Pesticide risks and benefits

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Definitions

Pests, diseases and weeds of major food crops are currently controlled in the European Union mainly with the use of plant protection products (PPPs – products, which are commonly referred to as "pesticides") which offer, in many cases, the only satisfactory method of limiting yield losses (Kalamarakis and Markellou, 2007).

Plant Protection Product (or pesticide product) means the pesticide active ingredient(s) and other components, in the form in which it is packaged and sold.

According to Council Directive 91/414/EEC "plant protection products" are active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to:

- protect plants or plant products against all harmful organisms or prevent the action of such organisms, in so far as such substances or preparations are not otherwise defined below;
- influence the life processes of plants, other than as a nutrient (e.g. growth regulators);
- preserve plant products, in so far as such substances or products are not subject to special Council of Commission provisions on preservatives;
- destroy undesired plants; or
- destroy parts of plants, check or prevent undesired growth of plants.

Pesticide means any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs,

or substances which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thinning fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport (FAO, 2002). Under the NSW Pesticides Act 1999, a pesticide is an "agricultural chemical product" as defined in the Agricultural and Veterinary Chemicals Code Act 1994 (Cwlth), namely: "a substance or mixture of substances that is represented, imported, manufactured, supplied or used as a means of directly or indirectly:

- destroying, stupefying, repelling, inhibiting the feeding of, or preventing infestation by or attacks of, any pest in relation to a plant, a place or a thing; or
- destroying a plant; or
- modifying the physiology of a plant or pest so as to alter its natural development, productivity, quality or reproductive capacity; or
- modifying an effect of another agricultural chemical product; or
- attracting a pest for the purpose of destroying it" (EPA, 2007).

Tab. 1. Classification of pesticides according to pest types. Table was obtained from U.S. EPA (2005)

Pesticides	Use
Algicides	Control algae in lakes, canals, swimming pools, water tanks, and other sites.
Antifouling agents	Kill or repel organisms that attach to underwater surfaces, such as boat bottoms.
Antimicrobials	Kill microorganisms (such as bacteria and viruses).
Attractants	Attract pests (e.g. to lure an insect or rodent to a trap).
Biopesticides	Biopesticides are certain types of pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals.
Biocides	Kill microorganisms.
Disinfectants and sanitizers	Kill or inactivate disease-producing microorganisms on inanimate objects.
Fungicides	Kill fungi (including blights, mildews, molds, and rusts).
Fumigants	Produce gas or vapor intended to destroy pests in buildings or soil.
Herbicides	Kill weeds and other plants that grow where they are not wanted.
Insecticides	Kill insects and other arthropods.

Miticides (also called acaricides)	Kill mites that feed on plants and animals.
Microbial pesticides	Microorganisms that kill, inhibit, or out compete pests, including insects or other microorganisms.
Molluscicides	Kill snails and slugs.
Nematicides	Kill nematodes (microscopic, worm-like organisms that feed on plant roots).
Ovicides	Kill eggs of insects and mites.
Pheromones	Biochemicals used to disrupt the mating behaviour of insects.
Repellents	Repel pests, including insects (such as mosquitoes) and birds.
Rodenticides	Control mice and other rodents.
Defoliants	Cause leaves or other foliage to drop from a plant, usually to facilitate harvest.
Desiccants	Promote drying of living tissues, such as unwanted plant tops.
Insect growth regulators	Disrupt the molting, maturity from pupal stage to adult, or other life processes of insects.
Plant growth regulators	Substances (excluding fertilizers or other plant nutrients) that alter the expected growth, flowering, or reproduction rate of plants.

The history and present time of pesticides

The first recorded use of insecticides was in 2500 B.C. by Sumarians, who used *sulphur compounds* to control insects and mites. Other methods arose as time went on, such as controlling body lice in China with *mercury* and *arsenical compounds* in 1200 B.C., burning sulfur to kill insects and using *salt* to control weeds in ancient Rome, controlling ants with *honey* and *arsenic* in 1600. Elemental sulphur, still in use today as an insecticide, together with other inorganic chemicals, such as *arsenic, mercury* and *lead* are frequently referred to as the "first generation" pesticides, which were applied to crops for many centuries, until the beginning of the 20th century (Committee on the Future Role of Pesticides in US Agriculture, 2000). The use of the first generation pesticides was largely abandoned because they were either too ineffective or too toxic, showing also a great tendency to accumulate in soil to the point of inhibiting plant growth. Moreover, with the passage of time, pests became resistant and tolerant to these pesticides.

Expanding agriculture to meet the needs of the growing population necessitated the application of more effective pesticides; thus, the "second generation" pesticides as they came to be known were developed, comprising *synthetic organic*

chemicals, which made their debut in the 1930s (Committee on the Future Role of Pesticides in US Agriculture, 2000).

The modern era of pesticides essentially began with the introduction in 1939 of the insecticide *DDT* (*dichlorodiphenyl trichloroethane*). The astonishing efficacy of DDT led to the development of a variety of chlorinated hydrocarbons, such as *gamma-lindane* and *toxaphene* which were quickly adopted in the agricultural practice (Daly et al., 1998).

In the 1940s, manufacturers also began producing large amounts of other synthetic pesticides, like *the organophosphates*, which, despite their greater toxicity to mammals and other non-target species, enjoyed considerable popularity because of their broad spectrum efficacy and rather low cost (Casida and Quistad, 1998).

Pesticide use to date has increased 50-fold since 1950 and currently there are thousands of synthetic pesticide products made up of more than 1000 different chemicals and combinations thereof (Miller, 2002). On the other hand, potential health risks of pesticides identified in toxicological and epidemiological studies include cancer, genetic malformations, neuro-developmental disorders and damage of the immune system (Pistl et al., 2004; Sanborn et al., 2004, 2007; McKinlay et al., 2008).

Rachel Carson's book *Silent Spring*, published in 1962 (Carson, 1962), first drew attention to the hazard of the widespread extensive use of pesticides for the environment (namely birds) and also for human health. The book resulted in big modifications to the policy on pesticides, leading to a ban on DDT and certain other pesticides.

The urgent ban to major "second generation" pesticides for valid reasons, apparently created the need for re-evaluation of pesticide applicability and for the development of a legal framework regulating their production and use. By the end of the 1960s, this need culminated in the creation of the *Environmental Protection Agency* (EPA) in the U.S.A., which was the first governmental agency taking actions against pesticide usage at that time (Walker et al., 2003).

In July 1991, after great difficulties encountered in the development of a harmonised framework for authorisation, use and control of plant protection products, the European Council adopted Council Directive 91/414/EEC concerning the placing of pesticides on the market. This Directive was one of the first major items of European legislation implementing not only the principle of subsidiarity, but also the precautionary principle. From the outset, it explicitly placed protection of human health and of the environment above the needs of agricultural production. According to its provisions, active substances in pesticide formulations are only approved for use in the EU if they have undergone

a peer-reviewed safety assessment. The active substances covered by the review programme were classified as follows:

- ***Existing:*** the active substances that were already in the market in July 1993 (date of Directive enforcement);
- ***New:*** the active substances introduced, or in the process of applying for marketing, since July 1993.

An essential provision of Council Directive 91/414/EEC is the evaluation of all existing active substances and other plant protection products (920 in total) and the creation of a list (referred to as *Annex I*) of active substances that are considered acceptable in regard to their impact on the environment, human and animal health, and therefore authorised for use in pesticide formulations within the Community.

Evaluation of both existing and new active substances is carried out through *a tiered approach*. For each substance, an initial *draft risk assessment report* (*DAR*) must be produced by a designated Member State; this is followed by a peer review by all Member States, which leads to a legislative decision regarding inclusion of the substance in the Community's list (*Annex I*) (EFSA, 2008).

Very drastic changes have occurred in the list of legally marketed pesticides over the last years in the EU as a result of the EU legislation on marketed pesticides. Approximately 704 active substances were banned, of which 26% were insecticides, 23% herbicides and 17% fungicides (Karabelas et al., 2009).

Nowadays, data required to support an application of a registration should cover all relevant aspects of the plant protection product during its full life-cycle. They should include:

- the identity and physical and chemical properties of the active ingredient and formulated product,
- analytical methods,
- human and environmental toxicity,
- proposed label and uses,
- safety data sheets,
- efficacy for the intended use,
- as well as residues resulting from the use of the pesticide product, container management, and waste product disposal (Karabelas et al., 2009).

Generation of such data for a single compound may take several years and costs a great amount of money (Damalas and Eleftherohorinos, 2011).

Benefits and hazards of pesticide use

Pesticides are widely used in agricultural production to prevent or control pests, diseases, weeds, and other plant pathogens in an effort to reduce or eliminate yield losses, maintain high product quality (Oerke and Dehne, 2004; Cooper and Dobson, 2007), and improve the nutritional value of food and sometimes its safety (Boxall, 2001; Narayanasamy, 2006). Pesticides are also applied in forestry, public health, homes and gardens (Aktar et al., 2009). They help to control hundreds of weed species, more than one million species of harmful insects and roughly 1,500 plant diseases (NACA, 1993; Ware and Whitacre, 2004).

The annual application of synthetic pesticides to food crops in the EU exceeds 140,000 tonnes (Eurostat statistical books, 2007), an amount that corresponds to 280 grams per EU citizen per year. Despite European policies to reduce pesticide use, EU statistics data show that the annual pesticide consumption has not decreased (Eurostat statistical books, 2007). According to OECD (2006) the consumption of pesticides in the Slovak Republic was 0.16 tons per km^2 of agricultural land in 2006.

Although pesticides are at the top of the list of dangerous pollutants, modern pesticides are fast-acting, some of them may be unique in their action against a specific pest, they can control large infestations, they are generally easy to apply, and lead to increased crop yield by reducing crop losses. Thus, from this point of view, pesticides can be considered as an economic, labor-saving, and efficient tool of pest management with great popularity in most sectors of the agricultural production (Cooper and Dobson, 2007; Damalas, 2009).

On the other hand, there is now overwhelming evidence that some of these chemicals do pose a potential risk to humans and other life forms and unwanted side effects to the environment. No segment of the population is completely protected against exposure to pesticides and the potentially serious health effects may occur in humans and animals (Aktar et al., 2009; Damalas and Eleftherohorinos, 2011).

The risk assessment of the impact of pesticides either on human health or on the environment is not an easy and particularly accurate process because of differences in the periods and levels of exposure, the types of pesticides used (regarding toxicity and persistence), and the environmental characteristics of the areas where pesticides are usually applied (Damalas and Eleftherohorinos, 2011).

Health and ecotoxicological risk assessment

Before any pesticide can be used commercially, several tests are conducted that determine whether a pesticide has any potential to cause adverse effects on hu-

mans and wildlife, including endangered species and other non-target organisms, or potential to contaminate surface water and groundwater from leaching, runoff, and spray drift. Effects in any non-target species may translate into ecosystem unbalance and food-web disruption that ultimately may affect human health and edible species (Damalas and Eleftherohorinos, 2011).

Health risk assessment

Regardless of the difficulties in assessing risks of pesticide use on human health, the authorization for pesticide commercialization in Europe currently requires data of potential negative effects of the active substances on human health. These data are usually obtained from several tests focused on e.g., ***metabolism patterns; acute, sub-chronic or sub-acute and chronic toxicity; carcinogenicity; genotoxicity; teratogenicity; generation study; and also irritancy trials*** using rodents as model mammals or in some cases dogs and rabbits (Matthews, 2006).

The respective toxicity tests for human health risk assessments are:

- ***the acute toxicity test***, which assesses the effects of short-term exposure to a single dose of pesticide (oral, dermal, and inhalation exposure, eye irritation, skin irritation, skin sensitization, neurotoxicity),
- ***the sub-chronic toxicity test,*** which assesses the effects of intermediate repeated exposure (oral, dermal, inhalation, nerve system damage) over a longer period of time (30–90 days),
- ***the chronic toxicity test,*** which assesses the effects of long-term repeated exposure lasting for most of the test animal's life span and intended to determine the effects of a pesticide product after prolonged and repeated exposures (e.g., chronic non-cancer and cancer effects),
- ***the developmental and reproductive tests***, which assess any potential effects in the fetus of an exposed pregnant female (i.e., birth defects) and how pesticide exposure may influence the ability of a test animal to reproduce successfully,
- ***the mutagenicity test*** which assesses the potential of a pesticide to affect the genetic components of the cell, and
- ***the hormone disruption test***, which measures the pesticide potential to disrupt the endocrine system (consists of a set of glands and the hormones they produce that regulate the development, growth, reproduction, and behaviour of animals including humans).

The acute toxicity experiments are required for the calculation of ***the median lethal dose (LD_{50})***, which is the pesticide dose that is required to kill half of the tested animals when entering the body by a particular route. For example, if the

substance is swallowed the figure is an oral LD_{50}, whereas if absorbed through the skin it is a dermal LD_{50}. In addition, the acute inhalation lethal concentration (LC_{50}), which is the pesticide concentration required to kill half of the tested animals exposed to a pesticide (for 4 hours), is also calculated. These endpoints are used for WHO and EPA toxicity classifications of pesticides and are shown in Tab. 2 and Tab. 3.

Tab. 2. Acute toxicity of pesticides according to WHO classification. Table was obtained from WHO (2010)

Class / Classification	LD_{50} for the rat (mg/kg BW)			
	Peroral		Dermal	
	Solids	Liquids	Solids	Liquids
Ia Extremely hazardous	< 5	< 20	< 10	< 40
Ib Highly hazardous	5–50	20–200	10–100	40–400
II Moderately hazardous	50–500	200–2000	100–1000	400–4000
III Slightly hazardous	> 501	> 2.001	> 1.001	> 4.000
U Unlike to present acute hazard	> 2.000	> 3.000	–	–

Tab. 3. Acute toxicity of pesticides according to the EPA classification. Table was obtained from EPA Registering Pesticides (2009)

Class	Signal words	Acute toxicity to rat		
		Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Inhalation LC_{50} (mg/l)
I	DANGER	< 50	< 200	<0.2
II	WARNING	50–500	200–2000	0.2–2.0
III	CAUTION	500–5000	2000–20 000	2.0–20
IV	CAUTION (optional)	>5000	>20 000	>20

Long-term studies exposing test animals at a range of pesticide doses allow defining the reference point below of which no adverse effects occur. This dose, known as ***No Observed Adverse Effect Level (NOAEL)*** or ***No Observed Effect Level (NOEL)***, is used to derive the ***acceptable daily intake (ADI)*** for humans, which is defined as the amount of chemical that can be consumed every day for a lifetime with no harm. It is worth mentioning that a 100-fold safety or uncertainty factor is taken into account in calculating the safe daily intakes of food by humans. This is done to overcome differences between animals that are used in the tests as well as differences between humans (inter-individual variability).

Pesticide and the environment

Pesticides may pose adverse effects on the environment (water, soil and air contamination, toxic effects on non-target organisms) (Burger et al., 2008; Mariyono, 2008).

In particular, inappropriate use of pesticides has been linked with:

- adverse effects on non-target organisms (e.g., reduction of beneficial species populations),
- water contamination from mobile pesticides or from pesticide drift,
- air pollution from volatile pesticides,
- injury on non-target plants from herbicide drift,
- injury to rotational crops from herbicide residues remained in the field,
- crop injury due to high application rates, wrong application timing or unfavourable environmental conditions at and after pesticide application (Aktar et al., 2009).

Regarding the adverse effects on the environment, many of these effects depend on the toxicity of the pesticide, the measures taken during its application, the dosage applied, the adsorption on soil colloids, the weather conditions prevailing after application, and how long the pesticide persists in the environment (Damalas and Eleftherohorinos, 2011). Many processes affect what happens to pesticides in the environment. These processes include adsorption, transfer, breakdown and degradation. Transfer includes processes that move the pesticide away from the target site. These include volatilization, spray drift, runoff, leaching, absorption and crop removal. Fate and behaviour of pesticides in the environment is shown in Fig. 1 (http://www.agf.gov.bc.ca/pesticides/c_2.htm#1).

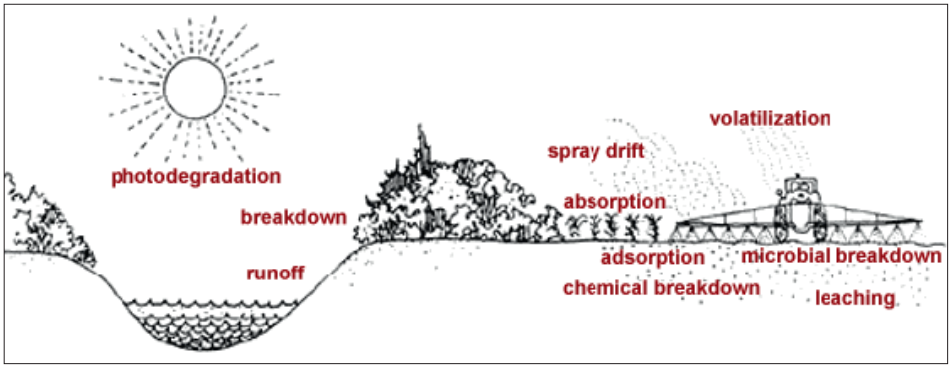

Fig. 1. Fate and behaviour of pesticides in the environment.
Figure was obtained from http://www.agf.gov.bc.ca/pesticides/c_2.htm#1

Pesticide exposure in humans

Although pesticides are developed through very strict regulation processes to function with reasonable certainty and minimal impact on human health and the environment, serious concerns have been raised about health risks resulting from occupational exposure and from residues in food and drinking water.

It is estimated that man and animals are exposed to more than 1.000 pesticides every day because of their widespread use and persistence in different environmental compartments – in the air, water, soil and plants.

Occupational exposure to pesticides often occurs in the case of agricultural workers in open fields and greenhouses, workers in the pesticide industry, and exterminators of house pests (Wilson and Tisdell, 2001; Maroni et al., 2006; Atreya, 2007; Soares and Porto, 2009; Martínez-Valenzuela et al., 2009). However, irrespective of whether the occupation involves the use of pesticides, the presence of such chemicals in the working environment constitutes potential occupational exposure. Evidently, workers who mix, load, transport and apply formulated pesticides are normally considered to be the group that will receive the greatest exposure because of the nature of their work and are therefore at highest risk for possible acute intoxications (Fenske and Day, 2005).

In some situations, exposure to pesticides can occur from accidental spills of chemicals, leakages, or faulty spraying equipment.

The exposure of workers increases in the case of not paying attention to the instructions on how to use the pesticides and particularly when they ignore basic safety guidelines on the use of personal protective equipment and fundamental sanitation practices such as washing hands after pesticide handling or before eating.

Several factors can affect exposure during pesticide handling:

The form of formulation of pesticide products may affect the extent of exposure. Liquids are prone to splashing and occasional spillage, resulting in direct skin contact or indirect skin contact through clothing contamination. Solids may generate dust while being loaded into the application equipment, resulting in exposure to the face and the eyes and also respiratory hazards (Fenske and Day, 2005).

The type of packaging of pesticide products can also affect potential exposure. For example, the opening of pesticide bags can result in some kind of exposure depending on the type of packaging in combination with the formulation of the active ingredient.

Also, ***the size of cans, bottles, or other liquid containers*** may affect the potential for spillage and splashing (Fenske and Day, 2005).

Moreover, ***adjuvant chemicals*** used in pesticide formulations to enhance their efficiency in terms of biological activity (e.g., enhance the contact between the active ingredient and its specific molecular target) as well as to facilitate application and reaching target species, may show toxicity themselves, thus contributing to the overall effect of exposure to a commercial pesticide product (Surgan et al., 2010).

Weather conditions at the time of application, such as air temperature and humidity, may affect the chemical volatility of the product, the perspiration rate of the human body, and the use of personal protective equipment by the users (Gomes et al., 1999; Fenske and Day, 2005). Wind increases considerably spray drift and resultant exposure to the applicator. The amount of pesticide that is lost from the target area and the distance the pesticide moves will increase as wind velocity increases, so greater wind speed generally will cause more drift. In addition, low relative humidity and high temperature will cause more rapid evaporation of spray droplets between the spray nozzle and the target than high relative humidity and low temperature (Gil et al., 2008).

General hygiene behaviour of workers during pesticide use can also have substantial impact on exposure. For example, workers who avoid mixing and spraying during windy conditions can reduce the exposure. Proper use and maintenance of protective clothing are considered important behaviours associated with reduced chemical exposures (Gomes et al., 1999).

Furthermore, ***the frequency and duration of pesticide handling*** both on a seasonal and lifetime basis affects the exposure. In particular, the exposure of an individual farmer that applies a pesticide once a year is lower than that of a commercial applicator that normally applies a pesticide for many consecutive days or weeks in a season (Fenske and Day, 2005).

In developing countries, farmers face great risks of exposure due to the use of toxic chemicals that are banned or restricted in other countries, incorrect application techniques, poorly maintained or totally inappropriate spraying equipment, inadequate storage practices, and often the reuse of old pesticide containers for food and water storage (Ecobichon, 2001; Asogwa and Dongo, 2009).

Exposure of the general population to pesticides occurs primarily through eating food and drinking water contaminated with pesticide residues, whereas substantial exposure can also occur in or around the home, when living close to a workplace that uses pesticides or even when workers bring home contaminated articles (Wilson and Tisdell, 2001; Jaga and Dharmani, 2003; Maroni et al., 2006; Soares and Porto, 2009).

Non-occupational exposure originating from pesticide residues in food, air and drinking water generally involves low doses and is chronic (or semi-chronic). However, clear links between individual pesticides and individual health effects

can only be shown in animal studies, but the doses used in these studies are far higher than the enforced legally pesticide limits (Harris and Gaston, 2004). Therefore, the risk to human health from these studies appears to be negligible. The actual acute exposure, however, may be higher than that anticipated due to certain food preferences, residue variability between individual food items and the greater than average consumption of a particular food item only at one sitting (Hamilton et al., 2004).

Approximately 300 different pesticides have been reported as contaminants of food products of European origin (Commission staff working document, 2012). Up to 50% of fruits, vegetables and cereals grown in the European Union are known to contain pesticide residues (Commission staff working document, 2012). Nonetheless, one out of twenty food items is known to exceed a current EU legal limit for an individual pesticide. Further, over 25% of fruits, vegetables, and cereals contain detectable residues of at least two pesticides (Commission staff working document, 2012). Processed food and baby food are also commonly contaminated. In addition, other sources, such as contaminated drinking water, dusts and spray drift contribute to human exposures.

As a result of pesticide use in or around the home, individuals can be exposed during the preparation and application of pesticides or even after the applications are completed, whereas delayed exposure can occur through inhalation of residual air concentrations or exposure to residues found on surfaces, clothing, bedding, food, dust, discarded pesticide containers, or application equipment. Pesticides have been measured in residential environments, most notably in indoor dust (Rudel et al., 2001, 2003; Colt et al., 2004, 2005; Bradman et al., 2006; Harnly et al., 2009; Roberts et al., 2009; Ward et al., 2009; Gunier et al., 2011). Several studies indicate that pesticide residues persist indoors due to the lack of sunlight, rain, temperature extremes, microbial action, and other factors that facilitate degradation (Roberts et al., 2009). Carpet dust is a good environmental medium for assessing long-term exposure in the home (Lioy et al., 2002; Gunier et al., 2011; Quirós-Alcalá et al., 2011). Previous studies have reported that concentrations of agricultural pesticides in carpet dust are higher in residences closer to treated fields and in farm homes (Lu et al., 2000; Curwin et al., 2005; Ward et al., 2006; Harnly et al., 2009).

Also, accidental poisoning with pesticides in the home is a possibility from pesticide use around the house or garden. Exposure is likely to occur from pesticide spills, improper use, or poor storage as a result of use without reading or accounting to the pesticide label. Pesticide mishandling such as transferring the products from their original packages into household containers and also the lack of compliance with instructions of the label can also be sources of exposure (Jaga and Dharmani, 2003).

However, the total level of population exposures to pesticides in Europe is unknown, but data from US population studies show that the majority of the population has detectable concentrations of pesticide metabolites in the urine (Mage, 2004; Bjørling-Poulsen et al., 2008).

Health effects associated with pesticide exposure

Worldwide it is estimated that approximately 1.8 billion people engage in agriculture and most use pesticides to protect the food and commercial products that they produce. Others use pesticides occupationally for public health programs, and in commercial applications, while many others use pesticides for lawn and garden applications and in and around the home (Alavanja et al., 2009).

Obviously, exposure to pesticides poses a continuous health hazard, especially in the agricultural working environment. By their very nature most pesticides show a high degree of toxicity because they are designed to kill certain organisms and thus create some risk of harm. Within this context, pesticide use has raised serious concerns not only of potential effects on human health, but also about impacts on wildlife and sensitive ecosystems (Stoate et al., 2001; Pistl et al., 2003, 2004; Berny, 2007; Power, 2010).

The World Health Organization has reported that roughly three million pesticide poisonings occur annually, resulting in 220.000 deaths worldwide (WHO, 1992). Agricultural pesticide poisoning is a major public health problem in the developing world, killing at least 250.000 – 370.000 people each year (Gunnell and Eddleston, 2003; Gunnell et al., 2007; Dawson et al., 2010). The world-wide deaths and chronic diseases due to pesticide poisoning number about 1 million per year (Environews Forum, 1999).

It is well accepted that ***acute poisonings*** cause health effects, such as *seizures, rashes*, and *gastrointestinal illness* (Solomon et al., 2007). Excluding acute poisonings, *contact dermatitis* is thought to be the most common health effect of pesticides, through either irritant or allergic mechanisms. Along with *eye injuries*, it is the health effect most likely to be seen and might be the only indicator of exposure.

Chronic effects, such as *cancer* and adverse *reproductive outcomes*, have also been studied extensively, and the results have been interpreted in various ways as evidence that pesticides are safe or are a cause for concern because they can be detrimental to human health. Genotoxic potential is a primary risk factor for long-term health effects such as cancer and reproductive health outcomes (Bolognesi, 2003).

The review by Alavanja et al. (2004) summarized studies examining the link between pesticide exposure and *cancer*. *Non-Hodgkin lymphoma* has been one

of the most extensively studied cancers. Associations between Non-Hodgkin lymphoma and exposures to phenoxyacetic acid, organochlorine, and organophosphate compounds have been reported.

Leukemia has also been studied extensively. Similar associations have been shown with *prostate cancer, multiple myeloma*, and *soft tissues sarcomas*. There is less supportive literature of an association between pesticides and other types of cancer, although there is some literature of an association between chlorinated compounds and *breast* and *testicular cancer* and *Hodgkin disease* (McCauley et al., 2006).

Occupational exposure to pesticides and adverse *reproductive effects* have been reviewed by Hanke and Jurewicz (2004). Employment in agriculture appears to be associated with the risk of infertility or congenital malformations in offspring, particularly orofacial cleft, as well as musculoskeletal and nervous system defects.

Many pesticides have been identified as *endocrine disruptors*, of these 46% are insecticides, 21% herbicides and 31% fungicides; some of them were withdrawn from general use many years ago but are still found in the environment (e.g., DDT and atrazine in several countries) (Mnif et al., 2011).

Exposure to pesticides has been associated with *altered immune response* (Pistl et al., 2003, 2004) that causes an increased susceptibility of exposed organism to viral, bacterial and parasitic infections and to tumours. It is known that farmers are population with a high risk of Hodgkin's disease, melanomas, multiply myeloma and leukemia (Lee et al., 2007; Dennis et al., 2010; Kokouva et al., 2011). An excessive incidence of non-Hodgkin's lymphoma (a cancer of the immune system) has been reported among farmers and other occupational groups working with pesticides (Pistl et al., 2004; Chiu and Blair, 2009; Hohenadel et al., 2011).

In some cases, it has been suggested that *neurological disorders* may be connected to pesticide exposure. Long-term effects of pesticides on the nervous system include cognitive and psychomotor dysfunction, and neurodegenerative and neurodevelopmental effects. Pesticide poisonings result in well-described acute and chronic *neurotoxic syndromes* (Sanborn et al., 2007). There is also extensive literature supporting the association of *Parkinson's disease* and other neurologic diseases and pesticide exposure (Brown et al., 2006; Van der Mark et al., 2012).

Young children are particularly vulnerable to adverse health effects that may result from pesticide exposures. Epidemiologic evidence of the neurodevelopmental toxicity of pesticide exposure during pregnancy is growing (Rauh et al., 2006; Engel et al., 2007; Eskenazi et al., 2007; Bjørling-Poulsen et al., 2008; Harari et al., 2010). The results obtained suggest that developmental pesticide exposure can cause delayed mental development detectable at 6–24 months of

age (Whyatt et al., 2004; Rauh et al., 2006; Eskenazi et al., 2007), with reduced motor functions and visual acuity and reduced short-term memory and attention being apparent later on. *In utero* and/or postnatal chronic exposures to organophosphorous pesticides have been associated with poorer neurodevelopment in children (Rauh et al., 2006; Engel et al., 2007; Eskenazi et al., 2007; Bouchard et al., 2010; Marks et al., 2010), altered fetal growth, low birth weight (Whyatt et al., 2004; Sathyanarayana et al., 2010; Wohlfahrt-Veje et al., 2011), and shortened gestational duration (Eskenazi et al., 2004). Animal studies have also shown that neonatal exposures to other contemporary-use pesticides such as pyrethroids are associated with impaired brain development (Imamura et al., 2002), changes in open-field behaviours, and increased oxidative stress (Nasuti et al., 2007). Epidemiologic studies have observed an association between residential proximity to use of agricultural pesticides and fetal death, neural tube defects, autism, Parkinson's disease, and childhood cancer (Nielsen et al., 2010).

In the review by Kamel and Hoppin (2004) of the health effects of pesticide exposure, the authors report that chronic pesticide exposure is associated with a broad range of nonspecific symptoms, including *headache, dizziness, fatigue, weakness, nausea, chest tightness, difficulty in breathing, insomnia, confusion*, and *difficulty concentrating.* Many of the studies indicate that pesticide exposure is associated with deficits in *cognitive function.* Of particular interest are the studies performed in areas where organophosphates are widely used (Bjørling-Poulsen et al., 2008).

The results on toxicity characterization of the 276 legally marketed active substances in Europe indicate that 32 out of the 78 fungicides, 25 out of the 87 herbicides and 24 out of the 66 insecticides are related to at least one health effect (e.g., carcinogenic, endocrine disruptor, reproductive and developmental toxicity, acute toxicity) (Karabelas et al., 2009).

The majority of active substances that are characterized as toxic are fungicides, regarding chronic effects, whereas mainly some insecticides are responsible for acute health effects. Regarding approved active substances, the current situation and trends that are shaped by EU legislation appear to have a significant impact on the conditions as well as on the approach to be taken in performing health impact assessment studies involving pesticides. A key characteristic of such studies is the significant latency of health effects due to rather long-time human exposure to low concentrations of pesticides (Karabelas et al., 2009).

Pesticide exposure in animals

Deliberate poisoning of domestic animals and wildlife with commercial formulations of pesticides has been documented worldwide since the early 1950s (Cramp, 1973; de Snoo et al., 1999; Fleischli et al., 2004).

The circumstances involving lethal exposures can be classified as due to accidents with the approved use, misuse, and deliberate abuse of pesticides. In the first case, animal poisonings occur when pesticides are applied to the approved target and at the proper application rate (Augspurger et al., 1996; Pain et al., 2004). In the second case, pesticides are not applied according to the specified conditions for use (Greigsmith et al., 1994; Guitart et al., 1996). In the last case, pesticides are used in a deliberate or illegal attempt to poison animals, and secondary poisonings in scavengers can occur because of the high doses of pesticide usually employed (Allen et al., 1996; Berny et al., 1997).

Monitoring studies of poisonings in domestic animals and wildlife have been conducted in France (de Snoo et al., 1999; Berny, 2007), Greece (Antoniou et al., 1997), Korea (Kwon et al., 2004), the Netherlands (de Snoo et al., 1999), Spain (Guitart et al., 1999; Motas-Guzmán et al., 2003), United Kingdom (Cramp, 1973; de Snoo et al., 1999), the Czech Republic (Modrá and Svobodová, 2009), and the United States of America (Forrester and Stanley, 2004).

The pesticides most frequently involved in animal poisonings are insecticides and rodenticides (Guitart et al., 1999; de Snoo et al., 1999; Motas-Guzmán et al., 2003; Berny, 2007). Poisonings by herbicides and molluscicides are also described, but the number of incidents is much lower (Burgat et al., 1998).

The use of specific pesticides in deliberate animal poisonings relies on several factors, such as the type of agriculture of the region, the popular knowledge of the toxicity of a specific product, and its availability in the local market (Navas et al., 1998; Grey et al., 2005). As the median lethal dose (LD_{50}) of some pesticides can be as low as 1 mg/kg of body weight (Dreisbash and Robertson, 1982; Hudson et al., 1984), the percentage of such active ingredients in the commercial formulations will greatly determine the risk of intentional poisonings by the use of these products.

Groups of pesticides involved in animal poisonings in European countries are shown in Tab. 4 (Martínez-Haro et al., 2008).

Nowadays, there are fewer cases of acute poisoning caused by high doses of toxic substances but there are more and more cases of chronic poisoning as a consequence of environmental pollution. Diseases caused by chronic exposure to toxic substances are very often non-specific, and manifested as a consequence of the immune system weakening or by decreases in weight gain in economically important animal species (Pistl et al., 2003, 2004).

Moreover, the accumulation of exogenous substances in tissues of economically important animal species also affects the safety and quality of food of animal origin.

Tab. 4. Groups of pesticides involved in animal poisonings in European countries. Table was obtained from Martínez-Haro et al. (2008)

Country	Period	n	%					References
			Fungicides	Herbicides	Insecticides	Rodenticides	Mollusquicides	
Greece	1990–1994	223	–	2.2	84.3	13.5	–	Antoniou et al. (1997)
France	1994–1995	144	–	–	69.4	30.6	–	de Snoo et al. (1999)
United Kingdom	1990–1994	262	–	1.1	27.9	69.9	1.1	de Snoo et al. (1999)
Netherlands	1990–1994	121	–	–	86.8	13.2	–	de Snoo et al. (1999)
Spain	1990–2005	260	0.8	3.5	66.1	26.9	2.7	Martínez-Haro et al. (2008)

Modrá and Svobodová (2009) reported the most frequent cases of poisoning in farm animals, horses, cats, dogs, wild animals, fish and honey-bees in the Czech Republic. Cases of acute poisoning with manifested clinical symptoms in ruminants are relatively infrequent. They are usually due to a gross breach of regulations governing the handling of toxic substances, non-observance of technological procedures, etc. An example of a gross breach of handling regulations for toxic substances and waste materials is the *DDT* cattle poisoning case that happened in 2002 at the Karlovy Vary region (Svejkovský et al*.,* 2003). The most frequent causes of poisoning in dogs at present still include *anticoagulation rodenticides*, and pesticides *carbofuran* and *metaldehyde*. *Anticoagulation rodenticides* poisoning may happen when dogs accidentally ingest a rodenticide bait in household but because of their easy availability, *anticoagulation rodenticides* are also often abused for intentional poisoning. Poisoning with *carbofuran* is always intentional and it occurs at hunting grounds where foxes or martens are the intended victims. Cat poisoning may sometimes occur as a result of an improper use of *synthetic pyrethroids* (Svobodová et al., 2008). Every year, the most frequent inquiries of owners and veterinary surgeons relating poisoning are about *metaldehyde-based moluscocides* in the case of dogs and about *synthetic pyrethroids* in the case of cats. Also frequent are inquiries about *rodenticides* (Modrá and Svobodová, 2009).

Wild animals can be considered as suitable indicators of contamination of individual ecosystems, particularly with pesticidal preparations. In spite of the increased attention paid to environmental contamination with pesticides, the incidence rate of acute pesticide poisonings is relatively low. In practice, the

death of wild animals due to acute poisoning is diagnosed relatively often, mostly intentional *carbofuran* poisoning cases.

In the 1970–1990 period pesticides were responsible for 6% of fish poisoning in the Czech Republic (Modrá and Svobodová, 2009).

The most important role in bee toxicology, however, is played by pesticides, and, in particular insecticides and, in some cases, also herbicides (*paraquat* and *diquat herbicides*). The largest number of mass poisonings of bees has been caused by *the insecticide Regent WP 50* containing *fipronyl* as the active ingredient. Its residual efficiency period is 21 days. The use of the preparation on oil rape against the rape blossom beetle has been banned since 2006. However, the danger of bee poisoning with pesticides still exists. Bees are still at risk of poisoning with *organophosphates, carbamates, pyrethroids*, and, in particular, with the newly introduced *neo-nicotinoid fungicides* (Modrá and Svobodová, 2009).

The illegal poisoning of wild predators, like fox or wolf, may be a significant threat for their populations and for other opportunistic scavengers like kites and vultures. Red kite is one of the most affected species by the illegal use of poisons, especially *carbamates aldicarb* and *carbofuran* (Cardiel, 2006). The high toxicity of these pesticides (acute oral LD_{50} less than 10 mg/kg) (Schafer et al., 1973; Hill and Camardese, 1984) and the significant content of the active ingredient make their granular formulations very attractive for the deliberate poisoning of domestic animals (Delaunois et al., 1997; Frazier et al., 1999) and wildlife (Mineau et al., 1999; Fleischli et al., 2004; Salyi et al., 2005). Aldicarb and carbofuran have also been involved in many fatal poisonings in humans (Gupta, 1994; García-Repetto et al., 1998; Nisse et al., 2002). The use of aldicarb and carbofuran has been banned in the last decade in Europe and North America due to the impact on non-target animal species observed with the labeled application (EPA, 1991; Council Directive 91/414/EEC; Mineau et al., 1999).

Carbofuran (the active ingredient of the preparation *Furadan*) has been the most frequent cause of poisoning in wild predatory birds in the Slovak Republic in the past 10 years. Illegal use of *carbofuran* used to be a widespread practice in vermin (foxes, martens, etc.) control. *Carbofuran* was added to various types of bait (dead calf, fish, etc). Lethal doses of carbofuran for birds are about 10 times smaller than for mammals. Because of its high toxicity for birds, the most frequent were the deaths of wild predatory birds. As of 13 December, 2008, carbofuran-based preparations were banned (http://www.dravce.eu.sk/page/).

One of the most widely used poisons to kill predators in many countries was also *strychnine*, which was finally banned in 1994 but it is still occasionally used for the deliberate poisoning of wildlife (Martínez-López et al., 2006). The source of strychnine used today is unclear, but old stocks, chemists or veterinarians are possibilities. A similar situation exists for the case of *endrin*. The use of this

organochlorine had been gradually restricted and then totally banned, but this is still being used for illegal poisonings of animals.

The deliberate poisonings of animals by banned compounds show that not only the ban on the use is important, but also that a more strict control of the distribution among professionals is needed. Apart of the restriction to authorized personnel, formulations of pesticides should contain *repellents* and *a lower percentage of the active ingredient* to reduce the risk of ingestion of lethal amounts by non-target animals (Mason and Epple, 1998; Sayre and Clark, 2001). Some repellents used or evaluated to reduce the risk of unintentional poisonings by pesticides in non-target animals are D-pulegone, quinine hydrochloride, methyl anthranilate, 2-heptanone, lithium chloride, ortho-aminoacetophenone, pine oil and extracts from plants (Mastrota and Mench, 1995; Ries et al., 2001). Additionally, the *incorporation of an emetic* could be useful, in some cases, to decrease the absorption of the toxic agent. Some manufacturers, for example, add *stenching agents* (of deterring odor), *an emetic* and *a blue dye* to the toxic herbicide *paraquat* (de Liñán, 2003), which is frequently involved in human poisonings (Klein-Schwartz and Smith, 1997).

Nowadays some highly toxic formulations are not frequently being involved in animal poisonings, which can be a result of a proper control of the use of specific formulations and/or a lower popular knowledge of the toxicity of such formulations. However, more efforts should be done to prevent the use of highly toxic formulations for the illegal and deliberate poisoning of animals, suicide or other criminal uses of these products.

Conclusions

With industrial development the risk of presence of xenobiotics in the environment, whether occasionally (emissions, accidents) or purposefully – by using of various kinds of potentially toxic chemical compounds as pesticides, has significantly increased. Nowadays, pesticides are considered to be the dominant chemical load of environment, therefore a matter of concern is revealing their effects on non-target organisms and health status of human and animals.

Pesticides have played a key role in providing reliable supplies of agricultural produce at prices affordable to consumers, improving the quality of produce, and ensuring high profits to farmers. Although pesticides are developed to function with reasonable certainty and minimal risk to human health and the environment, many studies have raised concerns about health risks from exposure of farmers (or other end-users of pesticides) and from non-occupational exposure of the population to residues found on food and drinking water. Several indicators have been used to assess the potential risk of pesticides to human

health and the environment. However, their use indicated reduced certainty, suggesting the need for development of alternative indicators that should increase the accuracy and reliability of pesticide risk assessment and thus contribute to reduction of the possible adverse effects of pesticides on human health and the environment.

The overall optimization of pesticide handling strictly according to the regulations and also considering the public concerns about pesticide residues in food and drinking water could contribute to reduction of the adverse effects of pesticides on human health and environment. All this may sound difficult, but seems to be a promising way for sufficient supply of safe food production within a viable agricultural production system.

New tools or techniques with greater reliability than those already existing are needed to predict the potential hazards of pesticides and thus contribute to reduction of the adverse effects on human and animal health and the environment. Some new methods were used in our studies in which the potential adverse effects of carbamate insecticide bendiocarb were observed.

Thus, the purpose of this monography is to present:

1. uses, mode of action, clinical signs and therapy after exposure to carbamate pesticides,
2. literature data about the adverse effects of carbamate bendiocarb,
3. results from our experimental studies with bendiocarb under *in vivo* and *in vitro* conditions,
4. description of some new methods for determination of the potential adverse effects of bendiocarb, or other pesticides.

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