce observable effects or adverse effects in the most sensitive animal species. In establishing the ADI for humans the NOEL is reduced by a safety factor, which take into account the uncertainties of the results of the investigations, the extrapolation from animals to humans, and the variations in sensitivity and life-style within the human population. When the toxicological background material is

considered sufficient, a safety factor of 100 is normally used (a factor of 10 for differences between species and 10 for differences within species (Fig. 7). Additional safety factors are occasionally used, for example, when the biological effect is considered to particularly serious or when uncertainty exists in the evaluation of the consequences of a finding. Safety factors of 1000 or even higher have occasionally been used, when a clear NOAEL cannot be established on the basis of available data, lowest observed adverse effect level (LOAEL) is sometimes identified and used to establish an ADI. On the other hand, MRL is based on field spraying trials and subsequent determinations of residues. These investigations include different methods of application, including those using the highest dosages and used in such a way that the lowest possible amount of residue is produced. The MRL is never established at a level higher than needed even if the established ADI value would allow a higher residue content. In practice, this means that the intake of most pesticides by the general population is well below the ADI. In the evaluation of the health risk, the possible total intake of the pesticide is calculated as if the concentration in all the food in which it can be present is at the MRL for each single food item. This mean that exceeding the MRL in one single sample does not automatically result in exceeding the ADI, as many samples normally are without detectable residues.

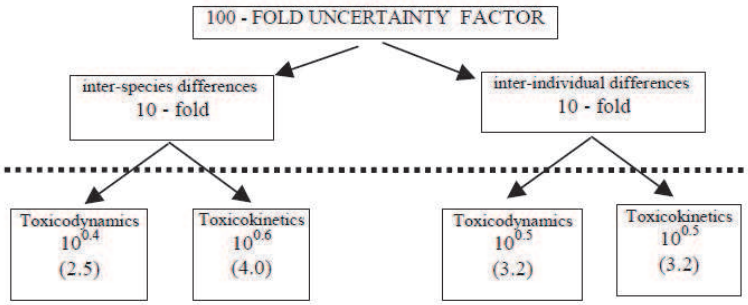

Fig. 7. Subdivision of the 100 -fold uncertainty factor, adapted from Walton et al., 2001.

4.2 Biomarkers in risk assessment

The field of biomarkers has been the object of increased interest in the past few years. The term biomarker is used to mean biological biochemical/molecular markers, which can be measured by chemical, biochemical or molecular biological techniques (Costa, 1996). Biomarkers are usually divided in three categories : biomarkers of exposure, of effect and of susceptibility (NRC, 1987). Additional subdivisions of and overlaps between different types of biomarkers should also be considered. For example, certain biomarkers of exposure, e.g. DNA adduct, may be also considered as biomarker of effect. Fig. (8) shows the fate and reactions of a xenobiotic in the human body and the types of tests available to investigate human exposure (Aldridge, 1986). Once a chemical is absorbed and distributed through the plasma pool, it attaches itself to the molecular target either directly or after metabolic activation, then a cascade of biochemical and physiological changes occurs, which triggers the morphological, clinical expression of toxicity. Evaluations of human exposure might be performed at any stage of this process but their significant is obviously different.

The best available tools are in the area of biomarkers of exposure is the of measurement of neurotoxic chemicals and their metabolites in biological fluid which provide useful and

reliable indicators of exposure (Henderson et al., 1987, Costa, 1996). An ideal biomarker of exposure is chemical specific, detectable in trace quantities, inexpensive and quantitatively relatable to prior exposures. Also, the binding of a toxicant to hemoglobin is considered a good biomarkers to measure cumulative internal dose due to repeated exposures, because red blood cells are long-lived (approximately 4 months in humans), while adducts to albumin reflect more recent exposure because albumin has a shorter lifetime in blood (20-25 days) (Henderson et al., 1987). Therefore hemoglobin adducts could be used as a biomonitoring technique for evaluating residues in food for specific pesticides which form arylamine-hemoglobin adducts (Sabbioni & Neuman, 1990).

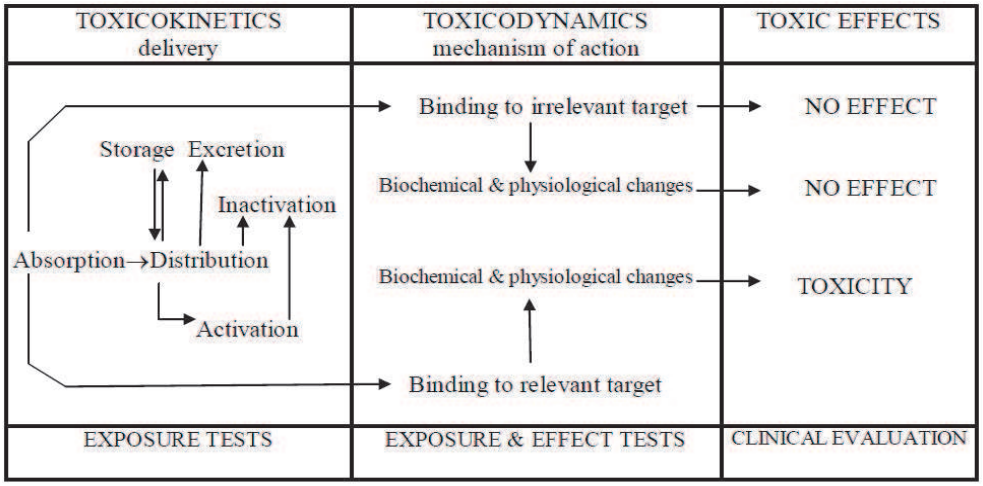

Fig. 8. Fate and reaction of a xenobiotic in human body, adapted from Aldridge, 1986.

Biomarkers of effect should reflect early biochemical modifications that precede structural or functional damage. Thus, knowledge of the mechanism(s) that led to ultimate toxicity is necessary to development specific and useful biomarkers. Such markers should identify early and reversible biochemical events that may also be predictive of later responses (Silbergeld, 1993). The oldest and probably still the best example of the application of such strategy to neurotoxic compounds is represented by the measurement of red blood cell AChE following exposure to OPs. Erythrocyte AChE, in particular, was found to be better correlated with brain or diaphragm activity than plasma ChE (Padilla et al., 1994). OPs such leptophos, EPN, cyanofenophos, trichloronate and salithion proved to cause irreversible ataxia in chicken, mice and sheep and their AChE inhibition stands for their acute toxicity, while NTE inhibition is responsible for their paralytic ataxia and can be used as a standard screening method for delayed neuropathy (El-Sebae et al., 1981). The precise measurement of ChE (erythrocyte or plasma) can be useful as a measurement for low level exposure to OPs in epidemiological research (Richter et al., 1986, Dyer et al., 2001). Recent studies conducted have shown that lower group mean plasma and erythrocyte ChE level in populations living adjacent to cotton fields which are sprayed regularly with OPs (Richter et al., 1986). Also, urinary alkylphosphates are sensitive indicators of OPs exposure, and have been shown to correlate with symptoms.

A comparative inhibition of rodent and human erythrocyte AChE by two anticholinesterase carbamates, carbaryl and carbofuran was evaluated by using Michaelis constant (K_m), maximum velocity (V_{max}), concentration of pesticide required to inhibit 50% of the enzyme activity (IC_{50}) and bimolecular rate constant (K_i) (Rao et al., 1994). Although there are inherent differences in kinetics of substrate hydrolysis between rodent and human erythrocyte AChE, the kinetics of inhibition *in vitro* by carbofuran and carbaryl as estimated by the comparative of ki are quite similar between species and may be useful in human risk assessment. Also, optical sensors can be used for detection anticholinesterases by immobilizing fluorescein isothiocyanate (FIC)-tagged ell organ AChE on quartz fibers and monitoring enzyme activity (Rogers et al., 1991). These biosensors detect concentrations of the carbamate insecticides such bendiocarb and methomyl and the OPs echothiophate and paraoxon in the nanomolar to micromolar range. On the other hand, malathion, parathion, and dicrotophos were not detected even at millimolar concentrations, but, longer exposure or prior modification of these compounds (i.e. to malaoxon, paraoxon) may increase the biosensors detection limits. These AChE biosensors are fast, sensitive, reusable, easy to operate and portable, so it show potential adaptability to field use. So, the measurement of blood AChE activity remains an excellent biomarker for exposure and effect of OPs exposure under both acute and chronic conditions.

The measurement of lymphocyte NTE has been suggested as a potential biomarker to monitor for OPIDP (El-Sebae et al., 1981, Bertoncin et al., 1985, Lotti et al., 1986 and Sigolaeva et al.,1999). The sensitivity of human lymphocyte NTE to several OP inhibitors is similar to that of the nervous system enzyme. Best example is its application in humans in an attempted suicide with chlorpyrifos in which, based on 60% inhibition of lymphocyte NTE, it was correctly predicted that a neuropathy would develop well after recovery from acute cholinergic poisoning had occurred (Lotti et al., 1986). Also, in order to assess the risk of OPIDP from exposure, it is useful to determine the relative potency of the oxon analogue for inhibition of NTE versus AChE (Lotti & Johnson, 1978) as well as using of the k_i values in preference to fixed-time I_{50} when making assessment of the neuropathic risk of OPs (Richardson et al., 1993). Also, pesticides may induce oxidative stress leading to generation of reactive oxygen species (ROS) and/or free radicals which are well known to be deleterious to many biological molecules and to produce a broad range of deleterious effects (Osman, 1999, Osman et al., 2000, Salama et al., 2001). The measurement of alteration in antioxidants or oxygen free radical scavenging enzymes can be used as biomarkers for exposure and effects.

4.3 Toxicokinetics of insecticides related to risk assessment

Tests exploring the toxicokinetics include measurements of the chemical or its metabolites in body fluids. Virtually all pesticide exposure can be assessed in this way, only depending on availability of analytical procedures. Furthermore, the understanding of the mechanism of action and the availability of a biomarker effect allows studies on quantitive relationships between the concentration of the compound or its metabolites in the body fluids and their effect on the target. Most OPs are activated to their corresponding oxygen analog by an oxidative desulfuration reaction, which is catalyzed by cytochrome P450 (Vasilic et al., 1987). Upon phosphorylation of AChE, a portion of the molecule, the leaving group, is released and excreted. Both the parent compound and the oxon can undergo a series of detoxication reactions that are mediated by various A-esterases (paraoxonase, carboxyesterase), by P450, and by glutathione transeferases. The leaving group, *p*-

nitrophenol in the case of parathion, which is also generated by hydrolytic cleavage, and alkylphosphates are excreted in the urine and can be quantified as an index of OPs exposure (Richter et al., 1986). For occupational exposures, pesticides are unusual in that dermal residues are often the most important source of systemic absorption. In general, respiratory exposure in the occupational setting is much less than dermal exposure, with the exception of exposure to aerosols, powders or dust, concentrated vapors, work in enclosed spaces, or pesticides which are gaseous at room temperature or on contact with water (especially the fumigants). Dermal absorption of drift may contribute to community exposures, and for evaluation of community exposure, monitoring of respirable residues is important in the research setting (WHO, 1993a). In agricultural communities little studies have been done to evaluate routes of exposure to communities exposed through skin and by aerosol inhalation to drift from adjacent fields, although some studies suggest significant systemic absorption of pesticides, resulting in ChE depression, among persons in such communities under selected conditions (Richter et al., 1986). The provision of dermal absorption data is required for the registration of agrochemicals, particularly in USA (Scott et al., 1992). Sharp (1987), and Maddy (1990) reported that exposure of users of pesticides containing active ingredients which have the potential of causing adverse effects, especially chronic effects, has to be accurately measured in order to make meaningful risk assessment and risks mitigation determinations. Analysis of residues on cloth pads that had been worn on various parts of the body may provide an overestimate exposure than in the case when such studies are done on humans or other primates.

Nutley & Cocker (1993) analyzed over 400 urine samples obtained from 140 workers with potential occupational exposure to OPs during various agricultural activities, sheep dipping or pesticide formulation. The measurement of dialkyl phosphate metabolites in urine provides a sensitive biological monitoring method suitable for use in the assessment of occupational exposure to many OPs. Metabolites were detected in people with exposure to OPs at levels below those that cause a decrease in ChE activity. OPs exposure among children living in two Seattle metropolitan communities were assessed by measuring urinary metabolites, and identified possible exposure risk factors through a potential interview. Concentrations of dialkyl phosphate compounds, the common metabolites of OPs, were significantly higher in children whose parents reported to pesticide use in the garden (Lu et al., 2001). Therefore, OP pesticides use should be avoided in areas where children are likely to play and the measurement of OP metabolites in postpartum meconium and/or urinary dialkyl phosphate metabolites is useful for monitoring exposure to OPs and is capable of detecting low levels of exposure not detected by depression of ChE activity. Moreover, the presence of DDE levels in organisms is a good biological indicator of chronic exposure to DDT (Woodruff et al., 1994). Also, V_{max} and K_m values for animal and human would be used to develop a physiological based pharmacokinetic (PB-PK)/physiologically based pharmacodynamic (PB-PD) model to predict the fate and toxicity of pesticides in animals and man (Knaak et al., 1993).

Although it is intuitive that pesticides which bioaccumulate and biomagnify are of special concern to those species that consume them, the relative contribution of these processes to toxicity is dependent on trophic level in the food web, life stage, physiological conditions favoring lipid mobilization (e.g. pregnancy, lactation), and reproductive strategy. DDT is one of best known organochlorine insecticides which accumulated in the food chain and known to be transferred from mother to offspring via milk (Wooley & Talens, 1971). The levels determined in human milk are more than 10 times higher than those in cow's milk

(Jensen, 1983). Also Due to the lipophilic nature of DDT and its principle metabolite, DDE, these compounds have been found in diverse human samples of serum, adipose tissue, and breast milk (Woodruff et al., 1994). The half-life of DDT in human adipose tissue is approximately 7.5 years, while the amount of serum DDT varied according to the levels of lipid circulating in the blood. The ratio between the levels of DDT in adipose tissue and blood was 300 to 1.

5. Risk characterization

Risk characterization is the last step of the risk assessment process. This step evaluates assessments of human health and ecological effects, identifies human sub-populations or ecological species potentially at risk, and delineates areas of uncertainty, limitations, and assumptions made in the risk assessment.

5.1 Effect of insecticides on non-target organisms

Pesticides occupy a rather unique position among the many chemicals that man encounters daily, as they are deliberately added to the environment. Ideally their injurious action would be highly specific for undesirable target pests. However, most of pesticides are not highly selective to many nontarget species, including humans, and other desirable forms of life that coinhabit the environment. The ecological risk assessment evaluates the likelihood of adverse ecological effects caused by any chemical, physical or biological entity (including pesticides) that induce adverse effects on the components (individuals, population, communities or ecosystem) (Norton et al., 1992, EPA, 1995). Pesticides may affect the non-target organisms by direct contact or through translocation from the sites of application through the various media. The extent to which translocation within the environment occurs will depend to a large degree on the physicochemical properties of the pesticides (Murphy, 1986).

Factors that affecting the risk assessment of pesticides include the application rate and time, sorption processes in the soil, uptake by crops, volatilization, biotic and abiotic transformation, mineralization, factors influencing the biodegradation of active ingredient in soils, mobility and leaching, and drinking water quality aspects (Pawlizki, 1991). The "Framework for Ecological Risk Assessment" which is developed for risk assessment of ecological effects is illustrated in Fig. 9 (U.S. EPA, 1995). This framework is conceptually similar to the approach used for human health risk assessment, but it is distinctive in its emphasis in two areas. First, ecological risk assessment can consider effects beyond those on individuals of a single species and may examine a population community, or ecosystem. Second, there is no single set of ecological values to be protected that can be generally applied.

The nature of environment exposures to chemicals and the population variability in response make it difficult to determine population risk from traditional epidemiological studies (Spear, 1991). This has given rise to attempt to predict risk from environmental transformation and transport, exposure mechanisms, and biological response probabilities. For readily degradable chemicals emitted at intervals, the ecological risk can be related to the time taken for the chemical to fall to a level causing no effect on most individuals, e.g. 95% of the species (Straalen et al., 1992). The deleterious effects of endocrine-disrupting chemicals in the environment on the reproductive success of wildlife population have been documented (Colborn et al., 1993). These deleterious health effects have been observed in the presence of numerous man-made chemicals. DDT applied in a mosquito control

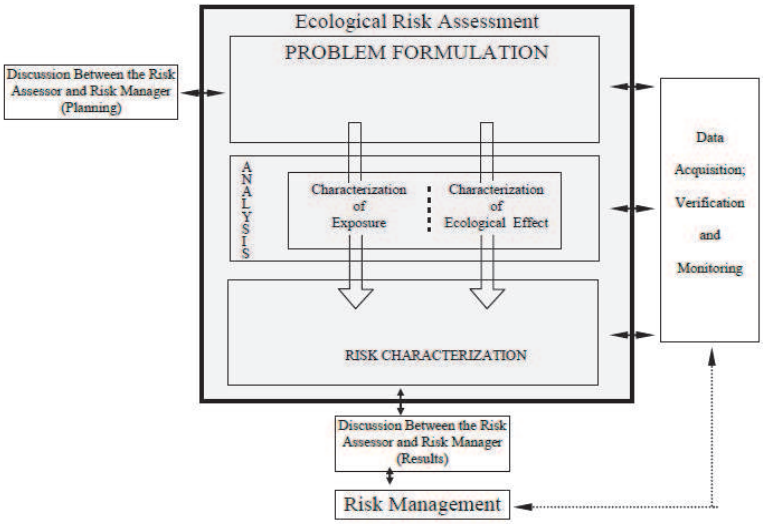

Fig. 9. Framework for ecological risk assessment, adapted from U.S. EPA, 1995.

program in a tropical or subtropical area may ultimately have adverse effects on species in Arctic regions (Murphy, 1986). Such small quantities that may be present in mud and surface waters are taken up by plankton and other food sources for phytophagous fish. The phytophagous fish are eaten by carnivorous fish. These fish may migrate and be ingested by birds in Arctic climates, such as falcons and eagles, in sufficient quantities to contribute doses of the insecticide or its metabolites that can affect avian reproduction. The reproductive parameters such as thinned eggshells and lowered the thickness index of American kestrels (*Faclo sparverius*) after exposure to kelthane at dietary concentration have been affected (Clark et al., 1990). Also, insecticides may affect bird populations by reducing the insect prey base available to the birds, while herbicides affect various bird populations through a variety of pathways, including a direct reduction of the food base of granivorous species, reducing invertebrate abundance by removing the plants that invertebrates depend on as food or habitat, and reducing nesting cover (O'Conner, 1992).

5.2 Endogenous and exogenous factors affecting human risk

For human health, a number of factors contribute to a wide range of risks, including endogenous factors such as genetic predisposition, age (embryo, fetus and children) and gender and exogenous factors which include diet, disease conditions, climate and past exposures. Endocrine disruption of the developing brain can permanently alter the behavior, whereas similar exposures of fully differentiated brain could be without effect (Kavlock et al., 1996). There are specific critical periods of sensitivity to endocrine disruption which vary for different organs and species. The unique changes in physiology during development may increase sensitivity to endocrine-disrupting agents. Also, adult males and females are affected by endocrine disruptors, and the physiologic states in the adult (e.g., early pregnancy) may enhance susceptibility. Infants and children are growing and developing. Their metabolic rates are more rapid than those of adults. Children generally receive greater dietary exposure in milligrams per kilogram of body weight (mg/kg bw) of

pesticides than adult, due to higher food intake rates (Whyatt and Nicholson, 1991). Also, there are differences in their ability to activate, detoxify, and excrete xenobiotic compounds. Both irritant and allergic inflammatory reactions are weaker in older patients (Harvell & Maibach, 1994). It is not clear why this occurs, but it could be due to an age-related decrease in percutaneous absorption or an age-related difference in the inflammatory cascade. Newborns, on the other hand, especially preterm neonates, have immature epidermal barriers, which can lead to potential problems with percutaneous absorption of toxins (Kravchenko, I., Maibach, 2003). All these differences can affect the toxicity of pesticide to infants and children, and for these reason the toxicity of pesticides is frequently differed in children and adults. The quantitive differences between children and adults are usually less than a factor of approximately 10-fold (NAS, 1993).

Many OPs appear to be better inhibitors of ChE, suggesting that this enzyme may be a more sensitive indicator of exposure. However, this is not true for all OPs. Furthermore, plasma ChE activity displays a higher variability because it can be affected by other exogenus agents (e.g., drugs) or physiological and pathological conditions (e.g., pregnancy or liver damage) (Chatonnet and Lockridge, 1989). In addition, genetic variants of human serum ChE exist (Lockridge, 1990). Individuals with atypical ChE, which occurs in homozygous form in 1 out of 3500 Caucasian and consists of a single amino acid substitution in position 70 (glycine instead of aspartic acid), have an abnormal response to muscle relaxant succinylcholine. It is known that genetic difference in detoxification enzymes and non-specific binding account for some of the inter-individual variation in susceptibility to anti-ChEs (Mutch et al., 1992). Esterases which hydrolyze OPs are called A-esterases and might be involved in their detoxification. Subjects with low serum A-esterase activity are more susceptible to the toxic effects of OPs (Brealy et al., 1980).

Specific factors that may contribute to excess cancer incidence among farmers include prolonged occupational exposure to sunlight, diet, contaminated drinking water, and occupational exposure to a variety of potential hazardous chemicals and biological agents (Blair et al., 1992). The exposure to these nonchemical factors could also adversely affect the nervous system resulting in effects similar to those produced by endocrine disruptors (Kavlock et al., 1996). Also, seasonal and regional variability of food consumption rates, possibly due to availability and prices and residue levels may be important contributors to interindividual variation of dietary exposures (Maclntosh et al., 1996). An increase in DDT accumulation was found in tropical areas and/or regions with greater agriculture activity (Lopez-Carrillo et al., 1996).

5.3 Exposure to mixtures

Humans are more likely to be exposed to chemical mixtures than to a single chemical under most environmental and occupational conditions. Many chemicals of the mixtures modify stratum corneum lipid fluidity as precutaneous absorption enhancers, and the skin barrier absorption rate which increase or inhibit the formation of more readily absorbable toxic residues and metabolites. When conducting risk assessments of chemical mixtures, the assessor must also consider factors that influence toxicity (i.e., chemical interactions). A toxicological interaction is a circumstance in which exposure to two or more chemicals results in qualitatively or quantitatively altered biological response relative to that predicted from the actions of a single chemical (NRC, 1980). The study of combined action or interaction of chemicals involves the challenges of how to characterize antagonistic,

additive, or synergistic action. It is therefore of crucial importance to understand the terminology that describe combined interaction of agents in terms of the mechanisms of action (Groyen et al., 1999).

Toxicokinetics and toxicodynamics can be altered in particular circumstances of exposure to mixtures (Lotti, 1987). For instance, as it often occurs in practical conditions of exposure to impurities and mixtures of pesticides, the toxicokinetics might be deeply influenced and the net toxicological effect remarkably changed. Examples include inhibition of the detoxification mechanisms as in the case of impurities of OPs or as in the case of mixtures of pyrethroids and OPs, and also accelerated biotransformation as in the case of liver enzyme induced by certain chlorinated pesticides. On the other hand, toxicodynamics might also be influenced by the competition for the target as in the case of some carbamates which prevent the delayed neuropathy caused by some OPs (Johnson, 1982). The acceleration of parathion metabolism in the gastrointestinal (GI) tract of lindane-pretreated rats could have been due to either a prolonged residence time of parathion or increase GI nitroreductase activity or both (Chadwick et al., 1990). The increased in nitroreductase activity may account for lindane-parathion interaction and could influence the metabolism, toxicity and risk assessment of many other environmental nitrocompounds that become toxic, mutagenic or carcinogenic upon reduction of their nitro-groups. Also, the chemical components in topically exposed mixtures may have significant effects on the prepenetration fate, penetration/distribution pattern, metabolism and precutaneous profile of parathion/drug in the mixture (Qiao et al., 1996). Therefore, multiple level interactive effects on parathion absorption must be considered into any effort to identify critical mechanisms that affect assessment of topically exposed mixtures.

Specific chemicals which individually did not inhibit GJIC at a given concentration, could, when mixed with other chemicals, which also did not inhibit GJIC at a certain concentration, may interact to inhibit GJIC (Kang et al., 1996). Also, because humans are exposed to many of this kind of estrogenlike chemicals in their food supply and because several combinations of these chemicals in mixtures can affect GJIC when no chemical single could. It is assumed that these chemicals might be tumor promoters of human breast cancers and thus could be entertained as possible contributors to the multistage nature of human carcinogenesis. Therefore, consideration of the adverse effects caused by exposure to mixtures must an integral part of protecting human health.

6. Conclusion

Risk assessment is a multidisciplinary task related to toxicology, analytical chemistry, biochemistry, molecular biology, health disciplines, politics, etc. The four key aspects of risk assessment are; hazard identification, dose response, exposure assessment and risk characterization. They are all driven by dynamics based on intake, absorption and effect.

Important advances have recently occurred in analytical methodologies that allow the determination of biomarkers of internal dose as part of national monitoring programmes. Once the risk assessment process is completed for a given pesticide, regulators begin the risk management step; to decide how much exposure will be allowed and, if necessary, establish risk reduction options to ensure that with reasonable certainty, a pesticide will not be harmful to humans.These risk assessments support two major types of regulatory decisions (Dearfield & Moore, 2005), the approval and registration of pesticides and the setting of standards for acceptable exposure levels in air, water and food. Using the conclusions of the

risk assessment, regulators can approve a pesticide as proposed, or adopt protective measures to limit its exposure (occupational or non-occupational). Decisions taken by regulators have important economical consequences for the industry that manufactures pesticides, the farmers, the workers and the consumers. Such consequences, justify the need for regulators to have well supported data related to the four steps of the risk assessment process. Risk assessment requires a robust analytical basis; studies addressed either to hazard identification or exposure estimation. Both have to be conducted under good laboratory practice (GLP) certification (OCDE, 1997).

There is a principle difference between pesticides and other environmental chemicals. Pesticides are approved by the authorities for use in the production of food crops. This means that in a number of cases residues are accepted in food. However, the pesticide residues in foods are very closely regulated. This, of course, does not imply that pesticide residues are accepted in other media such as drinking water and air. Approval by regulatory agencies of a pesticide demands that the health risk associated with exposure to the compound be evaluated by the regulating authorities. The joint Meeting of the FAO panel of Experts on Pesticide Residues in food and the Environment and the WHO Expert Group on Pesticide Residues (JMPR) normally convene annually, and the FAO Panel of Expert is responsible for reviewing pesticide use pattern (GLP) data on the chemistry and composition of pesticides, methods of analyzing pesticide residues, and for estimating MRLs that might occur following the use of a pesticide according to GAP. The WHO Expert Group is responsible for reviewing toxicological and related data on the pesticides and, where possible, for estimating ADI's for humans.

Risks can be minimized once the hazard and the routes of exposure to the hazard are understood. Therefore, pesticides must undergo a rigorous regulatory procedure designed to determine the hazard level of a product and assess the risks associated with that product before gaining approval and being placed on the market. There is also a need to force the authorities to give more emphasis on the health of the humans and treat the issue on a priority basis. Also, careful and prospective health studies are required to determine the actual exposure levels and the precise pesticides to which people are exposed. Without further studies, we cannot determine if these low-level chronic exposures can result in either short or long term health effects. In fact, what needs to be done immediately is to appraise the adverse health effects caused by the pesticides and if they are found to be dangerous beyond a certain level, restrictions should be imposed on their use as well as exposure to human health.

In conclusion, there is an urgent need to initiate necessary action to restrict sales of many of the most toxic pesticides, improving facilities for disposal of hazardous wastes, creating more awareness among the farmers and authorities in enforcing and ensuring the use of protective gear while handling pesticides. Farmers needs to be encouraged to reduce, if not eliminate the use of pesticides, with the introduction of incentives to the farmers to help them shift from synthetic pesticides to bio-pesticides and organic farming. Also there is a need to draw the focus of all individuals, families, communities and nations on this crucial issue and raise the demand for lesser exposure of the pesticides to humans and animals with a view to their well being. For general people, to reduce the risk from pesticides they have to eat organically and ecologically grown food, wash and peel vegetables and fruit, grow their own food, avoid fatty foods or trim fat from meat as persistent pesticides are stored in fatty tissue, cook vegetables rather than eat them raw all the time, cook meat and chicken

thoroughly, garden in a non-chemical way without pesticides, avoid using chemical and pesticide based head lice shampoos, keep away from areas that have been freshly sprayed with pesticides and if their job involve exposure to pesticides they should wear proper protective clothing.

7. References

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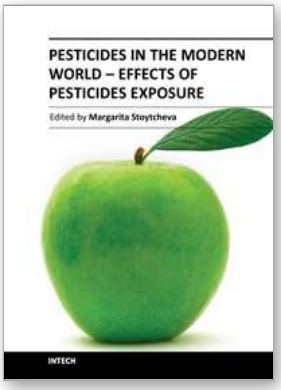

Pesticides in the Modern World - Effects of Pesticides Exposure

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The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950â€™s marked the beginning of the modern pesticides era and a new stage in the agriculture development. Evolved from the chemicals designed originally as warfare agents, the synthetic pesticides demonstrated a high effectiveness in preventing, destroying or controlling any pest. Therefore, their application in the agriculture practices made it possible enhancing crops and livestockâ€™s yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising worldâ€™s population. Nevertheless, the increase of the pesticide use estimated to 2.5 million tons annually worldwide since 1950., created a number of public and environment concerns. This book, organized in two sections, addresses the various aspects of the pesticides exposure and the related health effects. It offers a large amount of practical information to the professionals interested in pesticides issues.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821