1 Introduction

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INTRODUCTORY REMARKS

As consumers, we do not want pesticide residues in our food because they have no nutritional value and can potentially pose a risk to health. However, we need pesticides to ensure that a consistent supply of economical and high quality food is available and sometimes residues will remain in the food supply. As a compromise, we require that the amounts of these residues in our food and drinking water will not be harmful to our health and should be no more than absolutely necessary. Risk assessment, which uses scientific processes to meet these requirements, has progressed considerably in recent years.

This book aims to describe the issues surrounding pesticide residues in food and drinking water and, in particular, the issues associated with human exposure and consumer risk assessment. In broad terms, consumer risk assessment encompasses three areas of scientific disciplines – human toxicology, pesticide residue chemistry and dietary consumption – which are explored in further detail within this book.

This chapter will briefly introduce the contents of the book and will discuss some of the commonly asked questions associated with pesticide residues.

WHAT ARE PESTICIDES?

The term 'pesticide' covers a wide range of substances, including insecticides, acaricides, fungicides, molluscicides, nematocides, rodenticides, and herbicides. Pesticides[1] are not necessarily single chemicals of natural or synthetic origin but may be micro-organisms (e.g. fungi or bacteria) or components thereof (e.g. endotoxins from *Bacillus thuringiensis*), or even so-called 'macro-organisms', e.g. predatory wasps such as *Trichogramma evanescens*, specifically bred in large numbers to control caterpillars, aphids and other sucking insects. Pesticides are used widely in agriculture since significant economic damage can occur when insects, nematodes, fungi and other micro- and macro-organisms affect food and commodity crops. The quantity and types of pesticides required to ensure high crop yield and unblemished produce acceptable to the consumer vary, depending on climatic conditions, pest species and pest burdens.

Many pesticides of natural origin have been used throughout the history of agriculture. The pesticidal or repellent action of some plants forms the basis of an age-old practice of companion planting, where the proximity of one plant is

[1]The Food and Agriculture Organization of the United Nations (FAO) has defined a pesticide as a 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 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. Also included in the FAO definition are substances intended for use as plant growth regulators, defoliants, desiccants, or agents 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 or transport (FAO, 2003).

used to increase the yield of another plant which may be subject to attack by pests. Alternatively, pesticidal extracts from a particular plant type can be applied on or around another to control pests; examples include pyrethrum extracts (from a variety of daisies) or extracts from neem trees (*Azadirachta indica*). Other naturally occurring inorganic (e.g. arsenic or sulfur) or organic compounds (e.g. nicotine or strychnine) have been used for their pesticidal actions; many of these are extremely hazardous (i.e. poisonous) and pose a significant risk to users and to consumers of the produce, as well as a risk of accidental poisoning.

HISTORY OF PESTICIDE USE AND REGULATION

Large-scale use of pesticides began after World War II with the widespread use of organochlorine and organophosphorus compounds. Other chemical groups were subsequently developed and are used in agriculture today (e.g. triazine herbicides, carbamate insecticides and synthetic pyrethroids). However, pesticides are not a new development and have been used for centuries. For example, sulfur was used in classical Roman times for pest control in agriculture (Smith and Secoy, 1976). In the 19th century, highly toxic, mainly inorganic, compounds of copper, arsenic, lead and sulfur were used for the control of fungal diseases and insects.

HAZARD AND RISK

The World Health Organization (WHO) in 1995 provided specialist definitions for hazard and risk and associated terms such as risk assessment (WHO, 1995). These specialist meanings are used in assessing and explaining the risks of biological and chemical contaminants of food, including pesticide residues. They should not be confused with the normal dictionary meanings of risk and hazard, where the words ‘risk’ and ‘hazard’ are often synonymous.

Under the WHO definitions, risk assessment can be split into four different parts. First, in hazard identification, the possible adverse health effects of the chemical are identified from toxicological studies. Secondly, in hazard assessment, the toxic effects and characterization of the biological response in terms of the dose, i.e. the dose–response relationship, are considered and acceptable levels of dietary intake are derived. Thirdly, in exposure assessment, referred to as the ‘dietary intake estimate’ in this book, the dietary exposure of residues resulting from the consumption of food and drinking water containing residues is estimated. Finally, in risk characterization, the estimated dietary intake is compared with the acceptable levels of dietary intake or dose that were derived as part of the hazard assessment. In simple terms, if the dietary intake is less than this dose, then the risk is acceptable.

SCOPE OF THE BOOK

This section gives an overview and briefly introduces each chapter in the book: environmental fate, metabolism, food processing, toxicology, dietary consumption,

chronic and acute dietary intakes, natural compounds, international standards and explaining the risks.

OVERVIEW

Studies of the environmental fate, metabolism and food processing provide basic information for studying residue levels in food. Whereas toxicology describes the hazard, the dietary consumption, in combination with residue levels, provides the dietary intake. Chronic and acute consumer intake estimates compare dietary exposure with acceptable intakes derived from the toxicology. Natural compounds, for proprietary reasons, have not usually been studied as thoroughly as synthetic compounds and therefore the safety of these compounds is frequently less well known. The risk assessment of residues in food must be acceptable at the international level to protect the consumer and to prevent disruption of the international trade in food. The final chapter deals with the very important topic of risk communication.

Most pesticide residues occur in food as a result of the direct application of a pesticide to a crop or farm animal or the post-harvest treatments of food commodities such as grains to prevent pest attack. Residues also occur in meat, milk and eggs from the consumption by farm animals of feed from treated crops. However, residues can also occur in foods from environmental contamination and spray drift. In addition, transport of residues and sediment, e.g. in storm water run-off or leaching through the soil to ground water, may also contaminate drinking water sources.

Since the publication of Rachel Carson's book *Silent Spring* in the 1960s (Carson, 1965), there has been increased public concern about the impact of pesticides on the environment. Much of this concern was associated with the organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT) and dieldrin. These compounds have both high environmental persistence and high fat solubility which commonly lead to residues occurring in meat, milk and eggs. Most countries have now withdrawn the registration of these persistent organochlorine pesticides. However, residues are occasionally detected in food because of the environmental contamination that remains from historical usage of the chemical. For example, animals grazing on contaminated land readily consume residues, which can be detected in the fat. Grazing cattle may consume 1 kg of soil per head per day and so will ingest the residue directly from the soil as well as residue in the pasture or forage itself. Of the crops grown in soil contaminated with organochlorines, root crops are the most likely to take up residues.

It is possible to estimate dietary intake from the environmental fate, metabolism and food processing experimental data that are commonly submitted by the agrochemical companies. However, these estimates are usually large overestimates of dietary intake as a result of the 'worst-case' assumptions that are included. The most realistic estimate of dietary intake can be obtained by conducting a *Total*

Diet Study. These studies are conducted by a number of countries (WHO, 1999) and many still look at the levels of organochlorine residues in our overall diets. In general, some organochlorine pesticides are no longer detected and the dietary intake of others is slowly declining.

Another potential route by which residues can result in food is through spray drift at the time of pesticide application. Spray drift results in very little residue in our diet since the rate of application is usually far lower than on the directly treated crop. Nevertheless, the contamination can be devastating for an individual farmer whose crops become unsaleable as a result.

Environmental Fate

Studies of environmental fate aim to determine what happens to the pesticide once it has been applied by investigating the behaviour of the compound in soil and water systems. Of particular importance to the overall dietary intake is the potential for the compound to leave residues in water. The environmental properties of pesticides likely to result in contamination of surface water and ground water are persistence, mobility and water solubility. A widely used herbicide such as atrazine has these properties and is frequently detected in surface and ground waters. In contrast to food where most residues result from direct treatment, residues in drinking water usually result from this indirect environmental contamination. Dejonckheere *et al*. (1996) showed that, even though atrazine was often detected in drinking water in Belgium, its estimated dietary intake constituted only 0.3 % of the acceptable level, known as the *Acceptable Daily Intake* (ADI).

Pesticides are transformed in soil, water and air into metabolites and other degradation products. The transformations may be microbiological (metabolism), hydrolysis (reaction with water) or photolysis (broken down by sunlight). Transformation usually proceeds through small changes to the parent pesticide molecule through to complete mineralization to carbon dioxide, water, chloride, phosphate and so on. For some pesticides, the initial transformation products may also be residues of concern in food or drinking water and should be included in the risk assessment process. Some transformation products are more persistent than the parent pesticide, e.g. dichlorodipenylethylene (DDE) is more persistent than DDT.

Pesticide Metabolism

The metabolism of a pesticide compound is studied by administering a radio-labelled compound to the test animal or the test crop and then, after a suitable interval, examining the distribution of the radio-label. Tissues, milk and eggs are examined in farm animal studies, whereas in plants, the plant foliage, fruit, seeds or roots are examined. The next stage is to investigate the nature of the residue – how much is still unchanged parent pesticide and what are the identities

and amounts of metabolites and transformation products. Toxicological decisions are required on which metabolites need to be included with the parent pesticide in the risk assessment and which metabolites can be ignored because their amounts and toxicity are insignificant.

Plant and animal metabolic systems may conjugate the pesticide or a transformation product, i.e. chemically bond it to a natural compound such as a sugar. The conjugate will have different physical properties, e.g. a sugar conjugate is likely to be more water soluble, thus facilitating its elimination by an animal in the urine.

The results of metabolism studies are absolutely crucial before residue and food processing trials can begin. The metabolism studies tell us which compounds must be included in the residue tests of the processed samples. In some cases, the metabolite of one pesticide is another pesticide in its own right, hence suggesting that the risk assessment of the two should be combined.

Food Processing

The level and nature of residues in food can also be affected by commercial or domestic processing and preparation of the food. For example, food preparation will remove surface residues from some foods, e.g. mangoes or citrus, where surface residues are discarded with the peel. Specific studies are commonly conducted to investigate if the nature of the residue changes during processing and how much of the residue remains in the processed products. These food processing studies are a very important aspect of dietary intake estimates, particularly for those commodities that are consumed only after processing, e.g. cereal grains, or substantially after processing, e.g. grapes consumed as wine.

Changes to the nature of the residue during processing and the identification of transformation products, are commonly determined by studying the hydrolysis of the pesticide (reaction with water) at typical cooking temperatures. Hydrolysis experiments tell us which compounds must be included in the residue tests of the food processing studies.

The food processing studies themselves should simulate commercial processing practices as far as practicable. Thorough cleaning is often the first step in commercial processes and, depending on the nature of the residue, has the potential to remove a good part of surface residues, e.g. tomatoes and apples are vigorously washed before juicing, and wheat is cleaned to remove traces of grit and stones before milling. Experience tells us that residue levels in wheat bran are usually higher than in the original grain, while residues in flour are lower than in the grain – results which are hardly surprising since most residues are found on the grain surface. Fat-soluble residues tend to partition into the crude oil when oilseeds are processed. Water-insoluble residues tend to be depleted in clear fruit juices while attaching themselves to the pomace when apples or grapes are processed. Similarly, water-soluble residues in grapes have a greater chance of reaching wine than water-insoluble residues.

Toxicological Assessment

Toxicity studies aim to characterize the nature and extent of toxic effects caused by the pesticide and to find doses that cause no adverse effects in the test animals (*No Observed Adverse Effect Level* (NOAEL)). A wide range of studies from acute (i.e. short-term) to chronic (i.e. long-term) on laboratory animals is necessary, with dosing regimes and animal examination designed to investigate all kinds of effects such as tumour initiation and production, changed bodyweight gain, increased liver weight, changed blood properties, enzyme inhibition and foetal abnormalities.

The acceptable level of long-term dietary exposure, referred to as the *Acceptable Daily Intake* (ADI) for humans may be calculated by using a safety factor (usually 100) from the NOAEL for the most sensitive animal species (ADI = NOAEL/100). The ADI is used in the chronic risk assessment and is expressed as an amount of chemical per kilogram of bodyweight. Similarly, the acceptable level of short-term dietary exposure, referred to as the *acute reference dose* (acute RfD), for humans is calculated, where appropriate, with a safety factor applied to the NOAEL for the most sensitive animal species in the short-term toxicity tests. The acute RfD is used in the acute risk assessment and is also expressed as an amount of chemical per kilogram of bodyweight.

Diets and Food Consumption

Dietary intake of pesticide residues is calculated from residue levels in each food and the food consumption per person per day (i.e. the diet). Various methods have been used to assess diets for the human populations and for population sub-groups, e.g. children and infants.

At the international level, food balance sheets are used as a first estimate of *per capita* food consumption (WHO, 1997). The food balance sheets are based on a country's food production, imports and exports. Several countries' food balance data have been aggregated to produce regional diets, e.g. the European diet. Because waste at the household level is not considered, food balance sheets are usually overestimates of long-term average food consumption. In addition, dietary data for processed foods are sometimes missing, which prevents the use of processing studies for refining intake estimates beyond the raw commodity stage. Food balance sheet data do not, however, take into account differences in the diet within a population, the different consumption patterns of particular population sub-groups, e.g. infants and seasonal differences in consumption; nor do they allow for high consumption of a specific food by some individuals.

Some countries have surveyed thousands of households (e.g. household food consumption budget method), chosen to represent the population, in order to get a more accurate measure of food consumption over 24 hours. Other surveys have been based on detailed records of individual consumer's consumption of food over a 24 hour to 7 day period (e.g. diary record method). The subsequent

analysis of these survey data provides not only information on average consumption of many foods over the whole population, but also provides dietary data for various sub-populations such as infants, toddlers, men, women and ethnic groups. The detailed surveys provide data on the diets of those people who consume much more of a food than average (high-percentile consumers), which is particularly useful for acute dietary intake estimates. The detailed survey data are also used by some countries in their chronic intake estimates.

Chronic Dietary Intake

Chronic intake or exposure assessment (intake and exposure mean the same thing for residues in food and drinking water) provides us with the estimated amount of residue consumed daily with our food and drinking water in the long term. In theory, this is for a lifetime of dietary intake and in practice it is for at least several years of continuous dietary intake. It is concluded that the dietary intake of residues is safe if it is less than the ADI derived from the toxicology studies.

Accurate chronic intake estimates are difficult because crucial information may be missing and then 'conservative or worst-case assumptions' are substituted for data. For example, often only a small portion (no more than 1–5 %) of a crop is treated with a specific pesticide on a national basis, but in the absence of solid information we assume conservatively that it is all treated. As previously explained, because the information is not available, we assume that all of the crop is treated at the maximum rate permitted on the label and harvested at the minimum time interval permitted. Dietary intake estimates with these assumptions will produce values much higher than intakes in reality, but the estimates can be still useful for deciding if the intake is acceptable or needs more detailed investigation.

Total diet studies measure residue levels in food purchased at retail level and prepared for consumption. They provide the most realistic estimates of chronic residue intake and usually give much lower values than those calculated with the conservative assumptions.

Acute Dietary Intake

The focus of dietary risk assessment for pesticide residues has generally been on the risks arising from chronic dietary intake. However, recent attention has focused on the potential for acute dietary intake from pesticide residues. Two developments have led to this recent attention.

First, as chronic dietary intake methodology has improved, there has been a move away from 'worst-case' estimates of chronic intake. Whereas in the past there were always large conservative assumptions to account for lack of data, now with more data available the chronic intakes are more realistic and this has directed more attention to a greater need for an explicit consideration of acute dietary intake. Secondly, recent research, especially in the UK, has shown that

residue levels in individual carrots, apples or other fruits and vegetables are quite variable and that, for example, an individual carrot may have residue levels which are two to five times as high as the average residue level in its fellow carrots from the same field (PSD, 1997). In these circumstances, it is a legitimate question to ask about the effects of short-term residue intake that may be much higher, in a single meal or on a daily basis, than the chronic dietary intake. The methodology of acute dietary intake estimates aims to answer this question.

For an acutely toxic pesticide we need to take into account the person who eats a large portion of a specific food at one meal, or over a short time such as 24 hours and the highest possible residue that may occur in that food. Acute dietary intake estimate methodology takes all of these factors into account to calculate an estimated short-term dietary intake for each food. We conclude that this short-term intake is safe if it is less than the acute RfD derived from the toxicology studies.

Natural Toxicants

Plants, fungi and bacteria produce low-molecular-weight secondary chemicals (natural toxicants) thought to be aimed primarily at protecting the producing organisms from predators and competitors, e.g. aflatoxins produced by certain fungi. Such chemicals may be considered as natural pesticides. When such pesticides are present in food as intrinsic components or as contaminants, they raise food safety issues parallel to and, in many cases, of greater concern to public health than those posed by residues of manufactured pesticides. Unlike manufactured pesticides, natural pesticides have evolved for maximum deterrence without regard to their poisonous effects on mammals. Consequently, many natural pesticides are extremely poisonous to mammals, e.g. cyanogenic glycosides (cyanide-producing), present in the cassava plant and glycoalkaloids found in potato tubers under certain stress conditions (Johnston, 1991). This is illustrated by one incident in 1979 in which 78 boys in Lewisham, England became ill after eating a school meal which included potatoes with high glycoalkaloid levels. Seventeen of the children required hospital treatment (Consumers Association, 1994).

When organisms producing natural pesticides infect or contaminate food or drinking water, human exposure and risk assessment studies, as probing and as rigorous as those to which synthetic pesticides are subjected, are justified but are not usually available. Where data are available then they are often found to be far from benign. For example, Professor Bruce Ames of the University of Berkeley has cited 27 natural pesticides known to cause cancer in rodents, that are found in concentrations exceeding 10 mg/kg in several foodstuffs (Johnston, 1991).

International Standards

International agreements on pesticide residues in food rely on the work of the Codex Alimentarius Commission, established by the FAO and the WHO in 1962

to set standards for food in trade. The purpose of the Codex Food Standards Programme is the protection of the health of consumers and ensuring fair practices in the international trade in food. The main reason given by national governments for non-acceptance of Codex pesticide residue standards has been 'concern with dietary intake of residues'. Consequently, the Codex Committee on Pesticide Residues has devoted time and energy to improving the risk assessment process for residues in food. The current methodology for chronic risk assessment (WHO, 1997) is now generally accepted at the international level and attention has turned to acute dietary intake.

Codex maximum residue limits (MRLs) are recognized by the World Trade Organization (WTO) as the standards applying to food commodities in international trade and are assumed in the event of a trade dispute to represent the international consensus. National governments may be tempted to seek a trade advantage for their local industries by imposing unjustified standards on food to 'protect the health of their consumers'. The fine line between genuine health standards and standards imposed as a non-tariff trade barrier is not always clear, particularly where the details and methods are somewhat obscure. Codex procedures and detailed evaluations for each pesticide are published and have become increasingly transparent. Indeed, it is possible to trace the data and the reasoning supporting each standard for pesticide residues in food. Furthermore, the detailed calculations of the dietary intake are also now published.

Explaining the Risks

It is difficult for the public to understand the level of the risks associated with pesticide residues in their food and drinking water or for the regulatory or agrifood industry to effectively communicate the relative risks and benefits. Indeed, the risks associated with chemical residues is a complex matter and the technical complexity probably adds to consumer concern. In these authors' opinion, some people perceive the risks from pesticide residues to be much higher than justified from a detailed study of the evidence, while others are totally indifferent. We have therefore tried to explain the situation as openly, transparently and sincerely as possible and hope that people wanting to understand can make good use of the information presented. The following questions and discussion may help in this respect.

QUESTIONS ABOUT PESTICIDE RESIDUES IN FOOD AND DRINKING WATER

In this section we present discussion and answers to some common concerns about pesticide residues in food and water. Although the questions are simple and straightforward, the answers are not simple, because the subject is complex.

WHERE CAN I OBTAIN RELIABLE INFORMATION ON PESTICIDE RESIDUES?

Reliable information on pesticide residue issues is publicly available. However, when assessing any such information, it is worth examining the interests of organizations or groups making the information available, in order to see if those interests might influence the views expressed. Individuals in each stakeholder group (e.g. consumers, regulators and agrochemical companies) might have a very wide range of views, but the emphasis of the information made available is likely to be coloured by the interests of that particular stakeholder group. A plausibility check on such public statements therefore needs to take into account the interests involved. The following text helps to explain the interests of some of the stakeholder groups to help in this process:

- The agrochemical industry has made huge investments in generating scientific data to meet government regulatory requirements and has a commercial interest in presenting their pesticides as safe and effective.
- Consumer groups and activists need regular exposés of unsafe residues in food to maintain their profiles. Safety concerns raised by activists are frequently based on evidence that is taken out of perspective.
- Research scientists seeking research grants may try to influence research funding bodies by correctly timed and purpose-designed press releases or may overemphasize a safety concern in order to secure funding.
- The media are interested in selling newspapers or television time, which means priority for colourful and sensational stories. It is not generally in their interests to provide a completely objective balance to such stories.

One of the best sources of information on pesticide residues is from national regulatory authorities, many of whom make summaries of the evaluation of pesticides registration data available at a nominal cost, e.g. the United Kingdom's pesticide disclosure documents, available from the UK Pesticide Safety Directorate. These are very useful sources of detailed information on individual pesticides. They commonly include a summary not only of pesticide residue related data, but also other information, such as the exposure of operators or users and the effects on wildlife and the wider ecosystem.

A further authoritative source, which is also free from any national emphasis, is that of the Food and Agricultural Organization (FAO) and the World Health Organization (WHO). These international organizations jointly publish excellent material on pesticide residues and toxicology written by independent reviewers. The FAO and WHO systems rely on an expert panel of scientists chosen to be representative of a geographical spread of countries around the world, but principally chosen for their expertise. The scientists systematically review proprietary and published data, prepare summaries and explain reasoning and conclusions in a transparent manner. The FAO and WHO publications are an excellent starting

point for information about toxicology and residues in food of particular pesticides. However, only a limited number of pesticide compounds have been dealt with by the FAO and the WHO although these are generally those compounds which have the greatest propensity for leaving residues in food. Recent FAO and WHO reports are available directly from their respective websites.

Information on pesticide residues is also available on a number of official websites via the Internet. For example, the United States Food and Drug Administration (FDA) conducts a large-scale pesticide residue monitoring programme which is published in both paper and electronic form.

WHAT IS THE DIFFERENCE BETWEEN A RISK AND A HAZARD?

As outlined earlier in this chapter, in scientific terms, the words 'risk' and 'hazard' have specific and different meanings, as has been elaborated by the WHO (WHO, 1995).

To explain the difference in the two terms, let us consider a simple example, that of a high mountain such as Mount Everest. Mount Everest clearly poses a significant **hazard** given the number of lives that have been lost in attempting to conquer its peak. However, Mount Everest does not pose any **risk** unless you try to climb it, i.e. the risk is a function not only of the intrinsic hazard but also of the level of exposure. If you do not attempt to climb the mountain or you just stay in base camp, the level of exposure is zero or small and the level of risk will also be zero or small, respectively.

A pesticide chemical can be considered in the same way. Although it may be very toxic and therefore an extreme hazard, the level of risk to the consumer associated with the chemical will be dependent on the level of exposure, referred to as the dietary intake. If the chemical leaves no residues in the food, then there is no risk to the consumer. If on the other hand, the use of the chemical leads to high residues in food, then this will result in a risk. A risk assessment is then required in order to decide if the risk is low and acceptable in scientific terms.

In conclusion, the hazard that a chemical poses can be considered as being dependent on its intrinsic properties. On the other hand, the risk that a chemical poses also depends on the level of exposure, e.g. dietary intake, and can be thought of as the probability of an adverse outcome.

IF MY FOOD IS SAFE, DOES IT FOLLOW THAT THERE IS NO RISK?

No, the food may still pose a low level of risk despite being perfectly safe to eat. Indeed everything that we do in life has a risk associated with it and it is impossible to eliminate all the risks associated with eating food. Each type of food contains different risks, e.g. the risk of heart disease associated with saturated fats contained in most dairy and other farm animal products to the risk associated with the toxicity of the natural components of food.

Food is considered 'safe' when the level of risk is sufficiently low as to be considered minimal or negligible. This is analogous to a driver of a car who considers it 'safe' to drive along a quiet road in a well-maintained car; this, though, would not be risk free. In a similar way for pesticide residues, it is generally accepted by the scientific community that this 'safe' level of minimal or negligible risk is achieved when the dietary intake is within the ADI, and, when applicable, within the acute RfD.

WHY ARE PESTICIDE RESIDUES COMMONLY PERCEIVED TO POSE A SIGNIFICANT RISK TO CONSUMER SAFETY?

Total diet studies indicate that the level of pesticide residues as consumed are very low and are generally well within acceptable exposures, commonly a very low percentage of the ADI. However, when surveyed, the general public frequently perceive the risk associated with pesticide residues to be similar to that of smoking or driving a car. To understand why this is the case and whether this perception is justified, one needs to understand the factors that commonly influence the perception of risk by consumers. This perception is, perhaps, influenced by three main factors:

- the level of understanding of the nature of the risk by the consumer
- the amount of control that the consumer has over the risk
- the degree to which the consumer benefits from the risk.

To illustrate these three factors, let us consider again the example of a consumer driving a car to the grocers. The consumer has a relatively good understanding of the level of risk associated with the driving of a car. However, crucially, the consumer has control over the car and the associated risks and is also the beneficiary of the trip to the grocers.

In contrast, if we consider the case of pesticide residues in food, a consumer may have little understanding of how the risk is assessed and what it means. In addition, the consumer has only very limited control (perhaps some home-grown vegetables) and may believe that the only beneficiaries from the use of the pesticide are the farmers and agrochemical companies.

The above example helps to explain the apparent significant difference between an evidence-based evaluation of the risks posed by pesticide residues with the common public perception. However, this does not mean that regulators can be complacent about the risks since pesticide residues, and therefore dietary intake, can be high if pesticides are not properly controlled and significant misuse occurs. An example of this was in June 1992, when the illegal and gross misuse of the compound 'aldicarb' on cucumbers in Ireland led to at least 29 people being poisoned, with some requiring hospital treatment. A similar case was also reported in California involving watermelons contaminated with aldicarb. Luckily, incidents of this kind are rare; however, they do illustrate how pesticide residues can

pose unacceptable risks to human health when they are used in a way that differs significantly from the product label recommendations or statutory conditions of use, i.e. illegal misuse.

WHY IS CAUTION NEEDED WHEN INTERPRETING 'WORST-CASE' SCENARIOS USED IN THE EVALUATION OF PESTICIDES?

We should distinguish decisions relating to what is typically or actually happening from those that are based on 'worst-case' scenarios. What is 'worst-case'? In practice, the range of circumstances and possibilities is very wide; the worst-case scenario is the circumstance which will lead to the most extreme result but still has a theoretically possible chance of occurring in practice.

In making decisions about pesticides, regulators commonly use worst-case assumptions, particularly when more realistic evidence is not available. However, when we run a series of worst-case possibilities layered one on the other the estimated end result can be quite remote from reality, and yet the perception can be that such an end result is typical. For example, for pesticide residues we commonly see dietary intake estimates based on assumptions that a person consumes throughout a lifetime food always containing pesticide residues at the maximum allowable concentration. The purpose of such a calculation is to show that if safety is achieved under this worst-case then it will be safe under other circumstances. It is, of course, totally impossible to produce residues consistently at the maximum allowed, and only in a minority of cases are more than a few percent of crops treated with a specific pesticide. Furthermore, it is quite impossible that someone consumes every day a range of foods that have all been treated and that all of these have been harvested to contain residues at the maximum residue limit (MRL).

It is recognized that these 'worst-case calculations' can act as useful tools for regulatory agencies, who may decide that if the 'worst-case' is acceptable, then the risk is minimal and no further scientific studies are needed. However, difficulties arise when people misunderstand or misinterpret the worst-case scenarios and present them as a typical case and representative of the real situation.

HOW ARE SAFETY FACTORS DECIDED?

Safety factors, sometimes known as 'uncertainty factors', are used to convert the *no-observed-effect levels* (NOELs) or the *no-observed-adverse-effect levels* (NOAELs) from the animal toxicology studies to an ADI for humans. Safety factors are also incorporated into the derivation of acute RfDs.

The USA FDA (Food and Drug Administration, 1955) explained the basis for the safety factor then adopted and which is still largely in force today. The FDA, in predicting the quantity of a poisonous compound that may be consumed over a long period without hazard to man, deemed it reasonable and advisable to assume the following:

- that man is ten times more prone to injury from the compound than other warm-blooded animals;
- that the most sensitive humans are ten times more susceptible to injury from the compound than the average human.

Therefore, in dealing with new compounds to which humans have not been exposed extensively, it is proper to apply a combination of these two factors and use a combined safety factor of 100. A safety factor of less than 100 may be used if data on physiological or other effects on humans are available. A safety factor greater than 100 may be desirable if unusually alarming reactions have occurred from exposure of humans, or other animals, to the compound.

A WHO publication (WHO, 1990) reiterated the interpretation of the 100-fold safety factor as two 10-fold factors, i.e. one for inter- and one for intra-species variability, and explained the factors that might influence a choice of other safety factors. For example, when relevant human data are available, the 10-fold factor for inter-species variability may not be necessary. The quality of a study or difficulties of interpretation may suggest the choice of a higher safety factor.

ARE MIXTURES OF RESIDUES MORE TOXIC THAN THE INDIVIDUAL COMPONENTS?

Risk assessment for pesticide residues normally deals with one pesticide at a time or, at most, with a small group of related pesticides perhaps with the same or closely related residues. Questions have been posed about the toxicity of mixtures, such as, 'is the toxicity of a mixture higher than the added toxicities of the individual compounds?'.

This question is not easy to answer and, because of the multitude of possibilities, there can never be enough empirical data to cover each different combination of residues. Mumtaz *et al.* (1993) posed the question as to whether from a public health perspective the risk from mixtures is overestimated, underestimated or is realistic, and looked at possible mechanisms.

For example, if compound A reduces the liver function so that the liver detoxifies compound B much more slowly, we would expect compound B to be more toxic in the presence of compound A. However, if compound B is metabolized by the liver to a more toxic compound, then compound A would reduce the toxicity of B. In practice, the timing of administration, the doses, absorption, transport within the body and numerous complex mechanisms will all influence the process and make the simple explanation conceptually useful but unlikely to be more than part of the story.

The Joint FAO/WHO Meeting on Pesticide Residues replied to a question about the possible combined effects of pesticides (JMPR, 1996). The JMPR noted that interactions between pesticide residues, other dietary constituents and environmental contaminants could occur and the outcome, which cannot be predicted

reliably, may be enhanced, mitigated or additive toxicity. The JMPR report concluded that the safety factors that are used for establishing ADIs should provide a sufficient margin of safety to account for potential synergism (i.e. effects that exceed the sum of their combined effects).

WHY DO WE USE THE TERM 'ORGANIC FOOD'?

In the late 18th century, natural substances were classified according to the three 'kingdoms of nature', namely animal, vegetable and mineral (von Meyer, 1898), although a number of substances were found to be common to animals and plants and were classified as organic compounds, i.e. produced by organisms. In 1828, Wohler produced urea, an organic substance, from ammonium cyanate, an inorganic substance, demonstrating at least in this case and subsequently for others that production of an 'organic substance' did not necessarily require an organism. The terms 'organic chemistry' and 'organic compound' are, however, still retained for carbon compounds, the main components of plants and animals.

In the early 19th century a 'vital principle' was invoked to explain the ability of organisms to produce complex organic substances. Liebig (1842) expressed the opinion that the processes in plants and animals could best be explained in chemical terms and that 'vital principle' was of equal value with the terms 'specific' and 'dynamic' in medicine, i.e. 'vital principle' is just a learned name, not an explanation:

> *. . . . everything is specific which we cannot explain, and dynamic is the explanation of all which we do not understand; the terms having been invented merely for the purpose of concealing ignorance by the application of learned epithets.*

The terms 'organic farming' and 'organic food' appear to be a revival of the idea of drawing a distinction between substances produced in nature and those produced artificially or synthetically. There may be an intuitive belief that humans have been extensively exposed to natural compounds over the ages and that our metabolism and biological system are adjusted to them and render them safe. The belief may extend to synthetic compounds that, by the same logic, will be new to human metabolic systems and therefore cannot be detoxified and will be hazardous.

Biological systems are very complex and adaptable. A simplistic approach, such as an association of 'natural' with 'good' and 'synthetic' with 'bad' is useful in advertising but is difficult to justify when we begin looking at details of individual cases. This issue is discussed further later in this chapter.

Gardner (1957) described the organic farming movement in the USA, which maintained that food loses its health value if it is grown in soil that has been devitalized by chemical fertilizers and that artificial fertilizers and sprays had caused almost all of the nation's health disorders, including cancer.

'Organic food' and 'organically produced' are now useful marketing concepts. The market will supply the wants of those consumers especially concerned about the safety of pesticide residues in their food and who are willing to pay a premium for reassurance from vendors of the produce.

ARE PESTICIDE USES ON FOOD CROPS ADEQUATELY TESTED FOR CONSUMER SAFETY?

Before a pesticide is registered for use, the government pesticide regulatory authority requires the submission of a wide range of test data. These data are evaluated and an independent scientific assessment is conducted to ensure that the use of the pesticide is safe to the consumer, the user and the environment (including wildlife). Consumer safety is of crucial importance and pesticides are not registered if the scientific assessment indicates that residues in food pose an unacceptable risk.

Pesticide uses and the resulting residues in food and drinking water are highly regulated, particularly in the developed world, thus reflecting the high level of political and public interest. However, as previously discussed, the public tends to perceive the risks as higher than the scientifically assessed risks based on a detailed evaluation of the data by government authorities.

A further important consideration regarding the regulation of pesticide residues is that trade is involved. Governments and export industries may find that extensive data on residue levels and their safety are required by importing countries to gain trade access.

Political and trade interests combine to ensure that pesticides are extensively tested and studied before registrations are granted and that extensive regulatory requirements are developed. As a comparison, the use of veterinary drugs on food-producing animals is generally not of such high political and public interest (growth promotants are an exception) and the data requirements for veterinary drug uses are commonly less than those for pesticide uses.

WHAT IS 'ALARA'?

Exposure to chemicals in food and drinking water and to chemicals in the workplace are regulated by the use of two general principles. First, exposure should not exceed a pre-determined daily dose derived from a no-effect-level in animal experiments with the application of a safety factor. Secondly, exposure should be no higher than necessary when good practices are followed, i.e. 'as low as reasonably achievable' (ALARA). Permitted legal limits for residues in food and permitted legal exposure to chemicals by workers mostly derive from the 'as low as reasonably achievable' principle.

WHAT IS THE RELATION BETWEEN MRLs AND FOOD SAFETY?

The maximum residue limit (MRL) or tolerance for a pesticide residue is the maximum concentration of a pesticide residue legally permitted in or on a food

commodity. MRLs are based on the highest residues expected in or on a food commodity when the pesticide is used according to registered label instructions.

Label instructions originate from the application rate, interval between treatment and harvest, method of application, etc. found necessary for effective pest control under practical conditions but leaving a residue which is the smallest amount practicable, i.e. *as low as reasonably achievable*.

Foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable. Before an MRL is established, it must pass the hurdles of risk assessment (Figure 1.1).

It follows from the procedure used for establishing MRLs that they are based on the registered uses of a pesticide and have no direct calculated relationship to the ADI (acceptable daily intake) of the pesticide. The acceptability from a food safety point of view of the recommended limits for a particular pesticide is assessed from the long-term dietary intake of that pesticide, which is compared to the permissible intake of residue calculated from the ADI for a consumer, while the short-term intake is compared with the acute RfD for a consumer.

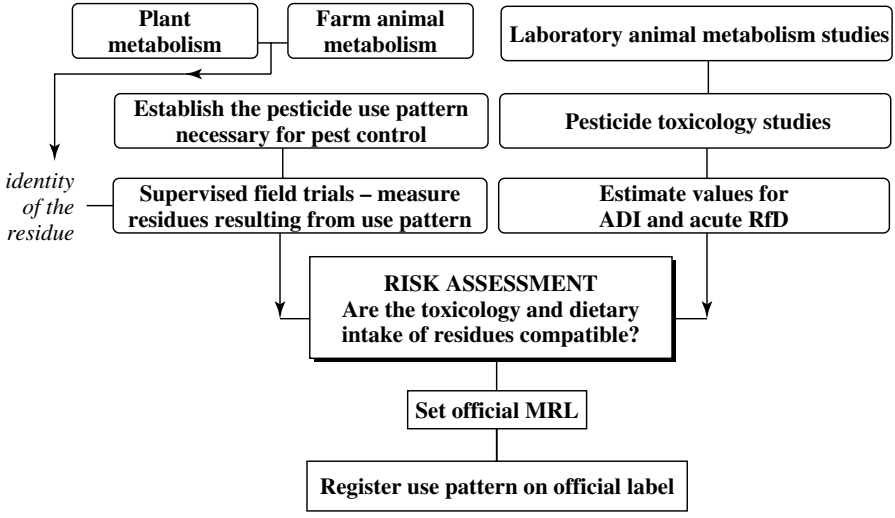

Figure 1.1 Risk assessment process before registration for pesticide residues in food: ADI, acceptable daily intake; acute RfD, acute reference dose; MRL, maximum residue limit or tolerance. Reprinted from Hamilton, D. J., Food contamination with pesticide residues, in *Encyclopedia of Pest Management*, 2002, Figure 1, p. 287, by courtesy of Marcel Dekker, Inc

HOW ARE 'NO DETECTED RESIDUES' INCLUDED IN THE DIETARY INTAKE ESTIMATE CALCULATIONS?

Analytical methods are used to measure the concentrations of pesticide residues in foods. Major progress has been made in the development of analytical methods for pesticide residues since the early days of pesticide residue regulation in the 1950s and 1960s. Colorimetric methods were the best methods available at that time. These methods had high limits of detection (LOD) by modern standards, being commonly around 1 mg/kg and even higher. If the residue levels were higher than the LOD, the analyst would report the values, but for lower concentrations in the food the analyst could only report 'not detected'. Pesticide regulatory officials often interpreted 'not detected' as 'nil,' but the real value could have been anywhere from zero up to the limit of detection.

Modern analytical methods mostly using gas chromatography (GC) or high performance liquid chromatography (HPLC) with very sensitive detectors routinely measure residue concentrations a hundred- or a thousand-fold lower than previously, i.e. at 1–10 μg/kg in food commodities. In principle, the same problem still exists, i.e. the method cannot 'see' residue levels below the lower limit. However, in many cases for dietary intake estimates, levels below the LOD are now sufficiently low as to be of little or no concern.

What values can we use in dietary intake calculations when the analyst reports 'not detected' or more likely now, 'less than limit of quantification' (LOQ)?

Some regulators use a conservative assumption that the actual residue is just below the LOQ and so justify use of the LOQ in the calculation. This is a plausible assumption when many of the values exceed the LOQ with some at 'less than the LOQ'. It is not plausible when all values are 'less than the LOQ' because the natural spread of values in a residue data population will ensure that if the highest value is just below the LOQ, the average or typical value will be much lower.

Some regulators use other assumptions such as '$\frac{1}{2}$ of the LOQ' or 'zero'. The '$\frac{1}{2}$ of the LOQ' has no scientific justification, but is a recognition that the LOQ is an unrealistic estimate of typical residue levels in the circumstances. Assumptions of 'zero residues' can be justified when there is supporting evidence apart from the analyses themselves. For example, if a pesticide is destroyed by processing (e.g. cooking), the assumption of 'zero residues' is reasonable for these processed foods.

In assessing residues below the LOQ in supervised trials, the FAO Panel of the Joint Meeting on Pesticide Residues (JMPR) uses the LOQ unless there is scientific evidence that residues are 'essentially zero' (FAO, 2002). The supporting evidence would include residues below the LOQ from trials at exaggerated treatment rates (i.e. above the maximum application rate) or relevant information from the metabolism studies.

In total diet studies, the pesticide treatment history of the samples is commonly not known although the reason samples have no detectable residues is probably

because the pesticide had not been used. In these circumstances, two estimates of dietary intake are sometimes made, one with residue results at 'less than the LOQ' set at the LOQ and one with these residues assumed to be at zero. If the two estimates arrive at two conclusions (acceptable and unacceptable intake), then more research is required on the analytical method to achieve a lower LOQ.

LOQs for pesticide residues in water are typically 100-fold or more lower than for the same residues in food, but the daily dietary consumption of drinking water is normally taken as two litres for an adult, which is higher than for any individual food. Experience shows that the LOQs for residues in drinking water do not normally lead to the sort of 'no detected residue' problem described above, in dietary intake estimates.

HOW DOES DIETARY INTAKE FROM RESIDUES IN DRINKING WATER COMPARE WITH THAT FROM RESIDUES IN FOOD?

The residues found in drinking water are of those compounds with some water solubility and their presence is likely to be as a result of widespread use in the water catchment area. The type of pesticides most commonly found in drinking water are herbicides with many uses in agriculture and other situations such as on railway lines and roadways.

Some compounds with sufficient water solubility and weak binding to soil particles are mobile down through the soil profile to ground water. Aldicarb, an insecticide, and atrazine, a herbicide, are two examples that have been found in ground water and in many places where ground water is used for drinking water.

Levels of residues found in drinking water are usually much lower than those found in food commodities and even when combined with the relatively high consumption of water, the estimated dietary intakes are usually very low.

Pesticide residues occur in drinking water mainly from environmental contamination, which is in contrast to residues in food where most residues occur from direct uses on crops producing food or animal feed. National authorities use various methods to set regulatory limits for pesticide residues (Hamilton *et al.*, 2003).

First, a drinking water residue limit may be calculated directly from the ADI (acceptable daily intake) by assuming a person of stated body weight (say 70 kg) consumes two litres of water per day and the intake is a percentage of the ADI (say 10 %).

Secondly, if the authority decides that residues should not occur in drinking water the limit may be set at the LOQ (limit of quantification) of the analytical method. An LOQ limit for a particular pesticide will usually be lower than a limit calculated from the ADI.

Thirdly, the authority may decide to set the limits by legislation.

Fourthly, where the pesticide has a direct use in drinking water, e.g. for mosquito control, the limit may be set at the level required for the pesticide to be effective for its intended use. It must also pass the risk assessment test for consumer safety.

ARE NATURAL CHEMICALS BENIGN AND SYNTHETIC CHEMICALS HARMFUL?

The common perception of the public is of nature as being benign, whereas man-made things are perceived as having destroyed our harmonious relationship with nature. In the area of chemicals, this idea is extended to suggest that natural chemicals are either benign or have low toxicity and that man-made synthetic chemicals are harmful. In truth, this belief does not live up to scrutiny with some of the most toxic chemicals known to man being produced naturally by plants and animals as part of their defence mechanisms (Ames, 1992). Indeed, it has been reported that the botulinus toxin produced naturally by C*lostridium botulinus* is approximately 30 000 times more toxic than 2,3,7,8-tetrachlorodibenzodioxin (TCDD) which is thought to be one of the most toxic man-made poisons; TCDD is the most toxic of the dioxin group of chemicals (Faust, 1990).

Of those natural chemicals that are consumed in food on a regular basis, many are found to be carcinogenic (cancer-causing) in rodent toxicological studies that are commonly required by regulators for man-made pesticides. Examples of these include D-limonene in orange juice, 5-/8-methoxypsoralen in parsley and parsnips, and caffeic acid found in a large number of crops, including apples, carrots, grapes and potatoes (Johnston, 1991). It has been reported that there are probably at least half a million naturally occurring chemicals in the food that we eat, ranging from low-molecular-weight flavour compounds to macromolecular proteins and polysaccharides (Fenwick and Morgan, 1991).

In response to the rhetorical question 'Are natural chemicals benign and synthetic chemicals harmful?', the answer is clearly 'no' since the statement is a gross simplification. Indeed, each chemical needs to be treated on a case-by-case basis in the scientific risk assessment. Scientific risk assessments are justified even for natural chemicals commonly found in food, when the dietary intake by consumers may increase significantly.

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ACRONYMS APPEARING IN THE BOOK

3-PBA	3-phenoxybenzoic acid
ADI	acceptable daily intake
ADP	adenosine diphosphate

ALARA	as low as reasonably achievable
ANZFA	Australia New Zealand Food Authority
ARC	anticipated residue contribution
ARfD	acute reference dose
ATP	adenosine triphosphate
BCF	bioconcentration factor
Bt	*Bacillus thuringiensis*
CAC	Codex Alimentarius Commission
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CSFII	Continuing Survey of Food Intakes by Individuals (USA)
CXL	Codex Alimentarius Maximum Residue Limit
DEEM™	Dietary Exposure Evaluation Model
EBDC	ethylene bisdithiocarbamate
EC	emulsifiable concentrate
EC	European Community
EDI	estimated daily intake
EMDI	estimated maximum daily intake
EMRL	extraneous maximum residue limit
EPA	(US) Environmental Protection Agency
ETU	ethylenethiourea
FAO	Food and Agriculture Organization of the United Nations
FBS	(FAO) food balance sheet
FDA	(US) Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetic Act (USA)
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act (USA)
FQPA	Food Quality Protection Act (USA)
GAP	Good Agricultural Practice
GATT	General Agreement on Tariffs and Trade
GC	gas chromatography
GEMS/Food	Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (WHO)
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
GSH	glutathione
GUS	Gustafson Ubiquity Score
HPLC	high performance liquid chromatography
IARC	International Agency for Research on Cancer (WHO)
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
IGR	insect growth regulator

IPCS	International Programme for Chemical Safety (WHO)
IPPC	International Plant Protection Convention
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOD	limit of determination
LOD	limit of detection
LOEL	lowest-observed-effect level
LOQ	limit of quantification
MRL	maximum residue limit
NAFTA	North American Free Trade Association
NDNS	National Diet and Nutrition Survey (USA)
NEDI	national estimated daily intake
NESTI	national estimated short-term intake
NMR	nuclear magnetic resonance (spectroscopy)
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRA	National Registration Authority for Agricultural and Veterinary Chemicals (Australia)
NTMDI	national theoretical maximum daily intake
OC	organochlorine (pesticide)
OECD	Organization for Economic Co-operation and Development
OIE	International Office of Epizootics
OP	organophosphorus (compound)
OPPTS	Office of Prevention, Pesticides and Toxic Substances (USA)
PAs	1,2-dehydropyrrolizidine alkaloids
PDP	Pesticide Data Program (USA)
PHI	pre-harvest interval
PMTDI	provisional maximum tolerable daily intake
PSD	Pesticide Safety Directorate (UK)
PTU	propylenethiourea
PTWI	provisional tolerable weekly intake
RAC	raw agricultural commodity
SC	suspension concentrate
SOP	standard operating procedure
SPS	sanitary and phytosanitary (measures)
STMR	supervised trials median residue
STMR–P	supervised trials median residue for processed foods
TBT	(Agreement on) Technical Barriers to Trade
TMDI	theoretical maximum daily intake
TMRC	theoretical mean residue concentration
TRR	total radioactive residue
UDMH	1,1-dimethylhydrazine

UF	uncertainty factor
UNECE	United Nations Economic Commission for Europe
USDA	United States Department of Agriculture
WHO	World Health Organization
WTO	World Trade Organization