Occupational and Residential Exposure Assessment for Pesticides

Edited by

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Series Preface

There have been tremendous advances in many areas of research directed towards improving the quantity and quality of food and fibre by chemical and other means. This has been at a time of increasing concern for the protection of the environment, and our understanding of the environmental impact of agrochemicals has also increased and become more sophisticated, thanks to multidisciplinary approaches.

Wiley recognized the opportunity for the introduction of a series of books within the theme 'Agrochemicals and Plant Protection' with a wide scope that includes chemistry, biology and biotechnology in the broadest sense. This series is effectively a replacement for the successful 'Progress in Pesticide Biochemistry and Toxicology', edited by Hutson and Roberts, which has run to nine volumes. In addition, it complements the international journals *Pesticide Science* and *Journal of the Science of Food and Agriculture*, published by Wiley on behalf of the Society of Chemical Industry.

Volumes already published in this series cover a wide range of topics, including environmental behaviour, plant metabolism and chirality, and a volume devoted to fungicidal activity. These together cover a wide scope and form a highly collectable series of books within the constantly evolving science of plant protection.

As I write this preface, I remain deeply saddened by the death in 2003 of Dr Junshi Miyamoto, who contributed so much to this series as my Co-Editor-in-Chief. More significantly, Junshi will be remembered for his lifetime achievements in agrochemical biochemistry, toxicology and metabolism – and not least for the energy he displayed in international activities aimed at harmonizing knowledge within the field of agrochemicals. He leaves us with a wealth of scientific publications.

Terry Roberts
Anglesey, UK
July 2004

THE SERIES EDITORS

Dr Terry R Roberts is an independent consultant, based in Anglesey, North Wales, UK. He was Director of Scientific Affairs at JSC International, based in Harrogate, UK, from 1996 to 2002, where he provided scientific and regulatory

consulting services to the agrochemical, biocides and related industries, with an emphasis on EU registrations.

From 1990 to 1996, Dr Roberts was Director of Agrochemical and Environmental Services with Corning Hazleton (now Covance) and was with Shell Research Ltd for the previous 20 years.

He has been active in international scientific organizations, notably the OECD, IUPAC and ECPA, over the past 30 years. He has published extensively and is now Editor-in-Chief of the *Wiley Series in Agrochemicals and Plant Protection*.

Dr Junshi Miyamoto (deceased) was Corporate Advisor to the Sumitomo Chemical Company for 45 years, since graduating from the Department of Chemistry, Faculty of Science, Kyoto University. After a lifetime of working in the chemical industry, Dr Miyamoto acquired a wealth of knowledge in all aspects of mode of action, metabolism and toxicology of agrochemicals and industrial chemicals. He was a Director General of the Takarazuka Research Centre of the Sumitomo Chemical Company, covering the areas of agrochemicals and biotechnology, as well as environmental health sciences. He was latterly President of the Division of Chemistry and the Environment, IUPAC, and in 1985 received the Burdick Jackson International Award in Pesticide Chemistry from the American Chemical Society, and in 1995, the Award of the Distinguished Contribution to Science from the Japanese Government. Dr Miyamoto published over 190 original papers and 50 books in pesticide science, and was on the editorial board of several international journals, including *Pesticide Science.*

Preface

Pesticides are a class of products essential for sustainable agriculture and good public health. Lack of clarity in some of the published literature and a general misunderstanding of the difference between the hazard of a pesticide and the actual risk have heightened public anxiety over the use of such materials. Of particular concern is the potential for pesticide residues to harm the health of adults and especially that of their children. To fully understand the potential risk that might occur when a pesticide is used, it is imperative that accurate and reliable estimates of exposure be available. This information, along with the toxicological profiles, enable risk assessors to determine whether the pesticide can be used without harming health and the environment.

This book documents the current state of knowledge in occupational (applicators and field workers) and residential exposure assessment and outlines the ways in which exposure data are used in assessing the risks of pesticides to humans. The importance of developing standardized methods for measuring exposure, building mathematical models and interpreting data to foster internationally harmonized, scientifically sound decisions is discussed. Because pesticides are used globally, the opportunities for international collaboration in generating the data and in assessing the risks are identified in each chapter and then discussed in the final chapter.

Many of the principles used in pesticide exposure assessment are applicable to other classes of chemicals, and it is hoped that this book will encourage cross-fertilization among disciplines. In particular, continued international co-operation and harmonization will be essential to ensure the protection of workers and the general public from the adverse effects of pesticides.

This book would not have been possible without the knowledge and dedication of all of the authors who generously contributed chapters to this text. We thank them for this and for their patience in seeing this project through to completion.

CLAIRE FRANKLIN AND JOHN WORGAN

July 2004

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Introduction and Overview

CLAIRE A. FRANKLIN[1] and JOHN P. WORGAN
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The purpose of this book is to document the current state of knowledge in the field of occupational and residential exposure assessment and to outline the ways that exposure data are used in assessing the risks of pesticides to humans in occupational and residential settings. Recommendations for improvements to exposure assessment are also proposed.

Over the past 30 years, there has been increasing awareness of the need to have estimates of exposure for workers applying pesticides, for field workers involved in handling pesticide-treated crops and for the general public who come into contact with pesticides in their homes, their gardens, their schools and other

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public places. In the early days, exposure estimates were carried out to understand why workers were getting sick after applying certain products or after working in the fields picking crops. Now, quantitative estimates of exposure have become an integral component of the regulatory decision-making process on whether a pesticide should be registered for use or remain on the market post-registration. Many jurisdictions also have regulations requiring companies to submit reports concerning adverse effects attributable to the use of their products, and epidemiology studies are carried out to study the health effects of pesticides on larger populations. Furthermore, data from all pathways of exposure are required, and the emphasis is now being placed on distributional data rather than point estimates. These developments have highlighted the need for accurate estimates of exposure over a wide range of circumstances or scenarios, hence leading to improved methods for analyzing pesticides and more precise ways of extrapolating the data.

ASSESSMENT OF RISKS TO HUMANS EXPOSED TO PESTICIDES

It is generally considered that the acceptability of a pesticide should be based on the nature and degree of risk it poses. This necessitates a knowledge of both the toxicity of the pesticide, as determined through extensive testing in animals, and the level of exposure to people under defined conditions to be able to fully characterize the risk. The defined conditions include such factors as the type of equipment (open or closed systems), application rate, the use of personal protective equipment, such as gloves and coveralls, and the type of job the worker performs. These conditions are then grouped into 'use scenarios'. Initially, the focus was on agricultural workers. More recently, there has been increased emphasis on non-occupational or residential risk assessment, especially determining the potential risks of pesticides to children.

THE FOUR STEPS IN RISK ASSESSMENT

Hazard Identification

This is carried out by testing the pesticide in a variety of animal species over a range of doses administered by the oral, dermal and inhalation routes at various life stages and for increasing durations of time ranging from a single acute exposure, a short-term exposure and a chronic (lifetime) exposure. Only toxic endpoints that are relevant to humans are used in the risk assessment. Although some of the acute and short-term studies are carried out by using the dermal and the inhalation routes of exposure, the bulk of the studies, including the long-term, reproduction and teratology studies, are carried out by using only the oral route. These data are appropriate for estimating risks due to exposure to pesticides via food residues. They are less useful for estimating worker and residential risk

because exposure is primarily via the dermal, and to a lesser extent, the inhalation route. To overcome this problem, the amount of pesticide that is absorbed through the skin (either the % absorbed or the rate of absorption) is estimated in animals. The absorption factor can then be used to calculate the absorbed dose, thus enabling comparison with the oral toxicity data.

There are scientific uncertainties involved in the conduct of a risk assessment. For example, toxicology data generated in animals are extrapolated to humans and there are different sensitivities within a human population. To deal with these uncertainties, regulatory agencies worldwide apply safety or uncertainty factors. A 100-fold safety factor (10 for species differences $\times$ 10 for sensitivity) is generally used, but this can range upwards or downwards depending on the nature of the data and the completeness of the database. In North America, an additional 10-fold factor is required unless there is evidence to show that children are not more sensitive to the effects of the pesticide. Following review of the toxicology data, consideration is given to which safety or uncertainty factors should be used in the next step.

Dose–Response Assessment

Margin of Safety Approach

Most chemicals do not cause toxic or adverse effects until a certain dose has been given. These are called *threshold chemicals*. The lowest dose level at which there are no adverse effects observed in the test animals is called the *No Observed Adverse Effect Level* (NOAEL) and is the starting point for the calculation of the reference dose. While the terminology used may differ among regulatory agencies, the concepts are similar. In North America, the term margin of safety or exposure is used, whereas in Europe an *Acceptable Operator Exposure Level* (AOEL) is used. Care is taken to choose the NOAEL for an effect which is relevant to humans and that the duration, frequency and route of exposure in the test animals are relevant to the human exposure.

The next step is to calculate a *reference dose* (RfD) by dividing the NOAEL by the safety or uncertainty factors appropriate for the pesticide under review. Additional safety factors can be used for severity of the toxicological effect, if sensitive sub-populations such as children are likely to be exposed to the pesticide and if there are scientific uncertainties in the data. This approach is used for establishing the risk from exposure to threshold chemicals.

Quantitative Risk Assessment

A different approach, called a quantitative risk assessment, is used for non-threshold effects, such as cancer. Sophisticated statistical models are used to extrapolate the experimental animal data obtained at high doses to the low exposures predicted in humans. The *linearized multistage* (LMS) model is frequently

used for regulatory purposes. From it, the lifetime cancer risk for an average daily lifetime exposure can be calculated.

Exposure Assessment

This is a critical component of risk assessment and is the focus of this book. If the exposure estimate is inaccurate, it can have serious ramifications on the decision. Too low and there might be unacceptable risks to people exposed to the pesticide. Too high and the pesticide might not be registered or the uses could be severely limited. Recently, there have been significant changes in the way that exposure assessments are carried out. Exposure assessment methodologies for agricultural and residential settings, including re-entry into treated areas, are discussed in the four chapters in Section One of this book.

It is important that the exposure estimate be realistic yet protective of human health and that it takes into account the frequency and duration of exposure. Uncertainties in the exposure assessment, including the fact that exposure studies are carried out under controlled circumstances, may be compensated for by using conservative assumptions such as maximum application rate, upper bound values and 100 % dermal penetration. These conservatisms can have a negative impact on the regulatory decision and could be avoided with access to more complete data.

Generic databases, such as PHED, EUROPOEM, ARTF and others, have been developed to increase the confidence in the exposure estimates since many more data points from a wide range of different studies are included. Details on how these databases are constructed, the different ways in which the data are normalized and recommendations on how databases can be improved and harmonized are discussed in Chapters 5 and 6.

Risk Characterization

Once the estimated human exposure level has been quantified, its acceptability is determined by comparing it to the reference dose. If lower than the reference dose, it is considered to provide a sufficient margin of safety and is therefore not associated with unacceptable health risks. During the risk characterization phase, consideration must be given to the strengths, limitations and uncertainties in the exposure and hazard assessments to accurately characterize risk and the potential for adverse effects.

One of the challenges is the necessity to convert the human exposure level into an absorbed dose to enable a comparison with the RfD to be made. This is discussed in detail in Chapter 9.

The importance of accurate and relevant exposure data to the reliability of the risk assessment derived from both the margin of safety approach and the quantitative cancer risk assessment cannot be over-emphasized.

RISK MANAGEMENT

Once the risks have been characterized, it may be necessary to reduce exposure levels if the pesticide is to be eligible for registration. This step is called *risk management* and entails exploring options for reducing exposure and recalculating the risks to see if they are within an acceptable range. The options range from limiting the amount of pesticide that can be sold, limiting the uses for the product, requiring different formulation types and packaging, restricting the type of equipment that could be used to load and deliver the pesticide, requiring applicators to wear gloves, coveralls, respirators or use 'closed-cab' systems, and establishing re-entry intervals to protect field workers. Regulatory agencies may also restrict use of a pesticide to trained certified applicators or require that registrants implement a product stewardship programme. North American regulatory agencies are increasingly favouring engineering controls, such as closed mixing/loading systems, closed cabs for application equipment and improved lower exposure formulations and packaging, as the most effective ways to reduce exposure and work to further improve engineering controls should continue. The protective values of some of these mitigation measures are discussed in Chapters 1 and 2. More complete and realistic data on the protective values of these mitigation measures could assist in the refinement of exposure assessments.

It must be determined whether the risk mitigation options selected are feasible and provide a realistic use pattern, and whether compliance can be enforced. Another significant consideration is that options are cost-sensitive and are unlikely to be accepted if their cost exceeds the economic value of the commodity on which the pesticide is to be used.

ADVANCES IN DATA INTERPRETATION

PROBABILISTIC APPROACHES

There is a transition away from using a deterministic approach in which high end or upper bound point estimates and default values are used towards using a probabilistic approach in distributional models which incorporate complex data sets to build realistic estimates of exposure. While probabilistic dietary exposure assessments can now be carried out routinely for many pesticides, available occupational and residential exposure data sets are typically insufficiently robust. Work on developing newer exposure databases (e.g. ARTF, ORETF, AHETF and EUROPOEM II) and distributional use pattern data would facilitate this transition. The topic of probabilistic exposure assessment is covered in Chapter 8.

RECOGNITION OF THE TIER APPROACH

Regulatory agencies have adopted an internationally accepted tiered approach to occupational exposure assessment. Similar tiered approaches are also used

for residential and dietary exposure assessments. The tiered approach was first presented by Henderson and colleagues at a workshop on 'Risk Assessment for Worker Exposure to Agricultural Pesticides' in the Hague in 1993. Each tier requires more refined and complex data and hence provides a more accurate measure of exposure. Assessments are typically started at lower, less complex tiers and proceed to higher tiers as required. This approach economizes resources and focuses efforts on chemicals of greatest concern. Tier 1 involves estimating exposure using generic data and conservative default assumptions such as 100 % dermal absorption, maximum application rate and upper bound hectares treated per day. If the exposure exceeds the RfD, a further refinement (Tier 2) may be made with validated supporting data on variables such as dermal absorption, use pattern (e.g. typical application rates and areas treated per day) or effectiveness of protective clothing and engineering controls. If the Tier 2 exposure estimate exceeds the reference dose, a field study (Tier 3) may be conducted. In most cases, a biomonitoring study, supported by complete knowledge of human pharmacokinetic data, would be required to provide a more accurate and realistic estimate of exposure. At the highest tier, a probabilistic assessment could be carried out by using distributional data from a modern generic exposure database or from an individual biomonitoring study, combined with distributional data on use pattern (e.g. rates of application and areas treated per day). This tiered approach is discussed in Chapter 5.

AGGREGATE EXPOSURE

Until recently, it has been generally accepted practice to assess pesticide exposure separately for each source (dietary, drinking water and residential). As a result of legislative changes, there has been a shift away from single-source, single-pathway and single-route assessments in North America for non-occupational exposure. Aggregate exposure assessment for a single active ingredient is carried out by combining exposures from all sources, including residential exposure, food residues and drinking water. The development of novel approaches and associated scientific challenges to aggregating exposure are discussed in Chapter 8.

CUMULATIVE EXPOSURE

For classes of pesticides that cause their toxic effects through a common mechanism of toxicity, the non-occupational exposures to all members of the class have to be aggregated and used in a cumulative risk assessment. In 2003, the United States Environmental Protection Agency (USEPA) published a framework outlining how cumulative risk assessments should be conducted. There is no question that this approach has provided significant challenges to toxicologists, exposure assessors and risk assessors. Much of the developmental work on how to conduct

cumulative risk assessments has been carried out on the organophosphorous (OP) pesticides since they act through a common mechanism of toxicity. The USEPA published a revised OP cumulative risk assessment in 2001 and will finalize registration decisions based on this assessment. In the USA, thirty two (32) different OP active ingredients registered for a wide range of agricultural and residential uses were included in the cumulative assessment. This complex assessment is very 'data-rich' and is based on probabilistic approaches as much as possible. As pointed out in this document, cumulative risk assessment cannot be achieved by adding up the aggregate risk assessment for each OP because many of these products are alternatives for each other and may not be used at the same time or for the same uses. Realistic exposure scenarios must be developed in order to define the times and routes of exposure to the critical pesticides linked to the common toxic effect. The task is complex, because the possibility exists that there may be concurrent exposures through multiple pathways to a number of pesticides from the same cumulative group. How aggregate and cumulative exposure assessments can be carried out is discussed in Chapter 8.

IMPACT OF NEW SCIENTIFIC ADVANCES

If the estimated level of exposure is less than the reference dose (RfD), the pesticide is considered to be safe to use. The aggregation (addition) of the amount of exposure received from each source will increase the total exposure to a level which may then exceed the RfD. In addition to aggregation increasing the level of exposure, the reference dose is becoming smaller because of the use of extra safety factors to protect children. The trend towards lower reference doses impacts both residential and worker risk assessments.

The need for aggregate and cumulative non-occupational exposure assessments, and lower reference doses for all assessments, means that some pesticides will fail lower-tier risk assessments and without more refined exposure data they might even fail higher-tiered assessments. For example, in North America many of the residential uses of the OPs have been discontinued as a result of the aggregate risk assessments. As a result, there has been increased emphasis on gathering better toxicology and exposure data to reduce the conservatisms that are contained in the current system.

POST-REGISTRATION MONITORING

Once a pesticide is in use, post-registration monitoring could be conducted to further characterize the potential exposure under conditions of typical use. Occupational exposure studies carried out for registration purposes are conducted in compliance with the label requirements. While regulatory agencies compensate for such controlled conditions through the application of safety factors and other conservative assumptions, post-registration monitoring of workers using typical *Personal Protective Equipment* (PPE), rates of application and treating

a typical number of hectares per day would provide additional insight into potential risk under conditions of actual use. Such data could also be useful in determining a distribution of exposures for probabilistic assessments. These post-registration monitoring studies could be conducted by using the passive dosimetry or biomonitoring techniques described in Chapter 1 and provide validation of pre-registration studies.

Post-registration monitoring could also be useful for aggregate exposure assessments for residential use pesticides. There is the potential for a pesticide to contaminate surface and ground water, dust, soil and surfaces in the home through direct application or 'track-in', as well as air. Given the requirement to conduct aggregate exposure assessment, it is important that there be post-registration monitoring data to provide realistic estimates of the pesticide levels in some of these media. Such data may also provide an indication of the relative significance of various exposure pathways. While not the subject of this present book, such an approach is used by regulatory agencies in higher-tier dietary risk assessments whereby refined monitoring data for foods (e.g total diet studies and market basket surveys) are used to provide realistic estimates of potential food exposure. Monitoring of pesticides in drinking water may also be required for some pesticides.

Many epidemiology studies have to rely on recall responses to questionnaires to estimate exposure for workers and the general population. The need for realistic and accurate measures of exposure for epidemiology studies is the topic of Chapter 7. Post-registration monitoring of residues in various media, and of workers or the general public using passive dosimetry and biomonitoring, would also provide better surrogates of exposure for epidemiology studies. Limited population-based biomonitoring studies have been carried out and provide an indication of potential exposure to pesticides in the general population. These studies are described in Chapter 4.

Some regulatory agencies also require the reporting of adverse effects. Such post-registration monitoring data can supplement and validate risk assessments for pesticides under re-evaluation and provide useful information for further risk mitigation and management.

HARMONIZATION OF REGULATORY APPROACHES

In the past few years, there have been increasing efforts towards international harmonization of approaches to pesticide exposure assessment. Harmonization allows exposure assessors to share expertise and resources and develop better methods. Ongoing efforts towards international harmonization are discussed in Chapter 10. The development of generic databases has provided an impetus for harmonization of methodologies for generating the data. Further harmonization would increase the number of studies that could be included in databases, thus improving the exposure estimates derived from them. The use of harmonized factors for dermal absorption and clothing penetration, plus protective factors

for clothing and equipment, as well as the use of consistent triggers for exposure assessments, harmonized route-specific considerations and generic transfer coefficients, would improve enormously the quality of the data and enable much larger databases to be built. New requirements for assessing residential exposure in the context of aggregate exposure have also spurred exposure assessors to develop common approaches and methodologies. Further development of common approaches and databases would significantly increase accuracy and confidence in residential assessments. To promote harmonization, it is essential that researchers and regulators have a common vocabulary and methods. One of the outcomes of this book is a glossary of terms, and its writing has benefitted enormously from the work of the Exposure Terminology Subcommittee of the International Program on Chemical Safety (IPCS) Exposure Assessment Planning Workgroup of the World Health Organization (WHO).

SUMMARY

Pesticides are a class of products that are essential for sustainable agriculture and for good public health, especially in light of the increase in vector-borne diseases such as 'West Nile Virus' and the ongoing challenge of malaria control. Public anxiety regarding the impact of exposure to pesticides on their health and that of their children underscores the importance of generating accurate and reliable exposure data so that appropriate decisions may be taken on the registration and use of these products. The need for monitoring data to identify where there might be problems resulting from the use of pesticides is also critical.

The field of exposure assessment is currently going through a rapid phase of development and in order to assist the reader in keeping up with this, a Reference List of Guidelines (Bibliography) is provided at the end of this book. It is recognized that this listing is not complete, but hopefully it will provide the reader with the basic sources from which more detailed and up-to-date searches may be conducted.

The ten chapters in this book cover various aspects of exposure assessment in agricultural and residential settings, ranging from generation of the data, building of databases to synthesize the empirical data, use of the data in epidemiology studies, new approaches to aggregate exposure assessment for a single pesticide, and cumulative exposure assessment for pesticides that have the same mode of toxicity, to a discussion of the importance of international harmonization on the generation and use of exposure data.

The goal of this text is to provide a critical assessment of the current state of knowledge of exposure assessment of pesticides and to provide recommendations to advance our ability to fully characterize and accurately assess their potential exposure and risks. While the focus is on pesticides, many of the principles are also applicable to other classes of chemicals and it is hoped that this book will help encourage cross-fertilization among various disciplines. Significant progress

has been made in the last decade, but further work is required in several key areas to meet the challenges posed by the newer developments described above. In particular, continued international co-operation and harmonization will be essential to ensure the protection of workers and the general public from the adverse effects of pesticides.

Section One

Exposure Assessment Methodologies

1 Assessment of Exposure for Pesticide Handlers in Agricultural, Residential and Institutional Environments

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INTRODUCTION

Occupational pesticide exposure holds a peculiar status within the field of occupational health and safety, both from a scientific and regulatory perspective. Methods for personal monitoring of dermal exposure first arose in the context of pesticide applications in agriculture, pioneered by scientists in the USA Public Health Service (Batchelor and Walker, 1954; Durham and Wolfe, 1962). These methods gained worldwide recognition in the early 1960s, and remain a component of exposure assessment practice today. This work pre-dated most personal monitoring methods that were developed for industrial workplaces.

Nonetheless, occupational hygiene – the science of workplace hazard recognition, evaluation and control – has turned its attention only belatedly to exposures in the agricultural workplace. The majority of scientists who investigated pesticide exposures through the 1980s came from disciplines allied more with the agricultural sciences than with the health sciences. Thus, for many years, standard occupational hygiene procedures were not applied to these populations.

In the past decade, however, the occupational health and safety community has directed greater attention to pesticide exposures among workers and their families. Initiatives, focused on minority workers, women and the children of workers, have also made pesticide exposure assessment a timely topic for scientific investigation and medical management. Finally, major new epidemiologic initiatives in both the United States and Canada have given new stimuli to the study of occupational pesticide exposure in farming (Alavanja *et al*., 1996; Arbuckle *et al*., 1999).

The purpose of this present chapter is to critically discuss study methodologies used to derive quantitative estimates of exposure associated with the mixing, loading and application of pesticides for agricultural, residential and institutional

scenarios. The exposure assessment methodologies presented here are also relevant to the assessment of post-application risks to workers, which is addressed in more detail in Chapter 2. This review will also comment on the exposure of children of pesticide workers, as they appear to be a sub-population at potentially high risk for exposures. This chapter will review basic characteristics of pesticide products and populations at risk, and will then focus on study design considerations, and methods for monitoring and assessment. A final section will discuss the differences between guideline studies conducted in support of regulation and operational studies and will make recommendations on ways to improve exposure studies.

PESTICIDE CATEGORIES

Pesticides are a heterogeneous group of chemicals developed to control a variety of pests. The term can be applied to microorganisms with biocidal properties, as well as to common household products. Pesticides are generally categorized according to the type of pest for which they have been shown to be efficacious. The primary categories are insecticides, herbicides and fungicides. Many other categories, such as wood preservatives, termiticides, rodenticides, algaecides, repellents and miticides, are also in use. An excellent resource book describing the various pesticide classes is available (Ware, 1994).

Pesticides are manufactured and sold in various formulations. The latter are composed of the technical active ingredient (also referred to as the *active* substance) and other chemicals, including water (*formulants*) which are designed to improve effectiveness, or may enhance storage or safety of the active ingredient. Persistence of the pesticide in the environment can also be affected by formulation. Types of formulation may be liquid or powder sprays (e.g. emulsifiable concentrates and wettable powders), dusts, aerosols or granular materials. The formulation may be designed to volatilize quickly, or to act in a slow-release or controlled-release manner. Knowledge of the formulation type can often prove useful in understanding the potential for worker exposures.

PESTICIDE HANDLERS

AGRICULTURAL PESTICIDE HANDLERS

Workers who mix, load and apply formulated pesticides may be classified into a single category of pesticide handlers. Such handlers 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 acute intoxications. The potential for development of long-term adverse health effects depends on such factors as frequency of application (times per season) and exposure duration (years of application). This worker population has been the subject of significant regulatory scrutiny, and exposure databases have been developed in both North America

and Europe to better understand the extent and variability of exposure. A comprehensive review of these databases has been published (van Hemmen, 1992), and is the subject of Chapter 5 in this book. A publication from an international workshop also provides an excellent review of these issues (Curry *et al*., 1995).

Exposure is also dependent on the type of task performed, and therefore it is important to collect data for each.

Tasks Performed by an Individual

- ***Mixing/loading*** – this work activity involves weighing or measuring the product in some fashion, mixing the measured concentrated product with a diluent, usually water, either inside or outside of the application equipment, loading the product (either neat or partially diluted) into the equipment either manually or via a pumping or other system, adding additional diluent if required, and mixing it in the application equipment. For some products, such as dust formulations, no diluent is used.
- ***Application*** – this task involves driving a vehicle which either pulls the application equipment or where the equipment is contained within the vehicle itself. This would include trucks (with tank and mounted spray rig), tractors (which pull a tank and spray rig), other self-contained units and aircraft (helicopters or fixed-wing planes), which are equipped with tanks or hoppers and spray, dusting or granular application equipment.
- ***Mixing/loading/application*** – this work activity involves all of the tasks involved in the application of the pesticide. This is the most common activity for farmers who apply their own pesticides. Commercial, for hire, applicators typically have separate tasks. There are also workers in greenhouse operations and residential settings where the typical equipment may be backpack sprayers, hand-held tank sprayers, push-type applicators and belly-grinders.
- ***Flagging*** – this activity occurs when pesticides are applied aerially. The workers position themselves, with a flag, at the edge of fields to be treated aerially to assist the pilot in identifying his line of flight in order to obtain complete coverage of the target area without significant overlap. Such workers may receive direct contact with the pesticide product or spray during the course of the application.
- ***Other activities*** – certain large application equipment may become heavily contaminated during the application operation and require 'clean-up'. Some application procedures may require an immediate second operation, such as soil incorporation of an herbicide immediately after application, or irrigation of a pesticide into a lawn soon after treatment. It may be appropriate in some circumstances to monitor exposure during such activities.

Factors Affecting Exposure

Exposure during specific pesticide handling events can be modified by several important factors, as follows:

- ***Type of equipment used*** – mixing and loading of pesticides can result in substantial exposures over brief periods; closed systems have been developed to mitigate such exposures, and when properly used and maintained, have proven effective. Applications with such equipment as air-blast (speed) sprayers produce much higher exposures than applications with ground-boom equipment, although most of the exposure occurs from mixing/loading the concentrate. Newer spray rigs are typically equipped with enclosed cabs which have ventilation systems that provide substantial protection against dermal exposure. They also reduce inhalation exposure to a level comparable to a National Institute of Occupational Safety and Health (NIOSH)-approved dust/mist or organic-vapour removing respirator. Performance criteria for closed cabs are published in the United States Environmental Protection Agency (USEPA) Worker Protection Standard (WPS 40CFR, part 170.240 (d) (5)) (USEPA, 1992).
- ***Formulation*** – different formulation types can produce very different exposure patterns. Liquids, such as emulsifiable concentrate (EC) solutions, and aqueous suspensions (ASs) are prone to splashing and occasionally spillage, resulting in permeation of clothing and skin contact. Emergency washing facilities are often required in proximity to mixing stations in order to prevent overexposures. Solids, such as wettable powders (WPs), granules and dusts, may present a plume of dust while being loaded into application equipment, so producing both a respiratory hazard and exposures to the face and eyes. Some of the newer water-dispersible granules (WDGs) have been formulated to drastically reduce this potential exposure to dust particles.
- ***Packaging*** – the type and size of packaging can also influence potential exposure. The opening of bags, depending on type, can result in significant exposure. The size of cans, bottles or other liquid containers may affect the potential for spillage and splashing. Many larger-volume pesticides are delivered in larger bulk and 'minibulk' containers, which when used in combination with the closed mixing/loading systems described above, significantly reduce handler exposure.
- ***Environmental conditions*** – climatological factors, such as temperature and humidity, may influence chemical volatility, perspiration rate and use of protective clothing. Wind can have a profound effect on spray drift, and resultant exposure to the applicator.
- ***Protective clothing and personal protective equipment*** – protective clothing, such as chemical-resistant gloves and coveralls, are often required during pesticide handling and application. Label requirements may also call for respiratory protection. Use of such personal protective equipment can dramatically reduce skin contact and inhalation exposures.
- ***Hygienic behaviour*** – worker care in regard to pesticide handling can also have substantial impact on exposure. Workers who avoid mixing and spraying during windy conditions can reduce their exposure. Proper use and maintenance of protective clothing are also important behaviours associated with reduced chemical exposures.

- ***Dual activities*** – in exposure studies for agricultural scenarios, mixing/loading tasks are often monitored separately from the application, even though the same individual may frequently perform both tasks, particularly in smaller farm operations. It has been observed that mixer–loaders typically have the highest exposure, mainly to their forehead, forearms and hands, for many scenarios, regardless of the type of application. This has been attributed to the fact that they are handling the concentrated pesticide. The advantage to conducting studies in this way is to permit identification of the principal sources of contamination, and to provide more detailed recommendations for personal protective equipment or other mitigation measures. For workers who conduct both tasks, the exposures from mixing–loading and from application are summed.
- ***Duration of activity*** – in addition to measuring the unit exposure for a worker on a daily basis for a particular scenario, exposure and risk assessment requires knowledge and characterization of the frequency and duration of exposure, both on a seasonal and lifetime basis. For example, an individual farmer may apply a pesticide once a year, while a commercial applicator may apply a pesticide for many consecutive days or weeks in a season. Since the exposure associated with mixing–loading is greater than for other activities, it is important to normalize the data with respect to the number of tank fills or kilograms of active ingredient handled.

Table 1.1 illustrates the influence of some of the above noted variables on unit exposure (μg/kg of active ingredient handled) for selected scenarios.

RESIDENTIAL AND INSTITUTIONAL PESTICIDE HANDLERS

Workers who mix, load and apply pesticides commercially in residential and institutional settings are often referred to as pest control operators (PCOs). Their potential for exposure is distinguished from agricultural pesticide handlers in a number of important ways. First, PCOs may handle pesticides every day, and may use the same compound with high frequency. Secondly, many of these workers have limited training, although many countries require workers who 'spray for hire' to be licensed. While they may be required to work under the supervision of a licensed pesticide applicator, they often have no supervisor on site during applications. Thirdly, this population has a relatively high turnover rate, and so exposure duration (years of exposure) may be limited. Finally, the volume of chemicals used for most residential and institutional applications is small when compared to agricultural applications.

Exposure studies of adults who handle pesticides in and around their homes would normally require the same methodologies used for agricultural and commercial applicators. Products that contain only a small proportion of active ingredient (typically 0.5–1.0 wt%) are sold directly to the public for lawn and garden use. Consumers who use these pesticide products generally have no formal training in mixing and application techniques, but are provided label instructions for proper handling.

Table 1.1 Effect of various factors on pesticide exposure. All data are unit exposure values (μg/kg of active ingredient (a.i.) handled), taken from PHED (1992). Values are central tendency measures based on high confidence data sets

Factor[a]	Exposure (μg/kg a.i.)[a]	
Formulation type (M/L)[b]	Dry flowable	163.7
	Granular	13.0
	Liquid	51.1
Protective clothing for M/L[c]	Gloves	51.1
	No gloves	6300.0
Engineering controls	Closed cab	11.0
For ground-boom applicator[d]	Open cab	33.0
Engineering controls for	Closed cab (air blast)	42.0
air-blast applicator[e]	Open cab (air blast)	561.7
Engineering controls for M/L	Open M/L	51.0
(liquids)[f]	Closed M/L	19.0
Application method[g]	Ground boom (open cab)	33.0
	Air blast (open cab)	828.2
	Aerial (fixed-wing and rotary)	9.7

[a] M/L, mixer–loader.
[b] M/L (open system) wearing single layer of clothing, plus gloves.
[c] M/L (open liquid system) wearing single layer of clothing (with and without gloves).
[d] Ground-boom applicator wearing single layer of clothing and gloves.
[e] Air-blast applicator wearing single layer of clothing and gloves.
[f] M/L (liquids) wearing single layer of clothing and gloves.
[g] Applicator wearing single layer of clothing (no gloves).

FAMILIES OF PESTICIDE HANDLERS

Increased attention has been directed at spouses and children of agricultural workers. The US National Institute for Occupational Safety and Health (NIOSH) has prepared a review of children's exposures to environmental health hazards, including pesticides associated with parental occupation (NIOSH, 1995).

The exposure metrics in studies of effects in children exposed as a result of their parent's occupational exposure to pesticides are frequently based on pesticide use records or on questionnaire data, rather than on actual measurements of pesticide exposure in children (Kristensen *et al*., 1996; Garry *et al*., 1996).

The exposure potential for children of agricultural families may be higher than for other child populations, since concentrated formulations of pesticides are stored and/or mixed, although not used in high concentration near the home. Another source of exposure may result from the inadvertent introduction into the home via various 'take-home' pathways. Several studies have also shown that agricultural workers bring contaminated clothing into the home (Chiao-Cheng *et al*., 1989; Clifford and Nies, 1989). Poor hygienic practices such as these

among pesticide formulators have been associated with measurable blood levels of pesticides (chlordecone or kepone) in family members (Cannon *et al*., 1978). Classic organophosphorous (OP) pesticide exposure symptoms in spouses and children of greenhouse workers have been reported (Richter *et al*., 1992).

A study in Washington State found that children living with agricultural workers and in proximity to tree fruit orchards may have more opportunity for exposure than children living in homes without such risk factors (Simcox *et al*., 1995). These findings were supported by an additional study which measured pesticide metabolites in children's urine (Loewenherz *et al*., 1997; Lu *et al*., 2000).

Current attempts to control such exposures are therefore aimed at reducing 'track-in' of pesticides from the outdoors, proper handling and cleaning of work clothing, and possible restrictions on children's activities during or following pesticide applications. In addition, agricultural workers should be cautioned regarding the dangers inherent in the use of acutely toxic pesticides in residential environments.

STUDY DESIGN CONSIDERATIONS

Exposure assessments may be conducted for one of four purposes: hazard evaluation leading to appropriate control efforts, monitoring to ensure compliance with workplace standards, dose–response characterization within the context of epidemiological studies, and estimation of dose or uptake for risk assessments. Assessment strategies and measurement techniques will differ depending on the purpose at hand.

Most studies of pesticide handler exposure have been conducted to obtain an estimate of their exposure when the pesticide is applied according to label directions. This exposure estimate is then used in the risk assessment conducted by regulatory agencies to determine whether the pesticide should be registered. The various safety (uncertainty) factors that are applied in the risk assessment compensate for the fact that some workers may not adhere to the label directions. A second type of study that would be useful is one in which the exposure to workers who are not adhering to the directions on the label would be measured. The impact that this has on the amount of exposure will be discussed later. Current risk assessment procedures require knowledge of the population at risk and the distribution of exposures within this population, as well as information on the toxicity of the compound under evaluation (NAS, 1983). The primary goal of conducting an exposure assessment in support of a registration request is to identify a study population which is representative of the population at risk, and to then conduct a sampling program that characterizes well the central tendency and variability of the exposures which these individuals receive.

In support of this goal, four fundamental study design concerns should be considered.

WORKER STRATIFICATION

Occupational hygienists have traditionally evaluated exposures according to job title or work activity within industrial settings (Corn and Esmen, 1979). Grouping workers in these ways tends to increase the precision of estimated mean exposures. One example of a worker grouping is the homogeneous exposure group, which has been proposed as a basis for reducing sampling burden for making compliance decisions (Hawkins *et al*., 1991). Assignment of workers to such groups can presumably be done *a priori* through knowledge of environmental conditions and time–activity patterns, although a subsequent analysis demonstrated that such classifications are not necessarily accurate (Kromhout *et al*., 1993).

In the case of agricultural worker exposure, researchers have traditionally sub-divided worker populations into such categories as pesticide mixer/loaders, applicators, flaggers and fieldworkers, recognizing that exposure processes are markedly different for these groups. The categorization of workers by van Hemmen (1992), according to work activity, environment and application techniques, represents the most thorough analysis to date of exposure variability within and across mixer/loader and applicator groups.

ROUTES OF EXPOSURE

Respiratory Exposure

Respiratory exposure assessments place great emphasis on the accurate measurement of environmental concentrations in the air breathed by the worker, and normally make simplifying assumptions regarding contact rate (standard respiratory volume) and absorption (100 % absorption).

Dermal Exposure

It is clear that the behavioural component of exposure is very important, and that uptake of chemicals through the skin can exhibit high variability. Since the primary route of exposure in pesticide handlers is through the skin, most work in this field has focused on characterizing deposition of chemicals on the skin and their subsequent absorption into the body. In the absence of actual data on dermal absorption, regulatory agencies may use default values ranging from 1 to 100 %, depending on the chemical characteristics and on the policy of their agency.

SAMPLING STRATEGY SELECTION

The fundamental issues in field study design can be outlined by a series of simple interrogatives: who, where, when, how long, how often and how many? The answers to these questions require substantial prior knowledge of worker populations and working conditions, as well as the toxicological and metabolic

characteristics of the pesticide. An optimal field study protocol would be constructed of an idealized study design, tempered by the practical difficulties inherent in human population studies, as well as financial limitations.

STATISTICAL ANALYSIS

The role of statistical principles in study design has been the subject of extensive discussion within the occupational hygiene community (Nicas *et al*., 1991; Teschke *et al*., 1994). Extensive analysis of air sampling data has led to the generalization that occupational exposures are log-normally distributed, both within and between workers (Rappaport, 1991). Analysis of data sets generated by the North American Pesticide Handlers Exposure Database (PHED) indicates similar distribution patterns (PHED, 1992). Most researchers in this field have concluded that the arithmetic mean exposure is the most appropriate statistic to summarize the central tendency of these types of exposure distributions for individual workers (within-worker), because of its direct relationship to cumulative dose under chronic low-level exposure conditions (Rappaport, 1991). However, the geometric mean exposure of a stratum of workers (between-worker) is the most logical basis from which to calculate exposure percentiles within the group (e.g. 95th, 90th and 50th percentiles). The variance in exposure for both individual workers and groups of workers is best described by the geometric standard deviation. Hawkins *et al*. (1992) have indicated that 6–11 samples may be sufficient to estimate mean exposures, but that larger sample sizes (20 or more) are needed to reliably estimate the variance. Buringh and Lanting (1991) have conducted modeling exercises of exposure, and have also concluded that exposure variance will likely be underestimated if too few samples are taken. In situations where only a few samples can be taken, a conservative (high) estimate of the variance can be employed. The application of statistical principles to study design is an important issue deserving of greater attention within the pesticide exposure assessment community.

PROTECTION OF HUMAN SUBJECTS

A number of governments have established common requirements for the protection of human subjects involved in research studies. These have been codified in the United States through the Code of Federal Regulations (40 CFR 26). In addition to this ‘common rule’, Section 12(a)(2)(P) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) provides that it shall be unlawful for any person to use any pesticide in tests on human beings unless they: (1) are fully informed about the nature of the tests and the potential health consequences, and (2) freely volunteer to participate.

In 1992, the USEPA published its Worker Protection Standard (WPS) Final Rule (USEPA, 1992). This WPS contains provisions intended to inform agricultural employees about the hazards of pesticides, and provides specific protective clothing requirements for pesticide handlers. In conducting any field study, the

investigator must ensure that the applicable provisions of the WPS regulations are being fulfilled. Generally, hazard information must be available for all workers, appropriate protective clothing must be provided, and decontamination sites and emergency assistance must be available. Volunteers for studies must receive adequate training prior to the conduct of the study, and should sign an informed consent document that delineates the potential hazards involved in the study.

PESTICIDE EXPOSURE MONITORING METHODS

The two primary methods for assessing exposure to pesticides are *passive dosimetry*, which is more commonly used, and *biological monitoring*.

Passive dosimetry measures the amount of pesticide that comes into contact with the skin, clothing and the breathing zone of the worker. From the late 1960s until the 1980s, large numbers of worker exposure studies were conducted using passive dosimetry methods which measured the amount of pesticide that came into contact with the skin of the worker and was measured on patches attached to the clothing or from extracts of the clothing. The amount of pesticide that was absorbed into the body was not measured. These studies were reviewed by Wolfe (1976) and Davis (1980). More recent, detailed discussions of these methods are presented in OECD (1997) and USEPA (1998).

PASSIVE DOSIMETRY

Estimation of Respiratory Exposure

Air sampling for occupational exposure to pesticides normally consists of measurement of pesticide concentrations in the worker's breathing zone, with a portable air-sampling pump and a sampling train which includes some type of collection device. The latter device, or sampling media, selected are based on the physical and chemical properties of the compound to be measured. Field workers may be exposed to chemical vapors, solid particulates or water-based aerosols. Examples of sampling media include membrane filters, sorbent tubes, polyurethane foam and charcoal. A discussion of pesticide exposure provides a useful review of methods for respiratory exposure measurement (Nigg *et al.*, 1990).

Estimation of Dermal Exposure

Dermal exposure sampling methods fall into three general categories: surrogate skin techniques, chemical removal techniques and fluorescent tracer techniques (Fenske, 1993a).

Surrogate Skin Techniques

(1) *Patches*. Surrogate skin methods involve placing a collection medium against the skin and subsequently analyzing it for chemical content. The most common

approach has come to be known as the *patch technique*. The latter was developed by US Public Health researchers in Wenatchee, Washington in response to potential acute intoxications among pesticides handlers (Durham and Wolfe, 1962). The technique has since become accepted as a standard internationally (WHO, 1986; USEPA, 1987). In most cases, ten patches are attached to clothing or directly to the skin on the following body regions: chest (1); back (1); upper arms (2); forearms (2); thighs (2); lower legs (2). Chemical loading on the patch (mass per unit area) is then extrapolated to the skin surface area of the appropriate anatomical region (Table 1.2).

The utility of the patch technique for quantitative exposure estimation presupposes that exposure is uniform across each body region; however, under some circumstances, this assumption is probably not valid (Franklin *et al*., 1981; Fenske, 1990). Despite such limitations, patch sampling can serve as a simple and cost-effective method for hazard evaluation and control through comparative studies. For example, a recent study of pesticide applicators in Brazil used patches to demonstrate a significant reduction in exposure due to changes in application equipment (Machado *et al*., 1992). Studies in greenhouses have also used patches to characterize the effects of ventilation (Methner and Fenske, 1994a). Numerous investigators have quantified protective clothing penetration by placing patch samplers inside and outside of the fabric barrier (Gold *et al*., 1982; Nigg *et al*., 1986; Keeble *et al*., 1988; Fenske *et al*., 1990; Nigg *et al*., 1992).

The composition and size of the patches used in dermal exposure studies are important considerations and should be based on the characteristics of the pesticide and the exposure scenario. For sprays, the use of papermaking pulp or

Table 1.2 Surface areas for regions of the adult body and locations of dermal exposure pads that represent these regions (USEPA, 1987)

Body region	Surface area of region (cm^2)	Patch location
Head	1300[a]	Shoulder, back, chest, head[b]
Face	650	Upper chest, head
Back of neck	110	Upper back
Front of neck + 'V' of chest	150	Upper chest, head
Chest/stomach	3550	Chest
Back	3550	Back
Upper arms	2910	Shoulders, upper arms
Forearms	1210	Forearms
Hands	820	Gloves or hand rinse
Thighs	3820	Thighs
Lower legs	2380	Shins
Feet	1310	Use socks

[a] Surface area for the head includes the 650 cm^2 face surface area.
[b] Exposure to the head may be estimated by using the mean of the shoulder, back and chest patches, or by using a head patch attached to the worker's cap.

alpha-cellulose is recommended, because high-quality alpha-cellulose will absorb a considerable amount of material without disintegrating. Preparative chromatography paper is also satisfactory for this purpose. Other appropriate materials include surgical gauze, clothing material and blotter paper. Patches constructed from surgical gauze are suggested for dry formulations such as dusts or granules.

(2) *Body garments*. Whole-body garments have been proposed as a standard method for measuring pesticide exposures for registration purposes (Chester *et al*., 1992; Teschke *et al*., 1994). Whole-body garments generally consist of long underwear garments or coveralls worn next to the skin with no protective layer. Thus, there is potential for penetration of residues through the garments to the skin and a resultant underestimate of exposure. 'Tyvek' coveralls have the advantage of being impermeable and therefore do not underestimate exposure to the skin. The garments typically represent the torso and limbs, but not the head, face, neck, hands and feet. Thus, the principle advantage of this method when compared to the patch technique is that no extrapolation to total surface area is required for the torso.

Body garments, such as gloves, can also be used to sample specific anatomical regions (Davis *et al*., 1983; Fenske *et al*., 1989; Brouwer *et al*., 1992). Some investigators have concluded that garment samplers such as gloves are likely to overestimate exposures (Davis *et al*., 1983), but others have found that glove measurements did not differ significantly from handwash measurements over an extended sampling period (Fenske *et al*., 1989).

No standard materials have been developed for whole-body garment sampling. Studies to date have used absorbent fabric such as cotton or cotton/polyester. Inner garments might consist of white cotton socks (feet), T-shirts (upper torso), briefs (lower torso) and thermal underwear bottoms and tops (the whole body, except hands, feet and head).

A key assumption of all of these techniques is that the patch or garment captures and retains chemicals in a manner similar to that of skin. This assumption, however, has not been validated systematically. Ideally, patches and garments, employed as dermal samplers, would be pre-tested for their ability to absorb and retain the particular chemical under study.

Chemical Removal Techniques

Washing or wiping the skin can remove chemical deposits, and chemical concentrations can be measured (Durham and Wolfe, 1962; Davis, 1980). Wash techniques are generally used only to assess hand exposure, while wiping techniques can, in theory, be applied to other skin surfaces.

(1) *Washes*. Several types of solutions or liquids can be used to collect handwash samples, including various types of aqueous surfactant solutions, and neat isopropanol or ethanol. The physico-chemical properties of the pesticide should guide selection of the rinse solvent, especially the octanol–water partition coefficient

(K_{ow}). The aqueous solutions may be preferred for the more water-soluble pesticides, whereas the organic solvents may provide better results for highly water-insoluble chemicals. The water used for preparing aqueous solutions should be either distilled or deionized if possible. Several commercially available surfactants have been used to prepare hand-rinse solutions ('Sur-Ten', 'Aerosol OT-75', 'Emcol 4500' and 'Nekal WT-27') at concentrations of about 0.01 %.

A wide array of procedures has been used to obtain hand-rinse samples, raising the likelihood that results across studies are probably not comparable. In some cases, test subjects place their hands in a large bowl (2–3 L) containing the rinse solutions, and rub their hands together in a washing motion. In other studies, the liquid is simply poured slowly over the hands, while the test subjects wring their hands in a washing motion, and the solution is collected in a wide-top container. The standard method described by Durham and Wolfe (1962) and Davis (1980) involves the hand placed in a plastic bag with solvent, and shaken for 30 s; the procedure is repeated with a new bag and solvent, and for each hand. The four bags are then pooled to provide a single handwash sample. This method has demonstrated good reproducibility in laboratory studies (Fenske and Lu, 1994). Handwash sampling should be conducted when workers routinely clean their hands, at scheduled breaks (lunch time), and at the end of the work shift. It is also recommended that a wash be conducted just prior to the initiation of the exposure monitoring to remove any pre-existing residues. The major drawback of handwash methods is that they do not necessarily remove the total amount of chemical deposited on the skin. It is remarkable that virtually no validation studies have been conducted for this technique during its nearly 40 years of use in the field. One study of chlorpyrifos skin exposure found that washing one minute after skin contact removed less than 50 % of the amount applied, and that washing one hour after contact removed less than 25 % (Fenske and Lu, 1994).

Removal efficiency was also observed to decrease with decreased skin loadings. These results indicate that data based on such methods may be highly variable, and will require appropriate removal efficiency studies as a part of method validation and quality assurance.

(2) *Wipes*. Skin-wipe methods have also been developed to assess pesticide applicator exposure to the hands, face and neck, but have not yet been validated. One laboratory study has reported that pesticides can be removed from the hands by wiping with relatively high efficiency (Geno *et al*., 1996). However, the wiping was conducted immediately following exposure, and neither the effect of skin residence time, nor the effect of concentration on removal efficiency, was determined. A recent field study of agricultural re-entry workers found that hand-wiping produced 6-fold lower exposure estimates than did hand washing under similar exposure conditions (Fenske *et al*., 1999). Skin wiping appears to be a relatively simple and convenient technique, but in light of these conflicting findings, it does not yet appear to be acceptable as a quantitative exposure assessment method.

Fluorescent Tracer Techniques

Visualization of skin exposure patterns with fluorescent tracers is a relatively new assessment method. Compounds known as fluorescent whitening agents (FWAs) were first demonstrated to be useful tools for characterizing skin deposition of pesticide sprays in the 1980s (Franklin *et al*., 1981; Fenske *et al*., 1985, 1986). Qualitative studies with tracers can provide important information about skin deposition patterns, protective clothing performance and work practices (Fenske, 1988). Exposure evaluations require introduction of the fluorescent tracer into the production system, and subsequent evaluation of workers in a dark area using long-wavelength ultraviolet illumination. The tracer compounds are not visible under normal lighting conditions, and so the patterns of exposure which workers view on their skin can come as quite a surprise.

The use of fluorescent compounds can be coupled with video-imaging analysis to produce exposure estimates over virtually the entire body (Fenske and Birnbaum, 1997). This approach requires pre- and post-exposure images of skin surfaces under long-wavelength ultraviolet illumination, development of a standard curve relating dermal fluorescence to skin-deposited tracer, and chemical residue sampling to quantify the relationship between the tracer and the chemical substance of interest as they are deposited on the skin.

This method was used to evaluate performance of chemical protective clothing during air-blast applications of ethion in citrus orchards (Fenske, 1993b) and demonstrated limitations in garment design. The method has also been used to examine pesticide exposure during greenhouse applications (Methner and Fenske, 1994a, 1994b). Several laboratories have adopted this method, or have developed similar approaches (Roff, 1994; Archibald *et al*., 1995; Bierman *et al*., 1998; Kross *et al*., 1996).

Fluorescent tracer techniques hold the promise of improved accuracy in assessing dermal exposures, as they require no assumptions regarding the distribution of exposure across skin surfaces. However, this approach also has several limitations. First, it requires introduction of the tracer compound into the agricultural spray mix. Secondly, there must be demonstration of a correspondence between pesticide deposition and deposition of the fluorescent compound for the production, such that the fluorescence can indeed be considered a 'tracer' of chemical deposition. Thirdly, range-finding and quality assurance studies may be needed to ensure the accuracy of tracer measurements. Fourthly, when protective clothing is worn by workers, the relative penetration of the pesticide and tracer needs to be characterized. All of these limitations make fluorescent tracer methods technically challenging.

Estimation of Exposure to Children in the Home

Studies of children's exposure to pesticides in residential settings have adopted the general strategy employed in agricultural re-entry monitoring; exposure occurs

post-application and is treated as the product of environmental concentrations and contact rate. Preliminary work in this area has focused on measurement of concentrations in air, on surfaces and in house dust (Hsu *et al*., 1990; Ross *et al*., 1991; Roberts *et al*., 1992; Simcox *et al*., 1995). Several recent studies have focused on children's exposures in agricultural communities (Loewenherz *et al*., 1997; Lu *et al*., 2000).

BIOLOGICAL MONITORING

Biological monitoring of pesticide exposures – the measurement of pesticides or their residues in biological fluids – has been conducted since the early 1950s, but has recently become the subject of renewed interest. Not all pesticides are amenable to biological monitoring. Pesticides that are rapidly absorbed and are neither sequestered nor metabolized to a significant extent, are usually good candidates, as are those for which a quantitative relationship between exposure and urinary metabolites can be established. Minimally, 80–90 % of the applied dose should be excreted in the urine within 5 d. It is difficult for investigators to maintain control over field volunteers for longer periods that this. Ideally, the pharmacokinetic model should demonstrate sufficient excretion in 1–3 d. Biological monitoring should not be considered if the pharmacokinetics in humans are not well characterized; reliance on animal data is insufficient. Biomarkers of effect, such as the measurement of enzyme activity, are not addressed here. Biomarkers of exposure will be the subject of this section, including monitoring of pesticide metabolites in urine and of parent compounds in saliva. Several reviews have been published on the general topic of biological monitoring of pesticides (Wang *et al*., 1989; He, 1993; Woollen, 1993; ICPS, 1996). Details for the conduction of a study that includes biological monitoring are contained in the 1987 USEPA Guideline for applicator exposure monitoring (USEPA, 1987).

Urinary Metabolite Monitoring

Measurement of pesticide metabolites in urine holds the potential for developing a more accurate estimate of internal dose, and is particularly useful when exposure is from multiple routes, oral, as well as respiratory and dermal, as is almost always the case for pesticide-exposed workers. If the total urinary output is collected, until either there are no detectable residues or background levels are reached (usually 48–96 h), the levels can be used to estimate the internal dose. Studies carried out in animals and humans for several pesticides have shown a good correlation between the amount of pesticide applied to the skin and the urinary output (Franklin *et al*., 1983, 1986; Popendorf and Franklin, 1987). However, there are limitations to using this approach. The pharmacokinetics of the pesticide must be known in humans, while those pesticides that are highly volatile are extensively metabolized to numerous minor metabolites or sequestered and are

unlikely to result in an accurate estimate of dose. A complete discussion of this approach is presented in Woollen (1993) and OECD (1997).

Urine sampling may be conducted on a 'spot' basis (e.g. end-of-shift or morning void), or as a complete 24 h sample. This latter sample, while more easily interpretable, is often difficult to obtain from workers. Sample collection is relatively simple and noninvasive, although issues of privacy and confidentiality need to be addressed. Laboratory analysis is generally complex, and therefore expensive. New techniques, such as enzyme-linked immunosorbent assays (ELISAs) show promise as simple and cost-effective analytical methods. Such methods, while useful to indicate exposure, are not suitable for quantifying exposure.

Urinary metabolite measurements from spot samples have sometimes been adjusted by urinary creatinine concentration to account for hydration effects. However, creatinine itself may exhibit substantial intra- and inter-individual variability (Alessio *et al*., 1985; Boeniger *et al*., 1993). Creatinine may be measured by using a colorimetric method known as the *Jaffe Reaction* (Boeniger *et al*., 1993), or a specific-gravity method (Alessio *et al*., 1985). Most clinical laboratories can perform these two analyses at relatively cow cost. Urine specimens, showing physiologically implausible low or high levels of creatinine or specific gravity, should be viewed as suspect and possibly disregarded in a field study.

Salivary Monitoring

Saliva has recently been explored as a practical medium for monitoring exposures to a few environmental chemicals, including pesticides (Nigg and Wade, 1992). Carbaryl concentrations in saliva were found to parallel those in plasma after gavage administration in rats, thus suggesting that saliva may be suitable for monitoring carbaryl exposure (Skalasky *et al*., 1979). Salivary concentration of ethion was measured among pesticide applicators (Nigg *et al*., 1993). Elevated salivary ethion levels were observed in applicators following ethion spraying as compared to controls, and urinary metabolites levels and salivary ethion levels were somewhat correlated ($r = 0.55$), hence leading the authors to conclude that saliva could be used to confirm ethion exposure.

More recently, the feasibility of saliva monitoring for the herbicide atrazine has been studied in a systematic manner by using an animal model (Lu *et al*., 1997a, 1997b). Salivary concentrations of atrazine were found not only highly correlated to plasma levels under varying conditions, but salivary levels represent the portion of atrazine (protein-unbound) in plasma with toxicological significance (Lu *et al*., 1998). This technique was used recently in a study of atrazine-exposed applicators, and levels measured in saliva corresponded well with pesticide-application activities (Denovan *et al*., 2000). Measurements of pesticides in saliva have great potential, due to both the convenience of sample

collection and to the expected reliability of salivary concentration as an indicator of tissue availability.

VALIDATION OF PASSIVE DOSIMETRY

One way to determine the accuracy of passive dosimetry at estimating dose would be to compare estimates derived from dosimetry with those from biological monitoring. Regulatory agencies receive studies conducted using both techniques, and while the following studies were not designed to validate passive dosimetry, they do indicate relatively good concordance between the two techniques.

ATRAZINE

Several studies using either passive dosimetry or biological monitoring, or both methods, were submitted by the registrant to assess exposure to workers in the US corn belt. The details of these studies are found in the USEPA Revised Human Health Risk Assessment (USEPA, 2002) and the USEPA Re-registration Eligibility Document (USEPA, 2003) on atrazine.

In the USA, the principal use of atrazine is in agriculture, and the major exposed workers are handlers who mix, load and apply atrazine to row crops. The passive dosimetry studies reported atrazine residues in terms of the parent compound only. The biological monitoring studies measured chlorotiazenes metabolites. The atrazine absorbed dose was 'back-calculated' from the measured metabolites based on a human excretion study. The results of the studies are reported in Table 1.3 and demonstrate fairly close concordance between the two methodologies.

Table 1.3 Comparison of biomonitoring and passive dosimetry data from atrazine exposure studies using closed mixing/loading systems and closed cabs (USEPA, 2002, 2003)

Exposure scenario	Crop type	Study type	Internal dose (μg/kg of a.i. handled)[a]	90th percentile[b]
Mixing/loading liquid	Corn, sorghum	Passive dosimetry	1.14	21.14
		Biomonitoring	1.28	9.68
Applying liquids with ground-boom application	Corn, sorghum	Passive dosimetry	1.59	64.70
		Biomonitoring	1.34	15.20
Mixing/loading/applying liquids with ground-boom application	Corn, sorghum	Passive dosimetry	2.77	25.10
		Biomonitoring	8.59	37.43

[a] a.i., active ingredient; geometric mean values.

[b] Passive dosimetry results are corrected for 6 % dermal penetration based on a study in humans.

The USEPA concluded that the unit exposures from both the passive and biological monitoring studies were within an order of magnitude of the values in the Pesticide Handler Exposure Database (PHED, 1992).

An additional biomonitoring study with greater than 100 replicates was not used in the risk assessment by USEPA due to the inability to relate results to the quantity of atrazine handled. The atrazine Reregistration Eligibility Document (RED) (USEPA, 2002) reports, however, that from this additional study, the range of daily dose per 'typical' agricultural handler of atrazine in various formulations using a variety of personal protective equipment and clothing and application equipment, confirmed the results of the concurrent biomonitoring and passive dosimetry results.

CHLORPYRIFOS

The USEPA reviewed a number of registrant-submitted studies to assess exposure to handlers applying chlorpyrifos in agricultural and residential settings (USEPA, 2001). The biomonitoring studies measured urinary concentrations of the primary chlorpyrifos metabolite and 'back-calculated' these to the absorbed dose of the parent. The passive dosimetry study results were corrected for 3 % dermal absorption from a human dosing study (Nolan *et al*., 1984). The results of the studies are reported in Table 1.4 and demonstrate fairly close concordance between the two methodologies.

Another study monitored exposure to fifteen homeowners during application of a 'ready-to-use' chlorpyrifos product. The total absorbed dose estimated from the passive dosimetry study ranged from 0.3 to 0.86 mg/kg/d, with a mean of 0.25 ± 0.25 mg/kg/d. Internal dose measured from the biological monitoring study ranged from 0 to 1.9 mg/kg/d, with an arithmetic mean of 0.49 ± 0.59 mg/kg/d and a geometric mean of 0.24 mg/kg/d, indicating relatively good agreement with the passive dosimetry results. It was postulated that ingestion of residues from the hands may have contributed to the higher biomonitoring results.

Another study monitored exposure to five workers using both passive dosimetry and biomonitoring during the application of chlorpyrifos as a termiticide. The mean absorbed chlorpyrifos dose of 4.27 mg/kg/d from the biomonitoring study was comparable to that measured in the passive dosimetry study (3.24 mg/kg/d).

In a third concurrent biomonitoring and passive dosimetry study, fifteen lawn care operators were evaluated. The geometric mean of the internal dose, based on biomonitoring was 0.4 mg/kg/d, and 0.079 mg/kg/d, based on comparable passive dosimetry.

USE OF PHARMACOKINETIC DATA

First, as made evident in the earlier discussion of personal monitoring methods, an accurate assessment of dermal contact exposure is technically challenging. Even whole-body garments worn close to the skin do not provide a complete assessment, as they miss such crucial areas as the neck, face, head and hands.

Table 1.4 Comparison of concurrent biomonitoring and passive dosimetry data[a] from chlorpyrifos exposure studies (USEPA, 2001)

Application method	Internal dose (μg/kg of a.i. handled)[b]
Mixer/loader/applicator using high-pressure hand wand (greenhouse ornamentals); 'Empire 20' formulation	
Biomonitoring	1.15 ± 1.13 ($n = 13$)
Passive dosimetry	3.85 ± 7.7 ($n = 13$)
Mixer/loader of the '50 W' formulation (ground application to low crops)	
Biomonitoring	11.7 ± 6.9 ($n = 6$)
Passive dosimetry	32.5 ± 24.2 ($n = 6$)
Mixer/loader of the '4E' formulation	
Biomonitoring	7.8 ± 10 ($n = 3$)
Passive dosimetry	9.6 ± 16 ($n = 3$)
Applicator – Ground boom open cab ('4E' formulation)	
Biomonitoring	2.1 ± 1.5 ($n = 9$)
Passive dosimetry	2.0 ± 1.4 ($n = 9$)
Mixer/loader – open mixing/loading ('4E' formulation)	
Biomonitoring	10 ± 21 ($n = 15$)
Passive dosimetry	6.2 ± 6.2 ($n = 15$)
Applicator air blast – open cab ('4E' formulation)	
Biomonitoring	13 ± 24 ($n = 15$)
Passive dosimetry	5.9 ± 6.0 ($n = 15$)
Mixer/loader/applicator (15 % granular)	
Biomonitoring	0.73 ± 0.33 ($n = 12$)
Passive dosimetry	0.3 ± 0.36 ($n = 16$)
Aerial mixer/loader of the '4E' formulation	
Biomonitoring	$3.9 + 8.5$ ($n = 13$)
Passive dosimetry	$1.1 + 0.60$ ($n = 15$)

[a] Passive dosimetry results – 3 % dermal and 100 % inhalation oral equivalent.
[b] a.i., active ingredient; mean ± standard deviation (std); n, number of handlers/workers.

Secondly, estimates of dermal absorption are generally based on simple models, with data from animal studies. These models frequently do not account for the time-dependent nature of absorption and can produce significant inaccuracies in dose estimates (Kissel and Fenske, 2000). In particular, existing models do not account for skin uptake following the workshift. Such uptake will occur until an effective washing event occurs. For many workers, this may occur many hours after the end of work (e.g. bath or shower at bedtime or the following morning). Biological monitoring can, in theory, provide a fully integrated estimate of dose, but the pharmacokinetic database required for proper interpretation is substantial (Woolen, 1993).

EXPOSURE MITIGATION MEASURES

Control or mitigation strategies for occupational exposures are normally expressed as a hierarchy, with engineering controls considered to be the first choice, administrative controls the second choice, and personal protection a choice of last resort. This approach has a sound basis in industrial hygiene practice and is outlined explicitly in the US Occupational Safety and Health Act of 1970. For pesticide handlers, however, this approach has not been adopted routinely. Rather, regulatory agencies worldwide have relied heavily on chemical protective clothing to mitigate exposures, and have made the use of such clothing a legal requirement for many compounds (USEPA, 1992; Easter and Nigg, 1992). While this is a sensible interim strategy, it should not be considered an adequate long-term control strategy for worker protection. Further efforts are needed to improve equipment design, application procedures and pesticide formulations to reduce exposures. Additionally, substitution of less hazardous compounds for pest control is the most certain means of preventing health risks for this population.

EXPOSURE STUDIES SUPPORTING REGISTRATION DECISIONS

Most regulatory agencies require worker exposure studies to be submitted by the registrant in support of registration. These studies are conducted using standardized protocols written up in guidance documents. In the United States, for example, the USEPA first produced guidelines for applicator exposure monitoring in 1987 (USEPA, 1987). More recently, agencies in North America and Europe have worked together to produce a harmonized guidance document in this area (Curry *et al*., 1995; OECD, 1997).

In many countries, such studies are to be conducted under standard procedures. For example, in the United States, studies are conducted under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Good Laboratory Practice (GLP) Standards (USEPA, 1989). These standards include well-defined quality assurance and chain-of-custody requirements. Comprehensive information regarding the implementation of GLP to pesticide handler field studies may be found in the work edited by Garner *et al*. (1992). Hawkins *et al*. (1992) have proposed a rationale and framework for the conducting of exposure assessments in support of risk management decisions, and outlined eight ‘good exposure assessment practices’ (GEAPs), essentially an extension of Good Laboratory Practices (GLPs) to field studies.

STUDY DESIGN FACTORS AFFECTING EXPOSURE VARIABILITY

All measurements of exposure will exhibit variability due to imprecision in sampling techniques or analytical procedures, and more importantly, due to the exposure conditions and the natural behaviour of the subject of study. If

variability is random, then the central tendency of the exposure distribution will represent true exposure, and the variance will provide an estimate of the certainty of the exposure value. If, however, some characteristic of the procedure causes measured exposure values to be skewed systematically, then the true value will not be accurately reflected in the central tendency of the data. Such an effect is referred to as *bias* in epidemiology and occupational hygiene (Checkoway *et al.*, 1989).

Pesticide exposure assessment studies conducted under current regulatory guidelines employ a sampling strategy in which a group of workers are recruited for the study and asked to conduct a single episode of pesticide handling, with the requirement that they apply the pesticide according to label directions. It is understood that this approach may reduce the exposure variability that might be seen in an uncontrolled situation. However, in most countries, it is illegal to apply pesticides in a manner that is inconsistent with the instructions on the label. Therefore, it would be inappropriate to require the registrant to conduct studies that did not adhere to label instructions.

SPECIFIC REQUIREMENTS FOR GUIDELINE STUDIES

Label Compliance

These requirements ensure that behaviours prohibited by the label will not occur, with a likely reduction in exposure values and their variability from those seen in an operational study. In particular, new chemical protective clothing is provided and workers are monitored to ensure adherence to its proper use. Field observations of current practice among pesticide handlers do not support these requirements as normal practices. In fact, dermal exposure is believed to result from inconsistent use, contamination and deterioration of chemical protective clothing. Similarly, guideline studies require that the spray application equipment be checked by experienced personnel for correct operation and application rate before the start of work. These actions are likely to eliminate or greatly reduce the incidence of accidents, mechanical repairs, and inadvertent overapplications due to miscalibration, resulting in reduced exposures when compared to normal agricultural practices.

Sample Size

Current guidance documents indicate that sample size should be based on the quality and nature of toxicological information, as well as on practical concerns related to the manageability of the field study; 10 to 15 measurements are recommended as a general guide. Teschke *et al.* (1994) have argued that a random sample of 10 is sufficient to calculate a mean exposure value, but that the variance derived from such a sample cannot be considered reliable. They concluded that for sample sizes less than 30, a conservative estimate of the variance should be employed in determining percentile distributions from exposure data.

There has been significant effort directed towards developing and using probabilistic techniques rather than the deterministic techniques for estimating exposure. The advantage of probabilistic methods is that they allow the full range of the exposure distribution to be characterized and used in the risk assessment. These techniques will help overcome the issues noted above but will require a fairly substantial database to accurately define the worker exposure distribution. A project has been initiated by the International Life Sciences Institute (ILSI) to develop guidelines on the use of probabilistic methods for pesticide worker exposure. A more detailed discussion of probabilistic methods is given in Chapter 8.

Observational Bias

Guideline studies normally last for one day. However, a worker's initial involvement in a study is a time when he or she is acutely aware that performance is under scrutiny. Thus, behaviour on the first day of the study is not likely to be typical. It has been a general observation in occupational hygiene that significant behavioural changes can occur among subjects on subsequent study days, with differences evident in their exposure values (i.e. exposure tends to increase). No current or proposed guidelines have addressed this issue, although it is common practice in many other human population studies to design procedures for controlling this effect.

Motivational Bias

What leads some workers to join pesticide exposure assessment studies when others do not? Since current human subjects guidelines require that participation in such studies must be voluntary, self-selection is a primary factor defining study populations. Several concerns can be raised here. First, financial incentives may be required to induce participation; yet workers who are paid for their participation may feel the need to perform well (i.e. to conduct applications in a careful manner). Secondly, those workers who routinely practice good health and safety may be much more willing to participate than those who feel that their normal behaviour will be viewed critically. Thirdly, in some cases a product undergoing registration review is perceived as highly beneficial among users. If so, they may develop 'loyalty' to the product, and be inclined to do the best they can to see that it garners approval.

Regulatory agencies are cognizant of uncertainties in estimating exposure due to worker motivational and observational biases, as well as the possibility that workers may not strictly adhere to the label directions when they are applying pesticides. As a result, regulators apply safety (uncertainty) factors and use conservative approaches to exposure assessment. For example, both the USEPA and Pest Management Regulatory Agency (PMRA) normalize exposure study data to the maximum application rate and use high end values for the amount of active ingredient used and for

the number of hectares treated to avoid underestimating worker exposure. These inherent conservatisms are discussed in the introductory chapter.

Teschke *et al*. (1994) have examined the available strategies for assessing fungicide exposure in the lumber industry and concluded that representative sampling in an operational setting would provide the most accurate assessment of current exposures, in contrast to following a guideline study approach. The rationale for this conclusion was threefold: (1) such studies were unlikely to represent the full range of conditions that influence exposure, (2) this approach did not allow enumeration of the exposed population, and (3) small numbers of measurements collected under the guideline study were likely to introduce bias into the exposure assessment. It is recognized that actual operational use studies cannot be carried out for pesticides that are not yet registered or when for economic reasons it is not possible to enumerate the total exposed population.

RECOMMENDATIONS FOR IMPROVEMENTS IN THE DESIGN OF GUIDELINE STUDIES

Population Selection

Study participants should have substantial experience with the activity under study, and they should use their own equipment on their own property. It is also important that a single individual should not be used repeatedly as a subject. The practice of using one individual to produce a large number of 'replicates', tolerated under the EPA guidelines, clearly has the effect of artificially reducing between-worker variability in the exposure data. Most workplace exposure studies indicate that between-worker variability is greater than within-worker variability (Hawkins *et al*., 1991; Rappaport, 1991). Regulatory agencies recognize that repeated use of one worker is not ideal and typical practice is to require as many individual workers as possible to be monitored. The OECD guidelines (OECD, 1997) recommend a minimum of ten workers.

Sampling Location

Current guidance documents provide little detail on proper sampling locations. They do, however, indicate that sampling locations must be representative of where the product is to be used. Multiple sites are recommended, but decisions regarding specific locations are left to study investigators. Regulatory agencies typically require approval of study protocols and look for a science-based rationale for site selection. It would be more transparent to outsiders if there were detailed published criteria for selection of sites to ensure that they were representative of sites of concern.

Sampling Season

Relatively little guidance is provided regarding when to sample. One notable effect of season is the proper use of protective clothing. In many parts of the

United States, for example, compliance with label requirements may occur in the spring, fall or winter, but not during the hotter months of summer. The effect of season on exposure has been documented in the timber mill industry, and it has been recommended that studies incorporate a seasonal component into their designs (Teschke *et al*., 1994).

Duration of Measurements

Full work shift samples should be collected whenever possible. Many exposure studies that are included in generic databases were of relatively short duration. For example, the USEPA (1987) guidelines require only that exterior sampling material have measurable levels of residues, resulting in some cases in samples of 10–20 min in duration. More recent guidelines stress the need for longer sampling periods (Chester, 1995; OECD, 1997).

Post-Registration Studies

Pesticide exposure assessment should not end with registration. Once a compound has come into general use, effective product stewardship should include periodic sampling of the exposed population and review of these data by regulatory agencies. Given the wide variety of equipment, application procedures and work practices, it is essential to determine whether in fact the exposure estimates derived from a combination of database information, assumptions, standard factors and controlled exposure trials reflect true exposure distributions in the exposed populations. Risk management decisions based on risk assessments, margins of uncertainty and feasibility considerations represent predictions that adverse health effects will not occur in the exposed population. Follow-up studies would ensure that these predictions were indeed accurate, and would provide a scientific foundation for altering regulations and conducting epidemiological research. The key design components of such post-registration studies would include the following: enumeration of the exposed population, stratification by worker group, random sampling within each strata, and calculation of the mean and variance of exposure within each group such that exposure distribution percentiles can be determined. If sample sizes are small in such studies, it would be necessary to employ conservative estimates of the variance.

CONCLUSIONS AND RECOMMENDATIONS

The field of pesticide exposure assessment is complex and challenging. Exposures occur through multiple routes and are highly variable. Risks associated with pesticide handling differ substantially for the different activities and from those experienced by agricultural re-entry workers. Different assessment and control strategies are needed for each population. Families of pesticide handlers can be

exposed to pesticides and consideration of their children as a vulnerable subpopulation will likely lead to changes in the agricultural workplace that will reduce exposures for workers and families alike. Professional training in the fields of occupational hygiene and exposure assessment is needed to enhance the scientific capabilities of researchers and public health officials responsible for evaluating and controlling pesticide exposures.

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2 Development of Risk-Based Restricted Entry Intervals

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INTRODUCTION

Agricultural workers are potentially exposed to pesticide residues when they enter pesticide-treated fields to perform a variety of hand-labor tasks, such as pruning, thinning, scouting and harvesting, required for the commercial production of agricultural crops. These exposures can occur in different crops throughout the growing season and can be of similar magnitude to exposures of workers who mix, load and apply pesticides (Worgan and Rozario, 1995).

However, the practical options for managing exposures through the use of personal protective equipment or engineering controls are considerably more

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limited for re-entry workers than for mixer/loaders and applicators. Thus, the establishment of *restricted entry intervals* (REIs), which are intended to provide sufficient time for pesticide residues to degrade to a safe level before allowing unprotected workers to enter a field, is the primary method for managing post-application exposures. This chapter briefly summarizes the history and evolution of REIs and discusses the approaches and data necessary to develop risk-based REIs for worker protection.

EVOLUTION OF RESTRICTED ENTRY INTERVALS

Much of what we know about the nature of re-entry exposures and risk comes from our early experience with organophosphate insecticides and the cholinergic poisoning episodes associated with workers contacting treated foliage following their use (Maddy *et al*., 1990). Over the twenty years from the initial introduction of the organophosphate insecticides, detailed analysis of the conditions producing illness of re-entry workers clearly established that foliar contact, and in a few cases possibly inhalation of airborne residues, were responsible for the cholinergic signs that developed. Recognition that foliar residues of pesticides declined with time (Gunther and Blinn, 1955) led to the concept that overexposure and resulting illness could be avoided by preventing workers from re-entering treated fields until residues had dissipated to 'safe' levels.

The practice of establishing pesticide restricted entry intervals (REIs) as a means of reducing worker exposures to pesticide residues on treated foliage was first developed by the state of California. In 1971, California adopted REIs for 16 organophosphate insecticides used on tree and vine fruits and during the subsequent 9 years expanded the list to include 21 organophosphorus compounds. The US Environmental Protection Agency (EPA) followed California's lead in 1974 and established 48-h REIs for 11 organophosphate insecticides and 2 non-organophosphorus compounds as part of 40 CFR 170, the Farmworker Safety Standards. California established 24-h REIs for all Toxicity Category I compounds shortly thereafter.

There are currently two approaches for setting REIs in the United States; one might be considered the past approach and the other the future approach. In the first approach, the EPA's Worker Protection Standards establish interim REIs based only on acute toxicity without any consideration of the crop, the work activity or exposure. Recognizing that risk is a product of toxicity and exposure, this approach is limited in that it only takes into account one-half of the risk equation. Nonetheless, this approach is the basis for most of the REIs currently in place in the USA. In the second approach, the EPA's re-registration process (as outlined in the Worker Protection Standards) requires the development of product, crop and activity-specific REIs based on the risk associated with any given use scenario. The advantage of this approach is that it takes into account both the toxicity and exposure components of the risk equation. Such an approach is the

basis for the development of REIs currently being set under the re-registration process in the USA and should eventually be the basis for all REIs.

For the most part, the REIs currently on US pesticide labels were set based on the requirements of the Worker Protection Standards. If a product has acute toxicity by the dermal route or due to eye or skin irritation that places it in Toxicity Category I, it has a 48-h REI on the product label. Toxicity Category II products receive 24-h and Toxicity Categories III and IV products receive 12-h REIs in accordance with the requirements of the Worker Protection Standards. The deficiency of this approach from a worker protection standpoint is that a high-exposure re-entry activity involving a Toxicity Category III product may present a greater risk than a low-exposure re-entry activity involving a Toxicity Category I product. Using the Worker Protection Standards' approach, the activity with the higher risk in this case, would end up with a shorter REI. This is the reason why the US regulatory process is moving toward the development of risk-based REIs.

The USEPA requires that a registrant specify a proposed REI on the product label. An REI and supporting data are required by the USEPA under 40 CFR 158.390 to support the registration of each end-use product that is in Toxicity Category I. An REI and supporting data are also required if the active ingredient is neurotoxic, teratogenic or oncogenic. Furthermore, an REI is required if adverse effects from worker re-entry are reasonably expected based on knowledge of the anticipated use patterns, work practices, toxicological considerations or epidemiological evidence, and the results of a risk assessment using a margin-of-safety approach (USEPA, 1996c).

DEVELOPMENT OF RISK-BASED REIS

Re-entry exposure monitoring studies were initially performed from an industrial hygiene perspective to characterize the magnitude of exposure by various routes, and from this early work the dermal route was determined to be predominant in most cases (Milby *et al.*, 1964). Such studies proved useful in establishing conditions responsible for worker illness following early re-entry to treated orchards (Popendorf and Spear, 1974). During the late 1960s and early 1970s, health experts found that worker re-entry exposures declined with declining foliar residue levels, and it was on this basis that the USEPA proposed initial guidelines for developing REIs (USEPA, 1984). At about this same time, researchers developed an empirical measure of residue transferability, now known as the *transfer coefficient* (*TC*). Popendorf and Leffingwell (1982) observed that the *TC* differed by type of activity and crop. Zweig *et al.* (1985) and Nigg *et al.* (1984) demonstrated the concept of a *TC* for both row crops and orchard crops. Subsequently, it became apparent that re-entry exposure was a function of degree of body immersion in treated foliage and the efficiency of transfer of the pesticide residue from the treated foliage to a worker's skin (Krieger *et al.*, 1990).

The 'Allowable Exposure Level Method', suggested by Spear (1980) and canonized by Adams (USEPA, 1984), is the basic method currently used in the USA

and Canada to set risk-based REIs. This method is considered to be the most complete approach for establishing risk-based REIs since it directly incorporates data on a pesticide's toxicity, residue dissipation and exposure for a given work activity and crop. REIs are established by determining the time at which the daily exposure for a given work activity and *dislodgeable foliar residue* (*DFR*) level is equal to an established safe level for the pesticidal active ingredient in question. A safe exposure for a given pesticide is estimated by dividing an appropriate toxicological *no observed adverse effect level* (NOAEL) by a safety or uncertainty factor, typically 100 when the NOAEL is from an animal study. However, depending on the severity of the endpoint, a higher factor might be used. If a NOAEL from an oral study is used as the basis for the safe level, an adjustment should be made for the fraction of active ingredient dermally absorbed.

REIs are established by determining the time (T) at which the daily exposure to the active ingredient is equal to an established safe dose level (ADD_{SL}). In the case of first-order dissipation kinetics for the *DFR*, the calculation of the restricted entry time (T) is as follows (Ross and Dong, 1996):

$$\begin{aligned} T &= \{[\ln\ (DFR_T)] - [\ln\ (DFR_0)]\} \times K^{-1} \\ &= \{\ln\ [(ADD_{SL} \times BW)/(TC \times ABS \times ED)] - \ln\ [DFR_0]\} \times K^{-1} \end{aligned} \quad (2.1)$$

where ADD_{SL} is the established safe daily dose (μg/kg/d), BW the body weight (kg), TC the transfer coefficient (cm^2/h), ABS the fraction of dermal absorption (unitless), ED the exposure duration (h/d), DFR_T the dislodgeable foliar residue at restricted entry time T (μg/cm^2), DFR_0 the dislodgeable foliar residue at time 0 (μg/cm^2) and K^{-1} the first-order rate constant from the slope of the *DFR* dissipation curve (h^{-1}).

The empirical measurements that may be used to develop a risk-based REI for a given compound/crop/work activity combination include the following: (1) a *DFR* decay curve, (2) a toxicological NOAEL or risk equivalent dose, and (3) activity-specific exposure data. The latter data specific to the work activity are usually treated generically since the exposures associated with any given re-entry situation are thought to be primarily influenced by physical factors, such as the nature of the work activity, the type of crop and the degree of contact with treated foliage, rather than the chemical-specific properties of the compound involved. Thus, it is assumed that it does not matter if it is compound A or compound B on the leaf surface. The exposure to one compound is assumed to be representative of the exposures to other compounds used in a similar manner. The *TC* for a given work activity is calculated by dividing the daily exposure (μg/h) for that activity by the *DFR* level (μg/cm^2) present on the treated foliage during the performance of the work activity. Likewise, the daily exposure (μg/h) for any *DFR* value can be calculated by multiplying the *DFR* value (μg/cm^2) by the activity-specific *TC* (cm^2/h).

Agricultural re-entry exposure studies are conducted to provide data that can ultimately be used to predict worker exposures during specific re-entry activities,

and indirectly can be used to estimated transfer coefficients (*TC*s) associated with a given work activity. In a typical worker re-entry study, a crop is treated with a pesticide formulation and, at designated intervals after application, workers are sent into the field to conduct specific work tasks (e.g. pruning, thinning, harvesting, etc.). At each re-entry time corresponding to a given work activity, leach punch samples are taken and measurements are made on the amount of pesticide residues in the composited leaf punch samples that can be dislodged from crop foliage, usually with dilute aqueous surfactant solutions. The amount of residues that can be washed off the leaf samples in the laboratory are termed the dislodgeable foliar residue (*DFR*), usually expressed in units of $\mu g/cm^2$ of leaf surface, with the surface area based on either one side of the leaf sample or both sides of the leaf sample. In addition, during these studies, measurements of pesticide residues found on the workers upon their return from the fields are made. The dosimeters typically worn by workers during these exposure studies are gauze pads, partial clothing (e.g. T-shirts) or whole-body dosimeters made from cotton or cotton blend fabrics. During the analysis, the gauze patches retrieved from the workers and representing specific body regions (such as head, hands, upper torso, lower torso, upper arms, forearms, upper legs, lower legs and feet) are extracted and analyzed for the active ingredient of interest. Similarly, in the case of whole-body dosimeters, the latter retrieved from the workers are carefully removed, cut into sections representing the standard body regions, extracted with solvent and analyzed for the active ingredient. Depending on the comprehensiveness of the study and the availability of analytical methods, measurements may also be made of inhalation exposures using personal air pumps and collection media, and total absorbed dose based on levels in urine over a period of days following the exposure (i.e. via biomonitoring measurements).

DATA NEEDED TO SUPPORT RISK-BASED REIS

DISLODGEABLE FOLIAR RESIDUES

The dislodgeable foliar residue (*DFR*), by analogy to other sorts of environmental exposures, is equivalent to a source strength term. Thus, the *DFR* represents the potentially available pesticide residue ($\mu g/cm^2$) with which the worker may come into contact. The current method for sampling dislodgeable foliar residues is derived from the original method developed by Iwata *et al.* (1977), although minor adaptations have been made by other investigators and discussed by Dong *et al.* (1991), ranging from leaf punch to whole-leaf sampling (Worgan and Rozario, 1995). The common extraction method for *DFR*s involves use of mild dilute detergent solutions to recover the residues. In the absence of measured *DFR* data, the application rate divided by the leaf area index of the crop (which is the one-sided surface area of the total foliage of a crop divided by the ground surface area on which the crop is growing) provides a crude estimate of the initial foliar residue on the crop, assuming uniform distribution of residues across the

crop (Bates, 1990). Because only a portion of the total initial residue estimated using the leaf area index approach is actually dislodgeable to workers, *DFR*s calculated using the leaf area index approach probably overestimate actual starting *DFR* levels based on monitoring.

The importance of dislodgeable foliar residues (*DFR*s) for worker re-entry exposures became apparent from the reported illnesses of field workers following treatment of crops with organophosphate pesticides. Because of variability due to sampling methods and, more importantly, differences in residue levels in the field due to uneven application, height differences in residue levels in foliage, etc., dislodgeable residue amounts on the leaves will vary from location to location within the treated field. As with many other types of environmental measurements, pesticide residues on crop foliage for replicate samples in the same field, taken on the same day, tend to follow a log-normal distribution. For example, a large monitoring study of dicofol residues, which considered three crops (oranges, cotton and apples) over a three year period demonstrated that all foliar residue measurements were well-described by a log-normal distribution (Wilkinson, 1993). There are certain factors that may potentially lead to variability in *DFR* levels. These include (1) crosswinds that may result in higher residues on the downwind side of the field than on the upwind side of the field, (2) hotspots where the applicator has turned at the end of the field to start application to a new row, and (3) variability due to overlap of application between rows. Such spatial heterogeneity may not result in a deviation from log-normality in the overall distribution of *DFR*s in the field, but may affect the observed variability of the entire set of *DFR* and worker exposure measurements. That is, all else being equal, a person working in an area of the field containing the high end of the range of *DFR* levels has a greater probability of receiving a higher exposure per unit time than a person working in a part of the field with lower *DFR* levels. Most *DFR* studies currently collect only two composite *DFR* values per re-entry date, and so it is not possible to adequately characterize the spatial distribution of residues in the field based on this limited number of composite samples.

The USEPA guideline OPPTS 875.2100 regarding dislodgeable foliar residue dissipation (USEPA, 1996a) requires that duplicate foliar samples be collected periodically for development of residue dissipation curves. The guidelines indicate that applications be made at the maximum label rate. Samples should be taken as soon as the spray has dried, and then at staggered sampling intervals. The guidelines suggest 1, 2, 5, 7, 14, 21, 28 and 35 d after pesticide application as an example sampling design. For more persistent pesticides, the Agency recommends sampling beyond 35 d. Control or baseline samples should be obtained immediately before pesticide application. In certain cases, *DFR* data from one site may be substituted for *DFR* data at another site when characteristics (e.g. climate and cultivation practices) are essentially identical. Background information on sampling of dislodgeable foliar residues is presented in Gunther *et al.* (1973) and Iwata *et al.* (1977).

From extensive measurements of residues on foliage for a wide variety of pesticides, it was noticed that the levels of residues declined with time. This process may be accounted for by using a dissipation function to describe the *DFR* at any given time (t) after application. Often, it has been assumed that the residue levels on the foliage will follow a monotonically decreasing decay curve which is exponential, namely:

$$\log\ (DFR_t) = \alpha - (\beta t),\ \text{or}\ DFR_t = \exp\ (\alpha - \beta t) \tag{2.2}$$

where α and β are fitted constants. If this fit is adequate (i.e. if R^2 is greater than 0.85), the day-zero *DFR* can be calculated as follows:

$$DFR_0 = \exp\ (\alpha) \tag{2.3}$$

and the half-life ($T_{1/2}$) is:

$$T_{1/2} = (\log\ 0.5)/(-\beta) \tag{2.4}$$

Sometimes, one encounters cases where Equation (2.2) does not yield a good fit to the data. An alternative form that is sometimes seen is a log–log relationship where several compartments exist (e.g. surface of leaf, interior of leaf, etc.) which are each associated with different half-lives:

$$\log\ (DFR_t) = \alpha - \beta\ [\log\ (t)] \tag{2.5}$$

Climatic factors such as humidity and temperature, as well as the specific physicochemical properties of the active ingredient, affect the rates at which the *DFR*s decline for a given crop. The initial *DFR*s tend to be lower on turf (of the order of 0.1 μg/cm^2 when a formulation is applied at slightly less than 2 lb of active ingredient (a.i.) per acre) than on treated crop foliage and tree fruit foliage (Krieger, 1995), probably in part due to the high surface area presented by turf. The type of formulation may affect the magnitude and persistence of residues (Krieger, 1995). Probably, both physical and chemical processes are involved in dissipation of foliar residues. For example, measurements of organophosphate residues verified that a portion of the residues on foliage and dust particles were converted to the more toxic oxygen analogues of the thio-organophorous compounds (van Hemmen *et al*., 1995). While the *DFR* remains an important index for understanding the magnitude of pesticide reservoir in a treated field, significant variations in the *DFR* are observed in field data due to imperfect spraying and incomplete coverage, leading to spatial heterogeneity in the field (van Hemmen *et al*., 1995). Furthermore, losses due to drift may occur outdoors, especially for low-volume and ultra-low-volume spraying techniques, and losses to soil are also likely to occur (van Hemmen *et al*., 1995). Because workers do not typically enter a treated field immediately after application, it is necessary to experimentally determine

the decay rate of the residues on the leaves in order to estimate the *DFR* at the anticipated time of re-entry. This decay rate is affected by many factors, including the chemical nature of the active ingredient, the degree of uptake by the crop, the characteristics of the foliage and climatic effects (sunlight, rain, wind and temperature) on the loss mechanisms for the chemical (Ebeling, 1963; Willis and McDowell, 1987; Bates, 1990). In a departure from the usual assumption of first-order decay, other forms of the dissipation curve occur. The exact nature of the decay curve may vary in form and slope. In many cases, the field data fit a 'biphasic' curve that could reflect the existence of a readily available pool of material and a less available pool of material, the different environmental transformation rates of different isomers of the active ingredient, or other factors. For example, biphasic dissipation has been observed in the case of endosulfan (Whitmyre *et al*., 2004; Antonius *et al*., 1998). In some cases, the decay kinetics may be best described by complex curves. Stamper *et al*. (1979) and Timme *et al*. (1986) have proposed power equations to provide a more accurate description of the decay process (van Hemmen, 1995).

SOIL DISSIPATION DATA

Dermal contact with pesticide-laden soils and particles contribute to exposures of agricultural workers who re-enter fields after pesticide application (Knaak *et al*., 1989). Soil dust also contaminates the surface of foliage in fields and contributes to the total residue reservoir on foliage with which workers may come into contact. Nigg *et al*. (1984) have suggested that differences in soil type and particle size distribution may have an impact on worker exposures. Because of the wide geographic variability in agricultural sites, the soil characteristics from site to site (e.g. particle size distribution, organic content, moisture content, pH, etc.) may vary significantly. Several occurrences of adverse human health effects have been documented due to re-entry exposures of workers to pesticide-contaminated soils, most notably resulting from use of ethyl parathion in citrus groves. These toxic responses resulted from dermal contact with high concentrations of paraoxon, and the toxic breakdown product of ethyl parathion, in soil dust contaminated under and around treated citrus trees (Gunther *et al*., 1976). Soil has been observed as a vehicle for transfer of pesticides to various parts of the body for workers engaged in harvesting tree fruit (Iwata, 1980). Similarly, some of the dermal exposure of strawberry harvesters and weeders to captan has been thought to be related to resuspended contaminated soil dust (Zweig *et al*., 1985). A special case for re-entry exposures to contaminated soils is re-entering drained rice-paddy areas and associated contact with soil containing pesticide residues. Knowledge of soil residue levels, the residue dissipation rate and soil adherence to skin is needed to assess dermal exposure resulting from contaminated soil. Values are available in the literature for soil adherence to use in assessing exposures, based on a number of studies, including, but not limited to, Driver *et al*. (1989), Que Hee *et al*. (1985), Roels *et al*. (1980) and Kissel *et al*. (1996). The USEPA occupational

test guidelines specify that duplicate soil samples be taken within the upper 1 cm of the test plot whenever re-entry worker activities at the treated site will expose workers to large amounts of soil (USEPA, 1996b). Typically, the fine material obtained from the soil samples sieved to less than or equal to 147 μm in diameter is extracted for analysis. Analytical results should be expressed in terms of μg of pesticide residue per g of fine material, also equivalent to parts per million (ppm), and μg of pesticide residue per cm^2 of surface area sampled at the treated site. The guidelines also indicate that soil methods should identify and quantify the parent compound and toxicologically significant metabolites and degradates (USEPA, 1996b). Specific requirements for describing the analytical methods, archiving of soil samples and samples of stable derivatives, and reporting requirements are also provided in the guidelines (USEPA, 1996b). Procedures are available for sampling and extraction of pesticides from fine dry soil particles (Spencer *et al*., 1977), sampling of pesticide residues from damp soils, and analysis of pesticides residues sorbed to surface soils (Smith and Gunther, 1978).

TOXICOLOGICAL ENDPOINT

While not an emphasis of this present chapter, it is important to note that any calculation of a risk-based REI will depend on having an appropriate toxicological benchmark available. These include benchmarks from acute neurotoxicity studies, no observed adverse effect levels (NOAELs) from subchronic studies (e.g. 90 d studies in rats, 21 d dermal studies in rats, rabbits or guinea pigs, and 90 d neurotoxicity studies in rats), developmental/reproductive studies (e.g. NOAELs for fetal effects), NOAELs from chronic studies (e.g. in rats and dogs) and cancer potency factors (or equivalent risk-specific doses) based on carcinogenicity testing, usually in rats and/or mice (Driver and Whitmyre, 1997). NOAELs, established based on studies involving multiple doses where adverse effects are observed in at least the highest dose group, are preferred. In certain cases where a NOAEL cannot be established (e.g. if adverse effects are observed in the lowest dose tested and other studies do not provide a clear NOAEL), the *lowest observed adverse effect level* can be used as the starting point for the toxicological benchmark, reduced by a modifying factor (typically 10, but can range up to 30), although there are uncertainties inherent to this extrapolation (de Raat *et al*., 1997). Toxicological benchmarks are often derived from various laboratory animal studies that have disparate routes of administration and various exposure regimens. A toxicological benchmark should be selected that is most appropriate to the given worker exposure scenario. Ross *et al*. (2001) have pointed out the limitations of toxicological benchmarks derived from currently designed standard studies, which include the following: (1) that the single dose or continuous exposure regimen in some animal studies may not represent the intermittent exposures experienced by field workers, (2) that the use of standard administration routes in many animal studies (e.g. oral) may not directly relate to the predominant exposure route for field workers (i.e. dermal), and (3) that dermal absorption at the

high doses used in dermal toxicity studies may not represent dermal absorption at the low dermal doses experienced by field workers, given the dose-dependence of dermal bioavailability.

ACTIVITY-SPECIFIC EXPOSURE DATA

The two types of data that are generated from studies of worker exposure during re-entry of treated fields are exposure measurements and measurements of dislodgeable foliar residues. The amount of exposure experienced by the worker during specific work activities is a direct result of the amount of pesticide available in the surroundings of the worker, the extent of contact with contaminated foliage and resuspension of deposited residues as a result of field activities (van Hemmen *et al*., 1995). Based on available research, there appears to be a good correlation between worker exposures (dermal and inhalation) and the amount of pesticide on the treated foliage; by far the strongest correlation is for dermal exposures (Worgan and Rozario, 1995). Such exposures may result from direct contact with residues on foliage, penetration of residues through clothing, movement of resuspended particles through or around the seams of clothing and deposition of residues onto skin. Worker activities in treated crops that are wet with dew or recent rainfall may lead to increased levels of dermal exposure.

Inhalation exposures for respirable particles resuspended during worker re-entry activities typically constitute only a very small fraction of total exposure. Nonetheless, inhalation exposures will occur and are dependent on available dust (see 'Soil Dissipation Data' section above) and wind conditions for outdoor exposures. Larger particles that are deposited in the upper respiratory tract and a portion of the respiratory tract which are cleared via mucocilliary transport may be transported to the mouth, where they are swallowed, thus becoming part of the oral dose contribution. The inhalation exposure route may not be measured in worker re-entry studies, because inhalation exposures are typically small in magnitude when compared to dermal exposure. While passive dosimetry using gauze patches to determine potential dermal exposures, as described by Durham and Wolfe (1962), is a relatively crude method, it is still commonly used for assessment of worker re-entry exposures. The use of whole-body dosimeters provides an improved residue collection mechanism that circumvents the need to extrapolate patch data to the entire surface area of a body part (e.g. hand, arm and leg). A limitation of passive dosimeters (gauze patch or whole-body) is that they provide a means of measuring only the amount that impinges on the dosimeter (i.e. the potential dermal exposure). Exposures do not occur uniformly across the body for any re-entry work activity; rather, there are certain areas (e.g. hands, forearms and chest) that receive the largest proportion of total exposure, depending on the crop type and work activity. Hands are typically the most exposed body part, even though the hands comprise only 4 % of the total body surface area. The direct measurement of absorbed dose is the main advantage of biological monitoring when compared to passive dosimetry (Worgan and Rozario, 1995).

Usually, the absorbed dose estimated by using biomonitoring methods is less than that estimated by using passive dosimeters, hand rinses or gloves, as illustrated by Krieger (1995) for strawberry harvesters. However, to be used effectively, the pharmacokinetics of the chemical need to be thoroughly understood (Worgan and Rozario, 1995).

For use of data from passive dosimetry, unless a dermal-route toxicology study is available for the endpoint of interest, it will be necessary to adjust the external exposures represented by the dosimeters for dermal absorption to estimate the absorbed per-event or time-averaged daily dose for the purpose of risk assessment. Dermal absorption of a pesticide contacting the skin is dependent upon the physico-chemical properties of the active ingredient, the state or condition of the skin, the nature of the material contacted (oily versus dry residue) and the concentration of the pesticide residue on the contacted skin (Worgan and Rozario, 1995; USEPA, 1992). The penetration of the skin by a pesticide can be approximated by Fick's law, whereby the flux of pesticide through the skin (μg per cm^2 of skin surface per s) is the product of the diffusion coefficient and the concentration gradient across the skin (Worgan and Rozario, 1995; USEPA, 1992). The time-limiting step in dermal absorption is the diffusion of the chemical across the stratum corneum. For simplification, the dermal absorption of a pesticide is often expressed as a percentage absorption of the total applied dose, usually for a time period of relevance to the re-entry workers, e.g. 8 or 24 h. Specific data for the compound under consideration or a structurally close surrogate chemical are, of course, highly desirable. In the absence of compound-specific data on dermal absorption, Worgan and Rozario (1995) have suggested a possible default value of 30 % based on currently available dermal absorption studies on a wide variety of pesticides in animals. This is supported by the work of Shah *et al*. (1987), in which the dermal penetration of 14 different ^{14}C-labeled pesticides was determined; in this study, the dermal penetration ranged from 0.3 to 30 % per 24-h period. Krieger (1995) has suggested a similar range for dermal absorption of pesticides, i.e. 0.1 to 35 % per 24-h period.

ESTIMATION OF TRANSFER COEFFICIENTS

The transfer coefficient (*TC*) is the conceptual term that links *DFR*s to worker exposures. The transfer coefficient is directly related to the degree of contact between the crop and worker (which is dependent upon the height and density of the crop) and the frequency and nature of worker contact for specific work activities (e.g. weeding, pruning, cutting, sorting/bundling and harvesting) The basis for estimating worker exposure to treated foliage is outlined in the following equation, where the *DFR* value is the estimated value for the actual day of re-entry:

$$\text{Exposure } (\mu\text{g/d}) = DFR\ (\mu\text{g/cm}^2) \times TC\ (\text{cm}^2/\text{h}) \times \text{Task duration (h/d)} \quad (2.6)$$

Thus, worker exposures are calculated based on the dislodgeable foliar residue (*DFR*) and the *TC*. If the *DFR* value is not known for the actual day of re-entry, it may either be interpolated from the dissipation curve or calculated as the 'Day 0' *DFR* multiplied by a dissipation function $D(t)$, or $DFR_0 \times D(t)$. If both exposures and *DFR*s are measured in a given study, then the following equation may be solved for *TC*, normalized per hour of task duration:

$$TC\ (\mathrm{cm}^2/\mathrm{h}) = [\text{Exposure } (\mu\mathrm{g/h})]/[DFR\ (\mu\mathrm{g/cm}^2)] \tag{2.7}$$

The *TC* can be thought of as the surface area of treated foliage contacted by the worker per hour. This is the 'general-case' *TC* calculation. However, there may be some special cases such as with cotton, where the *DFR* is expressed as ppm residues in the cotton bolls (i.e. μg/g of cotton bolls), in which case the *TC* is expressed as g cotton bolls/h. The *TC* is work-task-specific and crop-specific.

Initial attempts to determine a *TC* were based on the *DFR* and dermal exposures. Popendorf and Leffingwell (1982) found a linear relationship between the *DFR* level and dermal exposure to organophosphates over a broad range of values, although the ratio of *DFR* to exposure will vary depending on crop type and work activity (Worgan and Rozario, 1995). The approach by Popendorf and Leffingwell (1982) was further developed by Nigg *et al.* (1984) and Zweig *et al.* (1985). The range of *TC*s observed by these authors is 800 to 61 000 cm^2/h, with the value depending in part on the crop type and work activity. Zweig *et al.* (1985) reported an average *TC* of about 5000 cm^2/h across the studies they examined, based on 'one-sided' *DFR* values. This empirical factor of 5000 cm^2/h was proposed as a generic default for the *TC* for estimating dermal exposure when the dislodgeable foliar residue is known (Zweig *et al.*, 1985; Nigg *et al.*, 1984). However, this single default value does not adequately reflect the potentially wide range of *TC* values across different crops and across different work activities. Krieger *et al.* (1990, 1992) have presented *TC*s varying from about 1000 cm^2/h to as high as 400 000 cm^2/h for various worker re-entry activities involving different crops. An example listing of these *TC* values is provided in Table 2.1, based on field studies conducted by the Worker Health and Safety Branch, California Department of Pesticide Regulation (Worgan and Rozario, 1995).

The wide range of values observed for the *TC*s emphasizes the importance of the nature of the contact of workers with treated plants, and the body parts, motions and intensity of contact involved in specific work tasks. Recently, van Hemmen *et al.* (1995) have attempted to group *TC*s by activity type and contact type, based on Krieger *et al.* (1990, 1992), as follows:

- 'sort and select' activities (hand exposure only, e.g. for mechanical harvesting); $TC = 50$ to 800 cm^2/h.
- 'reach and pick' activities (hand and arm exposure, e.g. for tomato and strawberry); $TC = 500$ to 8000 cm^2/h.

Table 2.1 Example transfer coefficients for various re-entry worker activities[a]

Crop type	Work task	Transfer coefficient (cm^2/h)		Chemical used
		Standard clothing[b]	Plus PPE[b]	
Pole tomatoes	Harvesting	21 000	12 000[c]	Chlorothalonil
		—	17 000[d]	
		—	7 000[e]	
Bush tomatoes	Hand harvesting	9 000	—	Chlorothalonil
	Mechanical harvesting	1 000	—	
Lettuce	Cutting	—	13 000[e]	Folpet
	Packing	—	6 000[e]	
Strawberry	Harvesting	—	6 000[e]	Captan
		—	500[e]	Malathion
		—	2 000[e]	Dicofol
		—	1 000[e]	Naled
Peach	Harvesting	54 000	—	Azinphosmethyl
		24 000	—	Phosmet
Nectarine	Harvesting	7 000	—	Azinphosmethyl
Plum	Thinning	390 000	—	Captan
Apples	Harvesting	—	6 000	Azinphosmethyl
Grapes	Cane-cutting	17 000	—	Captan
	Harvesting	18 000	—	Captan

[a] Adapted from Krieger *et al*. (1990).
[b] Standard work clothing usually included shoes, socks, long pants and long-sleeve shirts; personal protective equipment (PPE) limited to gloves where indicated.
[c] New nylon gloves worn by workers.
[d] Previously used nylon pickers' gloves worn by workers.
[e] Rubber latex gloves worn by workers.

- 'search, reach and pick' activities (hand/upper body exposure, e.g. for tree fruit); $TC = 4000$ to $30\,000\,cm^2$/h.
- 'expose, search, reach and pick' activities (whole body contact, e.g. wine grapes); $TC = 20\,000$ to $140\,000\,cm^2$/h.

RISK MITIGATION

HISTORICAL BACKGROUND

Maddy (1976) has suggested a number of possible mitigation measures to reduce fieldworker exposure to pesticides on treated foliage. The major tool for reducing worker re-entry exposures is to restrict how soon workers may enter treated

fields after application. Although there continues to be interest in other exposure reduction strategies (e.g. the use of protective clothing, product reformulation and reduction in use rate), restricting the time of re-entry by the use of re-entry intervals is still the most widely used approach to prevent excessive exposure. This administrative measure to control worker exposure has evolved over a period of several decades, based on our understanding of the toxicology of pesticides and our ability to quantify worker exposure.

Before any quantitative measures of environmental exposure to pesticides (e.g. foliar and airborne residue levels) were equated with physiological responses (e.g. cholinesterase inhibition or cholinergic signs of overexposure), REIs were determined by committees composed of physicians, toxicologists and chemists (Milby, 1971). By the early 1970s, clear patterns of illness involving particular crops with particular insecticides emerged. Committees composed of experts who had experience with poisoning episodes would consider the circumstances that produced the alleged illness and based on this empirically determined knowledge they would develop a consensus opinion about the necessary REI. Factors considered included crop type (citrus, grape and peache/nectarine re-entry workers experienced the most frequent pesticide-related illnesses) and acute toxicity of the pesticide. The most acutely toxic pesticides were associated with a disproportionate number of illnesses. The resulting REIs were subjective and, thus changed as new information developed or as other factors such as weather or use conditions were considered.

After the first REIs were promulgated in California in 1971, more quantitative efforts were made to estimate REIs. In the 1970s, several investigators used the occurrence of a biological effect, specifically cholinesterase inhibition, as an index of exposures of workers to organophosphates (Worgan and Rozario, 1995). Serat *et al*. (1975) estimated an REI for an organophosphate insecticide based on the rate of dissipation of foliar residues and the rate of inhibition of plasma cholinesterase in peach harvesters exposed to the foliar residues. They proposed that the REIs should be set such that workers exposed each day to foliar residues at that level would not experience more than 30 % inhibition of plasma cholinesterase. Although inhibition of plasma cholinesterase can be an indicator of exposure, it is not as sensitive an indicator as urinary metabolite excretion. In addition, plasma cholinesterase inhibition may be less sensitive to inhibition than red blood cell (RBC) or brain cholinesterase, as observed with some inhibitors. Thus, acute illness could occur before there is significant plasma cholinesterase inhibition. Knaak *et al*. (1980) published a method for determining REIs for cholinesterase inhibitors. This method relied on published human exposure monitoring studies in which peach harvesters (Richards *et al*., 1978; Popendorf *et al*., 1979) or citrus harvesters (Spear *et al*., 1977) exposed to foliage treated with azinphos-methyl, phosalone or parathion were monitored for cholinesterase inhibition. The exposure periods monitored were of relatively short duration (5–10 d) and residues were not maximal, but the RBC cholinesterase levels were determined to have not been significantly inhibited. Knaak *et al*.

(1980, 1989) noted the use of multiple human monitoring studies as the basis for safe levels of foliar *DFR*s for organophosphates.

By utilizing rats, to which were administered different doses of cholinesterase inhibitors by dermal application, Knaak and co-workers established the relative potency of these insecticides for dermal exposure. This rat potency was then related to human safe levels by using proportional equations so that the dermal cholinesterase inhibiting potency of a reference compound could be adjusted to reflect the dermal potency of a compound whose safe level was being determined.

There are several disadvantages to this method of determining re-entry. First, it is limited to cholinesterase inhibitors. Secondly, it is not possible to determine the 'carryover' effect of multiple dermal exposures since the potency data are based on single-dose studies in rats. When humans are exposed for more prolonged periods to organophosphate pesticides during harvest, more significant cholinesterase inhibition does occur (Schneider *et al*., 1992). Finally, re-entry intervals based on such measures should be crop-specific. When re-entry workers are exposed to higher-exposure work tasks such as commonly occur for grapes, frank cases of poisoning have been observed to occur at the 'safe level' established in another crop (O'Malley *et al*., 1991). Popendorf (1992) has provided a thorough analysis of the published data on the decay of organophosphate compounds on foliage, and considerations regarding the kinetics for cholinesterase inhibition, reversion and regeneration. Such an elaborate approach is lacking for pesticides with other mechanisms of action (Worgan and Rozario, 1995).

Of concern is the relative insensitivity of RBC cholinesterase inhibition relative to brain cholinesterase for compounds such as mevinphos and butathiophos. This lack of sensitivity of RBC cholinesterase inhibition for some compounds may allow symptoms of overexposure to develop in the absence of significant change in the exposure endpoint being measured. Cholinesterase inhibition is not as sensitive as a measure of exposure when compared to urinary biomonitoring. The alkyl phosphate urinary metabolites of many organophosphates provide up to a 10-fold better detection of exposure than cholinesterase. Monitoring of the latter is also invasive and it is sometimes difficult to obtain compliance to validate estimates in humans. Cholinesterase monitoring values vary between laboratories using different methods and units of activity. This difference in reporting makes comparison between laboratories very difficult; because of this, California now requires laboratories to report all cholinesterase results in units referable to a common method (Henderson *et al*., 1998).

A method to set REIs would account for the rate of dermal absorption, the rate of foliar contact and the rate of change in cholinesterase. These factors were used in the Popendorf and Leffingwell (1982) 'Unified Field Model' for determining REIs. This model also accounts for the relative rate of *DFR* dissipation, and differences in potency based on the dermal LD_{50} of the pesticide. The Unified Field Model is an elegant technique that takes into account many variables affecting exposure and cholinesterase inhibition as a response. Ultimately, the rate of cholinesterase inhibition, and not a fixed level of inhibition, is the primary

determinant of health status. A rapid 20 % decline of RBC cholinesterase in minutes can be associated with more severe illness than a gradual decline. This model is predicated on a fixed diminution of RBC cholinesterase each day; however, worker re-entry exposures may typically be episodic in nature, hence leading to fluctuations in exposure levels over a given day or week. For all of these reasons, the use of cholinergic symptoms rather than cholinesterase inhibition as the measure of toxicity may be more appropriate.

As mentioned previously, dislodgeable foliar residues (*DFR*s) were used by Zweig *et al*. (1985) and Nigg *et al*. (1984) to develop approximate potential dermal exposures for harvesters using a generic *TC* of 5000 cm^2/h based on one-sided leaf areas. This generic *TC* was empirically determined by dividing the dermal exposure (μg/h) by the *DFR* ($\mu g/cm^2$) (see 'Estimation of Transfer Coefficients' section above). This first generic *TC* ignored the importance of variation due to crop foliage type and the nature of the work tasks. The role of exposure duration in determining the transfer of pesticide residues from treated crops would be found to require further evaluation (Krieger *et al*., 1990). Current thinking indicates that an equilibrium level of pesticide residues may develop on high-contact areas such as hands within an hour or two of exposure, whereby further contact of the affected body parts with foliage lead to no substantial increase in absorbed dose. This phenomenon, while yet to be conclusively demonstrated under controlled conditions, is more likely to occur in theory at high *DFR* levels than at low *DFR* levels.

COMPONENTS OF RISK MITIGATION – CONSIDERATION OF PERSONAL PROTECTIVE EQUIPMENT

A major data gap is the degree of penetration of pesticide residues through clothing following contact with treated crop foliage (Worgan and Rozario, 1995). Under hot and humid work conditions, penetration of pesticide residues through clothing may be enhanced by dampening of the clothing with sweat (Raheel, 1991) and/or plant juices generated by contact or certain work activities. There are a limited number of ways to mitigate the risk associated with worker re-entry exposures. As noted above, the REI, which is the time between pesticide application and worker re-entry contact with treated foliage, is the major mechanism for protecting workers from undue risk. *Personal protective equipment* (PPE) has a major impact on reducing the dermal absorbed dose. Quantitatively, the impact of PPE is typically indicated in a reduced effective transfer coefficient (*TC*). Because of differences in work practices, climatic conditions and the type and construction of clothing, uniform default values for protection factors provided by clothing may have limited value for application in all parts of the world. Most of the protection factor studies have been directed at the mixer/loader/applicator (Worgan and Rozario, 1995). However, for re-entry work situations, the distribution of contamination over various body parts may provide important clues for risk mitigation. For example, Zweig *et al*. (1985) have shown that strawberry

harvesters are mainly exposed on the hands, while weeders in the same crop were mainly exposed on the torso due to resuspension of pesticide-contaminated dust during weeding. In the United States, standard work clothing for re-entry activities such as harvesting may include long-sleeve shirts, long pants, shoes and socks. Additional PPE may include the use of protective gloves; the type of glove material and its permeability to the pesticide of interest may influence hand and overall dermal exposures. For certain worker re-entry activities, such as cotton scouting, coveralls may be worn, which impart additional protection. Dermal exposures for workers are typically calculated by using generic protection factors (*PF*s) that are applied to represent various risk mitigation options (e.g. the use of clothing and personal protective equipment (PPE)). The exact value for these *PF*s is not necessarily consistent across regulatory agencies. For example, the USEPA typically assumes that only a 50 % *PF* (i.e. 50 % reduction in exposures to the skin) is provided by a single layer of clothing. Assumption of a 50 % *PF* for a single layer of clothing is conservative and will likely overstate re-entry exposures for workers based on external passive dosimetry data. This approach is in conflict with the standard assumptions used by the California Department of Pesticide Regulation (DPR), whereby a 90 % *PF* (i.e. a 10-fold reduction in exposure) is assumed to be provided by each layer of clothing (Thongsinthusak *et al*., 1991a,b; DPR, 1995). There is evidence from actual field data on the penetration of various pesticides through various types of clothing that support a 90 % *PF* for work clothing, coveralls or overalls. Similarly, for hand exposures, the USEPA, California DPR, and Health Canada all assume a 90 % *PF* when chemical-resistant gloves are used.

POINT-VALUE VERSUS PROBABILISTIC METHODS OF SETTING REIS

An REI is the minimum time (hours or days) following application of a pesticide at which workers may safely re-enter agricultural fields. The USEPA requires that a registrant specify a proposed REI on the product label. An REI and supporting data are required by the USEPA under 40 CFR 158.390 to support the registration of each end-use product that is in Toxicity Category I, or if the active ingredient is neurotoxic, teratogenic or oncogenic, or if adverse effects from worker re-entry are reasonably anticipated based on anticipated use patterns, work practices, toxicological considerations or epidemiological evidence and the results of a risk analysis based on a margin-of-safety approach (USEPA, 1996c). Development of an REI takes into account the rate of dissipation of a pesticide on a particular crop. The method is work-task-specific, wherein exposure estimates are ultimately based on actual human studies in a crop related to the crop of interest. A number of factors influence re-entry worker exposure and the resulting absorbed dosage. These include, but are not necessarily limited to, the crop type, height and extent of foliage at time of contact, the nature of the work tasks (e.g. thinning, pruning and harvesting), weather conditions, extent of clothing and personal protective equipment (PPE), the decline curve for the *DFR*, spatial heterogeneity of the *DFR*

levels in the treated field and individual worker behavior (see 'Development of Risk-Based REIs' section above).

Because single point-values are typically used for each of the parameters, the restricted entry interval obtained may not necessarily be a central tendency value. Probabilistic modeling can better represent the impact of uncertainties resulting from the variability associated with each of the exposure-related parameters (Whitmyre *et al*., 1992a,b). The probability distribution of the REI (T) would be developed from repetitive iterations of Equation (2.1) (see 'Development of Risk-Based REIs' section above) based on the full ranges and distribution forms of the input parameters (e.g. body weight, *TC*, exposure duration and *DFR*). Deciding which input parameters can be varied over their distributions versus being expressed as a single point-value depends on the extent of data on each of the input parameters. For example, relatively few pesticides currently have the requisite distributional data on *DFR* and K^{-1} values. Ross and Dong (1996) have compared the REIs calculated using the conventional point-value approach with those based on a probabilistic approach. In the three cases studied by Ross and Dong (1996) – greenhouse harvesters, cotton scouts and nectarine/peach pickers – the 95th percentile value obtained using the probabilistic approach was roughly twofold lower than the 'extreme-case' value calculated as a 'worst-case' point estimate, and the 50th percentile value was 1/3 to almost 10-fold lower than the 'typical-case' point estimate. The REI was found to be significantly overpredicted when only a few extreme input parameter values (e.g. low body weight and high deposition) were used.

DATABASE DEVELOPMENT

GENERAL PURPOSE

Unlike the case of mixer/loader/applicator exposures where the Pesticide Handlers Exposure Database (PHED) has been available to obtain normalized exposures to pesticides for specific use scenarios (USEPA, 1995a,b), a completed publicly available database on worker re-entry exposures does not exist at the time of writing. The general concepts of such a database and how the information in it would be applied have been described (Nigg *et al*., 1984). The Agricultural Re-entry Task Force (ARTF), which consists of member companies who manufacture and/or distribute pesticides, is developing a worker re-entry database for use by its member companies. This database will contain generic *TC*s that are representative of specific crop types and worker activities, based on actual field studies sponsored by or purchased by the ARTF. These generic *TC*s can then be used to estimate worker re-entry exposures. This database will allow subsetting of the data by key variables that may affect the level of exposure. The worker re-entry exposure database will contain data on worker dermal and inhalation exposures, dislodgeable foliar residues, site location, meteorological conditions and other ancillary information (e.g. formulation type, method of application, restricted

entry times and conditions). Such a database can provide output reports on *TC*s on a whole-body basis and a body-part-specific basis. The latter would provide guidance for exposure mitigation methods once the body-part-specific *TC*s were used to calculate body-part-specific exposures for the use scenario of interest as applied to a specific formulation of interest.

POSSIBLE DATA SUBSETTING CRITERIA

Examples of the basic data subsetting criteria that would make sense to include in a re-entry exposure database could include crop type, worker activity, growth stage of the crop (related to crop height and degree of foliage), geographic region and level of clothing and protective equipment. Secondary subsetting criteria could include physical state *as applied*, application method used, application rate, season of the year and meteorological conditions (typical versus atypical, wind speed ranges, precipitation, temperature and presence or absence of dew during *DFR* sample collection).

Transfer coefficient data could be subsetted from a re-entry database based on the anticipated label-specified clothing, or the appropriate *TC* data for specific body areas could be adjusted by a generic clothing penetration factor (see 'Components of Risk-Mitigation. . ..' section above). Thus, it would be desirable to adjust or subset the available *TC* data based on the clothing scenario for the worker. For example, if an assessor was interested in a worker exposure scenario whereby the worker was wearing a short-sleeve shirt, one would indicate subsetting of the data based on 'outside' locations to select data for the outside forearm dosimeters. Conversely, data for chest and back exposures for short-sleeve or long-sleeve shirt scenarios would be subsetted for 'inside' or 'under clothing' dosimeter locations. Similarly, if gloves are not used in re-entry, 'outside' dosimeter locations for hand exposure or *TC* data would be selected. For whole-body dosimeter data, specific-body-part *TC* or exposure data are based on partitioning of whole-body dosimeters by body area.

A further description of dosimeter location that could be coded into a re-entry exposure database would be as follows:

- ***Outside dosimeters*** are on the outside of the outermost layer of clothing, in order to represent exposures resulting from contact of bare skin with the treated foliage.
- ***Dosimeters under normal clothing*** are placed in contact with skin (e.g. for forearms) or are outside of the undergarments but under normal clothing (e.g. for chest/back locations).
- ***Dosimeters under protective clothing*** represent those that are worn between normal clothing and protective clothing (e.g. protective coveralls) or under protective clothing but in contact with skin (as in the case of a forearm dosimeter for a worker wearing a short-sleeve shirt and protective coveralls).

- ***Dosimeters under normal and protective clothing*** represent dosimeters under both layers of clothing when protective clothing is worn over normal clothing.

STATISTICAL CONSIDERATIONS

Worker re-entry exposures result from contact with the foliage of treated crops, and should be a function of the *DFR* levels. Although the *DFR* values often follow a log-normal distribution, the associated worker exposures may follow a different distribution form. Worker re-entry exposures for a given day are a function of the contact with the foliage over an entire work day, and at a number of locations in the field. If comparison of exposures to long-term toxicological benchmarks is appropriate, then amortizing exposures over time may bring workers into contact with different levels of *DFR*s in the same field or in different fields. When this sort of environmental averaging occurs, the resulting exposure measurements often follow a normal distribution. However, there may be the case when the empirical distribution of the exposure values approaches or resembles a more complex distribution form.

Worker exposures may be measured by using (1) a whole-body dosimeter cut-up for analysis into body regions, (2) a garment that covers only certain body areas (e.g. a T-shirt), or (3) gauze patches. In the latter case, the amount analyzed is based on the area of the patch. In the first two cases, the area of the dosimeter and the area of the body region it represents are equivalent, and so no correction for surface area is necessary. In the case of gauze patches, the patch area (e.g. $25\,cm^2$) may be considerably less than the surface area of the body part (e.g. $1210\,cm^2$ for forearms). Thus, typically the amount collected (μg) is scaled to the body part based on the ratio of the body part area to the dosimeter area, e.g. in the case of forearms, (μg of residue) $\times$ ($1210\,cm^2$)/($25\,cm^2$). This assumes that the patch exposure is representative of the exposure for the entire body part and that the patch position on the body part is uniform across workers. These two conditions may not always be true. In addition, even if a patch dosimeter was entirely representative of a body-part exposure, one would expect higher variability in the recovered residues on the patches (typically $25\,cm^2$ in area) than for the entire piece of a whole-body dosimeter representing the body part (e.g. $1210\,cm^2$ for forearms). To the extent that patch location is not typical of exposed areas, the resulting calculated exposures could be biased low if they were positioned in 'protected' areas (e.g. near the elbow) or biased high if they represent 'hotspots' of exposure for that body part.

To the extent that the *DFR* values exhibit spatial heterogeneity across a field, heterogeneity of worker exposures may occur. Even if the *DFR* values were spatially uniform across a treated field, personal work habits or personal characteristics may result in between-worker heterogeneity. Climatic or meteorological factors may play a contributing role to the heterogeneity of exposures across studies or across re-entry dates. For example, a morning that starts with dew on the foliage, followed by an afternoon that is hot and humid, may result in higher

exposures than those occurring on a cool dry day. In the final analysis, one cannot predict with confidence that worker-exposure data will follow a particular statistical distribution. However, insights about the possible distributional form of worker re-entry exposure data can provide guidance for selection of the most appropriate tools for screening and analyzing these data and may help guide the development of statistical models that can provide scientifically defensible ways of investigating the effect of particular factors on worker exposures.

A number of standard statistical tools are useful for performing distributional analysis of re-entry exposure-related data. These include probit plots for normal and log-transformed data, as well as tests for normality ('goodness-of-fit' methods). The actual choice of methods would depend on the distributional form of the data. A central point is how the *TC* data from multiple studies may be reasonably combined. Within studies, different *TC*s for different restricted entry times (e.g. Day 0, 1, 3, 7, post-application) have been calculated representing different workers in the study. Hence, one question is whether the *TC*s within a given study vary across restricted entry times. Another question is whether the *TC*s vary across multiple studies for a given restricted entry time. The extent to which statistically significant differences are verified, (1) between studies for all restricted entry times or certain restricted entry times, or (2) within a given study between restricted entry times, determines the nature and extent of data grouping that can be made in a scientifically justifiable way. These questions bring up other grouping and comparison issues, such as whether there are regional and seasonal differences in the *TC*s. Such comparisons can be developed by attempting to group the appropriate data sets from the relevant studies and conducting the appropriate statistical tests for heterogeneity. For mitigation purposes, one can also perform statistical comparisons of patterns of exposure (i.e. distribution of total exposure or *TC*s across specific body regions, such as hands, forearms, legs, etc., for the same clothing and PPE scenarios) to see if there are differences from crop to crop, from one growth stage to another and from one region to another.

Thus, it would be useful for a re-entry database to contain statistical tools for evaluating distributional forms and comparing groups of data in order to identify subsets of sufficient homogeneity to estimate body-part-specific or whole-body *TC*s for given work activity/clothing scenario/crop type/restricted entry time (including all) combinations. A re-entry exposure database could provide for calculation and display of some basic summary statistics for a given selected subset of studies, such as:

- arithmetic mean and standard deviation for each group (appropriate for normally distributed data and for obtaining an average *TC* for estimating long-term exposures);
- geometric mean and standard deviation for each group (appropriate for log-normally distributed data);

- median (i.e. 50th percentile) and range (non-parametric estimators independent of distributional form);
- selected percentiles for *TC*s.

Some of these statistics are dependent on having an adequate sample size, as in the case of percentiles, where the ability to specify the values in the 'tails' of the distribution with a given degree of confidence is largely dependent upon the number of available values. For example, a minimum of 10 observations would be required to specify the 10th and 90th percentiles.

CONCLUSIONS AND RECOMMENDATIONS

Further work needs to be conducted in order to obtain a better understanding of the sources of variability in *DFR*s, *TC*s and re-entry worker exposure data. Stochastic methods may provide a way to better quantify the uncertainties associated with these data.

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3 Residential Post-Application Pesticide Exposure Monitoring

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INTRODUCTION

Pesticides are used both indoors and outdoors at residences, office buildings, schools, hospitals, nursing homes and other public facilities. A wide variety of pesticide products are available 'off the shelf' for use by the homemaker. These

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include preparations to control flies, roaches, ants, spiders and moths within the home, flea and tick sprays and shampoos for pets, insecticides for use on house plants and home gardens, and herbicides, insecticides and fungicides for lawn treatment. Many homeowners and landlords utilize professional pest-control services for routine indoor treatments or lawn care. In many parts of the USA, pre- or post-construction treatment for termite protection is essential. Exclusive of disinfectants and insect repellents, the most common indoor uses are for control of cockroaches and ants (crack and crevice treatment, baits, etc.), flies (sprays, pest strips, etc.), fleas (broadcast sprays and foggers) and rodents (baits). Outdoor uses in addition to lawn and garden care include perimeter and crawl space treatments for termites and crickets.

Pesticides may be periodically introduced into indoor air by direct application (e.g. insect sprays and bombs, disinfectant sprays and room deodorizers). In addition, there are often sources that continually emit vapors into the living space (e.g. continuous evaporation of residues from crack and crevice treatments and emissions from pest-control strips or other devices). Whether used inside the home or office, or outside on the lawn or garden, pesticides accumulate on indoor surfaces, especially in carpet dust, and also in upholstery and in or on children's toys (Lewis *et al*., 1994b, 1999; Simcox *et al*., 1995; Nishioka *et al*., 1996, 1999; Gurunathan *et al*., 1998).

Methods of measurement of pesticide exposures can be separated into two categories: direct and indirect (Bristol *et al*., 1984; Nigg *et al*., 1990). Direct methods measure a pesticide residue in environmental media or on the skin surface before it has entered the body in order to estimate the potential dose. Indirect methods estimate the minimum absorbed dose by measuring residues in excreta, body fluids or tissues after exposure has occurred. Examples of direct methods are those that determine residues in air, water, food and on surfaces. Indirect methods may involve determination of the levels of specific pesticides, their metabolites or biological indicators ('biomarkers'), such as protein- or DNA-adducts, in blood, urine, feces, sputum, sebum, cerumen or adipose tissue. This chapter covers direct measurement methods only.

INDOOR AIR

Pesticides applied indoors vaporize from treated surfaces (e.g. carpets and baseboards) and can be resuspended into air on particles. Many pesticides are semi-volatile (saturation vapor pressures between 10^{-2} kPa and 10^{-8} kPa at 25 °C) and tend to vaporize from treated indoor surfaces. The rate of volatilization will depend on the vapor pressure of the compound, the formulation (solvent, surfactants, microencapsulation, etc.), the ambient and surface temperatures, indoor air movement and exchange rates (ventilation), the type of surface treated and the elapsed time after application. The vapor pressure data for pure pesticides is frequently available and may be of value for assessing the relative importance

of potential respiratory exposures. Good compilations of vapor pressure data and other physical properties of pesticides are *The Pesticide Manual* (Tomlin, 2001), Howard (1991) and Wauchope *et al.* (1992).

For pesticides applied indoors, air concentrations typically drop rapidly for about three days after application as the pesticide is absorbed into furnishings or dissipates to the outdoor air. However, concentrations of the more volatile pesticides may still be 20 to 30 % of those on the day of application after as many as 21 days (Leidy *et al.*, 1993; Lewis *et al.*, 1994b). Air concentrations of pesticides having low volatilities, such as synthetic pyrethroids (many of which have saturation vapor pressures less than 10^{-8} kPa), tend to decline very rapidly after application as the aerosol settles (Koehler and Moye, 1995a). The rate of volatilization of microencapsulated pesticides is much slower than that of emulsifiable concentrates (Jackson and Lewis, 1979; Koehler and Patterson, 1991).

Dissipation rates will also depend on the method of application. Aerosol sprayers have been shown by some to result in higher post-application air levels than compressed air sprayers (Leidy *et al.*, 1993; Koehler and Moye, 1995a). Likewise, broadcast spraying has been shown to result in higher air concentrations than crack and crevice treatments (Fenske and Black, 1989). After an indoor application, air concentrations near the floor (at the breathing level for small children) may be several times higher than those at adult breathing levels (Fenske *et al.*, 1990; Lewis *et al.*, 1994b; Lu and Fenske, 1998). Broadcast and aerosol spray applications of chlorpyrifos [*O*,*O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl)phosphorothioate] have been reported to result in air concentrations that are several times higher at 25 cm above the floor than at 100 cm shortly after application (Fenske *et al.*, 1990). This vertical concentration gradient tends to disappear after several days (Lewis *et al.*, 1994b).

Pesticides applied to the foundation or perimeter of a building may penetrate into interior spaces, resulting in measurable indoor air levels. Lawn and garden pesticides and those applied to the foundation or perimeter of the house may be tracked indoors, where they can accumulate in house dust that may be resuspended into air (Nishioka *et al.*, 1996, 1999; Lewis and Nishioka, 1999). Termiticides, the efficacy of which depends on persistence, continually migrate from the building foundation into the living space by both the air route and 'track-in' of foundation soil (Wright *et al.*, 1994). Warmer weather may also increase volatilization of termiticides from the soil beneath the house, hence resulting in increased contributions to living spaces. Indoor air concentrations of pesticides applied outdoors tend to increase gradually over time after application, while outdoor air levels tend to decrease rapidly due to degradation by sunlight, soil microbes or other environmental factors and dissipation by wind and rain.

The importance of taking the indoor concentrations of pesticides into consideration when doing risk assessments is demonstrated in the study by Lewis *et al.* (2001). The potential inhalation exposure for diazinon following an indoor application was estimated to be up to 0.5 μg/kg/d. For chlorpyrifos, applied to the outside perimeter of the house, the potential inhalation exposure was up to

0.05 μg/kg/d for 12 d after the pesticide application. In addition to the inhalation of the pesticide, there is also dust/dirt tracked-in, and using the US Environmental Protection Agency (EPA) standard for ingestion or inhalation of resuspended dust of 100 mg/d, the maximum amount of diazinon or chlorpyrifos was 0.01 μg/kg/d. The residues found on the children's hands were estimated to give a potential exposure from repeated mouthing of as much as 1–1.5 μg/kg/d. The EPA subchronic acceptable daily intake (RfD) for diazinon of 0.9 μg/kg/d was exceeded in this study. The RfD for chlorpyrifos is 3 μg/kg/d and was not exceeded.

AIR MONITORING METHODS

Except for a few reactive pesticides that may be present in air at relatively high concentrations, integrative sampling (collection over a period of time) is necessary in order to obtain a sufficient quantity of the pesticide for analysis. General air sampling methodology for pesticides has been reviewed in depth in the past (Van Dyk and Visweswariah, 1975; Lewis, 1976), but not in recent years. Pesticide air sampling typically involves the collection of pesticides from air onto a solid sorbent or a combination trap consisting of a particle filter backed up by a sorbent trap. Solvent extraction and chemical analysis by gas chromatography or high performance liquid chromatography are most commonly employed (Hsu *et al*., 1988). General guidelines for monitoring of pesticides in indoor air are given in Chapter 8 of the EPA publication, *Post Application Exposure Guidelines: Series 875-Group B* (USEPA, 1998a). The Organization for Economic Co-operation and Development (OECD) post-application guidelines are currently under development and scheduled for completion in 2005.

Sampling media that have been shown to be efficient for collection of multiclass pesticides from air include the following: polyurethane foam (Bidleman and Olney, 1974; Orgill *et al*., 1976; Lewis *et al*., 1977; Lewis and MacLeod, 1982; Billings and Bidleman, 1980; Wright and Leidy, 1982); Chromosorb 102 (Thomas and Seiber, 1974; Hill and Arnold, 1979; Leidy and Wright, 1991); Amberlite® XAD-2 (Farewell *et al*., 1977; Johnson *et al*., 1977; Lewis and Jackson, 1982; Williams *et al*., 1987; Billings and Bidleman, 1983; Leidy and Wright, 1991; Wright *et al*., 1993; Lu and Fenske, 1998); Amberlite XAD-4 (Woodrow and Seiber, 1978; Jenkins *et al*., 1993); Tenax®-GC or -TA (Billings and Bidleman, 1980, 1983; Lewis and Jackson, 1982; Lewis and MacLeod, 1982; Roinestad *et al*., 1993); Porapak®-R (Lewis and Jackson, 1982); Florisil® (Yule *et al*., 1971; Lewis and Jackson, 1982). These sorbents appear to be about equally efficient for trapping most pesticides. Polyurethane foam (PUF) has enjoyed widespread popularity because it is more convenient to use and has much less resistance to air flow than the granular sorbents. However, a few of the more volatile pesticides may not be collected efficiently on PUF. Granular sorbents may be combined with PUF to extend the range of use to compounds with saturation vapor pressures greater than 10^{-3} kPa (Lewis and Jackson, 1982; Lewis and Gordon, 1996). A useful combination trap with low flow resistance can be assembled by 'sandwiching' 0.6 g of XAD-2 or Tenax-TA between two 22-mm

i.d. × 38-mm long pre-cleaned PUF plugs. This trap may be extracted, vacuum dried and reused without unloading it.

Samples may be collected over 24-h periods or for shorter periods of exposure time, depending upon the design of the study and the sensitivity of the method. When the usual gas or liquid chromatographic analysis procedures are used, air volumes of 0.01 to 1 m^3 are sufficient for occupational exposure levels (i.e. air concentrations of 0.1 to 10 mg/m^3) and 1 to 10 m^3 for non-occupational exposures (i.e. 0.01 to 10 $\mu g/m^3$).

For best exposure estimates, personal air monitors are recommended. These are usually small sorbent traps attached to battery-powered pumps weighing 0.2 to 1.2 kg that can be worn or carried by the subject under study. These systems have been described in the literature (Coker, 1981; Lewis, 1976; Lewis and MacLeod, 1982; Lewis and Wallace, 1989). They should be quiet in operation and easy to wear or transport. Sampling intakes are most often positioned in the 'breathing zone', but are probably best placed where they are not directly influenced by exhaled air. Attachment of the sorbent trap or inlet, oriented downward, to the clothing at the back of the neck is a good practice in most situations. However, the wearing of personal sampling pumps is generally not convenient for most participants in non-occupational studies, especially children. In such cases, the sampler may be kept close by the subject on a table, desk or counter top, during which time it may be operated by means of an AC-to-DC power converter/charger. For monitoring periods longer than 8–12 h, the latter procedure will usually be necessary due to limited battery life. Fixed-position area monitoring (e.g. indoor living space and outdoor patio areas), combined with activity logs, may also be used to estimate exposure. The portable pump-based systems used for personal exposure monitoring are also most convenient for area monitoring, provided that sufficient air volumes can be obtained.

In the United States, methods for several pesticides at occupational levels in air are given in the *National Institute for Occupational Safety and Health* (NIOSH) *Manual of Analytical Methods* (Eller, 1994). The NIOSH methods for organochlorines and organophosphates utilize small traps with a particle filter backed up by two Amberlite® XAD-2 resin beds. They are designed to be used with personal sampling pumps operating at flow rates of 0.2 to 1 L/min for maximum sample volumes of 60 to 240 L. Detection limits are in the 5 ng/m^3 to 600 ng/m^3 range.

There are two American Society for Testing and Materials (ASTM) International methods designed primarily for determining airborne pesticides at non-occupational levels. ASTM Standard D 4861 describes a sampling method and recommended analytical procedures for a broad spectrum of pesticides at concentrations in the 0.001 to 50 $\mu g/m^3$ range (ASTM International, 2003a), while D 4947 is a specific method for chlordane and heptachlor in indoor air (ASTM International, 2003b). D 4861 is based on EPA Compendium Method TO-10A, and is the method used in many large surveys conducted by the EPA (USEPA, 1999a). The sampling device employed by both the ASTM International and EPA methods collects airborne pesticides on a 22-mm o.d. × 76-mm long cylinder (or

'plug') of open-cell, polyurethane foam (PUF), density 0.022 g/cm^3, which may be used with or without a particle filter attached to the inlet. The methods are designed to be used with portable air sampling pumps capable of pulling about 4 L/min of air through the collector for a total sample volume not to exceed 5 to 6 m^3. Depending on the analytical finish, the minimum detection limits of the ASTM International methods range from <1 ng/m^3 to >100 ng/m^3. The World Health Organization (WHO) has published a method that is essentially identical to D 4861 (Lewis, 1993).

Most of the large studies employing the EPA/ASTM International method (e.g. the Non-Occupational Exposure Study (NOPES)) have not used a particle filter; however, one is recommended if pesticides associated with respirable particulate matter are likely to be present. While fine particles (1 μm or smaller) have been shown to be poorly retained by the PUF plug (Kogan *et al*., 1993), simultaneous, collocated sampling of residential indoor air with and without a quartz fiber particle filter showed no significant measurement differences even when sweeping and vacuuming activities took place in the same room (Camann *et al*., 1990).

Except for herbicide salts and a few other nonvolatile compounds, most of the pesticides will either be present in air primarily in the vapor phase or will volatilize from airborne particulate matter readily after collection on a filter (Lewis and Gordon, 1996). Many solid sorbent beds will collect particulate-associated pesticides along with vapors; however, recent studies have shown that some penetration of fine particulate matter (0.1 to 1 μm) may occur with PUF and Florisil (Kogan *et al*., 1993). Fine particles were not found to penetrate XAD-2 beds, presumably due to their retention by static charge. The backup trap should always be used, however, even for collecting nonvolatile pesticides (e.g. when sampling for airborne acid herbicides indoors). For example, as much as 20 % of airborne 2,4-D (2,4-dichlorophenoxyacetic acid), applied as the trimethylamine salt, has been detected on the backup PUF plug, presumably due to hydrolysis to the semivolatile free acid (USEPA, 1999b). The filter and sorbent bed should be extracted together for analysis to provide for better detection and to prevent misinterpretation of the analytical results with respect to original phase distributions.

The low-volume air sampling cartridge for pesticides described in EPA Compendium Method TO-10A and the two aforementioned ASTM International standards have been used in many studies to assess indoor, outdoor and personal respiratory air quality. The PUF cartridge with an open-face particle filter, shown in Figure 3.1, is commercially available from several vendors (e.g. Supelco Model Orbo 1000® and SKC Catalogue No. 226-124). A size-selective inlet for this method has been designed and used in several recent EPA indoor air studies. This is an integral system incorporating either a 2.5 μm or 10 μm inlet based on a design by Marple *et al*. (1987) and can be used at flow rates up to 4 L/min for up to 24 h (Camann *et al*., 1994; Lewis *et al*., 1994a). The glass sampling cartridge and particle filter are contained in a rugged high-density polypropylene

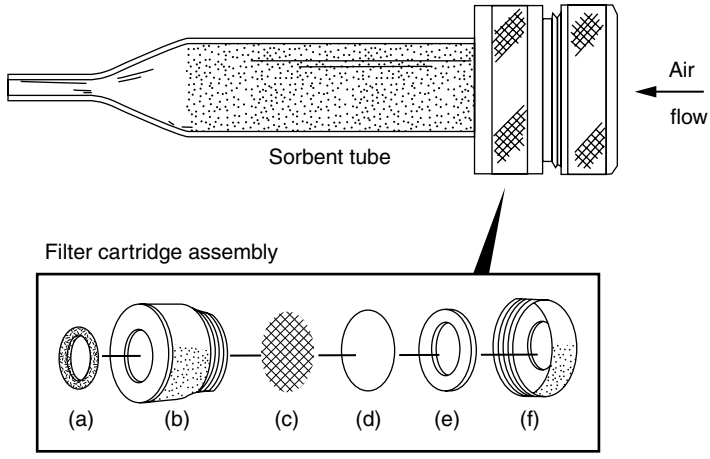

Figure 3.1 Simple air sampling cartridge with open-face particle filter: (a) O-ring seal; (b) filter holder; (c) stainless steel support screen; (d) particle filter; (e) PTFE filter gasket; (f) screw cap

case, which is highly resistant to breakage and tampering. The sampler, shown in Figure 3.2, is commercially available in the United States (URG Model 2500).

SAMPLING CONSIDERATIONS

Air sampling should be conducted within the residence or other building in the optimum locations to estimate human exposure (e.g. family rooms, bedrooms and office spaces). Occupant activity logs may be required in order to obtain accurate estimates of human exposure. The sampler may be conveniently positioned on a table, desk or counter top, during which time it may be operated by means of an AC-to-DC power converter/charger. For monitoring periods longer than eight hours, this will usually be necessary, due to limited battery life and to cover the sleep period. Typically, air intakes (inlets) should be positioned 1 to 2 m above the floor and oriented downward or horizontally to prevent contamination by nonrespirable dustfall. If two or more samplers are to be used for collocated sampling, intakes should be at least 30 cm apart for low-volume samplers (1 to 5 L/min). For determination of vertical air concentration profiles, the first sampler inlet may be placed as low as 10 to 15 cm above the floor.

Indoor residential sampling can be restricted because of available space or by homeowner objections. Equipment noise can also be an issue, depending on the size of the space being monitored, the acoustics of the area and the presence of occupants. Noise from sampling equipment used in residences, schools, offices and other relatively noise-free areas should be limited to 35 dB (1 sones) (ASTM International, 2003e). Many battery-operated portable pumps designed

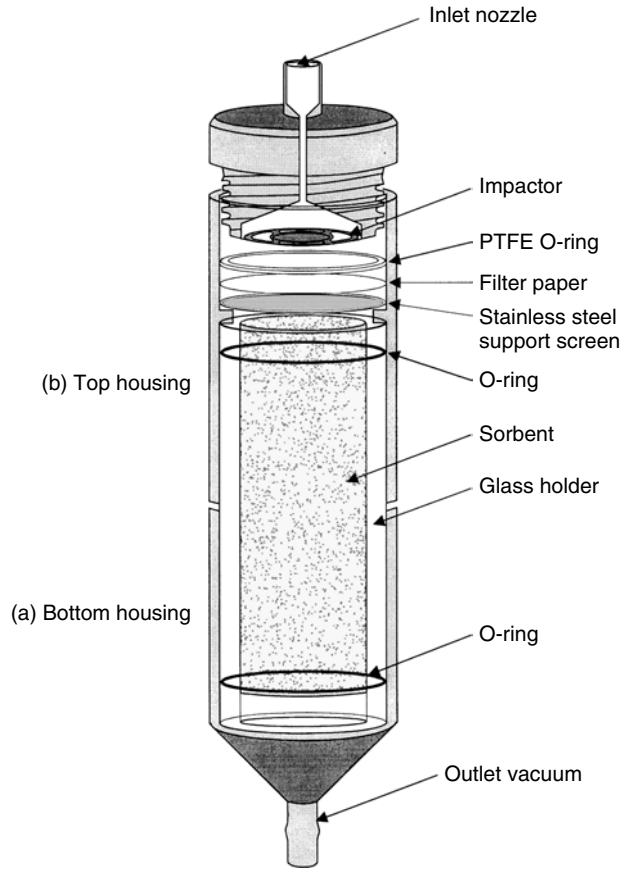

Figure 3.2 Air sampling assembly with size-selective inlet, particle filter and glass sorbent cartridge (note that sorbents other than PUF may be used)

for personal respiratory exposure monitoring are quiet enough for this purpose, although additional acoustic insulation may be required for use in bedrooms and family rooms. Non-industrial workplace monitoring is often more flexible with regard to space and noise restrictions. Security of sampling equipment should be considered in the plan. Typically, samplers that cannot either easily be tampered with, or changed by the homeowner or office worker, are preferable to those with exposed sampling elements or controls. For example, the possibility of electrical power disruption or contamination by onlookers or passersby should be considered in the sampling plan for any effort.

No method should be assumed to perform adequately unless it has been validated (preferably by the user) under the conditions of its intended application. At a minimum, the sampling media should be spiked with the analytes of interest (or

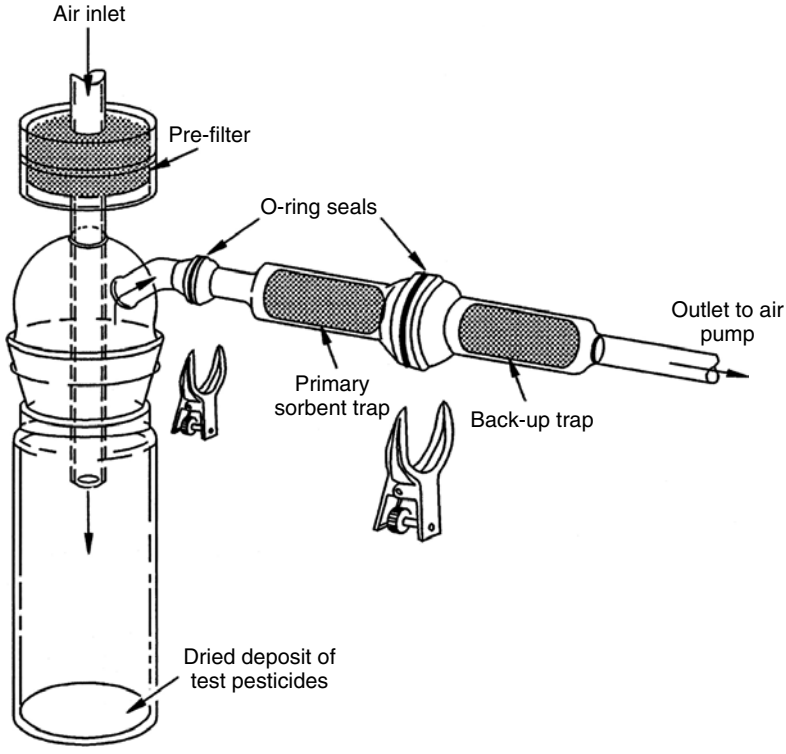

Figure 3.3 Low-volume pesticide vapor generator for determination of air sampling efficiencies

their isotopically labeled analogs) and subjected to the same or greater air flow rates and sampling volumes that will be encountered in the field. This dynamic retention test will usually provide a reasonable estimate of sampling efficiency. It is, of course, better to generate spiked atmospheres to be introduced into the sampler, but this is difficult for less volatile compounds. A simple low-volume vapor generator (Figure 3.3) that can be used for semivolatile pesticides is described in ASTM Standard D 4861 (ASTM International, 2003a). Sorbents and filters also need to be evaluated for storage stability, as well as artifact formation during the sampling process. Sampling media should be chilled or frozen immediately after sampling (including during transit to the laboratory) and be extracted as soon as possible after arrival at the laboratory. Extracts can usually be safely stored for extended periods (e.g. up to a year) at temperatures below $-20\,^{\circ}C$. Sampling media should not be stored for more than 30 d in a freezer unless kept under nitrogen. The use of isotopically labeled internal standards or other surrogates is very helpful in determining losses during storage, as well as during sampling and sample work-up.

At least 10 % of the samples should be quality control samples. Blank sampling cartridges should be taken to the field and returned to the laboratory for analysis; however, they should not be exposed to the air. Spiked sampling media may also be similarly transported as field controls.

INDOOR DISLODGEABLE (TRANSFERABLE) SURFACE RESIDUES

Residues are deposited onto both indoor and outdoor residential surfaces after the application of a pesticide formulation or by transfer from treated areas to non-targeted surfaces (e.g. transfer from lawn to carpet). Dislodgeable residues on exposed outdoor surfaces such as turf are typically short-lived. Indoor surface residues, however, may persist for long periods of time since they are largely shielded from environmental degradation and dissipation in the indoor environment. Human contact with contaminated surfaces may dislodge a portion of these residues, resulting in their transfer to the skin or clothing, where they may be absorbed or ingested through mouthing. Pesticide residues on residential surfaces may present a relatively important exposure route for infants and toddlers, since they spend much of their time on the floor and are more likely to come into intimate contact with yard dirt and lawns.

The parameter dislodgeable (or transferable) residue is defined as 'that part of the residue of a chemical deposited on a solid surface which may be transferred by direct contact to human skin or clothing' (ASTM International, 2003f). This is generally estimated by means of mechanical devices, although bare-skinned or clothed human subjects are sometimes used. Methods for determining dislodgeable residue transfer have included bare hand presses (Lewis *et al*., 1994b), gloved hand presses (Roberts and Camann, 1989), choreographed whole-body dermal contact (Vaccaro and Cranston, 1990; Vaccaro, 1993), whole-body garments combined with an aerobic exercise routine (Ross *et al*., 1990), gauze wipes (Geno *et al*., 1996; Lu and Fenske, 1998), and various sampling media that are pressed, dragged or rolled across the surface at known contact pressures and rates or times (Hsu *et al*., 1990; Ross *et al*., 1991; Vaccaro and Cranston, 1990; Lioy *et al*., 1993; Edwards and Lioy, 1999).

MECHANICAL SAMPLING METHODS

The three primary devices used in recent years to estimate skin-transferable pesticide residues from carpets and floors are the Polyurethane Foam (PUF) Roller (Hsu *et al*., 1990; Lewis *et al*., 1994b; ASTM International, 2003f), the Drag Sled (Vaccaro and Cranston, 1990), and the California Roller (Ross *et al*., 1991). These three methods have been rigorously evaluated and subjected to 'round-robin' testing (USEPA, 1997a) for inclusion in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Subdivision K guidelines (USEPA, 1998a).

PUF Roller

The PUF roller sampler was designed to measure dislodgeable residues that may be transferred to a small child's skin from contact with floor surfaces. This device is the basis of the ASTM Standard Practice D 6333. Dislodgeable pesticide residues are collected by transfer to an annular ring of medium density (0.029 g/cm^3) open-cell, polyether-type polyurethane foam (8.9 cm o.d. × 8 cm wide), which is rolled across the floor at a constant speed and applied pressure. The PUF sampling ring is slipped over a cylindrical metal axle that functions as the front wheel of the PUF roller apparatus. The apparatus is typically constructed of aluminum and consists of a frame with two permanent rear wheels and the detachable axle cylinder on the front (Figure 3.4). Weights are attached to the roller frame to apply the desired downward force on the PUF roller ring (sampling pressure). A total weight of 3.9 kg provides a sampling pressure of 8000 Pa, corresponding approximately to that of a 9 kg child crawling (6900 Pa) or walking (8600 Pa). A handle is connected at the rear of the roller frame to push or pull the device across the floor surface with the aid of a template or similar measuring device to identify the area to be sampled. The axle cylinder is fitted with a clean PUF ring, and the roller is pushed at a constant rate of approximately 10 cm/s over a distance of 1.0 m and then immediately pulled in the reverse direction back over the same sampling area at the same rate of speed, ending at the original starting position (in some cases, however, the PUF ring is rolled in one direction only.) The total surface area sampled is 800 cm^2. At the conclusion of the traverse, the PUF ring is removed from the detached axle cylinder and placed in a sealed container for transport to the laboratory for analysis.

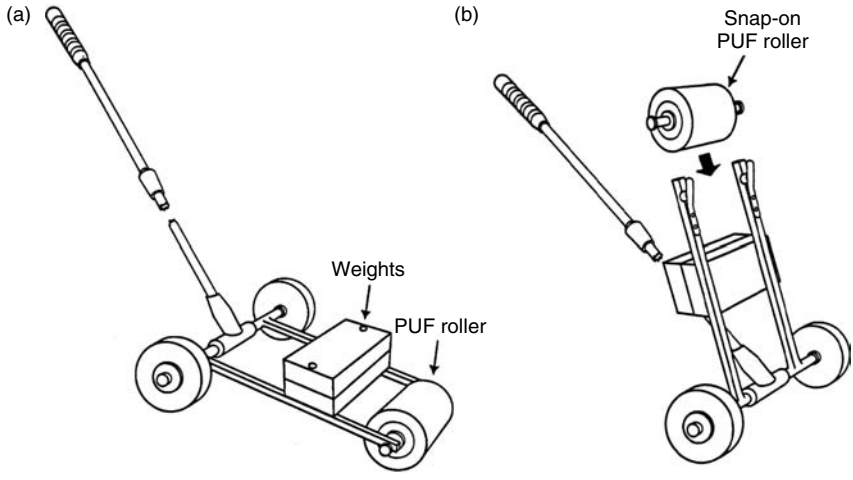

Figure 3.4 PUF roller: (a) in position for sampling; (b) axle cylinder/frame assembly

The effects of varying contact pressure, traverse speed and traverse distance on the sampling efficiency of the PUF roller have been evaluated (USEPA, 1996a). The increase in the amount of transferred chlorpyrifos (applied by broadcast spray to nylon plush carpeting as Dursban® LO) was found to be proportional to the contact pressure over the tested range of 2400 to 18 000 Pa. The amount transferred increased from $8.0 \pm 1.4\,\mu g$ at 2400 Pa to $26.8 \pm 5.2\,\mu g$ at 7300 Pa and to $46.6 \pm 17.8\,\mu g$ at 18 000 Pa. Little or no effect of traverse speed was observed. Only slightly less was picked up at 30 cm/s than at the normal sampling speed of 10 cm/s ($21.4 \pm 5.8\,\mu g$ versus $26.8 \pm 5.2\,\mu g$). The length of the carpet strip traversed by the PUF roller was varied from 0 cm (stationary for 3 s) to 25 cm, 1.0 m, 3.0 m and 10.0 m to evaluate its effect on transfer. The amount of transfer to the PUF ring increased very uniformly with distance traversed over the first 3 m of carpet, but the rate of transfer decreased thereafter. The 3 s stationary contact resulted in the transfer of $1.3\,\mu g$ of chlorpyrifos from the nylon plush carpet to the PUF. The amounts collected were $3.4\,\mu g$ over 25 cm, $12.7\,\mu g$ over 1 m, $58.3\,\mu g$ over 3 m, and $80.3\,\mu g$ over 10 m. However, multiple passes over the same 1-m strip of treated carpet showed no significant change in the transfer rate for up to 20 passes.

The PUF roller is usually used with dry sampling media. Hsu *et al*. (1990, 1993) reported the transfer efficiency (ratio of the transfer rate to the pesticide deposition rate) of a broad spectrum of dried pesticide residues (organochlorine, organophosphate, carbamate, phenolic and pyrethroid) from spiked aluminum foil to the dry PUF roller to be similar to that for a dry hand press (heel only) (PUF, mean 7.5 %; hand, mean 9.2 %). However, subsequent laboratory tests and field studies have shown that the dry PUF roller collects two to three times more dislodgeable pesticide residues from nylon plush carpets than the dry hand (palm only) pressed 10 times at 7300 Pa along an adjacent 1 m section of carpet (USEPA, 1996a). Moistening the PUF ring with water or other aqueous media has been shown to increase transfer rates several-fold, but results in analytical difficulties and may substantially increase measurement variability when the targeted analytes are extracted with nonpolar solvents (USEPA, 1996a). A 'sweat simulator' solution composed of a 70:30 aqueous phosphate buffer:acetonitrile mixture has been used successfully to collect dislodgeable residues of several pesticides (primarily acid herbicides) from carpet and turf (Nishioka *et al*., 1996, 1999).

Drag Sled

The drag sled surface sampler (Figure 3.5) is a simple device constructed of a 7.6-cm × 7.6-cm × 1.9-cm thick block of wood or other material, which is used to hold down a 10-cm × 10-cm piece of denim cloth sampling medium as it is dragged across the floor. The bottom of the block is covered with solvent-rinsed aluminum foil and the denim patch is placed over the foil. Staples or push-pins are typically used to secure the sampling medium to the block. A 3.6 kg weight is centered on top of the block to provide a downward pressure of 4500 Pa. The

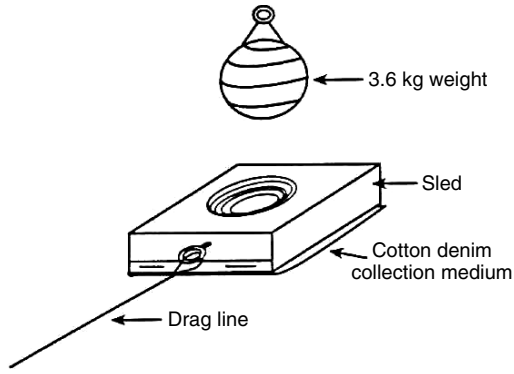

Figure 3.5 Drag sled device

sled is pulled at 8 to 12 cm/s along a 1.2 m path by means of an attached cord (e.g. a 60-cm to 90-cm nylon fishing line), sampling 925 cm^2 of floor area.

Increasing the contact pressure exerted by the drag sled on a treated nylon plush carpet had relatively little effect on the transfer of chlorpyrifos residues to the cloth sampling medium (36 ± 13 μg at 2100 Pa, to 56 ± 28 μg at 4500 Pa, and to 43 ± 10 μg at 15 600 Pa). Increasing the traverse speed of the drag sled reduced the amount of chlorpyrifos transferred from 56 ± 28 μg at 7 cm/s to 31 ± 21 μg at 20 cm/s. The amount of transfer increased relatively uniformly with traverse distances up to 10 m. Static (3 s) transfer of chlorpyrifos to the sled averaged 0.6 μg, or about half of that transferred to the PUF roller. The mean amounts transferred to the drag sled cloth increased from 4.2 μg over the first 17 cm traversed, to 8.6 μg over 92 cm, 124 μg over 3 m, and 302 μg over 10 m.

California Roller

The California roller is basically a large, weighted 'rolling pin' that is used to press a piece of polyester–cotton percale bedding material onto the floor to collect residues. The roller consists of a large (13-cm o.d. × 63-cm long) cylinder constructed from poly(vinyl chloride) (PVC) pipe, covered with a foam cushion (1-cm thick × 51-cm long), and fitted with end caps and handles (Figure 3.6(a)). The roller is weighted with 11.4 kg of steel shot ballast placed inside the cylinder to provide a total weight of 14.5 kg. The applied pressure is approximately 2300 Pa. The sampling medium is a 43-cm × 43-cm square piece of bed sheet made from 50 % combed cotton and 50 % polyester, 180 thread count. When sampling, the bed sheet is placed on the floor surface, covered with a plastic sheet, and the roller is rolled over it ten times in each direction (20 passes).

It is important that the operator does not exert any additional downward force when moving the roller back and forth over the sample medium. This has proven to be a difficult task to accomplish by hand. Therefore, a sled assembly

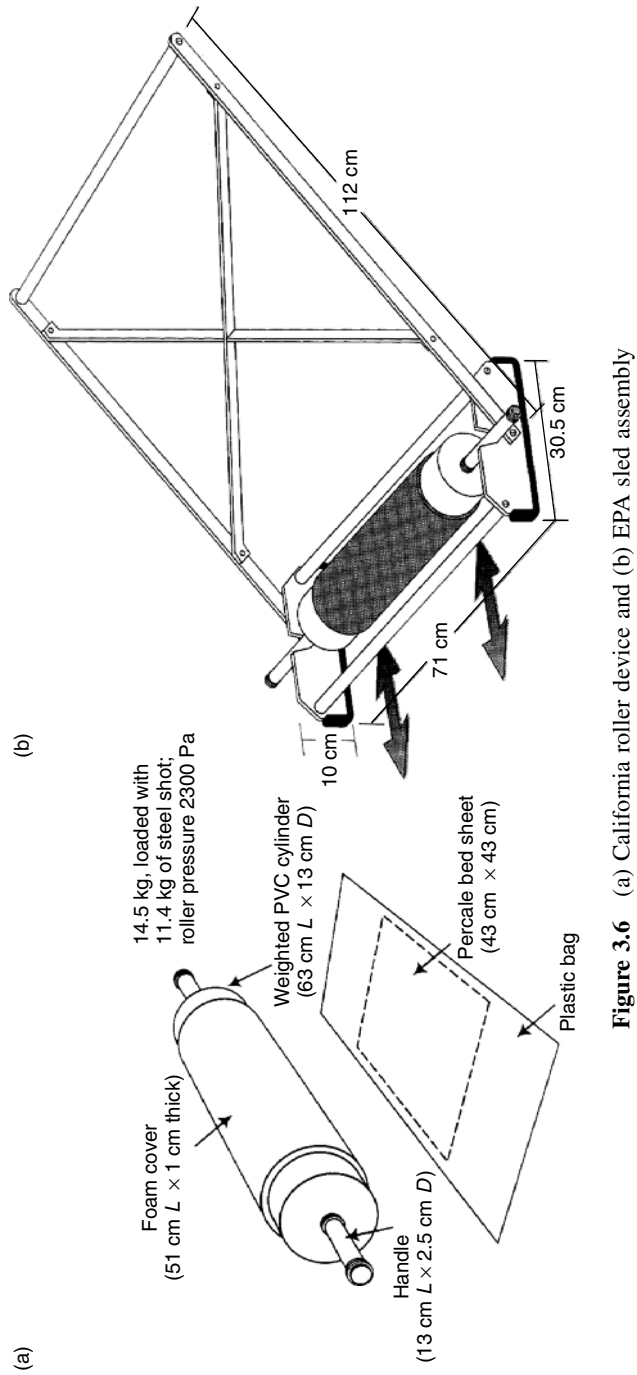

Figure 3.6 (a) California roller device and (b) EPA sled assembly

(Figure 3.6(b)) has been designed by the EPA that will allow the roller to roll smoothly and with uniform pressure across the sampling area (USEPA, 1997a). While the use of the sled is a marked improvement over hand operation, the framework of the assembly is large and can be difficult to maneuver in home environments. In addition, the heavy weight of the apparatus makes it difficult to lift, especially when the technician is a small person.

Problems have also been encountered with maintaining the position of the collection medium during sampling. The bed sheet has been found to migrate significantly as the heavy roller moves across it unless it was firmly anchored to the carpet (e.g. by pinning to the carpet backing). Under low-humidity conditions, the plastic sheet covering the bed sheet has tended to adhere by static charge to the roller, so necessitating the use of heavier plastic sheeting.

METHODS COMPARISONS

Amounts Transferred

The mode of sampling is different for each method. The PUF roller picks up residues by rolling contact of the pliable foam sampling medium with the floor surface; the drag sled operates through a wiping motion with a thick cotton fabric, while the California roller presses a thin cloth sheet against the surface. The characteristics of the three methods and their comparison with adult human hand presses are summarized in Table 3.1. All three mechanical methods have been subjected to comparative performance evaluation for collection of formulated pesticide residues from carpets and vinyl flooring. The performance of each method has also been compared to human hand presses (USEPA, 1996a, 2000a). No biases have been observed with respect to the direction of traverse when the samplers were used on plush or level-loop nylon carpets. However, for carpets that do not have uniform and level surfaces, some directional bias may be encountered, especially in the case of the drag sled.

Parallel comparisons of the PUF roller and drag sled with human hand presses (10 successive presses (Table 3.2), palm only at 6900 Pa, onto adjacent areas of carpet) showed that the drag sled picked up 6 to 11 times (mean 7.7, $n = 8$) as much chlorpyrifos, methoprene (isopropyl 11-methoxy-3,7,11-trimethyldodeca-*trans*-2,*trans*-4-dienoate) and piperonyl butoxide (2[2-butoxyethoxy]ethyl-6-propyl piperonyl ether) residues from nylon plush carpet as the dry hand press, while one pass with the PUF roller removed 1.5 to 4.9 times (mean 2.9, $n = 8$) as much as the hand (USEPA, 1996a). Ratios were similar for new vinyl flooring (drag sled: mean 7.1, $n = 9$; PUF roller: mean 3.6, $n = 9$), but transfer rates were higher by several orders of magnitude for the vinyl flooring. A recent comparison using water-moistened media reported that chlorpyrifos transfers for nylon plush carpet were similar for the drag sled and hand press (performed in the same manner) and that the PUF roller picked up 33–36 times as much as the skin (Lu and Fenske, 1999).

Table 3.1 Characteristics of the three principal dislodgeable residue methods and hand press

Property	California roller	Drag sled	PUF roller	Human hand press
Contact motion	Press	Drag	Roll	Press
Sampling medium (material)	Percale bed sheet (50 % cotton, 50 % polyester)	Denim weave cloth (predominantly cotton)	Polyurethane foam cylinder (open-cell, polyether type, 0.029 g/cm^3)	Skin on palm of hand
	43 cm × 43 cm	10 cm × 10 cm	8.9 cm o.d. × 7.6 cm long	
Total area of exposed medium	1849 cm^2	57.8 cm^2	212 cm^2	64 cm^2
Pressure exerted through sampling medium	2300 Pa	5900 Pa	8000 Pa	6900 Pa
Sampled carpet area	1849 cm^2	930 cm^2	760 cm^2	640 cm^2 (10 presses)
Number of passes over sampled carpet area	20	1	2	1
Sampling speed over carpet	20 cm/s	10 cm/s	10 cm/s	1 press/s

Table 3.2 Comparison of transfer of fresh dried formulated pesticide residues from floor covering by drag sled, PUF roller and human hand presses

Floor covering	Pesticide	Transfer rate, $\overline{x} \pm s$ (ng/cm^2)		
		Drag sled[a] ($n = 6$)	PUF roller[a] ($n = 6$)	Hand presses[b] ($n = 18$)
Plush carpet (used)[c]	Chlorpyrifos	5.6 ± 3.2	1.8 ± 1.0	—
	Piperonyl butoxide	7.0 ± 4.0	2.2 ± 1.1	—
	Pyrethrin I	1.0 ± 0.9	0.2 ± 0.1	—
Plush carpet (used)[d]	Chlorpyrifos[c]	9.2 ± 3.7	2.9 ± 0.3	1.3 ± 0.8
	Methoprene	2.5 ± 0.7	0.8 ± 0.5	0.3 ± 0.2
	Piperonyl butoxide	128 ± 52	58 ± 12	17 ± 10
	Pyrethrin I	38 ± 22	16 ± 3	—
Sheet vinyl (new)	Chlorpyrifos	1890 ± 1430	780 ± 440	250 ± 200
	Piperonyl butoxide	1660 ± 990	630 ± 390	300 ± 210
	Pyrethrin I	192 ± 49	116 ± 68	39 ± 42

[a] Mean and standard deviation of transfer rates for single passes over floor covering surface using dry sampling media (contact areas of 930 cm^2 for drag sled and 760 cm^2 for PUF roller).
[b] Mean and standard deviation of transfer rates for 10 consecutive dry palm-only hand presses contacting 640 cm^2.
[c] Sampled 0 to 2 d after application.
[d] Sampled 6 to 8 d after application.

Sampling Precision

In 1997, the EPA conducted a 'round-robin' evaluation of the PUF roller, drag sled and California roller. The 'round-robin' tests were carried out by six experienced technicians, three of whom were employed by pesticide registrants and three by contractors who conduct pre- and post-application monitoring studies for registrants. Seven separate tests were performed, each using a formulation containing three target pesticides (chlorpyrifos, natural pyrethrins and piperonyl butoxide) applied by broadcast spray to new plush nylon carpeting. Each participant independently collected three replicate samples by using the PUF roller, the California roller, and the drag sled methods. Samples were collected in a randomized manner from various areas of the treated carpet and along both dimensions of the carpet. Sampling precision was found to be high for measurements by all three methods (Table 3.3). The overall results (mean % relative standard deviation (RSD), $n = 21$) revealed the drag sled to have the best sampling precision (25.4 %), followed by the California roller (30.7 %) and then the PUF roller (37.9 %). The mean transfer efficiency (ratio of the transfer rate to the pesticide deposition rate) was highest for the California roller (5.0 %), followed by the drag sled (2.1 %) and the PUF roller (1.7 %). The mean transfer efficiencies observed in this study were substantially higher than those reported in earlier studies of this type.

Table 3.3 'Round-robin' comparison of three dislodgeable residue methods (mean % transfer and % standard deviation of 21 replicates)[a]

Sampler	Chlorpyrifos	Pyrethrin I	Piperonyl butoxide	Overall average
PUF roller	1.4 % (28.3 %)	1.9 % (45.7 %)	1.8 % (39.7 %)	1.7 % (37.9 %)
Drag sled	1.9 % (23.5 %)	2.1 % (26.8 %)	2.3 % (25.4 %)	2.1 % (25.4 %)
California roller	4.2 % (27.1 %)	4.2 % (35.2 %)	6.6 % (29.7 %)	5.0 % (30.7 %)

[a]Mean % transfer and relative standard deviation (in parentheses) for seven tests, with three replicates per test.

Ease of Use

Information relating to ease of use, simplicity, time requirements and other criteria for each of the test methods was also obtained during the 'round-robin' test by means of written subjective evaluations and critique by each volunteer. The drag sled and PUF roller methods were rated high in overall ease of use, while the California roller was rated low.

Of the three techniques, the PUF roller most closely approximates the human hand press in the quantities of pesticide residues collected per unit area of surface sampled, although it collects several times as much as the dry palm of the hand. The pliable foam sampling material, especially when wetted, more closely resembles human skin than the cotton fabrics used by the drag sled and California roller. However, since the transfer rates for the latter two devices are much higher than that of the PUF roller, they are less prone to yield non-detectable results in the field.

HAND-HELD WIPE SAMPLING

Surface wipes are appropriate for determining dislodgeable residues from bare floors and other hard residential surfaces (e.g. table and counter tops, window sills, cabinets, appliances, dinnerware and children's toys). However, residential wipe sampling techniques for pesticides have not yet been standardized and are unlikely to accurately reflect the transferability of surface residues to skin. Typically, cotton gauze or filter materials, dry or wetted with solvents, held in the hand are used to wipe a defined area (McArthur, 1992). Surface areas of 100 to 1000 cm^2 are normally defined for wiping by marking with tape or using a template (Ness, 1994). Comparison of various wipe materials for lead in dust found them to be very comparable for hard, smooth surfaces; however rough surfaces (e.g. unfinished plywood) were found to yield poor recoveries (Chavalnitikul and Levin, 1984). Cotton gauze and other materials have been used dry or wetted for surface wipe monitoring to assess cleanup effectiveness in areas contaminated by polychlorinated biphenyls (PCBs) and chlorinated benzo-*p*-dioxins (Michaud *et al*., 1994; Rappe *et al*., 1985; Slayton *et al*., 1998).

The US Occupational Safety and Health Administration (OSHA) recommends glass-fiber filter material (air sampling filters), dry or wetted with 2-propanol, for determining surface residues of pesticides (OSHA, 1999a). An EPA method uses two 10-cm × 10-cm surgical gauze sponges made of 6-ply cotton (Sof-Wick® 2375, Johnson & Johnson Medical, Inc., Arlington, TX, USA), each wetted with 10 ml of 2-propanol, to collect pesticide residues from residential human hands, indoor surfaces and farm implements (Geno *et al*., 1996; Harding *et al*., 1995). For indoor surfaces, the sampled area was wiped with a straight-line hand motion with each of the two gauze dressings, frequently turning them to provide fresh wiping faces. The first gauze dressing was used to wipe in one direction; the second for wiping in a direction orthogonal to the first. The same technique was used with the previously mentioned acetonitrile/phosphate buffer as the wetting agent to collect lawn herbicide residues deposited on window sills and 29-cm × 29-cm Formica® sheets placed on tabletops inside homes (USEPA, 1999b). Other EPA studies have employed cotton cloth fabric moistened with 100 % acetonitrile to wipe malathion [diethyl(dimethoxythiophosphorylthio)succinate] residues from painted drywall, vinyl flooring, carpet surfaces and cotton suit material (USEPA, 1998b).

Fenske *et al*. (1990) used surgical cotton gauze sponges wetted with distilled water to determine chlorpyrifos residues on residential indoor surfaces. Cotton balls wetted with 2-propanol as swabs were the choice of Wright *et al*. (1993) for collecting pesticide residues from hard residential surfaces (furniture, floors and walls), aided by a metal template with a 2.5-cm × 30.5-cm opening. Currie *et al*. (1990) used a similar technique. Slayton *et al*. (1998) compared cotton gauze wetted with saline solution (to simulate perspiration) or hexane with dry wipes for efficiency at recovering PCBs from concrete surfaces. The saline wipes were found to be 2 to 4 times as effective as dry wipes, while hexane wipes were 25 to 100 times more effective.

Wet wipe sampling is generally not recommended for carpet, upholstery and other fabric-covered or soft surfaces because the solvent may be absorbed into the surface being sampled. Wipes of soft surfaces also are less likely than wipes of hard surfaces to reflect the dermal exposure potential (Ness, 1994). However, Lu and Fenske (1999) recently reported the use of cotton gauze wetted by misting with distilled water to wipe carpets freshly treated with a chlorpyrifos formulation (Dursban® L.O.) and found it to be 23 to 24 times more efficient than transfer to dry palm presses.

If wet wipes are used, care must be exercised to avoid damaging the surfaces being monitored. Solvents other than water may remove substances (e.g. furniture and floor waxes) from the surface that can cause analytical interferences. In addition, if the solvent is capable of extracting the pesticide residue from beneath the surface being wiped, the residue recovered may overestimate the amount of dislodgeable residue. Special care should be taken when using flammable solvents indoors. Toxic solvents should never be used in occupied buildings. While 2-propanol and ethanol are relatively safe for use in occupied indoor

environments, reasonable care should be observed so that solvent residues are not left on children's toys, dinnerware, etc. Wipes wetted with acetonitrile/phosphate buffer solution should be avoided in the latter case. These solvents may also damage finished wood surfaces and remove waxes.

When wipe sampling is performed by hand, it is difficult to maintain a constant application of force against the surface, which may result in variable removal efficiencies. The motion used (straight, 'S' or 'Z' movements) and direction of wiping also need to be standardized for repeatability. The Lioy–Weisel–Wainman (LWW) sampler was designed to wipe smooth, hard surfaces with constant force (Lioy *et al*., 1993). The method as originally reported used a 37-mm polyethylene filter mounted on a 4-cm × 4-cm movable block that is drawn across the surface along a track at constant downward pressure to sample a surface area of 100 cm^2. It was subsequently adapted to use a 50-mm × 55-mm polycarbonate filter moistened with water (Rich *et al*., 1999) or a 47-mm Empore® octadecyl C-18 extraction disk (3M Company, St. Paul, MN, USA) (Gurunathan *et al*., 1998). The Empore disk material is a porous membrane of fibrilated polytetrafluoroethylene (PTFE) into which are embedded small octadecyl-bonded silica particles (8 μm, 6-nm pore size) (Hagen *et al*., 1990). The C-18 particles make up about 90 wt% of the material. These filter disks are popular for the analytical extraction of pesticides and other organic compounds from water. The LWW sampler was developed for the determination of trace elements in dust, but it has been used with Empore C-18 filter disks to determine chlorpyrifos residues on bedroom dresser tops after broadcast spraying (Gurunathan *et al*., 1998).

General guidance on wipe sampling is given in Chapter 6 of the Subdivision K, Series 875, Group B Guidelines (USEPA, 1998a). Detailed surface wipe procedures and references are presented in Ness (1994).

MECHANICAL AND HAND PRESSES

While dislodgeability data is usually obtained for the purpose of estimating the potential transfer to the skin, human hand presses are generally not practical monitoring tools for determining transferable pesticide residues: the nature of human skin varies between individuals, as do the size and geometry of the hand; it is difficult to determine and control the pressure applied; the hand can only be pressed infrequently (e.g. once or twice per day) on treated surfaces for both safety and health considerations; the solvents used to recover the pesticide residue may affect the nature of the skin; pesticide residues may be absorbed into the skin to the extent that they are not fully recoverable. Lewis *et al*. (1994b) reported the first use of human hand presses to determine the dislodgeability of aged pesticides on floors in residences, but the purpose of their use was for comparison with the PUF roller. In this study, the field technician washed his hand with soap and water, allowed it to dry for 5 min, and then pressed the palm only ten times on a scale covered with hexane-rinsed aluminum foil to achieve a uniform weight of 5.4 kg, which compares to a pressure of 6900 Pa.

For sample collection, the hand was pressed ten times on the carpet, progressing from one end to the other of a 10-cm × 100-cm area framed by the template (total area sampled, 640 cm^2). The PUF roller was used to sample adjacent areas of similar size. After pressing in each of three areas of the carpeted room, the hand was carefully rinsed with 70 mL of pesticide-quality 2-propanol, which was collected in a clean sample bottle. Only one hand press was performed per day.

Mechanical devices have been used to press the human hand and other sampling media onto surfaces with uniform pressures. An inflatable cuff from a sphygmomanometer (blood pressure kit), pressed down with a lead weight on the back of the hand or onto a holder for sampling media, has been designed and evaluated on carpet, vinyl flooring and painted drywall (USEPA, 1998b). In studies with this device in which the whole hand was pressed at 10 300 Pa onto carpet immediately after treatment with malathion, the transfer efficiency from carpet to hand ranged from 6.5 to 10.4 % (mean 8.9 %) of the original loadings. Transfer efficiencies from vinyl flooring and painted drywall were substantially lower (means of 0.5 and 0.4 %, respectively), presumably because less of the surface of the hand came into contact with residues on these hard surfaces than was the case with the carpet pile. However, the differences appear to be too large to be explained by the degree of hand contact. The hand presses were compared with presses made with human cadaver skin, pig skin, PUF and cotton fabric. In all cases, the dislodgeability of malathion residues from carpets was substantially greater than that from the hard surfaces: 3.1 % versus 0.13 % and 0.17 % for cadaver skin; 4.2 % versus 0.46 % and 0.99 % for pig skin; 20.7 % versus 0.38 % and 0.22 % for PUF; 22.6 % versus 0.05 % and 0.06 % for cotton fabric (means for carpet versus means for vinyl and drywall).

Single hand palm presses at 6900 Pa on new nylon plush carpet treated with an EC formulation of 0.125 % chlorpyrifos, 0.025 % pyrethrins and 0.25 % piperonyl butoxide showed mean transfer efficiencies of 0.32 to 0.48 % ($n = 6$) for dry palms and 0.90 to 2.6 % for palms wetted with water, 0.3 % dioctyl sulfosuccinate sodium salt (DSS) solution and human saliva (USEPA, 2000a). Transfers from treated used carpet were similar except for piperonyl butoxide, which were two to three times higher for new carpet (Table 3.4). Transfer efficiencies for the same formulation applied to new sheet-vinyl flooring (USEPA, 2000b) were three to ten times higher than those for carpeting: 1.4 to 3.6 % for the dry hand presses and 4.1 to 11.9 % for the wet hand presses (Table 3.4). All of the wetting agents substantially increased the transfer efficiencies over that of the dry palm. Within the error of measurement (typical % RSDs of 30–60 %), appreciable differences between the mean pesticide transfer efficiencies with a saliva-moistened and a water-moistened palm were apparent. The ratios of the transfer efficiencies of pesticides from carpet to moistened hands ranged from 1.9 to 7.8 for new carpet, 2.1 to 4.0 for used carpet, and 2.4 to 3.4 for sheet vinyl. These results suggest that it is the wetness of the saliva rather than its 'stickiness' or viscosity that is primarily responsible for the enhanced pesticide transfer with the saliva-wetted

Table 3.4 Dry and wet palm transfer efficiencies[a] of pesticides from one press onto plush new carpet, used carpet and vinyl flooring treated by broadcast application (mean ± standard deviation of six replicates (%)); wet-to-dry palm press ratios given in italics

Hand condition	Chlorpyrifos	Pyrethrin I	Piperonyl butoxide
New carpet			
Dry	0.48 ± 0.32	0.32 ± 0.15	0.44 ± 0.23
Moistened with:			
Water	1.64 ± 1.04 (*3.4*)	2.50 ± 1.57 (*7.8*)	2.58 ± 1.29 (*5.9*)
Human saliva	1.21 ± 1.00 (*2.5*)	1.87 ± 1.38 (*5.8*)	2.03 ± 1.04 (*4.6*)
DSS[b]	0.90 ± 0.32 (*1.9*)	1.39 ± 0.44 (*1.4*)	1.72 ± 0.42 (*3.9*)
Used carpet			
Dry	0.17 ± 0.16	0.75 ± 0.42	0.22 ± 0.24
Moistened with:			
Water	0.36 ± 0.17 (*2.1*)	1.54 ± 0.69 (*2.0*)	0.77 ± 0.35 (*3.5*)
Human saliva	0.47 ± 0.38 (*2.7*)	1.64 ± 0.86 (*2.2*)	0.87 ± 0.56 (*4.0*)
Sheet vinyl flooring			
Dry	1.53 ± 0.73	3.64 ± 2.21	1.41 ± 0.73
Moistened with:			
Water	5.22 ± 3.02 (*3.4*)	11.87 ± 7.25 (*3.3*)	4.85 ± 2.95 (*3.4*)
Human saliva	4.38 ± 2.83 (*2.9*)	8.89 ± 4.66 (*2.4*)	4.06 ± 2.64 (*2.9*)

[a] Transfer efficiency (%) = 100 × (transfer coefficient (ng/cm^2))/(mean 24 h surface loading (ng/cm^2)).
[b] DSS, dioctyl sulfosuccinate sodium (solution).

palm. Pressing wetted palms on the carpet more than five times was found to remove the wetting agent; therefore, these tests were limited to single presses.

GENERAL SAMPLING CONSIDERATIONS

At least three samples should be collected in the room being monitored. Unless the monitoring protocol requires otherwise, the areas to be sampled should be selected in a manner that reflects the average exposed surface areas. For floors, typically one sample should be taken near a doorway, one in the center of the room and one near a corner. Grid sampling may also be used to collect wipe samples from floors and other large surfaces. Random location sampling weighted to reflect the frequency of potential human contact, used by the USA National Institute of Occupational Safety and Health (NIOSH) for work areas and weighting factors for floors, walls and other surfaces in offices, have been established (NIOSH, 1988; Ness, 1994). The use of a template or masking tape to mark the sampling areas is recommended. If surface wiping is performed, it should be conducted in a manner that is as uniform in applied pressure and motion as possible. Wipes should be folded and turned periodically to expose fresh sampling media to the surface (Ness, 1994). The area chosen for sampling should be at least 30 cm from walls that may have received crack and

crevice treatments. The direction of traverse, where applicable (e.g. PUF roller and drag sled), should be varied, especially for carpet that has a visible 'hand' (pile direction) or wear pattern.

In conducting studies to determine temporal decay rates, sampled areas should be identified so that the same areas are not 're-sampled' pre-application and post-application. Likewise, if deposition coupons (e.g. α-cellulose filter paper or cotton gauze patches backed with aluminum foil) are placed on the floor during application of the pesticide formulation to estimate initial deposition rates, care should be exercised to avoid sampling in the areas covered by the coupons during subsequent monitoring visits.

The dislodgeability of a pesticide residue may depend on the condition of the surface. For example, new carpets are typically more stain-resistant and have more uniform piles, and thus they may behave differently than soiled and worn carpets. The presence of excessive moisture levels in carpeting, as may be the case shortly after a wet cleaning operation, may also affect the dislodgeability of residues, possibly yielding higher than normal results. Wax on vinyl and hardwood floors may affect dislodgeability, as may pits, cracks and crevices in the surface.

Once sampling is completed, sampling media should be placed immediately in appropriate clean, sealed containers and placed on ice or dry ice for return or shipment to the laboratory. The sealed containers should be placed in a freezer maintained at $-20\,^{\circ}C$ or lower until extracted. Media should not be stored for more than about two weeks. Frozen extracts may be safely stored for 90 d or more. At least 10 % of the samples should be quality control samples. Blank media should be taken to the field, briefly removed from the containers to air, and then returned to the laboratory for analysis.

TURF DISLODGEABLE RESIDUES

Many homeowners use herbicides, insecticides and fungicides for turf grass treatment. At least 12 % of US households employ commercial lawn care companies (Whitmore *et al*., 1993). Residues may also be left on lawns after direct applications to turf grass or from drift of pesticides applied to ornamentals, gardens or perimeters of buildings. The lifetimes of pesticide residues on turf are generally short relative to those on indoor surfaces. Rainfall, sunlight, volatilization, erosion, microbial degradation and removal of grass clippings reduce or eliminate most residues in a matter of days or a few weeks. Post-emergence acid herbicides such as 2,4-D and dicamba (3,6-dichloro-2-methoxybenzoic acid) are typically applied in the form of amine salts, which possess extremely low vapor pressures, although they also possess relatively high water solubilities and are rapidly depleted by rainfall. Organophosphate insecticides (e.g. diazinon and chlorpyrifos) tend to vaporize quickly unless applied in granular formulations. The lawn and shrub fungicide, chlorothalonil (tetrachloro-isophthalonitrile), tends to persist longer on turf than most pesticides due to its low volatility and low water

solubility (USEPA, 1999b). Some of the chemicals used in these studies are no longer registered for use on residential turf (e.g. diazinon, chlorpyrifos and chlorothalonil) in either Canada or the USA.

The determination of turf dislodgeable pesticides is important both for the assessment of potential chronic exposures which may occur within a few hours or days after application and for estimating the degree of transfer from lawn to home by 'track-in'. Studies have shown that walking over treated turf as much as one week after application results in transfer of residues to carpet dust that were proportional (3–4 %) to the dislodgeable residues on the turf (USEPA, 1997c; Nishioka *et al*., 1996). The median 2,4-D floor dust level in the living room was 6 $\mu g/m^2$, with a range of 1–228 $\mu g/m^2$, on all carpeted floors in occupied homes (Nishioka *et al*., 1999). Resuspension of 2,4-D residues tracked indoors from lawn applications has been recently reported to be the major source of the herbicide in indoor air (USEPA, 1999b).

The PUF roller moistened with acetonitrile:phosphate buffer has been shown to collect 0.01 to 0.27 % (mean 0.17 ± 0.06 %) of residues left from broadcast spray applications of several herbicide, insecticide and fungicide formulations to fescue grass 4–8 h after treatment (Nishioka *et al*., 1996; USEPA, 1997c). Adults walking across the treated plots transferred 1.6 to 3.2 % (mean 2.6 ± 0.8 %) of the turf dislodgeable residues to carpet dust collected with the HVS3 vacuum sampler (CS_3, Bend, OR, USA). Little difference in transfer efficiency was observed for the PUF roller on granular and spray applications of chlorpyrifos; however, 18 % of the turf residues from the granular formulation was transferred by walking to carpet dust versus only 1.6 % for the spray formulation.

The PUF roller, drag sled, and California roller have been subjected to comparative evaluation for performance on turf grass by the EPA (USEPA, 1997b). In the first of two tests performed, the PUF roller and drag sled methods were evaluated on fescue turf grass treated by broadcast spray with a mixed formulation of 0.17 % chlorpyrifos and 1.41 % chlorothalonil (Ortho Dursban Ready-Spray® Outdoor Flea and Tick Killer and Ortho Multi-Purpose Fungicide Daconil 2787® Plant Disease Control). The second test was designed to evaluate the California roller method alongside the other two methods, and a mixture of 0.06 % 2,4-D, 0.007 % dicamba and 0.03 % mecoprop [2-(4-chloro-2-methylphenoxy)propanoic acid] (Trimec® Southern) was used. The sled assembly previously described (USEPA, 1997a) was used with the California roller, and the sampling medium (percale sheet) was securely held in place by a plastic sheet held down with tent pegs. Dry sampling media were used in both tests.

In the first test, conducted in July under hot and relatively dry conditions, the grass was cut to 5 cm and raked prior to application of the chlorpyrifos/chlorothalonil mixture. Deposition rates were determined by strategic placement of 10-cm × 10-cm cotton gauze coupons backed with aluminum foil. The test plot was allowed to dry for 4 h before sampling. The mean transfer efficiencies for chlorpyrifos were 2.37 ng/m^2 (0.087 %) for the PUF roller and 1.05 ng/m^2 (0.039 %) for the drag sled. The transfer efficiencies were much higher for

chlorothalonil: 401 ng/m^2 (0.293 %) and 240 ng/m^2 (0.173 %), respectively. The sampling precisions were high: 30.8 % and 50.3 % for chlorpyrifos, with 62.0 % and 19.3 % for chlorothalonil, respectively.

For the second test, conducted in October under relatively cool and wet conditions, the grass was cut to 7.5 cm. At this turf height, the drag sled was unstable and could not be used. Transfer efficiencies for the PUF roller were 4.89 ng/m^2 (0.171 %) for 2,4-D, 0.66 ng/m^2 (0.184 %) for dicamba and 2.48 ng/m^2 (0.257 %) for mecoprop. The efficiencies were two to three times higher for the California roller, i.e. 15.63 ng/m^2 (0.560 %) for 2,4-D, 1.78 ng/m^2 (0.504 %) for dicamba and 5.19 ng/m^2 (0.548 %) for mecoprop. Unlike the case with carpeting, sampling precision was much better for the California roller, ranging from 10.1 to 12.2 % versus 43.7 to 47.7 % for the PUF roller.

Problems were encountered with grass clippings and other debris that adhered to the sampling media and had to be mechanically removed prior to extraction and analysis. The problem was particularly serious for the PUF roller. The drag sled and the California roller also collected small amounts of clippings and debris, but these could be easily removed by the laboratory analyst. The PUF sleeve, on the other hand, collected much larger quantities of the debris, and it adhered more strongly, hence making removal tediously difficult. The contribution of residues contained on grass clippings and other debris may contribute substantially to the total residue transferred. However, the contribution may vary widely with turf conditions and the target analyte. For example, separate extraction and analyses of the debris collected by the PUF roller indicated contributions ranging from 5 % for chlorothalonil and 25 % for chlorpyrifos in the first test, with up to 70 to 97 % for the acid herbicides applied in the second test.

Washing, wiping and vacuum techniques have also been employed to estimate foliar residue dislodgeability from turf grass (Popendorf *et al*., 1975; Goh *et al*., 1986; Sears *et al*., 1987; Cowell *et al*., 1993; Black and Fenske, 1996). In one of these techniques, boots wrapped with cotton cheesecloth are used to determine the transfer of turf residues to the shoe soles (Sears *et al*., 1987). Another was somewhat similar to the PUF roller, employing the use of a PUF-covered paint roller (Cowell *et al*., 1993).

The Outdoor Residential Exposure Task Force (ORETF), a Limited Liability Corporation comprised of 33 agrochemical manufacturers, formulators and distributors, recently evaluated various test methods for determining dislodgeable turf residues (Klonne *et al*., 2001; Rosenheck *et al*., 2001; Fuller *et al*., 2001). The ORETF tested eight methods, including modified versions of the PUF roller, drag sled and California roller. The latter, modified by adding a handle and changing the sampling medium to a large (68-cm × 99-cm) piece of 100 % cotton sheeting (200 thread count), was selected as the recommended method (Fuller *et al*., 2001). Although the modified California roller gave the most consistent results among users and formulations, the handle design, unlike the EPA sled, does not isolate the roller from pressure that might be applied by the operator.

The ORETF protocol (ORETF, 1998) calls for a minimum of one pre- and six post-application replicate samples to be taken from a treated plot no smaller than 93 m^2. The grass is to be mowed to 'normal' cutting height immediately prior to treatment. The plot may not be watered during the first 24 h post-application (unless label directions call for 'watering-in') and watering should be kept to a minimum thereafter until completion of the tests. At least three replicate samples are to be collected from each test plot prior to treatment and at intervals after treatment beginning as soon as the spray dries to 14 d, provided that sufficient analyte is collectable for accurate quantitation (twice times lower limit of detection) or the active ingredient has not decayed more than three 'half-lives'. Samples are to be immediately cooled or frozen after collection and stored at or below $-15\,^{\circ}C$ for analysis 'as soon as possible following collection'. Quality control measures include field spikes performed in triplicate at two concentration levels and control matrices. Field data required include site description (location, topography and size), turf characteristics (type, variety and blade height), maintenance performed during testing (mowing and watering), weather data, etc.

The EPA recently conducted a study to determine the transfer efficiencies of several common pesticides used on ornamental turf grass (USEPA, 2000c). St. Augustine grass, cut to a height of 5.5 to 7.5 cm, was sprayed with an emulsifiable concentrate containing 0.068 % chlorpyrifos, 0.47 % chlorothalonil and 0.013 % cyfluthrin, and allowed to dry for 24 h. Palm-only hand presses showed transfer efficiencies of 0.05 % for chlorpyrifos, 1.3 % for chlorothalonil and 2.9 % for cyfluthrin, when the hand was dry (Table 3.5). Transfer efficiencies for saliva- and water-moistened hands were two to three times higher in the case of chlorpyrifos and chlorothalonil and 1.4 times higher for cyfluthrin. The PUF roller collected more than twice as much chlorpyrifos as the dry hand press, but only about 30 % more cyfluthrin (Table 3.5). The PUF roller recoveries for chlorothalonil, however, were less than 75 % of those for the dry hand.

General guidance on sampling turf dislodgeable residues is given in Chapter 4 of the Subdivision K, Series 875, Group B Guidelines (USEPA, 1998a).

Table 3.5 Hand press and PUF roller transfer efficiencies[a] of pesticides from St. Augustine turf grass treated by broadcast application (mean ± standard deviation of six replicates (%)); wet-to-dry palm press ratios given in italics

Device	Chlorpyrifos	Chlorothalonil	Cyfluthrin
Hand palm press			
Dry	0.05 ± 0.03	1.29 ± 0.29	2.93 ± 1.53
Moistened with:			
Water	0.12 ± 0.08 (*2.5*)	3.06 ± 0.98 (*2.4*)	4.02 ± 1.21 (*1.4*)
Human saliva	0.16 ± 0.14 (*3.4*)	2.72 ± 1.12 (*2.1*)	4.18 ± 1.47 (*1.4*)
PUF roller, dry	0.10 ± 0.05	0.92 ± 0.29	3.87 ± 0.96

[a] Transfer efficiency (%) = 100 × (transfer coefficient (ng/cm^2))/(mean 24 h surface loading (ng/cm^2)).

HOUSE DUST AND TRACK-IN SOIL

Pesticide residues on house dust and soil that accumulate in carpets and on other residential indoor surfaces may present a chronic exposure risk, especially for young children. Dust and soil particles smaller than 100–200 μm in diameter may adhere to skin, clothing and other objects, where they may be ingested through mouthing. Smaller particles (e.g. < 20 μm) may be resuspended into air where they can be breathed into the upper respiratory system and lungs (Thatcher and Layton, 1995; Micallef *et al*., 1998; Lewis *et al*., 1999). Inhalable (< 10 μm) and respirable (< 2.5 μm) particles constitute the greatest risks for airborne particle-associated pesticide residues. Human activities such as walking on a carpet have been reported to result primarily in the resuspension of 5 to 25 μm particles (Lefcoe and Inculet, 1975; Thatcher and Layton 1995). EPA studies found indoor particulate 2,4-D levels to be higher in homes with active children and pets (USEPA, 1999b). Concentrations (in $\mu g/m^3$) measured on 10 μm particles were two to ten times higher than those on 2.5 μm particles, with concentrations declining on particles larger than 10 μm. Lewis *et al*. (1999) found that pesticide concentrations (in μg/g) in house dust are much higher on inhalable and respirable particles than on larger particles. Other studies have shown that a person walking across a floor can cause the concentrations of respirable airborne particles to more than double at a height of 2 m above the floor (Thatcher and Layton, 1995). Home vacuum cleaners are particularly prone to dispersing fine dust particles into the air via the mechanical action of the 'beater' bar and leakage through the walls of the vacuum bag.

Surface dislodgeable residue methods and air sampling generally do not yield useful information on potential residential exposures to pesticides bound to dust and soil. Surface wipes and adhesive lift sampling (Demyanek *et al*., 1995) are likely to collect particles larger than the maximum size for skin adherence. It is also difficult to accurately determine the mass of dust collected by wipe sampling. The particle collection efficiencies of the PUF roller, drag sled and California roller have not been determined, but like wipes, they do not distinguish between residues that are associated with dust and those that are not. Even with collection of larger particles, these methods may not collect enough material to detect dust-associated residues.

Various methods have been used to collect vacuum-dislodgeable dust from floors and upholstery (Que Hee *et al*., 1985; USEPA, 1989; Roberts *et al*., 1991; Farfel *et al*., 1994; Lanphear *et al*., 1995; Lioy *et al*., 1993; USEPA, 1995, 1996b). The approach most commonly employed by industrial hygienists is based on drawing dust by means of a personal air sampling pump operating at 2–3 L/min onto a particle filter held in a plastic cassette. The filter cassette is held close to the surface being sampled. The method is sometimes referred to as the *Dust Vacuum Method* (DVM) (Que Hee *et al*., 1985). A modification of this method developed by the Midwest Research Institute (MRI) was the so-called *Blue Nozzle* sampler, which utilized a 5-cm × 10-cm sampling nozzle and a 110 V rotary vane pump to draw larger quantities of dust through the same type of filter

cassette (Constant and Bauer, 1992; USEPA, 1995). Its sampling efficiency was reported to be only 44–59 % for dust sampled from bare concrete, linoleum and wood floors. Another MRI design pulled dust through a rigid 2.5-cm i.d. plastic pipe into a cyclone and deposited it onto a filter in a cassette holder at the bottom of the cyclone (Dewalt *et al.*, 1995). A hand-held vacuum cleaner was used as the vacuum source.

Such vacuum sampling methods typically do not collect adequate quantities of dust for pesticide residue analysis and are not amenable to large surfaces, such as floors. Consequently, the EPA designed the HVS3 cyclone vacuum sampler (Figure 3.7), which is capable of collecting enough dust for pesticide residue analysis, at a constant sampling rate, and in a highly reproducible manner (Roberts *et al.*, 1991; USEPA, 1995). The sampler consists of a 1-cm × 12.4-cm flat sampling nozzle, particle collection cyclone, glass or PTFE catch bottle and flow control system mounted on a standard upright vacuum cleaner (Royal Commercial Cleaner, Model 662, 6 A, Royal Appliance Manufacturing Company, Cleveland, OH, USA) to provide suction. The cyclone has a nominal cut point of 5 μm at a flow velocity of 40 cm/s. In efficiency tests conducted according to ASTM F 608 (ASTM International, 2003c), the sampler has been shown to collect 67–69 % of test dust from plush and level loop carpet and to trap 99 % of the vacuumed dust in the cyclone catch bottle. Additional tests with spiked test dust have demonstrated greater than 97 % recoveries of several common pesticides (Roberts *et al.*, 1991). The method has been evaluated for efficiency at collecting and retaining floor dust and the pesticides associated with it. It has been subjected to 'round-robin' testing and standardized for collection of dust from carpets and bare floors (ASTM International, 2003d). It should be noted, however, that the HVS3 does not efficiently remove deeply embedded carpet dust.

The amount of dust that can be collected by the HVS3 will vary greatly according to the dust loadings on the floor. Vacuuming of a 1 m^2 area of carpet typically collects 0.5–10 g of dust. The collected dust is retained in the catch bottle, which is capped and kept chilled or frozen until analyzed. The standardized methodology calls for the collected dust to be passed through a sieve to exclude particles larger than 150 μm prior to extraction and analysis. The sieved sample normally ranges from 10–60 % of the bulk dust sample (average, ca. 50 %). These amounts of dust will permit the quantitative measurement of 0.05 μg/g or less of most pesticides.

Simultaneous, collocated sampling of carpeted floors with the HVS3 and PUF roller (wetted with acetonitrile:phosphate buffer) in homes after lawn treatments with 2,4-D showed that the PUF roller collected about 1 % of the vacuum-dislodgeable dust (Nishioka *et al.*, 1999). Laboratory comparisons between the dry PUF roller and HVS3 on used nylon plush carpet demonstrated that the PUF roller collected 1.4 % (standard deviation (s.d.) = 1.2, $n = 8$) as much *trans*-permethrin and 1.7 % (s.d. = 1.2, $n = 8$) *cis*-permethrin as the HVS3 (USEPA, 2000d). In-home sampling of used carpets with dry PUF roller media resulted in measurements of pesticide loadings (in μg/m^2) that were <1 % to 7 % of

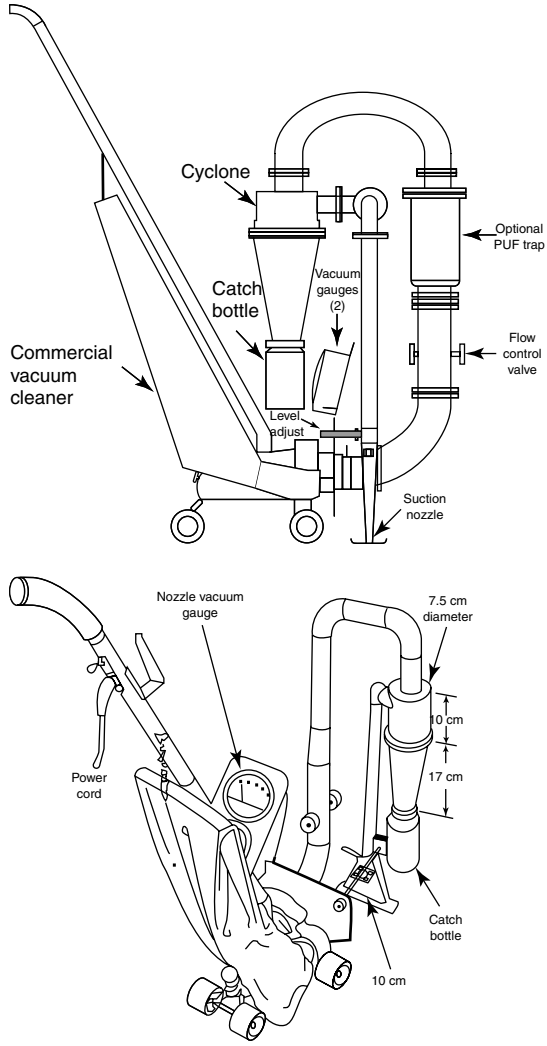

Figure 3.7 HVS3 cyclone vacuum sampler

those determined by the HVS3 (USEPA, 2000d). Following recent applications of chlorpyrifos, however, the PUF roller has often been found to yield surface loading values much closer to those of the HVS3 (Lewis *et al*., 1994b; USEPA, 1999c), in particular, soon after treatments.

Wang *et al*. (1995) modified a canister vacuum cleaner by fitting it with a special nozzle and using polyethylene or polypropylene filter bags of the type used for air pollution control to collect the vacuumed dust. The cone-shaped

filter bags were fitted inside the nozzle section. The sampler was shown to retain 93–99 % of particles down to 0.1 μm. There has been no reported use of this sampler for pesticide monitoring, however.

Home vacuum cleaners have also been used to collect floor dust for pesticide residue analysis (Starr *et al*., 1974; Davies *et al*., 1975; Roinestad *et al*., 1993; Colt *et al*., 1998); however, standard (unlined) vacuum cleaner bags do not retain fine particles well. As much as 25–35 % of the dust in the 2–4 μm size range may be lost during collection by penetration of the vacuum bags (IBR, 1995). Additional losses of fine particles may occur due to adherence to the walls of the vacuum bags. The collection efficiency of particles smaller than 5 μm is also low for the HVS3, since the cyclone inlet cuts off at that point. Side-by-side comparisons of the HVS3 and a conventional upright vacuum cleaner in university dormitory rooms revealed the HVS3 to be more efficient for particles smaller than 20 μm (Willis, 1995). This study also showed that both types of vacuum devices collected particles down to at least 0.2 μm in diameter (Figure 3.8). Since concentrations of pesticides on house dust increase rapidly on particles smaller than 25–50 μm in diameter (Lewis *et al*., 1999), analytical results for dust collected with household vacuum cleaners may be lower than those obtained with the HVS3. However, no significant differences in the concentrations of pesticides were found by the National Cancer Institute (NCI) in house dust collected with the HVS3 from 15 homes and that collected from the homeowners' vacuum cleaner bags (Colt *et al*., 1998). Another study of nine daycare centers yielded higher results for pesticides and polynuclear

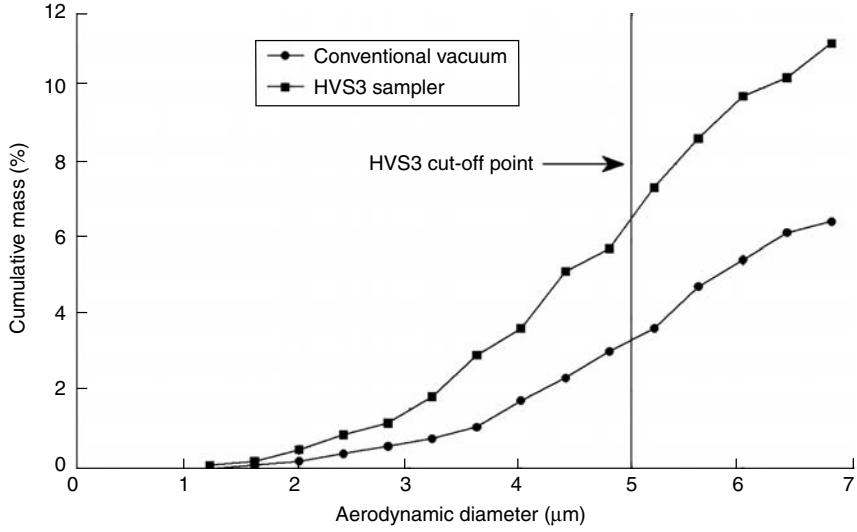

Figure 3.8 Fine particle collection efficiencies of the HVS3 and typical home vacuum cleaner

aromatic hydrocarbons (PAHs) in dust collected in standard vacuum cleaner bags in most cases (USEPA, 1999c). In the NCI study, the HVS3 sample was collected from carpets throughout the house, while the EPA collected the HVS3 sample from a single room on one day. In both cases, the bag sample was taken from the home or facility vacuum cleaner and represented dust collected over an unknown period of time and from multiple locations within the building. Consequently, concentration differences in the two types of samples reported by the EPA may have reflected a lack of both spatial and temporal homogeneity of the dust.

The HVS3 cyclone has also been incorporated into a vacuum-dislodgeable dust sampler of upholstered furniture (USEPA, 1996b). This device, called the HVFS (CS_3, Bend, OR, USA), employs a canister vacuum cleaner to pull air through a notched metal nozzle (upholstery style) connected by a flexible PTFE hose to the HVS3 cyclone and catch bottle assembly, which is transported by a shoulder sling. A household canister vacuum cleaner (Royal Can Vac® Model 3004, 10 A) is connected to the cyclone to provide suction. The HVFS was evaluated on two popular coverings of sofa cushions: flat polyester–cotton (53 % cotton and 47 % polyester) and velvet (65 % cotton and 35 % polyester) on 10.2-cm × 58.4-cm × 58.4-cm high-density polyurethane foam cores. The air flow through the HVFS was adjusted to 14.4 L/s with a pressure drop across the nozzle of 28 kPa for the flat polyester–cotton cushion and 11.6 L/s at 87 kPa for the velvet cushion. The collection efficiency ranged from 88.3 % ($n = 7$, $s = 2.7$) for light (0.1–1 g/m^2) loadings of house dust and 90.2 % ($n = 7$, $s = 3.1$) for moderate to heavy loadings (1–5 g/m^2). While its performance on other types of surfaces has not yet been evaluated, the HVFS may be readily used on curtains, window sills, shelving, etc. Its use on floors would be inconvenient, but feasible.

Several other types of hand-held vacuum samplers have been used to collect dust from residential surfaces. One of these, the Baltimore Repair and Maintenance Study Cyclone Sampler (BRMCS) (Farfel *et al*., 1994), has been evaluated against the HVFS. The BRMCS uses the same cyclone and catch bottle assembly as the HVS3, but a different nozzle and vacuum source. The vacuumed dust is sucked into the cyclone via a semi-rigid Tygon® hose (2.54-cm o.d.) that is notched on the sampling end to simulate a nozzle. Suction is provided by a small, hand-held vacuum device (Royal Hand Vac®, Model 553, 2 A). The collection efficiency for the BRMCS was determined to be 44.1 % ($n = 6$, $s = 3.8$) for plush nylon carpet, 61.1 % ($n = 6$, $s = 6.7$) for level loop carpeting, 71.8–87.8 % ($n = 6$, $s = 3.5$) for upholstery and 84.7 % ($n = 3$, $s = 2.3$) for wood surfaces (USEPA, 1996b).

Another dust sampler that uses a hand-held vacuum cleaner but is capable of collecting large dust samples was designed by Rudel *et al*. (2001). The method employs a Eureka Mighty-Mite® vacuum cleaner (8 A) (The Eureka Company, Bloomington, IL, USA) with the dust bag replaced by a 19-mm × 90-mm cellulose Soxhlet extraction thimble contained in a special PTFE sampling module.

This has been used on carpets, bare floors, window sills and furniture, typically collecting 1.4 to 12 g (mean, 4.5 g) of bulk dust in 45 to 90 min sampling periods.

Roberts and Camann (1989) used presses with hands gloved with solvent-extracted cotton jersey gloves and worn over powderless surgical gloves to determine pesticides associated with house dust in carpets. Whole hand (ca. 322 cm^2) presses (both hands, 2 s duration) onto new nylon plush carpet inoculated with spiked and unspiked house dust resulted in mean recoveries of 1 % for chlorpyrifos and chlordane (1,2,3,4,5,6,7,7a,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene), 0.45 % for dieldrin [(1*R*,4*S*,4a*S*,5*R*,6*R*,7*S*,8*S*,8a*R*)-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimetha nonaphthalene], and 0.34 % for carbaryl (1-naphthylmethylcarbamate). By comparison, a single dry palm press (6900 Pa) onto a used carpet containing dust found to have very high concentrations of *cis*- and *trans*-permethrin [(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate] resulted in the transfer of 0.6 % (mean of 8 presses) of the insecticides (USEPA, 2000a). Wetting the palm with water or saliva increased the transfer efficiency 7- to 15-fold. Brouwer *et al*. (1999) used a finely powdered fluorescent whitening agent to determine the transfer efficiencies of dust from glass surfaces to bare and cotton-gloved hands. Bare, whole-hand presses resulted in a mean 2 % ($n = 18$) transfer for high loadings and 0.14 % ($n = 3$) for low loadings. However, when cotton gloves were worn, the transfer efficiency increased by a factor of 70, due presumably to the porosity of the fabric.

A novel device was designed to estimate the dislodgeability of dust-associated pesticide residues by skin contact (Edwards and Lioy, 1999). Called the 'EL Sampler', the device consists of a spring-loaded assembly that permits the sampling medium to be pressed lightly (12 g/cm^2 or 1160 Pa) onto the surface to be monitored. A 10-cm × 15-cm Empore C-18 extraction membrane was used for the sampling medium. The material was chosen after controlled experiments on particle adhesion showed it to pick up the same distribution of test dust particle sizes as the human hand. In studies in which the EL sampler was pressed onto polyethylene surfaces coated with house dust and then sprayed with a solution of pesticides in 2-propanol, the device was found to collect 35 %, 31 %, 32 % and 18 %, respectively, of chlorpyrifos, diazinon (*O*,*O*-diethyl *O*-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl] phosphorothioate), malathion and atrazine (6-chloro-N^2-ethyl-N^4-isopropyl-1,3,5-triazine-2,4-diamine). Parallel studies with human hand presses (full hand at 6.8 kg = ca. 6900 Pa) yielded collection efficiencies of 42 %, 29 %, 43 % and 21 %, respectively.

Pesticides in vacuum-dislodgeable dust may be quantified either in terms of concentration (e.g. μg/g of dust) or surface loading (e.g. μg/cm^2 of surface sampled). Both values are useful in assessing the degree of contamination. However, the surface loading may be more important for estimating potential exposure since it reflects the quantity of dust that may be available for human contact.

NON-TARGET SURFACE DEPOSITION MONITORING

Deposition monitoring is useful both for determining or confirming the application rate at the time of treatment and for assessing contamination of non-targeted areas during and after treatment. Deposition on non-target surfaces may occur as a result of spray drift during application or settling of the suspended aerosolized formulation shortly after application. Longer-term post-application deposition of pesticides on surfaces may result from the settling of resuspended dust (dust 'fall-out') or condensation of pesticide vapors (dry deposition). The most commonly used monitors for deposition monitoring are α-cellulose filters and cotton gauze, typically 10-cm × 10-cm in size, and are most often referred to as a deposition 'coupon'. The paper or cloth monitors are generally backed with aluminum foil to prevent 'break-through' or contamination from the surface. Denim or other types of cotton cloth (Byrne *et al*., 1998; Krieger *et al*., 1997), filter paper (Wang *et al*., 1987), aluminum foil (Ross *et al*., 1990; Fenske *et al*., 1990, 1991), gauze pads (Das *et al*., 1983; Gold and Holcslaw, 1985), carpet swatches (Wright and Leidy, 1982), Formica sheets (Nishioka *et al*., 1999), Mylar sheets (Lavy *et al*., 1980), Petri dishes (Boreland *et al*., 2002; Tovey *et al*., 2002), metal, glass or porcelain dishes (Wright and Jackson, 1971; Wright *et al*., 1984; Waldron, 1985; Currie *et al*., 1990) and other collectors (Ness, 1994) have also been used as deposition monitors on residential indoor surfaces. Evaporative losses of pesticides from deposition coupons may be significant, especially in the case of coupons made from non-adsorbent materials, even for pesticides with very low vapor pressures. Consequently, for accurate determination of deposition rates, coupons must be removed for analysis immediately after the pesticide application. To prevent losses by evaporation in transit to the laboratory, the coupons should be placed, if possible, in a sealed vessel containing an appropriate solvent (e.g. one that will be used for extraction). An alternate, but less effective, approach is to place the coupons in sealed containers and freeze them as soon as possible. Rigid, non-adsorbent deposition monitors (e.g. metal or porcelain plates) should be wiped or rinsed in the field at the time of collection to recover the residues.

Coupons have also been used to estimate dissipation rates. For such use, it is best if the coupons are made of materials representative of household furnishings, flooring or other residential surfaces (i.e. fabrics, carpet, wood and Formica), and they should be placed on or near the surfaces they represent. Replicate coupons (e.g. three) should be placed at each location for best characterization, and field spikes are particularly important. Coupons should be exposed pre-application and at several time intervals post-application to provide sufficient measurements to project residue 'half-lives'. The same measures to prevent or limit the evaporative losses given above should also be exercised in order to assure that the coupons reflect the residues remaining on the surfaces being evaluated at the time of collection.

General guidance on deposition coupon use is given in Chapter 6 of the Subdivision K, Series 875, Group B Guidelines (USEPA, 1998a).

DERMAL EXPOSURE MONITORING

Dermal exposure monitoring techniques applicable to agricultural workers have been reviewed by Fenske (1993). The α-cellulose filters and cotton gauze monitor, typically 10-cm × 10-cm in size, may also be used on humans to estimate dermal exposure during application of pesticides (Durham and Wolfe, 1962; Davis, 1984; Gold and Holcslaw, 1985; Kurtz and Bode, 1985; Nigg and Stamper, 1985). In this application, the monitors are frequently called 'dermal patches' or 'dosimetry pads'. Industrial hygienists are concerned with exposure of pest control operators who apply pesticides in and around the home and commercial buildings, and regulators are concerned with both worker and bystander exposure. The focus of the discussion in this present chapter pertains primarily to exposure of residents both applying pesticides and coming into contact with residues after application. There is a discussion of these parameters as they pertain to workers and bystanders to agricultural applications in Chapter 1.

Dermal exposures may occur when homeowners apply pesticides around the home or when residents come into contact with contaminated surfaces. Infants and toddlers constitute the population of greatest concern for incidental dermal exposure as they are more apt to have intimate contact with floors, turf and other residential surfaces and generally wear less clothing indoors (Fenske *et al*., 1990; Lewis *et al*., 1994b; Zartarian and Leckie, 1998). Very young children also frequently engage in 'mouthing' of their hands, which may result in ingestion of dermal residues. Monitoring of hand residues has typically been used to estimate dermal exposures of residential occupants. Residues on the hands are important both from the standpoint of their potential availability for ingestion through mouthing and because the hands are more likely than other parts of the body to be contaminated during handling and use of pesticide products or by contact with contaminated surfaces.

ESTIMATING HAND EXPOSURE

Hand-rinses or washes have long been employed for collecting hand residues from agricultural workers and pesticide applicators (Durham and Wolfe, 1962; Kazen *et al*., 1974; Davis, 1980; Sell and Maitlen, 1983; Zweig *et al*., 1983; Davis, 1984; Grover *et al*., 1985; Fenske *et al*., 1986b; Aprea *et al*., 1998; Fenske *et al*., 1998). Various aqueous surfactant solutions, 1 % aqueous sodium bicarbonate or alcohols (either 2-propanol or ethanol in concentrated or dilute solutions) have been most widely used for this purpose. In the 'bag-wash' method, the wash solution is placed in a plastic bag (e.g. a 1.9 L sealable freezer bag) that is slipped over the hand and secured around the wrist and then shaken vigorously to assure good contact with the skin (Davis, 1984). Another popular approach is to rinse the hand with solvent delivered by a laboratory wash bottle and collect the rinsate through a funnel into a bottle (Atallah *et al*., 1982; Lewis *et al*., 1994b). Open vessels have also been used in the manner of wash basins for handwashes

(Knaak *et al*., 1986). A less-used procedure called the 'Cup Method' utilizes an aerosol spray device that permits reproducible washing of small areas (e.g. 5 cm^2) of the skin (Keenan and Cole, 1982). The device delivers the solvent through a spray nozzle mounted inside of a small cup that is pressed against the skin. The solvent wash drains through a short drip tube in the cup and is collected in an attached sample bottle. Another approach that has been used to sample small areas of skin (e.g. 3-cm × 3-cm) involves wiping with Whatman 'smear-tabs' (Whatman Inc., Clinton, NJ, USA) (OSHA, 1999b). Smear-tabs are made of hardened cellulosic filter paper and are 5-cm long with a 2.5-cm circular sampling disk at one end. They have been used to determine residues of polychlorinated biphenyls on the forehead, nose, cheeks and hands of workers (Smith *et al*., 1982) and skin exposure to pentachlorophenol by occupants of log homes (NIOSH, 1986). However, the latter two methods may not recover a sufficient sample of the pesticide residue for quantitative measurement unless sampling is performed on several areas of the skin.

When alcohols are used for handwashes or rinses, especially in concentrated form, evaporative losses may be encountered, particularly with the open hand-rinse or basin approach. Alcohols may also extract plasticizers or other additives from plastic bags and should always be evaluated for analytical interferences before use. The use of aqueous solutions may be limited by analytical constraints, especially for the determination of low-level residues. As previously discussed, aqueous media can cause extraction and analysis problems for neutral-extractable pesticides. Hydrolysis of some pesticides (especially carbamates and organophosphates) may also occur in aqueous solution.

The use of hand-rinses on small children has not been common practice. Lewis *et al*. (1994b) have reported problems in administering 2-propanol handwashes on young children due mostly to the reaction of the child to the sensation of 'coldness' as the solvent evaporated from the skin.

Hand-wipes for the determination of pesticide residues have seen limited use until recently. Hirai and Tomokuni (1993) have used cotton balls wetted with 70 % ethanol to determine chlordane levels on workers hands. Geno *et al*. (1996) developed a hand-wipe technique utilizing two 10-cm × 10-cm 'Sof-Wick' surgical gauze sponges (*vide supra*), which are sold in sealed packages of two sterile pieces. The technique calls for each of the two sponges to be wetted with 10 ml of pesticide-grade 2-propanol and used sequentially to thoroughly wipe the entire surface of the hand, being careful to thoroughly wipe each digit and in between. Immediately following sampling, the sponges are placed in a solvent-rinsed, oven-dried wide-mouthed glass jar with a PTFE-lined lid and an additional 50 ml of 2-propanol is added to the container before sealing with PTFE tape and packing on dry ice for transport to the laboratory. While children are capable of performing the wipes of their own hands under the supervision of a field sampling technician, the wiping procedure should be performed by a parent or the technician if the child is under two years of age.

Hand-wipes are much easier to perform and have been shown to be as effective or better than handwashes at recovering pesticide residues. Laboratory studies with adult volunteers have demonstrated that the 2-propanol wipe method quantitatively removes pesticides that were freshly applied to the skin (USEPA, 1996a). Adult skin was spiked by rubbing and pressing the hand on aluminum foil onto which measured quantities of emulsifiable concentrate (EC) formulations of chlorpyrifos and pyrethrins had been deposited and allowed to dry. Immediately after the transfer (ca. 30 s), before the pesticides could be absorbed through the epidermis, the hand was wiped and the foil rinsed to recover all residues. Quantitative (ca. 100 %) recoveries of residues transferred to the skin at levels ranging from 2 to 250 $\mu g/m^2$ were obtained (Geno *et al*., 1996; USEPA, 1996a). The recovery efficiency of the wipe was significantly higher than that reported for alcohol rinses. For example, Fenske and Lu (1994) reported a 43 % recovery of chlorpyrifos residues from human hands with 10 % 2-propanol in water immediately after exposure to dried formulations. Undiluted ethanol was reported to remove only 30 % of the residue with residence time on the skin having no effect on recovery (Fenske and Lu, 1994). A single bag wash of the hand with 10 % aqueous 2-propanol was found to recover 67–78 % of captan (*N*-trichloromethylthio-4-cyclohexene-1,2-dicarboximide), which is less efficiently absorbed by the skin, immediately after exposure (Fenske *et al*., 1998). A double bag washing resulted in 78–91 % recoveries.

Similar studies with aqueous surfactants, human saliva and a saliva surrogate as wetting agents for hand-wipes have yielded recoveries of about 50 % of freshly applied pesticides from the hand (Camann *et al*., 1993a; Majumdar *et al*., 1995; USEPA, 2000e). In these studies, three adult male volunteers spiked first one hand and then the other by pressing the palm at a pressure of ca. 10 000 Pa onto 14-cm × 14-cm pieces of aluminum foil to which 50 μL of an EC formulation of 184 ng/μL chlorpyrifos, 714 ng/μL pyrethrin I [(*Z*)-(*S*)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclopenta-2-enyl (1*R*)-*trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropane-carboxylate] and 1 μg/μL piperonyl butoxide had been applied. The hands were then wiped with 'Sof-Wick' cotton gauze sponges wetted with the appropriate liquid. Two saliva surrogates were evaluated: 1.3 % dioctyl sulfosuccinate sodium salt (DSS) (Surtan®, Sigma Chemical Company, St. Louis, MO, USA) in deionized water and a saliva substitute used to treat salivatory deficiency (Olsson and Axéll, 1991). The artificial saliva (AS) was composed of mucin (35 g), xylitol (20 g), potassium chloride (1.2 g), sodium chloride (0.85 g), magnesium chloride (0.05 g), calcium chloride (0.2 g), calcium carbonate (0.35 g), calcium phosphate (0.35 g) and benzalkonium chloride (0.02 g) in 1 L of deionized water. Each subject used his own saliva, collecting 50 mL in a PTFE bottle. Immediately after each hand press, the exposed hand was wiped sequentially with two gauze sponges, each wetted with 5 mL of saliva, AS or DSS, and the sponges were placed in containers with 50 mL of methanol, pending analysis. The results of replicate analyses, corrected for analytical recovery, are presented

Table 3.6 Hand-wipe removal efficiencies for dried residues by wetted cotton gauze sponges (mean ± standard deviation (%))[a]

Wetting agent	Chlorpyrifos	Pyrethrin I	Piperonyl Butoxide
Human saliva	52.0 ± 13.4	52.3 ± 9.3	40.7 ± 13.6
Artificial dental saliva	47.1 ± 11.4	41.6 ± 7.0	37.7 ± 13.4
Dioctyl sulfosuccinate, 1.3 %	51.7 ± 9.7	61.8 ± 12.9	51.4 ± 9.3
2-Propanol, 98 %	104.3 ± 10.7	91.8 ± 27.6	ND[b]

[a]Number of replicates for chlorpyrifos and pyrethrin I = 12 for 2-propanol wipes and 6 for saliva and saliva surrogates. Number of replicates for piperonyl butoxide = 5.
[b]Not determined.

in Table 3.6, along with the results obtained from similar 2-propanol hand-wipes for comparison.

AS and DSS hand-wipes may more accurately estimate the potential dislodgeability of pesticide skin residues by mouthing action than alcohol wipes. However, problems with storage stability and analytical difficulties associated with water limit the usefulness of these wipes for routine exposure monitoring (Majumdar *et al*., 1995).

Cotton and nylon gloves have been used to estimate hand exposure in agricultural operations (Durham and Wolfe, 1962; Davis, 1980; Zweig *et al*., 1983; Fenske *et al*., 1986b; Camann *et al*., 1993b). However, gloves, body patches and body garments can often provide an overestimation, especially if they come into direct contact with the pesticide formulations during applications (Davis *et al*., 1983; Fenske *et al*., 1986b; Camann *et al*., 1993b). Cotton fabrics have also been shown to retain more dust than skin does, due to the porosity of the material (Brouwer *et al*., 1999). Gloves are somewhat impractical to use in residential monitoring when the study subjects are the residents, particularly in the case of small children.

WHOLE-BODY EXPOSURE

Fluorescent Tracers

Fluorescent compounds, such as fluorescein [9-(*o*-carboxyphenyl)-6-hydroxy-3*H*-xanthen-3-one], Uvitex® OB [2,2′-(2,5-thiophenediyl)bis(5-*t*-butylbenzoxazole)], 4-methyl-7-diethylaminocoumarin and Tinopal® CBS-X [4,4″-bis (2-sulfosterylbiphenyl)] have also been used to estimate dermal exposure via visual imaging of the luminescence (Fenske *et al*., 1986a, 1986b; Fenske, 1988; Fenske and Elkner, 1990; Archibald *et al*., 1994; Archibald 1995; Black and Fenske, 1996; Brouwer *et al*., 1999). In these techniques, the fluorescent tracer is generally mixed with the pesticide formulation before application and the hands, face and other parts of the body are then examined in a darkened area under ultraviolet light to determine areas of dermal contact. Video imaging is

usually performed, employing a process known as 'Video Imaging Technique to Assess Dermal Exposure' (VITAE) (Fenske and Birnbaum, 1997). However, there are several precautions that need to be exercised when using fluorescent tracers to estimate dermal exposure. The tracer may not accurately correlate with the behavior of the pesticide of interest if it has substantially different physico-chemical properties (e.g. solubility, vapor pressure and k_{ow}).

Reflectance

Attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy is another technique recently reported to have been applied to the determination of pesticide residues on human skin and residential surfaces (Doran *et al.*, 2000). While this technique gave good results when evaluated in the laboratory for three pesticides at 0.5 to 5 $\mu g/m^2$ skin loadings, field use would be very limited by the size and transportability of the instrument and the liquid-nitrogen coolant for the detector. Whatever the method, surface residues are also difficult to measure quantitatively *in situ*, especially on the skin.

Whole-Body Dosimetry

Whole-body dosimetry has also been used to estimate residential occupant exposures to pesticide residues, with particular emphasis on estimating exposures of infants and toddlers (Ross *et al.*, 1991). Typically, undyed cotton or cotton/polyester garments are worn on the upper and lower body, legs, arms, feet, hands and head. The wearer of these garments contacts contaminated surfaces in or around the home for a prescribed period of time in a manner that simulates a child's typical activities. The entire garment set is then packaged, transported to the laboratory and extracted for analysis. The garments may be extracted individually or collectively. Major disadvantages of this technique are that large volumes of solvent are required for extraction and there are no 'standard' garments that can be used for the purpose (Fenske, 1993). The methodology is also impractical for use on residents.

Guidance for conducting dermal exposure monitoring, including whole-body dosimetry studies, may be found in Chapter 7 of the Subdivision K, Series 875, Group B Guidelines (USEPA, 1998a). In addition, detailed procedures and protocols for dermal sampling may be found in Ness (1994).

POST-APPLICATION FATE, TRANSPORT AND REDISTRIBUTION OF PESTICIDES

The persistence of a pesticide residue will depend on its physico-chemical properties. Volatility, water solubility, reactivity and biodegradability are properties that govern the longevity and mobility of a compound in the environment. However,

the environmental factors that degrade pesticides (sunlight, rain, wind, temperature extremes and microbial action) are largely absent indoors. The indoor environment is also a closed system in which pesticides move between media by volatilization and condensation (the 'chromatography effect') or by resuspension and settling of dust. Consequently, pesticide residues can persist for months or years indoors as opposed to days or weeks outdoors.

All organophosphate (OP) insecticides are semivolatile and will vaporize from surfaces after applications. The most volatile OP is dichlorvos (2,2-dichlorovinyl-dimethyl phosphate) (vapor pressure (v.p.) $= 7 \times 10^{-3}$ kPa at 25 °C). Dichlorvos (DDVP) has been a common household insecticide for many years, particularly in slow-release insecticide strips and flea collars for cats and dogs. Several studies showed that air concentrations of 100 $\mu g/m^3$ or greater were not unusual in rooms in which DDVP pest strips were deployed (Leary *et al.*, 1974; Lewis and Lee, 1976). While the pesticide is still registered in the United States for use in pest strips, foggers and flea collars, its use as declined dramatically since 1988, and it is currently undergoing special review for registration by the EPA. The indoor use of other OP pesticides, such as chlorpyrifos (v.p. $= 2.5 \times 10^{-6}$ kPa at 25 °C) and diazinon (v.p. $= 1.1 \times 10^{-4}$ kPa at 20 °C) has also been declining in favor of pyrethroid insecticides. Many countries have reduced or eliminated domestic uses of OP pesticides.

The majority of pyrethroid insecticides have low volatilities. The heavily used synthetic pyrethroid permethrin is classified as nonvolatile on the basis of its vapor pressure (1.3×10^{-9} kPa at 20 °C) and is rarely found in indoor air. However, it has recently been reported to be the major pesticide residue found in house dust (USEPA, 2000d). Cypermethrin [(±)-α-cyano-3-phenoxybenzyl-(±)-*cis,trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate] and cyfluthrin [cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylate] are two other low-volatility pyrethroids commonly used for indoor flea and cockroach control.

The influence of the volatility of a pesticide on measurable indoor air levels is evident by comparing semivolatile chlorpyrifos with nonvolatile permethrin. Room-air concentrations of these two insecticides were found to be comparable (means of 30 and 42 $\mu g/m^3$, respectively) 0–2 h after broadcast spraying, but the air levels of permethrin declined so rapidly that nothing (<1 $\mu g/m^3$) could be detected in air after 8 h, while chlorpyrifos levels remained high at 31 $\mu g/m^3$ (Koehler and Moye, 1995b). Immediately after spraying, permethrin is most likely present in air as an aerosol, which undergoes little or no volatilization after deposition.

There may be significant temporal and spatial variations in the concentrations of pesticides in the indoor environment, especially if monitoring is performed after an indoor application. Air concentrations typically drop rapidly for about 3 d after application as the pesticide is absorbed into furnishings or dissipates to the outdoor air. However, concentrations of the more volatile pesticides may

still be 20 to 30 % of those on the day of application after as much as 21 d (Leidy *et al*., 1993; Lewis *et al*., 1994b). Dissipation rates will also depend on the method of application. Aerosol sprayers have been reported by some to result in higher post-application air levels than compressed air sprayers (Leidy *et al*., 1993; Koehler and Moye, 1995a). Likewise, broadcast spraying has been shown to result in higher air concentrations than crack and crevice treatments (Fenske and Black, 1989). However, Lu and Fenske (1998) recently reported finding little differences in air concentrations for chlorpyrifos applied by pressurized broadcast spraying and aerosol (fogger) release. One day after treatments, chlorpyrifos levels averaged 23–64 $\mu g/m^3$ for broadcast application and 43–48 $\mu g/m^3$ for the fogger. Air concentrations of chlorpyrifos declined more rapidly after aerosol release than they did after broadcast spraying, declining on the second day by 75 and 50 %, respectively. Seven days later, air concentrations were similar (aerosol, 0.4–8.6 $\mu g/m^3$; broadcast, 0.9–8 $\mu g/m^3$).

When there has not been a recent broadcast application, pesticide levels in the air of most rooms vary little with vertical distance from the floor (Leidy *et al*., 1993, Lewis *et al*., 1994b). However, for several days or more after an application, air concentrations near the floor where small children spend much of the time may be several times higher than those at adult heights (Fenske *et al*., 1990; Lewis *et al*., 1994b; Lu and Fenske, 1998). This is particularly true for broadcast and aerosol spray applications, where concentrations of chlorpyrifos have been found to be more than four times higher at 25 cm above the floor than at 100 cm 5 to 7 h after application (Fenske *et al*., 1990). Lu and Fenske (1998) observed concentration gradients for chlorpyrifos when samples were taken at 25, 100 and 175 cm above the floor after broadcast and aerosol treatments of carpeted floors, but the gradients had largely disappeared after 3 to 5 d. Conversely, Lewis *et al*. (1994b) found air concentrations of chlorpyrifos to be twice as high at 12 cm as at 75 cm 2 d after crack and crevice treatment and 1.5 to 2 times as high at 8 and 15 d post-application. Koehler and Moye (1995a) reported concentration gradients after broadcast application of chlorpyrifos up to 175 cm. Leidy *et al*. (1993) found diazinon levels to be higher at 1.2 m than at ceiling level 21 d after crack and crevice treatment but to have equalized after 35 d. On the other hand, Lewis *et al*. (2001) reported no significant differences in diazinon air concentrations measured at 10 and 75 cm above the floor 1 to 12 d after crack and crevice treatments in the monitored room. Although the synthetic pyrethroids *d*-phenothrin [3-phenoxybenzyl(1 *RS*)-*cis*,*trans*-2,2-dimethyl-3-(2-methyl-prop-1-enylcyclopropanecarboxolate] and *d*-tetramethrin (3,4,5,6-tetrahydrophthalimido-methylchrysanthemate) have relatively low vapor pressures (1.6×10^{-7} and 9.4×10^{-7} kPa, respectively), they have been found in room air immediately after crack and crevice treatment at 752 and 1040 $\mu g/m^3$, respectively, but declined rapidly to 2 to 3 $\mu g/m^3$ and showed no concentration differences at vertical heights of 25 and 120 cm after the decline (Matoba *et al*., 1998).

The rate of volatilization of microencapsulated pesticides is much slower than that of emulsifiable concentrates (Jackson and Lewis, 1979; Koehler and

Patterson, 1991). Indoor air levels of chlorpyrifos applied as a microencapsulated formulation were measured at 3.1 $\mu g/m^3$ 0–2 h after broadcast spraying and 5.2 $\mu g/m^3$ after 24 h, compared to 30 and 15 $\mu g/m^3$, respectively, for the emulsifiable concentrate (Koehler and Moye, 1995a). After 48 h, levels were still about double for the emulsifiable concentrate application (8.5 $\mu g/m^3$ versus 4.0 $\mu g/m^3$).

Unfortunately, it is not possible to accurately predict rates of volatilization or project air concentrations based on vapor pressures. Even when ambient conditions, substrates and formulations are similar, emission rates for pesticides will depend on other factors such as the concentration and molecular structure of the active ingredient. Jackson and Lewis (1981) compared emission rates from three kinds of pest control strips in the same room under constant conditions of temperature ($21 \pm 1\,^{\circ}C$) and humidity ($50 \pm 20\,\%$) and found that room air concentrations over a period of 30 d were much higher for diazinon than for chlorpyrifos, but similar to those for propoxur [2-(1-methylethoxy)phenylmethylcarbamate]. On 'Day 2', room air levels were 0.76 $\mu g/m^3$ for diazinon, 0.14 $\mu g/m^3$ for chlorpyrifos and 0.79 $\mu g/m^3$ for propoxur. After 30 d, the air concentrations were 1.21, 0.16 and 0.70 $\mu g/m^3$, respectively. The vapor pressure of diazinon is nearly 100 times higher than that of chlorpyrifos and nearly 1000 times lower than that of propoxur (4×10^{-7} kPa at $20\,^{\circ}C$).

Most acid herbicides such as 2,4-D and glyphosate [*N*-(phosphonomethyl)glycine] used on lawns are applied in the form of amine salts that possess extremely low vapor pressures; hence, they may be found in air only at low concentrations and mostly associated with suspended particulate matter. For example, 2,4-D was detected in the air inside of 64 of 82 homes commercially treated with the herbicide (Yeary and Leonard, 1993). The time-weighted average concentration over 7 h on the day of application was determined to be 34 ng/m^3 in six homes with the highest measured air levels. Residues of 2,4-D in indoor air and on interior surfaces of residences receiving lawn treatments have been shown to increase for a week or more after the application (Nishioka *et al*., 1999; Lewis and Nishioka, 1999). Triazine herbicides, which have limited residential use for preemergent control of weeds in turf grass, are more volatile than acid herbicide salts, but are still largely classified as nonvolatile. There have been very few reports of their presence in indoor air. Atrazine (v.p. $= 3.7 \times 10^{-8}$ kPa at $20\,^{\circ}C$) has been reported at concentrations of 3 to 12 ng/m^3 in the indoor air of farm residences and homes near agricultural operations (Camann *et al*., 1993c; Mukerjee *et al*., 1997).

Somewhat water-soluble pesticides such as acid herbicides will be washed from foliar surfaces and into subsurface soils by rainfall. For example, dislodgeable turf residues of 2,4-D after a 2.54-cm rainfall have been reported to be only 1–5 % of those found at 4–8 h after application (Nishioka *et al*., 1996; USEPA, 1997c). However, dew or rain on aged turf residues may increase their dislodgeability (Nishioka *et al*., 1996). OP insecticides are semivolatile and will vaporize from surfaces after applications. Chlorpyrifos vaporizes rapidly from lawns if applied in aqueous formulations. Diazinon, which is used on lawns as well as indoors, dissipates even more rapidly. However, the persistence of OP

pesticides on lawns is enhanced in granular formulations. The dislodgeability of granular formulations by human foot traffic is also much greater than that of liquid formulations (USEPA, 1997c).

The presence indoors of 2,4-D, carbaryl and chlorothalonil, which are applied exclusively outdoors, implies that residues have been transported from outdoors (already stated in the 'Turf Dislodgeable Residues' section above). For typical homes, 'track-in' was found to be the most significant route of transport of 2,4-D residues from the lawn to the indoors. For high-activity homes, transport via an indoor–outdoor dog, the applicator's shoes and by children, was estimated to account for about 58, 25 and 8 % of the indoor residues, respectively. Spray drift and post-application aerial intrusion were minimal contributors (<1 %), except for homes in which outdoor shoes were not worn indoors and which had low pet activity. Resuspension of floor dust was the primary source of 2,4-D in indoor air, on table tops and on window sills. Indoor air concentrations of 2,4-D increased from non-detectable before lawn treatment to 0.2 to 10 ng/m^3 (PM_{10},[1] 10 μm inlet) after homeowner application, with about 65 % of the total particulate 2,4-D associated with respirable particles (<10 μm). 2,4-D associated with <1 μm and smaller particles made up 25–30 % of the total mass. Detectable residues of 2,4-D were found in air and on all surfaces one week after application (Figure 3.9). The surface concentration gradient followed the occupant traffic pattern through the house. Post-application floor surface loadings of 2,4-D in the living areas ranged from 1 to 228 μg/m^2 on carpeted floors and from 0.2 to 20 μg/m^2 on bare floors, compared to 0 to 0.8 μg/m^2 (median, 0.5 μg/m^2) pre-application.

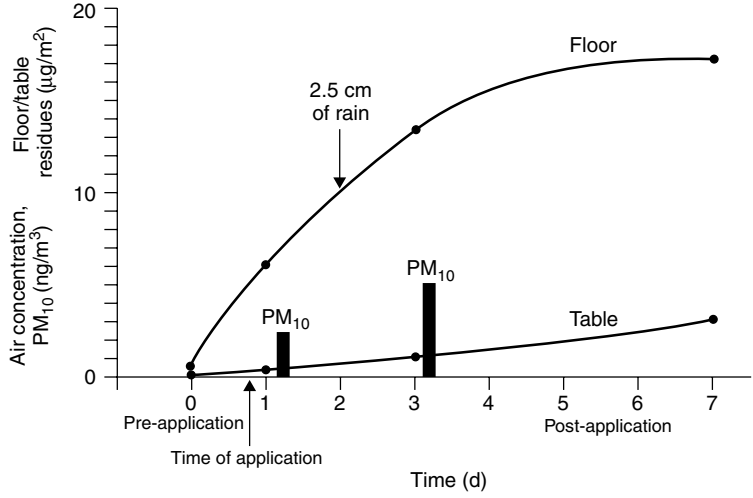

Figure 3.9 Temporal profile of 2,4-D residues inside a home before and after application of 2,4-D to the lawn; note that 2.5 cm of rain fell 24 h after the application

[1]Particle with aerodynamic diameter less than 10 μm.

About 1 % of the 2,4-D in floor dust was dislodgeable (PUF roller wetted with acetonitrile:phosphate buffer) and potentially available for dermal contact. 2,4-D residues on window sills and tables followed a similar traffic gradient, with surface loadings of 0.2 to 20 $\mu g/m^2$ (none were detectable before application). In homes in which occupants removed their shoes at the entryway, 2,4-D loadings on floors were typically an order of magnitude lower than in those in which shoes were worn.

Residential pesticide use indoors is heaviest during the spring and summer months when pest infestations are greatest. In addition, warmer weather results in more rapid volatilization of termiticides from the soil beneath the house, so increasing their concentrations indoors. Consequently, indoor air concentrations are typically highest during the summer months. For example, in an EPA study in Jacksonville, Florida, the mean indoor air concentrations of 25 pesticides were 2.3 $\mu g/m^3$ in summer, 1.2 $\mu g/m^3$ in spring and 0.81 $\mu g/m^3$ in winter (Whitmore *et al.*, 1994). Since insect populations are generally larger in more moderate climates, pesticide usage and corresponding exposure levels are greater in the southern latitudes of the northern hemisphere. For example, the EPA found total indoor levels of pesticides to be six to eight times higher in Jacksonville, Florida than during the same seasons in Springfield, Massachusetts.

CONCLUSIONS AND RECOMMENDATIONS

Simple and reliable methods for the estimating of respiratory exposure to pesticides in residential indoor air have been standardized for integrated sampling periods of 8 to 24 h (ASTM International, 2003a; Eller, 1994; USEPA, 1999a). However, measurements taken over a period of about two weeks after a pesticide application are usually required to obtain a reasonable estimation of occupant exposure. Repeated visits over a two-week period to residences to set up equipment and collect daily air samples is burdensome to occupants. Therefore, devices that can continuously sample over periods of up to several weeks would be very beneficial for post-application exposure assessment, as well as for estimation of chronic respiratory exposures. Diffusion-controlled passive samplers are commercially available for inorganic gases and volatile organic chemicals (vapor pressures above 10^{-2} kPa) and most can be deployed for long periods because of their low effective sampling rates (Lewis *et al.*, 1985; Berlin *et al.*, 1987; Koutrakis *et al.*, 1993). Such passive sampling devices (PSDs) containing appropriate sorbents (e.g. Tenax or XAD) would collect pesticide vapors but not aerosols or pesticides attached to airborne dust particles. Since the diffusion coefficients for semivolatile pesticides are much lower than those for volatile organic chemicals and most semivolatile compounds can not be efficiently thermally desorbed, the PSD would have very low sensitivity for most pesticides. However, a PSD with an effective sampling rate of about 1 cm^3/min for a given semivolatile pesticide should collect a sufficient quantity of analyte (0.2 to 20 ng)

over a two-week period to permit measurement by typical methods employing low-volume solvent extraction.

A recently developed technique, i.e. solid-phase microextraction (SPME), which collects vapors on a micro-fiber coated with a gas chromatographic polymer phase (Chai and Pawliszyn, 1995; Grote and Pawliszyn, 1997), may be more promising than typical PSDs for long-term sampling as it permits the entire collected sample to be analyzed. The SPME fiber can be exposed directly for rapid assessment of air quality or withdrawn into a tube that controls diffusion to the fiber for long-term sampling.

Another relatively new approach to long-term estimation of pesticides in air is the adaptation of semipermeable polymeric membrane devices (SPMDs) designed to collect nonpolar pesticides from water. One such SPMD device, currently under evaluation by the EPA, consists of thin-walled polyethylene tubing filled with the lipid triolein (Huckins *et al*., 1990). SPMDs collect gaseous pesticides by absorption through the tubing into the triolein solvent, which is extracted and analyzed. While the sampling rates of SPMDs are not diffusion-controlled, air concentrations can be estimated from the air–triolein partition coefficient, k_{OA}, of the compound of interest. SPMDs may be much more sensitive than diffusive samplers and have been used for sampling periods of up to two months to detect pesticides and polychlorinated biphenyls in ambient air at concentrations in the pg/m^3 range (Ockenden *et al*., 1998a, 1998b).

Whatever their design, passive samplers will collect only pesticide vapors. Therefore, air measurements made with them will not always be appropriate for estimating total respiratory exposure, especially in the case of low-volatility pesticides and pesticides tracked indoors on soil particles. In addition, some pesticides may undergo chemical degradation on sorbents or in solvents over such long sampling periods. Therefore, internal standards or other means will need to be used to assure acceptable analyte recoveries.

Whereas air monitoring data are relatively easy to acquire and interpret in terms of human exposure, dislodgeable and transferable residue data are neither. Among the several methods used to estimate the transferability of pesticide residues from residential floor and lawn surfaces to human skin, only the PUF roller has been extensively evaluated and its use standardized (ASTM International, 2003f). Of the three most popular devices (PUF roller, drag sled and California roller), the contact motion and physical composition of the sampling medium of the PUF roller appear to best approximate the contact between a child's skin and the surface. While the dislodgeable residues picked up by the dry PUF roller exceed those picked up by dry palm presses, they are quantitatively closer to those transferred to the skin (especially to wet skin) than transferable residues determined by either of the other two methods. On the other hand, the transfer efficiency of the dry PUF roller is so small (1–2 % of applied pesticide) that attempts to collect transferable residue data in residential environments often result in little or no surface-dislodgeable residues being detected even when skin wipes of child occupants' hands yield readily measurable residues (Lewis and

Nishioka, 1999). The use of PUF moistened with water or aqueous solvents significantly increases the transfer efficiency, but causes analytical problems for neutral pesticides and poor reproducibility, probably because of the tendency for the moistening agent to be transferred to the carpet or other surface being evaluated. The transfer efficiency for the drag sled with dry denim sampling media is about the same as that for the dry PUF roller. However, moistened denim is rapidly wiped dry, so that the use of wet media with the drag sled does not appear to be practical. The California roller has a much higher transfer efficiency, but its large size limits its use in residences. The performances of newer devices such as the LWW and EL samplers (see above) have not been fully demonstrated in the field, and they are likely to recover even less surface residues than the PUF roller.

None of the aforementioned transferable residue devices are designed for sampling upholstered and non-flat or irregular surfaces from which occupants may receive exposures to pesticides. It should be possible to develop a smaller version of the PUF roller or modified EL sampler that can be applied to many of these surfaces, especially upholstered furniture. The current EL sampler can be used on small flat surfaces, such as window sills and table tops. There are presently no methods available for determining transferable residues on small, highly irregular surfaces, such as those on children's toys. Surface wipes with alcohol or other suitable solvents may be used to determine total surface loadings only if the surface is non-porous and the solvent does not extract pesticides from the interior of the object. Conversely, in some cases the device (or wipe solvent) chosen may not efficiently remove all of the surface residues. It is important, therefore, that all methods be tested to the extent possible on the targeted surfaces before the beginning of a study and that methodologies are fully described in the published findings.

Collection of house dust samples is often useful for estimating exposure through dust ingestion or inhalation of resuspended dust, as well as for general characterization of the residential environment. Only the HVS3 sampler has been standardized for this purpose (ASTM International, 2003d) and the term 'vacuum-dislodgeable' is meant to apply exclusively to residues collected with this device. Other means of collecting house dust from carpeted and bare floors may be more or less efficient at dust extraction or small particle recovery. The HVS3, which does not have an agitator, removes dust that is loosely bound to or lightly embedded in carpeting. It is more efficient at collecting inhalable particles than typical home vacuum cleaners; therefore, HVS3 vacuum-dislodgeable house dust may more closely correspond to that which is readily accessible for human exposure through both the respiratory and dermal contact/non-dietary ingestion routes. For overall characterization of the living environment, analysis of home vacuum cleaner contents may serve equally as well. Assessing the role of house dust in human exposure is complicated by lack of knowledge as to the bioavailability of dust-bound pesticides and a poor understanding of exposure routes.

The issue of determining skin residues and interpreting their meaning in the context of human exposure is even more complicated. From a practical monitoring standpoint, hand-wipes are easy to use and are safer and more convenient for use in the residential environment than handwashes, especially if the solvents are flammable. If performed properly, the rubbing action of wipes can also be more efficient at removing skin residues than rinses or washes. They have also been shown to be better tolerated by small children than rinses (Lewis *et al*., 1994b). The only standardized method for determining pesticide residues on the hands is an OSHA method that uses 2-propanol-wetted glass fiber filters. It is unlikely that such a method would be efficient or effective for determining whole-hand residues in a non-occupational setting, especially on children. 2-Propanol hand-wipes using soft cotton gauze surgical sponges have, however, been demonstrated to be easy to use on infants and toddlers, although the alcohol may extract some subcutaneous residues. Studies on adults have shown that they remove nearly 100 % of freshly applied pesticide formulations. Saliva or aqueous surfactant wipes are about half as efficient, but are likely to be much more comparable to the removal efficiency of 'mouthing'.

During the course of a post-application monitoring study, skin residues may vary in a more irregular manner than residential surface residues; therefore, skin residue measurements taken once a day may not be representative of daily means. If biological monitoring is also part of the exposure study, complete removal of hand residues may result in reduced levels of pesticide residues or metabolites in the subject's blood or urine if the skin is wiped one or more hours prior to collection of the body fluids. This problem may be ameliorated by 'spot-sampling' small areas of the hands (e.g. with 2-propanol-wetted PUF swabs), but at the expense of reduced sensitivity and the risk of obtaining non-representative data due to non-uniform contamination of the skin. In the case of a small child's hands, the quantities of pesticides recoverable from spot-sampling may not be sufficient for detection or quantitation. Estimation of exposure by 'mouthing' not only requires realistic skin surface residue data, but also detailed knowledge of 'mouthing' behavior.

Pesticide residues in air and on residential surfaces represent an exposure risk to all occupants, but small children are potentially the most vulnerable. Infants and toddlers spend more time indoors and generally wear less clothing than adults. Their breathing zones are closer to the floor, where vapor concentrations and resuspended house dust concentrations are apt to be highest. They have higher body surface-to-weight ratios than adults, have more intimate skin contact with the floor and may frequently have wet, sticky hands that are several times as efficient at dislodging surface residues than dry skin (USEPA, 2000a,b). They engage in much more 'mouthing' activities (hands, toys and furniture) than adults. Consequently, pesticide residues that are on surfaces or that are transferred to the skin may be ingested, hence resulting in much higher doses than might result from dermal absorption. It has been estimated that children under the age of five ingest 2.5 times more soil and dust from around the home than

adults, yet they possess only about 20 % of the body weight (Hawley, 1985). Food dropped onto the floor or other residential surfaces, and subsequently eaten, presents another route by which pesticide residues can be transferred and ingested by small children.

The Food Quality Protection Act (FQPA) in the USA and the Pest Control Products Act (PCPA) in Canada mandate that potential risks to infants and small children be specifically addressed. When assessing the 'food' use of a pesticide, in order to assure 'that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide's chemical residues', the FQPA and PCPA in the case of threshold effects call for an 'additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure' to be applied to estimating risks to infants and children. A different margin of safety may be used only if, on the basis of reliable data, such a margin will be safe for infants and children. In Canada, these same requirements also apply to 'non-food-use' pesticides.

More studies are needed, however, to better estimate the exposures of small children to residential pesticides. Better methodologies need to be developed and applied to more accurately determine surface-to-skin and skin-to-mouth transfer efficiencies, pesticide bioavailability from ingested dust and the relationship of child-activity patterns to residential exposures. Such studies are essential before reliable exposure assessments can be made.

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4 Residential (Non-Dietary) Post-Application Exposure Assessment

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INTRODUCTION

Pesticides applied in and around homes by both professional applicators and consumers are used in different ways for different purposes: (1) indoor uses (e.g. floor sprays or foggers for fleas) and outdoor uses (e.g. treatment of wasp nests and ant mounds; use of antimicrobial products in swimming pools), (2) turf uses (e.g. granular applications for control of soil-dwelling insect pests, pre-emergent and post-emergent herbicide sprays) and ornamental uses (e.g. foliar sprays for shrubs), (3) home garden uses (e.g. fungicide dusts for tomatoes), and (4) structural pest control uses (e.g. structural treatment or insecticidal soil barriers to protect against termite invasion). The majority of US households use pesticides (Whitmore *et al*., 1992) and these uses present opportunities for exposure during intended, label-directed use, misuse and accidents. Other sources of indoor exposure to pesticides for the general population may be from ambient air, food, water, ambient particles and indoor house dust (Wallace, 1991, 1993; Jenkins *et al*., 1992; Pellizzari *et al*., 1993; Whitmore *et al*., 1994).

Following the use of products in and around the home, post-application chemical exposures to consumers may occur in a variety of microenvironments that correspond to the daily activities in which adults and children engage. These activity patterns may place individuals in contact with chemicals (e.g. transferable residues – residues potentially transferred from a treated surface to skin or clothing during gardening, lawn chemical exposures following re-entry onto treated turf and chemical emissions from treated surfaces inside the residence). To understand the potential health significance of these exposures it is necessary to characterize their sources and estimate their magnitude. In response to these needs, efforts have been undertaken to develop methodologies for quantifying pesticide and other chemical exposures in soil, air, food and water (Thompson *et al*., 1984; Ott, 1985; McKone, 1991, 1993; Cal-EPA, 1994; Curry *et al*., 1994; Vaccaro *et al*., 1996; Wallace, 1987, 1989, 1990, 1991; Wallace *et al*., 1982, 1984, 1985, 1986, 1987a,b,c, 1988, 1989, 1991a,b).

Exposure assessments often assume that exposure can be linked by single parameters to ambient concentrations in air, water, soil and food products. However, for human populations, total exposure assessments that include time and activity patterns and microenvironmental data reveal that an exposure assessment is most valuable when it provides a comprehensive view of exposure pathways and identifies major sources of uncertainty. Thus, we see the need to address many types of 'multiples' in the quantification of exposure and dose, such as multiple media (air, water and soil), multiple exposure pathways or multiple routes (ingestion, inhalation and dermal) and multiple target tissues for dose and effect, as delineated in the US Food Quality Protection Act of 1996. These multiples are called *aggregate exposure* when a single chemical is involved and *cumulative exposure* when multiple chemicals with the same toxicological effect are involved (ILSI, 1998). The United States Environmental Protection Agency (USEPA), in response to the Food Quality Protection Act of 1996 (FQPA, 1996), has been revising exposure monitoring guidelines which emphasize nonoccupational, residential exposure to pesticides; these guidelines are referred to as Series 875, *Occupational and Residential Exposure Test Guidelines; Final Guidelines.* Of specific interest is the *Post-Application Monitoring Test* (USEPA, 1996c; Whitford *et al*., 1999). The Series 875 guidelines provide information and protocols relevant for persons required to submit post-application exposure data under 40 CFR 158.390 (Figure 4.1). Generally, these data are required under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) when certain toxicity and/or exposure criteria have been met for a given pesticide (Driver and Wilkinson, 1996).

Although at a low level relative to occupational exposures, it is becoming apparent that a major source of chemical exposures for the general population results from the use of products in and around the home (Whitmore *et al*., 1994; Hill *et al*., 1995). Information and data regarding pesticide health-related incidences can be obtained from the American Association of Poison Control Centers (website: http://www.aapcc.org), the US Environmental Protection Agency (website: http://www.epa.gov/pesticides) or state regulatory

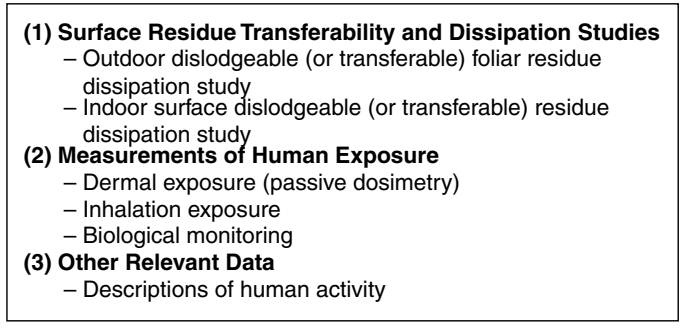

Figure 4.1 The USEPA Series 875 Guidelines

agencies, e.g. the California Department of Pesticide Regulation (website: http://www.cdpr.ca.gov.).

Given recent and renewed scientific and regulatory interest in children's health, and the passage of the FQPA and the ongoing Toxic Substances Control Act (TSCA) High Production Volume Chemicals program in the USA, it is perhaps not surprising that the potential health risks associated with exposure to chemicals, such as pesticides, occurring in and around the home are being evaluated much more carefully now than in the past by regulatory agencies in many different countries (Driver and Wilkinson, 1996).

KEY FACTORS TO CONSIDER IN RESIDENTIAL EXPOSURE ASSESSMENT

The residential exposure assessment process presents numerous challenges and data sources which must be taken into consideration (Figures 4.2–4.5).

POPULATION AT RISK

The age distribution in the residential population spans a wide range of age groups (infants, toddlers, teenagers, adults and the elderly) which tend to be

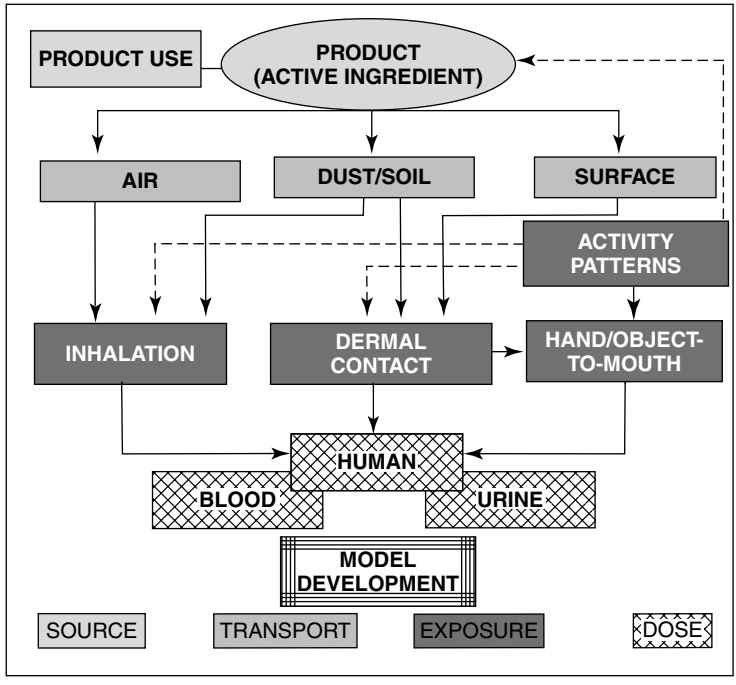

Figure 4.2 Factors involving models for residential exposure assessment

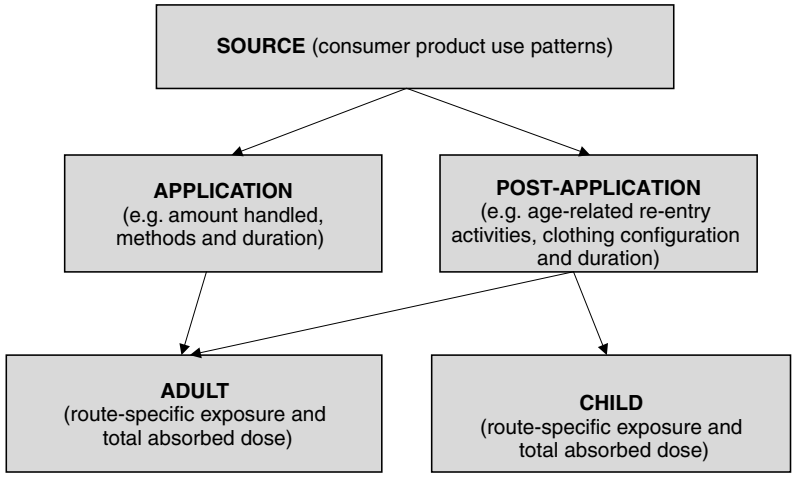

Figure 4.3 Overview of non-dietary (residential) exposure assessment

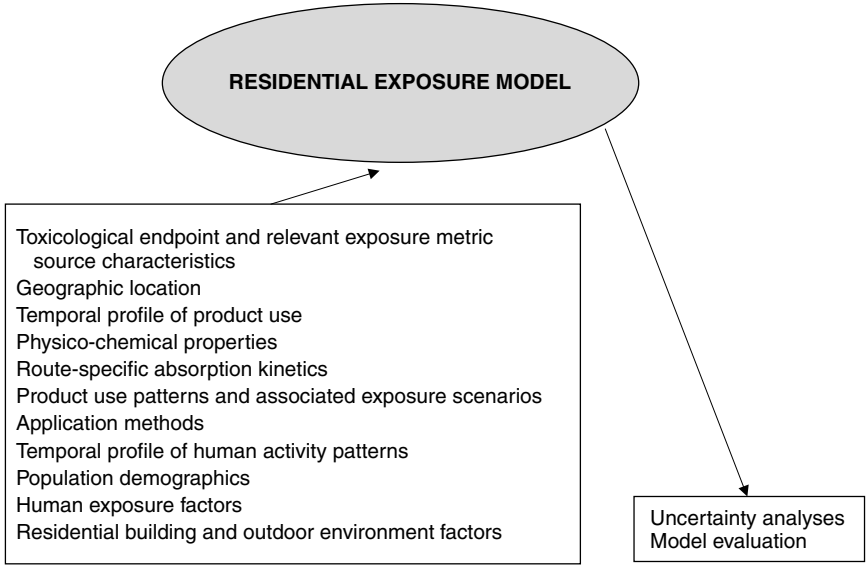

Figure 4.4 Key components of residential exposure assessment (analyses)

more female-dominated and include family members at home with an illness. The magnitude of exposure will vary because body weight, surface area and inhalation rates differ between age, gender and activity level.

The route and magnitude of exposure will vary. Infants and toddlers spend time crawling and playing on floors and carpets, may wear little clothing (e.g.

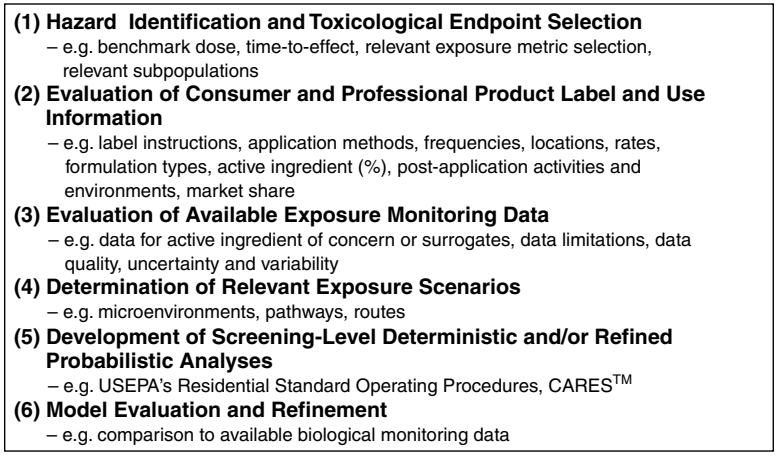

Figure 4.5 Residential exposure assessment – stepwise process

only diapers), breath air which is nearer the floor and spend most of their time indoors when compared to adult members of the same family. These differences are important because the floor and carpets may receive pesticide applications, less clothing means more opportunity for the pesticide to transfer directly from the carpet to the skin, and some studies have shown higher concentrations of pesticides in the air near the floor (the breathing zone for children).

EXPOSURE FREQUENCY, DURATION AND HUMAN TIME–ACTIVITY PATTERNS

The exposure frequency (the number of days per year and years per lifetime) and duration of exposure (minutes or hours of exposure to an agent for a given day on which exposure occurs) are critical variables for estimating residential exposures to pesticides. These are a function of product use patterns, human activities that bring individuals in contact with areas that may contain a pesticide, and the nature of the population's mobility, all of which limit the total number of days and years an individual may be exposed to a site-specific contaminant. For instance, a baby crawling on a floor, a person exercising on the carpet, an adult applying pesticides in the backyard, or teenagers playing touch football on the front lawn are but a few activities that can bring a person into contact with a pesticide when the floor, carpet or lawn has been treated.

SOURCE CHARACTERISTICS

Important factors in determining the impact of sources in the residence on exposures are the nature of the source (e.g. consumer product or professional application), how it is released (fine respirable aerosols, non-respirable coarse

aerosols or vapor release) and the source strength (roughly proportional to the concentration of the chemical in the source or product).

PHYSICAL, CHEMICAL AND BIOLOGICAL PROPERTIES

In the case of chemical pesticides, these include factors such as molecular weight and vapor pressure that determine the rate of evaporation into air of the pesticide in an applied material such as paint, or the release from aqueous solution. In the case of biological agents, these include, for example, pathogenicity to humans, allergenicity, infectious dose levels and aerosol particle size distribution.

RESIDENTIAL BUILDING FACTORS

The basic characteristics of the rooms and building in which residential exposures occur, as well as the ventilation configuration (i.e. number of windows and doors open, the rate of mechanical ventilation and air mixing, and the rate of infiltration of outside air) will determine the extent and rate of dilution of the agent of interest in a specific indoor air setting.

STUDY DESIGN CONSIDERATIONS

Techniques and study designs for measuring residential exposures have historically been less defined than other assessments. It is exceedingly difficult to write study design protocols that encompass all exposure scenarios since human activities are so diverse. Testing flexibility is also required in exposure assessments, since pesticides applied around a residence needs to account for how a pesticide is used (fogging, crack and crevice, and carpet treatment), and knowing that human activity has the possibility of leading to extremes (high and low) or considerable variability. Requiring studies with rigid protocols might produce precise exposure estimations under one set of conditions while proving a poor and inaccurate predictor of exposure under differing circumstances.

A consensus has developed from the scientists conducting residential exposure assessments; screening-level or initial ‘tier’ exposure estimates need to be obtained from those activities and pesticide applications that maximize human contact potential with the pesticide such as a baby crawling on a treated surface. Assessments which conclude minimal risk to humans from maximum exposures are then used to predict minimal risk at lower exposures.

As discussed in Whitmyre *et al.* (1992a,b), a number of these factors are associated with a wide range of variability across an affected population, resulting in uncertainties. Thus, the true distribution of exposures across the population would likely span several orders of magnitude. Rarely are all of these issues resolved by the exposure data available for a given assessment. Therefore, efforts to collect the data should focus on the minimum needed to conduct a scientifically credible analysis and meet the goals of the assessment in its risk management context.

HUMAN ACTIVITY PATTERNS

Residential risk assessment to pesticides typically involves more than one source and multiple pathways and routes, e.g. a given active ingredient may be used for multiple indoor applications, and in some cases, for outdoor applications. In some cases, the applications may overlap with respect to timing (calendar days). The potential co-occurrence of applications and potential exposures requires temporal product use information. Such information is rarely available.

For purposes of screening-level assessments, while multiple applications may exist for a given pesticide, e.g. indoor residential exposures may originate from pesticide applications to ornamental and landscape plantings, typically a 'worst-case' or 'high-end' exposure scenario is selected for the initial assessment. For example, turf grass broadcast application is the use pattern that often serves to provide the 'worst-case' estimates of human contact and exposure for most outdoor uses of a pesticide.

Outdoor turf studies are typically conducted in those areas of the country where the product is expected to be used. The highest labeled rate is applied during the time of year that would correspond to local use. Samples from the turf site are obtained prior to and immediately after the pesticide treatment. A typical outdoor study will take many more samples shortly after the application when the pesticide is at its highest concentrations and will thereafter take fewer samples as the study time increases. The samples are taken in time after application to determine how fast the pesticide dissipates after application. However, they additionally measure how well the pesticide transfers from the turf to skin or clothing.

Indoor exposure assessments can be more complex than outdoor assessments. The indoor assessments are often complicated by the fact that pesticide application methods and their placement within the indoor environments are very diverse and include, for example, crack and crevice treatment, carpet treatment, room foggers, moth repellents, residual termiticides, disinfectants and pet products. This diversity also means that potential human contact with the residues may range from a low probability (crack and crevice treatment) to a higher probability (indoor broadcast treatment such as an indoor total release fogger) because of the nature of the application and the variability in activities that may bring individuals in contact with treated areas. Furthermore, the varied characteristics of the source (e.g. formulation type, application methods, room of application and duration of emission) and the indoor residential environment (e.g. room size, air exchange rates, temperature and types of surfaces, such as carpet, upholstery, vinyl, etc.) significantly influence exposure potential.

The many uses of an indoor pesticide require that exposure estimates should be based on the most likely application that will lead to the highest probability of dermal and inhalation contact. For instance, a broadcast carpet treatment is generally presumed to result in more pesticide surface residue being accessible to individuals than the amount or accessibility of residue when the pesticide is placed inside an insect bait station.

The typical end-use product and application method chosen as representative of the 'extreme-case' exposure scenario must be used to attain the highest permissible rate allowed by label directions. Sampling for indoor residues should consider all potential sites where appreciable residues are expected and are accessible. For instance, dermal contact may come from exposure to the pesticide as a residue on carpets, vinyl tile, upholstery and counter tops, while airborne residue (vapor- or particle-phase) may provide the source of inhalation exposure. The measurements taken are linked specifically to the method of application.

QUANTITATIVE EXPOSURE ASSESSMENT

Accurate exposure and biological monitoring data are crucial to the evaluation of residential exposure and risk estimates since the potential health risks associated with a pesticide depend on the amount of exposure to the pesticide, its toxicity and the susceptibility of the exposed population. Prediction of whether adverse health effects will occur in humans can be made by comparing the exposure estimate to the No Observed Adverse Effect Level (NOAEL) derived from the animal toxicity data. Uncertainty arises from the 'input data' used in an assessment, e.g. variability in time–activity patterns, contact with exposure media, bioavailability, exposure duration, frequency of product use and differences in the route of exposure in humans from that in the animal studies (since absorption, distribution, metabolism and elimination kinetics may differ substantially by exposure route).

ESTIMATION OF ABSORBED DOSE

The challenge is to be able to measure the absorbed (internal) dose in humans, particularly in the context of estimating potential total absorbed dose from all possible sources and routes (aggregate exposure). Several approaches have been used and each requires additional data or assumptions to convert the amount measured to the absorbed dose. A measure of the pesticide in the ambient air, water and food would indicate the potential exposure, but would not provide an acceptably accurate estimate of absorbed dose to be used with confidence in a quantitative estimation of exposure. The preferred approach for measuring the actual amount of pesticide that comes in contact with biological exchange boundaries, e.g. the skin, the lungs and the gastrointestinal (GI) tract, for a defined period of time is to measure 'personal contact' exposure. This can be done by using whole-body cotton dosimeters to measure dermal exposure, by measuring air concentrations in the breathing zones of adults and children, and by analyzing the concentration in food as eaten ('market basket sampling'). The resultant sum is an amount known as the *contact* or *applied dose*. Absorption of the pesticide through each of the biological exchange boundaries is necessary to estimate absorbed dose and is a function of the concentration and duration of exposure.

The best, but sometimes more difficult, approach would be to measure the amount of pesticide or its metabolites in blood or target tissues (biological monitoring) taken periodically through the exposure period. To derive an accurate estimate of absorbed dose, knowledge of the pharmacokinetics of the pesticide would also be required. In some cases, the absorbed dose can be estimated from the amount of pesticide excreted in saliva, urine and/or feces.

The different types of 'dose' have been defined for purposes of exposure assessment (USEPA, 1992a). Applied (contact) dose is the amount of the agent directly in contact with the body's absorption barriers (biological exchange boundaries). Internal (absorbed) dose is the amount of the agent crossing the absorption barriers and, therefore, available to undergo metabolism, transport, storage and/or elimination. Delivered dose (body burden) is that portion of the internal dose that reaches a tissue of interest. Biologically effective (target) dose is that portion of the delivered dose that reaches the tissue or sub-cellular sites of toxicological action.

DAILY EXPOSURE ESTIMATION

Once there is a measure of the concentration of the pesticide in the exposure medium (air, water, food, etc.) in contact with the body or the actual concentration that comes into contact with the body, a daily dose metric can be calculated (e.g. maximum, average, geometric mean, etc.). This typically involves developing a mathematical equation that expresses dose as a function of pesticide concentration and other important parameters referred to as human exposure factors (USEPA, 1999a). In the context of this discussion, the term *human exposure factor* refers specifically to: (a) human characteristics, such as body weight, surface area, life expectancy, inhalation rates for air and consumption rates for food, drinking water and soil; (b) human behaviors, such as activity patterns, occupational and residential mobility and consumer product use, which are used by exposure assessors to calculate potential dose.

CALCULATION OF DAILY ABSORBED DOSE

Starting with a general integral form of the equation for exposure, several dose equations can be derived depending on boundary assumptions (USEPA, 1992a). One of the most important is the Average Daily Exposure or Dose (*ADE* or *ADD*) equation, which calculates an average absorbed dose over the time period of interest and is widely used by the USEPA (and other regulatory agencies) when assessing many non-cancer health effects (USEPA, 1992a).

The *ADD* can be calculated by dividing the total potential dose by the product of body weight and an averaging time, where total potential dose is equal to the product of four factors: (a) concentration of the agent in an environmental medium that is in contact with the outer boundary of the body; (b) intake rate, which is the rate of inhalation for air, rate of ingestion for water, food and soil

contaminants, and body surface area for dermal exposure; (c) duration, which is the length of time contact occurs between the agent and the person; (d) exposure frequency, which is how often contact occurs (USEPA, 1992a). This is given by the following equation:

$$ADD = \frac{C \times IR \times ABS \times ED \times EF}{BW \times AT} \tag{4.1}$$

where *ADD* is the average daily dose (e.g. mg/kg per day), *C* the concentration of the agent in a carrier medium (e.g. mg/L, mg/g, mg/m^3 or mg/cm^2), *IR* the intake rate, i.e. the inhalation rate (amount of air breathed per unit time) (e.g. m^3/day), ingestion rate (amount of water or food consumed per unit time) (e.g. L/day or g/day) or body surface area exposed (cm^2/h), *ABS* a route-specific absorption fraction, *ED* the exposure duration, i.e. time of contact at specified values for *C* and *IR* (e.g. years), *EF* the exposure frequency, if intermittent, number of times exposures occur (e.g. days/year), *BW* the body weight for an exposed person or average for an exposed population (e.g. kg) and *AT* the averaging time, i.e. period over which the dose is averaged (e.g. days).

The general *ADD* equation described above is applicable when intake rate, exposure duration, exposure frequency, body weight and pesticide concentration remain constant over the time period of interest. If they change over time, then it is necessary to use either a summation or integration approach to calculate potential dose (USEPA, 1992a).

CONSTRUCTING PLAUSIBLE RESIDENTIAL EXPOSURE SCENARIOS

When data from actual exposure studies are not available, a major challenge confronting residential exposure assessors is deciding how best to construct a plausible scenario and evaluate it quantitatively to obtain a realistic estimate of potential dose. Decisions about which values to use for critical human exposure factors are central to resolving key exposure and dose-related questions successfully. Depending on the complexity and comprehensiveness of a particular exposure assessment, literally hundreds of variables may need to be considered, as, for example, with multi-chemical, multi-pathway assessments. Although typically only a relatively few human exposure factors cause most of the variability and uncertainty in the final estimate, it is not always clear at the outset which are most important and which have minimal or negligible effects.

Quantified values for human exposure factors are best determined on a case-by-case basis, with site-specific and source-specific circumstances driving choices about appropriate values for intake rates, exposure duration and frequency, body weight, averaging time and other related variables affecting calculation of the *ADD*. Each exposure assessment is unique and the assessor must construct a scenario and tailor related human exposure factors to fit the conditions at hand.

Consequently, it is difficult, and potentially misleading, to make generic statements about which scenarios and human exposure factors are most appropriate.

SCREENING-LEVEL ASSESSMENT

One type of exposure assessment that does lend itself to general discussion is a 'screening-level' assessment. The latter refers to a preliminary evaluation that is usually cursory and relatively quick and inexpensive. Moreover, it is general in nature rather than either site- or situation-specific. Typically, screening-level assessments are performed using readily available (i.e. published) recommended values for human exposure factors to give the assessor a sense of (1) whether preliminary evaluation suggests the possibility of adverse health risks, thereby indicating the need for more in-depth analysis, or (2) the approximate range of exposures that might be expected in the general population under normal, everyday conditions, which is helpful for placing site- and situation-specific estimates into perspective.

UNCERTAINTY AND VARIABILITY

The five factors that determine the precision or reliability of an exposure assessment are as follows:

- specification of the problem (scenario development);
- formulation of the conceptual model (the influence diagram);
- formulation of the computational model;
- estimation of parameter values;
- calculation and documentation of results, including uncertainties.

An uncertainty analysis involves the determination of the variation of imprecision in an output function based on the collective variance of model inputs. One of the five issues in uncertainty analysis that must be confronted is how to distinguish between the relative contribution of variability (i.e. heterogeneity) versus true certainty (measurement precision) to the characterization of predicted outcome. Variability refers to quantities that are distributed empirically – such factors as soil characteristics, weather patterns and human characteristics – which come about through processes that we expect to be stochastic because they reflect actual variations in nature. These processes are inherently random or variable, and cannot be represented by a single value, so that we can determine only their moments (mean, variance, skewness, etc.) with precision. In contrast, true uncertainty or model specification error (e.g. statistical estimation error) refers to an input that, in theory, has a single value, which cannot be known with precision due to measurement or estimation error.

RESIDENTIAL EXPOSURE MONITORING METHODS

Measurement of the post-application residential exposure is, in many ways, more complicated than the agricultural re-entry since there may be multiple sources and routes of exposure, varying amounts of time spent in contact with these sources and a much wider age and health range in the exposed population (USEPA, 1991, 1999a). Chemicals such as pesticides that are released into or otherwise enter the residential environment tend to partition into various compartments, either through direct dispersion in indoor air or through adsorption onto surfaces that serve as 'sinks' from which material can subsequently be released into the air (Ross *et al*., 1990, 1991). A detailed discussion of the measurement of pesticides in the residential environment is presented in Chapter 3.

DERMAL AND HAND/OBJECT-TO-MOUTH EXPOSURE STUDIES

While inhalation exposure and indoor air quality have received the most attention to date, there are a number of non-inhalation exposure pathways that are likely to be of equal or greater importance in regard to human residential exposures to pesticides and other chemicals. These include potential dermal exposure to dislodgeable or transferable chemical residues from surfaces such as floors and carpets, or from hard surfaces resulting from the use of formulations for cleaning and disinfection. These measurements can also be used, in conjunction with other factors, e.g. hand-to-mouth frequency, saliva removal efficiency and surface area of hands-involved mouthing events, to estimate potential incidental ingestion of surface contaminants by children (e.g. 0–2 years old). Several studies and/or reviews provide examples of non-inhalation residential exposures and the complexities involved (CTFA, 1983; Turnbull and Rodricks, 1989; Driver *et al*., 1989; Calvin, 1992; Harris and Solomon, 1992; Harris *et al*., 1992; Vermiere *et al*., 1993; ECETOC, 1994; USEPA, 1996a). Dermal exposure modeling methods have been developed based on transferable residue measurements, concurrent with human volunteer passive dosimetry measurements following pesticide application (Ross *et al*., 1990, 1991).

HUMAN ACTIVITY EXPOSURE MONITORING STUDIES

Human volunteer monitoring studies often involve the use of whole body dosimetry, air sampling or biological monitoring methods. These study designs vary, however, and the activities engaged in by the volunteers are documented, whether choreographed or 'normal'. Choreographed activities provide the advantage of being able to better relate environmental measurements to actual human exposure during specific interactions with the environment (such as crawling across a carpet following treatment) (Ross *et al*., 1990, 1991). Jazzercise™-based routines have been used in some studies to provide reproducible and 'upper-bound'

measurements of potential pesticide exposures (inhalation and dermal) following treatment of surfaces (e.g. carpets and lawns). Jazzercise™ is an exercise program consisting of a set number of routines each lasting approximately 20 min. The study volunteers are usually led through the exercises by a certified Jazzercise™ instructor. The exercises selected are those that will bring the volunteers into repeated intensive contact with a pesticide-treated surface, such as carpet. Healthy adult volunteers are provided with a complete set of dermal passive dosimeters, i.e. long underwear consisting of long-sleeved shirt, tights, socks and gloves made of thin cotton. Volunteers enter the rooms treated with a pesticide and are assigned to specific areas within each room (or area on a lawn). The volunteers then perform the Jazzercise™ routines and at the conclusion of the program are asked to place the clothes – gloves, socks, tights and shirt – individually into separately marked plastic bags.

MODELING METHODS

Estimating or modeling potential indoor and outdoor residential exposures is a complex task and requires the use of available exposure monitoring data in conjunction with label and use information. Furthermore, evaluation of uncertainty and validation of predictive models are important to establish scientific credibility. Residential exposures are typically estimated for adult applicators and for both adults and children during post-application activities. Depending on the toxicological effect being evaluated, route-specific exposures may be calculated separately, or a total absorbed dose may be estimated. In the case of children, the total absorbed dose may include contributions from the dermal and inhalation routes and from incidental ingestion (such as from hand-to-mouth contact). Typical residential exposure assessments address the following:

(1) potential consumer applicator exposure (dermal and inhalation);
(2) potential post-application inhalation exposure;
(3) potential post-application dermal exposure;
(4) potential post-application ingestion exposure.

The models and methods used for purposes of estimating potential residential exposure (and absorbed dose) continue to be refined and validated as new monitoring studies become available. The goal is to simulate actual exposure conditions as closely as possible. The following sections present an example of a simplistic screening-level exposure assessment calculation for a consumer product, followed by a discussion of how more refined, probability-based or uncertainty analysis methods can be used. Screening-level methods typically include conservative bias in the form of ‘default’ assumptions that are used in the absence of directly relevant and robust exposure monitoring data and other information. These methods can be used to predict potential exposure. However, it

may be necessary to refine the screening-level assessment, if excessive health risk is suggested, to determine more realistic estimates of the potential distribution of exposures and corresponding health risks. This is often referred to as the 'tiered' approach to exposure and risk analysis. Initial tier calculations can typically be characterized as highly conservative, sometimes even as 'theoretical upper-bound estimates'. The overall conservatism results from a variety of sources, including the use of studies based on human activities (e.g. Jazzercise™) that overestimate exposures associated with more typical residential activities (e.g. walking, crawling and sitting), the use of conservative 'clothing scenarios' (e.g. no clothing being worn by infants and children), the use of conservative methods for estimating the transport and fate, and relative bioavailability of chemical residues on days following application, etc.

It is desirable to also develop distributional expressions of exposures and absorbed doses to more accurately reflect the underlying mathematical variability and uncertainty associated with key variables included in the analysis and to determine how conservative the initial screening-level estimate is, i.e. what percentile it represents (e.g. 50th, 75th, 90th, 95th, etc.). This latter representation of exposure and absorbed dose more adequately characterizes the overall uncertainty and conservatism in the inherent assessment and provides more information to the risk manager for decision-making purposes.

To illustrate residential modeling constructs, Appendix 1 provides general algorithms associated with two approaches for estimating potential dermal and non-dietary ingestion exposure, referred to as the *micro-activity* and *macro-activity* approaches (Hubal *et al.*, 1999). In the micro-activity approach, exposure is modeled as a series of mass transfers or removals resulting from each discrete dermal contact event (e.g. right hand contacting toy for 10 s, fingers contacting mouth for 3 s, etc.). In the macro-activity approach, dermal exposure is modeled by using empirically derived transfer factors or coefficients (dermal contact rates) to 'lump' the mass transfer associated with a series of contact events in a pre-specified time domain (ILSI, 1998; Hubal *et al.*, 1999). The Residential Exposure Assessment Spreadsheet Tool (REX)/(available from www.infoscientific.com), for example, employs the macro-activity method while the EPA's Office of Research and Development's Residential-Stochastic Human Exposure and Dose Simulation (SHEDS) model for pesticides has, in some cases, relied on the micro-activity approach (Zartarian *et al.*, 2000).

In the micro-activity version of SHEDS, for example, sequential dermal and non-dietary ingestion exposure and dose–time profiles are simulated by combining measured surface residues and residue transfer efficiencies with actual micro-level activity data quantified from videotapes (Zartarian *et al.*, 2000). Given that the sequence of dermal loading and removal processes is captured from videography data, such exposure profiles can be used to generate hypotheses regarding time-dependent dermal exposure and absorption which have traditionally assumed a fixed concentration at the skin surface. In contrast, REX aggregates the micro-events into transfer factors (or coefficients) based on evidence of dermal

equilibrium with surfaces contaminated with dry surface residues (Ross *et al*., 1990, 1991; ILSI, 1998). With both dermal modeling constructs, information on frequency and duration of hand-to-mouth activities can then be used as the basis for estimates of ingested residues. Furthermore, in both cases exposure and dose profiles can also be developed for different time domains based on the toxicological metrics of interest (e.g. daily, sub-acute or sub-chronic time-weighted averages). In addition, these modeling tools are useful to evaluate the apparent relative contributions of different exposure pathways and routes. When combined with product-use information and time-activity data, temporal exposure and dose profiles can also be used to construct 'calendar' views of exposure events, cumulative dose and how exposures can be mitigated, if deemed necessary. Temporal aggregate and cumulative exposure models, such as CARES, LifeLine, Calendex and SHEDS, have been developed for this purpose.

TIERED APPROACHES TO EXPOSURE ASSESSMENT

As described in the USEPA's Exposure Assessment Guidelines (USEPA, 1992a), a tiered approach to exposure assessment and the underlying exposure modeling provides a means for time-efficient and cost-effective utilization of resources for decision-making purposes. The quality of scientific information/data, the kind and degree of professional judgements/assumptions, and the level of sophistication (e.g. deterministic, point-estimates versus probability-based simulation, etc.) that are incorporated into tiered exposure assessments and modeling processes should be appropriate to the purpose for which the assessments will be used. Table 4.1 provides some exemplary model 'selection criteria' as recommended

Table 4.1 Some considerations in the selection of models (USEPA, 1997a)

Selection criteria
• Appropriateness of the model's assumptions *vis-à-vis* the analysis objectives
• Compatibility of the model input/output and linkages to other models used in the analysis
• The theoretical basis for the model
• Level of aggregation, spatial and temporal scales
• Resolution limits
• Sensitivity to input variability and input uncertainty
• Reliability of the model and code, including peer review of the theory and computer code
• Verification studies and relevant field tests
• Degree of acceptance by the user community
• Friendliness, speed and accuracy
• Staff and computer resources required

in the EPA's Guiding Principles for Monte Carlo Analysis (USEPA, 1997a) to facilitate appropriate matching of the exposure assessment's objectives to the capabilities and degree of uncertainty provided by available models.

DETERMINISTIC (POINT-ESTIMATE) EXPOSURE ASSESSMENTS

These are intended for 'screening-level' purposes and will tend to overestimate potential exposures because of the use of conservative assumptions and values for multiple variables. The combination of multiple conservative assumptions and overly simplistic models often results in exposure estimates that are in the 'high-end' (i.e. greater than the 95th percentile) of the actual exposure distribution or even higher than the maximum expected value. The latter estimate is referred to as a Theoretical Upper-Bound Estimate (TUBE). Thus, deterministic (point-estimate) exposure assessments intended for screening-level purposes will often be significantly influenced by uncertainties and assumptions that bias towards 'high-end exposures' such that the resulting estimate represents either a theoretical upper-bound or an upper percentile of the actual distribution of potential exposures. In the context of a 'tiered approach' to exposure assessment, if conservative screening-level exposure estimates result in a risk assessment that is considered to not pose unacceptable health risks, then the assessment may not require additional refinement. However, if the screening-level assessment suggests exposure levels that may not be considered 'safe', the assessor should carefully reconsider the modeling approach used and should consider the use of more realistic assumptions, alternative models, data quality objectives and appropriate uncertainty analyses.

PROBABILISTIC EXPOSURE ASSESSMENTS

When necessary, the assessor should consider the use of more advanced analysis methods (e.g. probability-based methods or more sophisticated/rigorous models) and focused data collection efforts to facilitate the development of a modeling approach that will result in estimates that are more representative of the actual exposure distribution. In the case of data collection, the value of information that could be gained is an important part of justification for the reduction of uncertainties by further study.

REPORT WRITING

Regardless of the level of sophistication, the exposure model(s) used for a given purpose/situation should be accompanied by sufficient documentation and reporting so that the assumptions, underlying mathematical and statistical procedures, data quality and transformations, input and output, validation procedures, minimally required data and intended use and limitations are transparent and clearly defined. These are essential components of good exposure modeling practices. Such practices ensure that an appropriate level of understanding can be achieved

by users and individuals making decisions based on the results obtained from a given model. The following components have been adapted, in part, from recommendations of the American Industrial Health Council (AIHC) (1994) to provide adequate documentation for models used in the context of exposure assessments.

PROTOCOL/USER'S GUIDE

Every exposure assessment should have a protocol written before its initiation. This protocol should first state the purpose of the exposure assessment and the model(s) used therein. It should also include the variables to be evaluated (i.e. a clearly defined assessment endpoint), the level of detail needed, how uncertainty will be addressed, and the relationship of uncertainty to the conclusions that may be drawn. Furthermore, the protocol should describe each of the other principles of practice noted below in sufficient detail so that the assessment is clearly adequate for the purpose. Similarly, exposure models used in assessments should be accompanied by adequate documentation regarding procedures for using the model, plus the minimum information that is required as input data and software references and computer system requirements.

GENERAL DESCRIPTION OF EXPOSURE MODEL

The model or set of models to be used in the exposure assessment to relate the presence of a substance to human exposure/absorbed dose should be stated. The model's general description should provide enough detail so that the user or reviewer understands the input variables, underlying mathematical algorithms and data transformations and output/results, such that the model can be easily compared to other alternatives. The basis for each model, whether deterministic, empirical or statistical, should be described. The statement of the model should include which variables are measured and which are assumed. A description should be provided of how uncertainties in the parameters and the model itself are to be evaluated and treated.

DETAILED DESCRIPTION OF MODEL INPUTS AND OUTPUTS

Descriptions of model input variables, e.g. data collection methods, analytical methods, data transformation procedures, etc., should be stated. Furthermore, appropriate statistical measures should be included for both input variables and model results (output) to facilitate qualitative and quantitative evaluations of uncertainty and appropriate interpretations.

EXPOSURE MODEL VALIDATION

Validation of an exposure model involves two primary processes: (1) verifying the underlying mathematical and statistical procedures, and (2) evaluating the

model's overall predictive accuracy and precision through comparisons to relevant empirical data. In the absence of adequate empirical data, statements should be made regarding the absence of model validation studies and any plans for future validation should be described.

QUALITY ASSURANCE PRACTICES

Procedures should be established and recorded to ensure that an acceptable quality level is associated with input data extraction and use, model execution and validation procedures. The procedures described by the EPA's Good Automated Laboratory Practices (GALP) should be considered, where applicable.

ARCHIVING

Model protocol/procedures, inputs and outputs, and other relevant information/documents should be retained so that they are retrievable for a specified period.

RECOMMENDED GENERAL PRINCIPLES FOR EXPOSURE ASSESSMENTS

In addition to the exposure model 'documentation components' noted above, the American Industrial Health Council (AIHC) (1994) and USEPA (1997a) have recommended data, particularly those based on Monte Carlo simulation, that are also relevant for simulation models being used as part of the overall assessment process. The USEPA has also issued guidelines for data quality assessment (USEPA, 1996b) relevant to model documentation. Some of these principles are listed below; more details are provided in USEPA (1992a, 1997b), AIHC (1994) and Burmaster and Anderson (1994).

(1) Describe all formulae and validation procedures.
(2) Calculate and present deterministic point estimates (based on regulatory agency recommended methods) in contrast to distributional representations.
(3) Present the results from univariate (or multivariate) sensitivity analyses of the deterministic calculations to identify the inputs suitable for probabilistic treatment, and then discuss any variables not included in the sensitivity analysis.
(4) Consider restricting the use of probabilistic techniques to the most significant exposure pathways/routes.
(5) Provide detailed information on the input distributions selected.
(6) To the extent possible, describe how the input distributions (and their parameters) capture and represent both the variability and the uncertainty in the input variables.

(7) Use measured data to inform the choice of input distributions whenever possible, after making sure that the data are relevant and representative of the demographic, spatial and temporal situation.
(8) Discuss the methods and report the 'goodness-of-fit' statistics for any parametric distributions for input variables that were fitted quantitatively to measured data.
(9) Discuss the presence or absence of moderate to strong correlations between or among the input variables.
(10) Provide detailed information and graphs for each output distribution.
(11) Perform probabilistic sensitivity analyses for all of the key inputs represented by a distribution in the Monte Carlo analysis in such a way as to distinguish the effects of variability from the effects of uncertainty in the inputs.
(12) Investigate the numerical stability of the (a) central moments (mean, standard deviation, skewness and kurtosis), and (b) the tails of the output distribution of the simulation.
(13) Present the name and the statistical quality of the random number generator used.
(14) Discuss the limitations of the methods and of the interpretation of the results, including the source, the nature, and the possible effects of any unresolved sources of bias not explicitly included in the analysis, and indicate where additional research or measurements could improve the analysis. In addition, a sensitivity analysis should be performed to assess the influence of the input parameters on the exposure assessment; this can also be used to illustrate the effect of subjective judgments on the exposure assessment (including Delphi-derived information).
(15) Finally, the results of the modeling, e.g. stochastic simulations based on the comparison of available exposure measurements (such as surface residue transferability and passive dosimetry), can be validated by comparison with the concurrent biomonitoring data for a surrogate chemical following broadcast carpet treatment in homes. These comparisons are usually based on data obtained for adults or adult volunteers simulating the activities of infants and children (e.g. playing with blocks, crawling on the floor, etc.).

STANDARD OPERATING PROCEDURES

The most recent effort to develop guidance for residential exposure assessment methods has been initiated by the USEPA's Office of Pesticide Programs in the Standard Operating Procedures for Residential Exposure Assessment (USEPA, 1996b, 1997c, 2001). The passage of the FQPA mandated the USEPA to immediately begin routinely addressing non-dietary and non-occupational pesticide exposures for the general population. These are exposures that can occur in a residential setting (or other areas frequented by the general population) and that

do not occur as part of the diet or as a result of participation in occupational practices. Such exposures may include breathing vapors while inside a treated home, exposures to children playing on a treated lawn, or exposures attributable to the mouthing behaviors of infants and children. Prior to the passage of the FQPA, the USEPA addressed these kinds of exposures on a case-by-case basis, typically in the 'special review' process. The intent of the USEPA Standard Operating Procedures (SOPs) is to provide a means for consistently calculating single-pathway, screening level exposures and not to provide guidance on other related topics such as aggregate (multi-source to a given pesticide) or cumulative (multi-source to two or more pesticides with a presumed common mechanism of toxicity) exposure assessments. These SOPs are the backbone of the USEPA's current approach for completing initial tier (screening-level) residential exposure assessments. However, the state-of-the-science continues to evolve since the release of the original document in 1997 and the emphasis of industry, as well as academia and others, has clearly focused on the scientific and policy issues raised by the implementation of the FQPA and use of the first-generation SOPs. Thus, revisions to the SOPs are continually ongoing in order to reflect the development of scientific information and the development of refined methods for estimation of potential residential exposures to adults and children.

Additional guidance for dermal exposure assessment methods and dermal permeability coefficients for some organic chemicals are contained in the USEPA's dermal exposure assessment guidance document (USEPA, 1992b). Given that skin surface area and body weight are closely correlated, total skin surface area to body weight ratios for use in residential exposure assessments have been recommended (Phillips *et al*., 1993). Another excellent source for methodology and data relevant to consumer product exposure assessments is ECETOC (1994).

A number of relevant data sources exist for key variables or factors used in performing residential exposure assessment. Data of use in estimating human exposures (e.g. distributions of body weights and skin surface areas, inhalation rates and residential occupancy periods) can be obtained from the American Industrial Health Council's *Exposure Factors Sourcebook* (AIHC, 1994) and the USEPA's *Exposure Factors Handbook* (USEPA, 1999a), which is currently being updated. Residential 'environmental factors' such as air exchange rates have been summarized by Pandian *et al*. (1993) and refined by Murray and Burmaster (1995). Human time–activity data in the USA have been summarized by USEPA (1999a), and compiled in the *THERdbASE* software (Pandian and Furtaw, 1995). Multiple data sources for time–activity data have been included in the USEPA's Consolidated Human Activity Database (CHAD) which is available via the Internet.

CONCLUSIONS AND RECOMMENDATIONS

Given that the potential for post-application exposures largely exists due to product use in and around the home, the need to develop and validate models for prediction of multi-pathway, multi-route exposures and absorbed dose is

evident. Historically, efforts have focused on indoor air and associated inhalation exposures. Jayjock and Hawkins (1993), for example, have explored the complementary roles of indoor air modeling and data development in improving the level of confidence in estimates of indoor inhalation exposures. More recently, dermal and incidental ingestion exposures have been the focus of monitoring and modeling efforts, e.g., the Outdoor Residential Exposure Task Force, Non-Dietary Exposure Task Force, OP Case Study Group and Residential Exposure Joint Venture (Zartarian and Leckie, 1998; USEPA, 1999b). Multi-pathway, multi-route modeling efforts for pesticides include the Residential Exposure Assessment (REX) model, the Stochastic Human Exposure and Dose Simulation (SHEDS) model, the Cumulative and Aggregate Risk Evaluation System (CARES), Calendex and LifeLine. The use of real-world data to validate residential exposure models is critical to developing estimates that are more representative than 'worst-case' estimates typically obtained from modeling approaches that have not been validated (Whitmyre *et al*., 1992a,b).

Other research activities related to residential exposure assessment currently being sponsored by the USEPA include the National Human Exposure Assessment Survey (NHEXAS) (website: http://www.epa.gov/heasd/edrb/nhexas.htm). In addition, the USEPA concluded a Co-operative Agreement, referred to as the Residential Exposure Assessment Project (REAP) with the Society for Risk Analysis (SRA) and the International Society of Exposure Analysis (ISEA) which resulted in a reference textbook (Baker *et al*., 2001) describing relevant methodologies, data sources and research needs for residential exposure assessment. The REAP and other efforts complement other USEPA initiatives, such as the development of the Series 875 guidelines, and will facilitate a sharing of information and other resources between the USEPA, other Federal and State agencies, industry, academia and other interested parties.

Residential exposures to pesticides and other chemicals are estimated by means of either monitoring and/or predictive modeling but, unfortunately, little or no guidance is available for those attempting such estimates. Key areas requiring attention include the following:

- characterization of temporal product-use patterns (particularly the likelihood of co-occurrence of more than one product-use event) and associated demographic and post-application activity information relevant to occupants of homes using products;
- source characterization, including emission rates, surface deposition, transferability to human clothing and skin and physico-chemical factors driving fate and transport processes;
- the complex interaction over time of environmental media residue concentrations with humans resulting from variable time–activity patterns that determine subsequent residential exposures (inhalation, dermal and incidental ingestion);
- identification of the fundamental principles, concepts and methods for conducting multi-pathway/multi-route residential exposure assessments, including

unique pathways such as incidental dermal exposure to dislodgeable or transferable pesticide residues from treated lawns, incidental ingestion of contaminated soil particles during gardening, hand-to-mouth transfer by infants and children, dermal exposure to dislodgeable pesticide residues from carpets and other treated surfaces, and incidental ingestion of post-application residues in food;
- characterization of key human exposure factors (ranges and distributions of factors such as age-specific inhalation rates, product use patterns and human time–activity data) and residential building factors (distributional data on housing stock type, number and size of rooms, air exchange rates, source emission rates and sink effects, i.e. adsorption/desorption from various surfaces in the home) that influence residential exposure and dosimetry;
- continued development and validation of methods for measuring and modeling indoor chemical fate processes (e.g. volatilization from surfaces, dislodgeable residue kinetics, etc.), chemical concentrations in complex matricies, such as house dust, and human intake (e.g. incidental ingestion, inhalation and dermal exposure);
- development and validation of methods for extrapolating from short-term monitoring data to long-term exposure scenarios, and for extrapolation of adult monitoring data to children;
- continued development and application of methods for quantifying uncertainty and variability (e.g. Monte Carlo methods) in residential exposure (and risk) estimates;
- the development and use of effective methods for comparing and communicating residential exposure and risk estimates to risk managers and the general public.

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APPENDIX 1 DERMAL EXPOSURE MODELING

Understanding the Variables Involved in Assessing Dermal Exposure Assessment: Macro- and Micro-Event Modeling

INTRODUCTION

The relative significance of the dermal route has been recognized in various occupational settings (e.g. agricultural worker re-entry into pesticide treated crops) and

more recently in the residential environmental (Popendorf, 1976; Fenske *et al*., 1990; Ross *et al*., 1990, 1991; Lewis *et al*., 1994; Zartarian and Leckie, 1998). A variety of direct (skin surface sampling) and indirect (environmental surface sampling, videography, etc.) measurements of dermal exposure have been developed, including the following: surrogate skin surface methods; cotton dosimeter patches and garments (Ross *et al*., 1990, 1991); removal methods; hand rinses or wipes (Fenske and Lu, 1994; Lewis *et al*., 1994); videotaping of human volunteers and analysis of dermal exposure-related variables (Zartarian *et al*., 1995, 1997); video imaging of skin surfaces exposed to fluorescent tracer compounds and surface sampling methods (Archibald *et al*., 1994, 1995; Black and Fenske, 1996); surface extraction, surface wipes and vacuum methods for dust, drag sleds, rollers and hand press (Popendorf, 1985; Ross *et al*., 1991; Roberts *et al*., 1992; Lioy *et al*., 1993; Lewis *et al*., 1994). However, the study designs that utilize these methods of dermal exposure measurement do not consistently characterize spatial and temporal variability and other key processes necessary to develop and validate realistic physical-stochastic predictive models.

Dermal exposure (and subsequent absorption kinetics) represents a dynamic, complex process with multiple, potential rate-limiting phenomena and highly variable factors (Ott, 1985; McKone, 1991; USEPA, 1992, 1996; Matoba, 1996; Zartarian and Leckie, 1998; Hubal *et al*., 1999). In environments such as the residence, this complexity can be attributed, in part, to time-dependent dislodgeability or transferability for different surface types (e.g. foliage, carpet and hardwood floors), spatial variability in surface concentration, environmental conditions (e.g. temperature and humidity) and related differential dermal 'body-part' surface area loading and removal rates as a function of human time–activity patterns and biomechanical variables (e.g. frequency and duration of body-part surface area contacted and the associated pressure exerted on the area of environmental surface contacted). Dermal exposure assessment to subpopulations, such as infants and children, must also address secondary pathways, such as incidental ingestion associated with hand-to-mouth behavior. Furthermore, the relative bioavailability of a given agent from various exposure media is often uncertain (Driver *et al*., 1989a,b; USEPA, 1992).

The development of more realistic models of dermal exposure is being facilitated by a variety of research programs initiated, in part, due to the requirements of the Food Quality Protection Act (FQPA) of 1996. This amendment to the Federal Insecticide, Fungicide and Rodenticide Act establishes a single, consistent, health-based standard for pesticide residues in food, emphasizes child safety and formalizes the EPA's strategic approach to a better understanding of non-occupational exposures in the residential environment, including those via the dermal route. Research programs include the EPA-funded National Human Exposure Assessment Survey and industry-sponsored exposure data development activities, such as the Outdoor Residential Exposure Task Force and the Non-Dietary Exposure Task Force, both formed, in part, to respond to the EPA's recent call for improved estimates of residential exposure. Two alternative approaches to

physical-stochastic modeling (i.e. macro- and micro-based) for estimating dermal exposure, based in part on the data development initiatives noted above, are presented here.

Modeling Residential Re-entry Dermal Exposures

Indoor and outdoor use of pesticide chemicals present opportunities for dermal exposure. The FQPA requires the USEPA to estimate potential multi-pathway, multi-route exposure (dermal, inhalation and incidental ingestion) during and following use of pesticide products in and around the home. Furthermore, potential residential exposures to children continues to receive emphasis in discussions surrounding federal legislative and regulatory initiatives, including the FQPA. Dermal exposure of children in the residential environment, following the use of a consumer or professional pesticide product, may occur through contact with different surfaces (e.g. carpets, rugs, hardwood floors, turf, treated pets, etc.). Residential exposure modeling, including the dermal route, involves a variety of influential factors, as illustrated earlier in Figure 4.2. Approaches to post-application dermal exposure modeling in the residential environment (indoor and outdoor) have relied on the use of environmental surface and dermal dosimetry measurements in conjunction with assumptions regarding 'representative' or 'worst-case' time–activity patterns for subpopulations of interest (Ross *et al.*, 1990, 1991; Vaccaro *et al.*, 1996; ILSI, 1998; USEPA, 1999).

A more recent 'macro-event'-based approach to post-application dermal exposure modeling involves the use of body-part-specific 'transfer factor' (*TF*) point-estimates and/or underlying distributions. The unitless *TF*s represent an activity-specific basis for estimating dermal loading (g/cm^2) for various anatomical regions from compound-specific transferable residue data (g/cm^2).

The general equation for estimating potential body-part-specific dermal exposure can be described as follows:

$$\begin{aligned} &\textit{Post-Application Dermal Exposure}_{\text{BodyPart}}(\text{g}) \\ &\quad = \sum [(\textit{Transfer Factor}_{\text{BodyPart}}) \\ &\qquad \times (\textit{Transferable Residue})(\textit{Surface Area}_{\text{BodyPart}})] \end{aligned} \tag{4.2}$$

where the transfer factor (*TF*) (unitless) is the 'generic' body-part-specific factor relating transferable residue values to the 'Jazzercise™-equivalent' dermal exposure, the transferable residue (g/cm^2) (chemical-specific) is the mass of residue per unit surface area transferring from a treated surface to a 'surrogate skin' collection medium (e.g. cotton dosimeter), and the surface area (cm^2) is the skin surface area represented by a specific body part.

The transfer-factor-based dermal modeling approach can be illustrated for estimating potential post-application dermal contact with floor surfaces on which aerosols have deposited by using the Jazzercise™ study conducted by Ross *et al.*

(1990, 1991). This study provides a means for conservatively estimating potential post-application dermal exposures to treated surfaces following the use of indoor total release foggers by using a high-contact, but reproducible activity. The procedure for estimating potential dermal exposure is based on the use of 'transfer factors' (*TF*s) derived from the human volunteer dermal dosimetry and treated carpet 'transferable-residue' measurements based on an indoor roller method (Ross *et al*., 1990, 1991).

The Ross *et al*. (1990) study measured the transfer of pesticide residues (chlorpyrifos and *d-trans* allethrin) from carpeted floor to five human subjects wearing dosimeter clothing following the use of home-fogger devices. Subject motions were standardized by using 20-min (18.2 min routine, plus entry and exit times) aerobic dance routines (Jazzercise™). This method provided reproducible dosimeter exposure measurements and derivation of transferable residue estimates – transfer of surface residues to exposed subjects. The study was conducted in recently constructed hotel rooms in Sacramento, CA, USA. Two hours after fogger treatment, the rooms were vented for 30 min by opening the windows. Sampling methods included aluminum fallout sheets (400 cm^2) and cotton dosimeter clothing (socks, gloves, pants and shirts).

The Ross *et al*. (1991) study demonstrated the use of a standardized, reproducible method for measuring transferable residues to supplement the study conducted by Ross *et al*. (1990). The monitoring device (the California Department of Food and Agriculture (CDFA) or California Department of Pesticide Regulations (CDPR) roller) was a cylinder that was rolled over a cotton cloth that was placed on the treated surface (i.e. a carpet). The method was shown to transfer 1–3 % of potentially available pesticide material from nylon carpeting to the collection media (cotton cloth). Transfer from carpet to cloth was found to be highly correlated with transfer to cotton clothing worn by persons exercising on the carpet (Ross *et al*., 1990).

It is important to note that transfer factor-based modeling inherently considers only the activities and time domain included in the dermal monitoring study from which the factors are derived. Therefore, if the study design, such as the case with Jazzercise™, represents a high-contact activity, it must be placed in perspective with more representative time–activity profiles (ILSI, 1998; USEPA, 1999). For example, dermal exposures associated with 20 min of Jazzercise™ (whether on indoor or outdoor surfaces) may be similar to or greater than an entire day of exposure (non-sleeping period) associated with more representative activities (e.g. sitting, walking, playing on floor surfaces, etc.) on the same surfaces (and with all other product use and environmental conditions being equivalent) (ILSI, 1998).

INTEGRATED PHYSICAL-STOCHASTIC DERMAL MODEL

The following section presents a practical, integrated physical-stochastic dermal model that represents a synthesis of the above described approach (transfer-factor-based), and shows the relationship with another commonly used dermal exposure

metric, i.e. the transfer coefficient, and provides for incorporation of other key deterministic variables.

Macro-Based Dermal Exposure Methodology

The following four elements are presented as part of the integrated dermal exposure assessment methodology/model:

(1) multiple environmental surfaces, multiple dermal surfaces and dermal contact;
(2) single environmental surface, single dermal surface and dermal contact;
(3) hand-to-mouth contact;
(4) time-dependent dermal contact.

Scenario 1

Exposure medium: environmental surfaces
Environmental surfaces: multiple
Exposure route: dermal contact
Dermal surfaces: multiple

- ***Inputs***

M_{env}	mass of chemical applied to environmental surfaces (g)
F_{env}	fraction of chemical depositing on environmental surfaces
A_{env}	area of environmental surfaces treated (cm^2)
J	number of zones in environmental surfaces
$F_{chem,\ j}$	fraction of chemical applied to environmental surface zone j
$F_{area,\ j}$	fraction of area in environmental surface zone j
$F_{dis,\ j}$	fraction of chemical dislodgeable from environmental surface zone j
A_{der}	area of dermal surfaces affected (cm^2)
K	number of regions in dermal surfaces
$F_{area,\ k}$	fraction of area in dermal surface region k
$F_{trans,\ j}®_k$	fraction of chemical transferred from zone j (environmental surface) to region k (dermal surface) per contact
$F_{mod(j,\ k)}$	exponential factor that modifies $F_{trans,\ i}®_k$, based on the contact number
$N_{con(j,\ k)}$	number of region-k (dermal surface) contacts with zone j (environmental surface) per hour (#/h)
T_{exp}	exposure duration (h)

In Scenario 1, a certain amount of chemical (mass = M_{env}) is applied to multiple environmental surfaces. In indoor environments, surfaces could include the

following: carpet, vinyl, wood, tile, drywall, wallpaper, particle board, marble, and granite covered floor, wall and counter-top surfaces; furniture coverings; object surfaces (e.g. toys, plants, appliances, etc.). In outdoor environments, surfaces could include grass, plant, soil, fence and concrete coverings, furniture coverings and object surfaces (e.g. toys, trampolines, etc.). A fraction of the chemical that is applied does not deposit on the surfaces. It can disperse in the air medium and be transported through air-flow away from the room and/or deposit on the application equipment, including the applicator. The fraction that deposits on the environmental surfaces is denoted by F_{env}.

In a residential setting, multiple environmental surfaces can be explained by two different situations. In one situation, a chemical can be broadcast homogeneously in a living room that has a partly carpeted and partly wood-covered floor. In this case, there are two environmental surfaces ($J = 2$), namely carpeted and wood-covered floor. In the other situation, when a chemical is sprayed in a carpeted room along the edges formed by the floor and the side walls, three homogeneous environmental zones ($J = 3$) can be assumed to be created. The first-assumed homogeneous surface is the carpeted floor area close to the edge, the second the carpeted floor area away from the edge and close to the center of the room, and the third the side wall area close to the edge.

The homogeneously different environmental surfaces are designated as follows: zone j, $j = 1, 2, \ldots, J$. The total area of all of the environmental surfaces is denoted as A_{env}, while $F_{\text{area, } j}$ and $F_{\text{chem, } j}$ refer to zone j area as a fraction of A_{env} and to chemical depositing on zone j as a fraction of M_{env}, respectively.

When a chemical deposits on an environmental surface, only a certain fraction can be physically dislodged from the surface. The characteristics of both the chemical and the surface dictate that not all of the chemical which has deposited on the surface can be dislodged. The fraction that can be dislodged from the environmental surface zone j is denoted as $F_{\text{dis, } j}$. For a given environmental surface, $F_{\text{dis, } j}$ can be estimated by using a form of either solvent-extraction, multiple-drag or multiple-roller studies.

Similar to the concept of multiple-environmental surfaces, the dermal surfaces contacting the different environmental surfaces can be divided into multiple surfaces. The homogeneously different dermal surfaces are designated as follows: region k, $k = 1, 2, \ldots, K$. The total area of all of the dermal surfaces is denoted as A_{der}.

For a single contact of a dermal surface region with an environmental surface zone, the fraction of chemical transferred from the latter to the former is set to $F_{\text{trans, } j®k}$. The latter is a function of the characteristics of the chemical, the environmental surface and the dermal surface. In addition, with increasing contact number, $F_{\text{trans, } j®k}$ decreases; in other words, ($F_{\text{trans, } j®k}$ for contact number 1) > ($F_{\text{trans, } j®k}$ for contact number 2) > $\cdots$ > ($F_{\text{trans, } j®k}$ for contact number N). To account for this decreasing $F_{\text{trans, } j®k}$, a modifier is used. This is

represented as an exponential function, i.e. $e^{-(F_{\text{mod},(j,\ k)} \times (n-1))}$, where $F_{\text{mod},\ (j,\ k)}$ is the exponential factor that modifies $F_{\text{trans},j}®_k$ and n is the contact number. As an example, if $F_{\text{mod},\ (j,\ k)} = 0.1$, for contact number 1 ($n = 1$), the modifier is 1.00, for contact number 2 ($n = 2$), the modifier is 0.905, for contact number 3 ($n = 3$), the modifier is 0.819, ..., etc.

The numbers of contacts of the different dermal surfaces with the different environmental surfaces are denoted by $N_{\text{con},\ (j,\ k)}$. The units for this variables are in number of contacts per unit time (e.g. # contacts/h). If an exposure duration is known (T_{exp}), the total number of contacts during that duration is obtained by multiplying $N_{\text{con},\ (j,\ k)}$ and T_{exp}.

- ***Assumptions***

(1) Before, during and after the dermal surfaces contact with the environmental surfaces, the concentrations of chemical on both of these, i.e. the environmental surfaces and the dermal surfaces, remain homogeneous.
(2) The mass in the environmental surfaces is assumed to be infinite. This gross assumption is interpreted as that every contact of a dermal surface with an environmental surface is with a *new* area. Usually, the transfer of chemical from the different environmental surfaces to the different dermal surfaces does not reach the limit of what is available. In the case where this is possible, the calculations have to be modified accordingly. A possible modification is used below in Scenario 3.
(3) When a dermal surface contacts an environmental surface, the entire dermal surface area is assumed to be in contact.

- ***Calculations***

Environmental surface zone *j* concentration (g/cm^2) = (mass in zone j)/(area of zone j):

$$C_j = \frac{M_{\text{env}} \times F_{\text{env}} \times F_{\text{chem},\ j}}{A_{\text{env}} \times F_{\text{area},\ j}}$$

Concentration of chemical dislodgeable from environmental surface zone *j* (g/cm^2):

$$C_{\text{dis},\ j} = C_j \times F_{\text{dis},\ j}$$

Ratio of areas (region *k*/zone *j*):

$$R_{(j,\ k)} = \frac{A_{\text{der}} \times F_{\text{area},\ k}}{A_{\text{env}} \times F_{\text{area},\ j}}$$

Normalized contribution of environmental surface zone j to dermal surface region k (g/cm^2) for $N_{\text{con, }(j,\ k)}$ contacts:

$$C_{k\leftarrow j} = C_{\text{dis, }j} \times F_{\text{trans, }j\to k} \times \sum_{n=1}^{\left(N_{\text{con, }(j,\ k)} \times T_{\text{exp}}\right)} \left(\mathrm{e}^{-\left(F_{\text{mod, }(j,\ k)} \times (n-1)\right)}\right) \times R_{(j,\ k)}$$

Concentration remaining in environmental surface zone j after $N_{\text{con, }(j,\ k)}$ contacts (g/cm^2):

$$C_{\text{rem, }j} = C_j \times \left\{1 - F_{\text{dis, }j} \times \sum_{k=1}^{K} \left[F_{\text{trans, }j\to k} \times \sum_{n=1}^{\left(N_{\text{con, }(j,\ k)} \times T_{\text{exp}}\right)} \left(\mathrm{e}^{-\left(F_{\text{mod, }(j,\ k)} \times (n-1)\right)}\right) \times R_{(j,\ k)}\right]\right\}$$

Total mass on dermal surface region k (g):

$$M_k = A_{\text{env}} \times \sum_{j=1}^{J} \left(C_{k\leftarrow j} \times F_{\text{area, }j}\right)$$

Dermal surface region k concentration (g/m^2):

$$C_k = \frac{M_k}{A_{\text{der}} \times F_{\text{area, }k}}$$

Total mass remaining on environmental surface in zone j (g):

$$M_{\text{rem, }j} = C_{\text{rem, }j} \times A_{\text{env}} \times F_{\text{area, }j}$$

Total mass on dermal surface (g):

$$M_{\text{der}} = \sum_{k=1}^{K} M_k$$

Total mass remaining on environmental surface (g):

$$M_{\text{rem, env}} = \sum_{j=1}^{J} M_{\text{rem, }j}$$

Average fraction of chemical that can be dislodged from the environmental surface:

$$F_{\text{dis, env}} = \sum_{j=1}^{J} \left(F_{\text{dis, } j} \times F_{\text{area, } j} \right)$$

Transfer factor for dermal surface region *k* from environmental surface zone *j* = (concentration in dermal surface region k)/(dislodgeable concentration in environmental surface zone j):

$$TF_{k \leftarrow j} = \frac{M_k}{C_{\text{dis, } j} \times A_{\text{der}} \times F_{\text{area, } k}}$$

Overall transfer factor for dermal surface region *k* = (concentration in dermal surface region k)/(dislodgeable concentration in total environmental surface):

$$TF_k = \frac{C_k}{\left(\dfrac{M_{\text{env}} \times F_{\text{dis, env}}}{A_{\text{env}}} \right)}$$

Overall transfer factor = (concentration in total dermal surface)/(dislodgeable concentration in total environmental surface):

$$TF = \frac{\left(\dfrac{M_{\text{der}}}{A_{\text{der}}} \right)}{\left(\dfrac{M_{\text{env}} \times F_{\text{dis, env}}}{A_{\text{env}}} \right)}$$

Transfer coefficient for dermal surface region *k* (m^2/h) = (mass on dermal surface region k)/[(exposure duration) × (dislodgeable concentration in total environmental surface)]:

$$TC_k = \frac{M_k}{T_{\text{exp}} \times \left(\dfrac{M_{\text{env}} \times F_{\text{dis, env}}}{A_{\text{env}}} \right)}$$

Overall transfer coefficient (cm^2/h) = (mass on total dermal surface)/[(exposure duration) ×(dislodgeable concentration in total environmental surface)]:

$$TC = \frac{M_{\text{der}}}{T_{\text{exp}} \times \left(\dfrac{M_{\text{env}} \times F_{\text{dis, env}}}{A_{\text{env}}} \right)}$$

Relationship between *TC* and *TF*:

$$\frac{TC}{TF} = \frac{A_{\text{der}}}{T_{\text{exp}}}(\text{cm}^2/\text{h})$$

Scenario 2

Exposure medium: environmental surface
Environmental surface: single
Exposure route: dermal contact
Dermal surface: single

- ***Inputs***

M_{env}	mass of chemical applied to environmental surface (g)
F_{env}	fraction of chemical depositing on environmental surface
A_{env}	area of environmental surface treated (cm^2)
F_{dis}	fraction of chemical dislodgeable from environmental surface
A_{der}	area of dermal surface affected (cm^2)
F_{trans}	fraction of chemical transferred from environmental surface to dermal surface per contact
F_{mod}	exponential factor that modifies F_{trans} based on the contact number
N_{con}	number of dermal surface contacts with environmental surface per hour (#/h)
T_{exp}	exposure duration (h)

Scenario 2 is a subset of Scenario 1, with $J = 1$ and $K = 1$. All uses of the subscripts j and k have been removed.

- ***Assumptions***

The assumptions applied to Scenario 1 are also applied here.

- ***Calculations***

Environmental surface concentration (g/cm^2):

$$C_{\text{env}} = \frac{M_{\text{env}} \times F_{\text{env}}}{A_{\text{env}}}$$

Amount of chemical dislodgeable from environmental surface (g/cm^2):

$$C_{\text{dis}} = C_{\text{env}} \times F_{\text{dis}}$$

Ratio of areas (dermal/environmental):

$$R = \frac{A_{\text{der}}}{A_{\text{env}}}$$

Normalized contribution of environmental surface to dermal surface (g/cm^2) for N_{con} contacts:

$$C_{\text{der}\leftarrow\text{env}} = C_{\text{dis}} \times F_{\text{trans}} \times \sum_{n=1}^{(N_{\text{con}} \times T_{\text{exp}})} \left(e^{-(F_{\text{mod}} \times (n-1))}\right) \times R$$

Concentration remaining in environmental surface (g/cm^2):

$$C_{\text{rem}} = C_{\text{env}} \times \left\{ 1 - F_{\text{dis}} \times F_{\text{trans}} \times \sum_{n=1}^{(N_{\text{con}} \times T_{\text{exp}})} \left[e^{-(F_{\text{mod}} \times (n-1))}\right] \times R \right\}$$

Total mass on dermal surface (g):

$$M_{\text{der}} = A_{\text{env}} \times C_{\text{der}\leftarrow\text{env}}$$

Dermal surface concentration (g/m^2):

$$C_{\text{der}} = \frac{M_{\text{der}}}{A_{\text{der}}}$$

Total mass remaining on environmental surface (g):

$$M_{\text{rem}} = C_{\text{rem}} \times A_{\text{env}}$$

Transfer factor for dermal surface from environmental surface (based on dislodgeable concentration):

$$TF = \frac{C_{\text{der}}}{C_{\text{dis}}}$$

Transfer coefficient (cm^2/h) (based on dislodgeable concentration):

$$TC = \frac{M_{\text{der}}}{T_{\text{exp}} \times C_{\text{dis}}}$$

Relationship between *TC* and *TF*:

$$\frac{TC}{TF} = \frac{A_{\text{der}}}{T_{\text{exp}}} \ (\text{cm}^2/\text{h})$$

Scenario 3

Exposure medium: dermal surface on hands
Exposure route: oral (hand-to-mouth)

- ***Inputs***

C_{hand}	concentration of chemical on hand dermal surface (g/cm^2)
A_{hand}	area of hand dermal surface (cm^2)
F_{dis}	fraction of chemical dislodgeable from hand dermal surface
A_{con}	area of hand dermal surface contacted by mouth during each contact (cm^2)
F_{trans}	fraction of chemical transferred from hand dermal surface to mouth per contact
N_{con}	number of hand dermal surface contacts with mouth per hour (#/h)
T_{exp}	exposure duration (h)

- ***Assumptions***

(1) Before, during and after contacts of the mouth with the hand dermal surface, the concentration of chemical on the hand dermal surface remains homogeneous.
(2) The loss of mass in the hand dermal surface with every contact with the mouth is estimated and applied for subsequent contacts.
(3) For each contact of the mouth with the hand dermal surface, the same fraction of the hand dermal surface area is assumed to be contacted.

- ***Calculations***

Concentration of chemical dislodgeable from hand dermal surface (g/cm^2):

$$C_{dis} = C_{hand} \times F_{dis}$$

Ratio of areas (contact/hand):

$$R = \frac{A_{con}}{A_{hand}}$$

Normalized contribution of hand dermal surface to mouth (g/cm^2) for ($N_{con} \times T_{exp}$) contacts:

$$C_{mouth \leftarrow hand} = C_{hand} \times F_{dis} \times F_{trans} \times R \times \sum_{n=1}^{(N_{con} \times T_{exp})} (1 - F_{dis} \times F_{trans} \times R)^{(n-1)}$$

Concentration remaining on hand dermal surface (g/cm^2):

$$C_{\text{rem}} = C_{\text{hand}} \sum_{n=1}^{(N_{\text{con}} \times T_{\text{exp}})} (1 - F_{\text{dis}} \times F_{\text{trans}} \times R)^n$$

Total mass in mouth (g):

$$M_{\text{mouth}} = A_{\text{hand}} \times C_{\text{mouth} \leftarrow \text{hand}}$$

Total mass remaining on hand dermal surface (g):

$$M_{\text{rem}} = C_{\text{rem}} \times A_{\text{hand}}$$

Transfer factor for dermal surface from environmental surface (based on dislodgeable mass):

$$TF = \frac{M_{\text{mouth}}}{M_{\text{dis}}}$$

Transfer coefficient (cm^2/h) (based on dislodgeable concentration):

$$TC = \frac{M_{\text{mouth}}}{T_{\text{exp}} \times C_{\text{dis}}}$$

Micro-Based Dermal Exposure Methodology (SHEDS)

As an alternative to the macro-based methods described above, Zartarian *et al.* (2000) have described a micro-activity approach as incorporated into 'Residential-SHEDS'. Sequential dermal and nondietary ingestion exposure and dose–time profiles are simulated by combining measured surface residues and residue transfer efficiencies with actual microlevel activity data quantified from videotapes. Because the sequence of dermal loading and removal processes is preserved, such exposure profiles can improve estimates of time-dependent dermal absorption, which have traditionally assumed a fixed concentration at the skin surface. With information on frequency and duration of hand-to-mouth activities, these profiles can also improve estimates of ingested residues that are otherwise difficult to quantify. Exposure and dose profiles also provide various metrics of toxicological interest (e.g. peaks, averages and instantaneous values) and information about the relative contribution of exposure pathways. When combined with activity data, profiles can provide information on how exposures and doses occur and how they can be mitigated.

The Residential-SHEDS algorithms are presented in Zartarian *et al.* (2000). For each specified exposure scenario, the model randomly selects an individual

from the National Human Activity Pattern Survey (NHAPS) and simulates a sequence of object contact events (with object categories for smooth surfaces, textured surfaces, nothing, food, water, grass and mouth) during each sequential location–activity combination reported in the individual's daily diary (Zartarian *et al*., 2000). Each object contacted is associated with an exposure pathway (i.e. skin-to-surface residue contact, skin-to-water contact, hand-to-mouth contact or object-to-mouth contact) that allows the model to select the appropriate exposure and dose equation for each contact event. The model then performs time steps through every 5 s intervals in the simulated individual's day, combining proximity-specific surface residues with randomly sampled exposure factors for the appropriate pathway equation. The initial and final values are calculated for each sequential contact event in the person's database, and time profiles are generated for dermal exposure, nondietary ingestion, mass of metabolite in the blood compartment and mass of metabolite eliminated using pathway-specific equations. Exposure and dose metrics of interest are extracted from the time profiles, and the entire process is repeated 1500 times to yield histograms for the specified exposure scenario (Zartarian *et al*., 2000).

The Residential-SHEDS model currently assumes simple first-order linear absorption from the skin and gastrointestinal tract into the body and first-order urinary elimination of the pesticide metabolite from the body. The model construct contains a number of other assumptions that can be refined with more research. For example, removal and loading of chemicals at the skin surface is assumed to be instantaneous and independent of number of skin-to-surface contacts, and the model does not track which portion of the skin contacts residue from one contact event to the next. For a given application method and post-application time, deposited concentrations on targeted surfaces are assumed to be the same throughout a residence; nontargeted surfaces in the same residence are also assumed to be uniform, but may be different from targeted surfaces. Surface residue loadings are 're-sampled' for each simulated residence. The model time step is of the order of seconds (based on available skin-to-surface contact duration data), except during sleeping activities, when 30 min is used (the optimal time step for minimizing error in approximating the exact analytical solution to the differential exposure and dose equations with numerical difference equations). Because little information is available on the physical and chemical fate of pesticide residues indoors, nonparticle-bound residues are assumed for up to 30 d post-application, and aerosol deposition and evaporation at the skin surface are not currently included. The individuals sampled are assumed to live in residences with independent indoor and lawn pesticide applications. The initial daily exposure and dose is assumed to be zero for a given individual. During a sleeping event, the child's skin is assumed to contact nontargeted surface residues. Legs, arms, torso and feet are treated as a single skin surface because body-part-specific micro-activity data are currently lacking, except for hands and mouth. Because of the lack of data concerning the penetration of pesticide residues

through clothing and the percentage of skin surface that is clothed, the role of clothing is currently neglected in the model.

Residential-SHEDS is a useful tool for identifying data needs to encourage research so that the model can be evaluated and used reliably to make predictions when measurements are not feasible. In particular, the model can now be used as a research tool to identify critical data needs and relative contributions of pathways and model inputs, and can be used for regulatory purposes after it has been evaluated.

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Section Two

Databases and Models

5 Generic Operator Exposure Databases

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INTRODUCTION

The application of pesticides is widespread in agriculture and elsewhere, and the concomitant risks depend on their toxicity, and duration and frequency, as well as the level of exposure (Henderson *et al*., 1993; Krieger and Ross, 1993). Exposure may be incidental or almost continuous. This is true not only for workers (occupational exposure), but also for the general public and people who may be considered as bystanders, who are not involved in the actual occupational activities with pesticides, but are close enough to get exposed. In this present chapter, only operator exposure will be discussed because agricultural re-entry modelling is discussed in Chapter 2 and residential post-application exposure modelling in Chapter 6 of this book.

The application of pesticides to crops can be carried out with all sorts of equipment, which may be hand-held or vehicle-drawn. In special cases, applications may be carried out by airplane or helicopter. Most applications are carried out by using spraying techniques, but the application may also be conducted using dusting techniques or by the spreading of granules. Special cases include the application of pesticides to seeds in commercial treatment plants or during the sowing process. In greenhouses, pesticides may be applied through the same systems that are used for irrigation. In almost all cases, the loading of the application equipment can be considered as a separate activity from application, although the same person may carry out the two tasks. The various factors that influence exposure include type of job (e.g. mixer/loader and applicator), type of formulation (e.g. powders, granules, micro-encapsulates (van Hemmen, 1992a; Gimeno, 1966) and liquid), amount of pesticide handled and type of equipment. The size and opening of the container have been indicated as important variables for the level of exposure (unpublished observations by the Central Science Laboratory (CSL), UK (Hamey, Pesticide Safety Directorate (PSD), UK, personal communication)). The type of engineering controls (e.g. closed loading systems, closed cabs, etc.) can also be a significant determinant of exposure (PHED, 1992). Wind direction, wind speed and relative humidity may vary appreciably throughout the seasons,

but also over the day (van Hemmen, 1992a). The above factors, in combination with the size and structure of the field plots to be treated and work methods and hygienic practices of the operator, may widely increase the variation in exposure observed in field studies.

Exposure may also occur during cleaning of spray tanks and pesticide containers, and during maintenance (e.g. cleaning of nozzles). More detailed discussions of these factors have been given in the chapters in Section 1 of this text.

Exposure estimates that are required for risk assessment may be obtained from chemical-specific field studies, or from extrapolations from other field studies. This requires high-quality exposure data that have been obtained under conditions relevant for the exposure and use scenarios under consideration (Krieger *et al*., 1992; Fenske and Teschke, 1995; Krieger, 1995; Turnbull *et al*., 1995). For risk assessment purposes, the exposure data obtained for relevant use scenarios can be compared with an appropriate accepted exposure level (e.g. Acceptable Operator Exposure Level (AOEL)) based on the toxicological profile of the compound.

The generic approach to exposure assessment based on the grouping of uses into scenarios where activities are similar was presented by Franklin *et al*. (1982). This approach was further advanced by Hackathorn and Eberhart (1985), who discussed the development of a database for predictive exposure modelling. The basic idea behind the development of such databases is that the level of exposure, when in a suitable format, can be extrapolated for 'similar-use' scenarios. Currently, it is assumed that for mixing/loading, the main differentiation is for formulation type (i.e. between powders, granules and liquids) used for hand-held application equipment, vehicle-mounted equipment or aerial equipment. For application, the main differentiations used are upward or downward spraying and hand-held or vehicle-mounted spraying and some aerial application scenarios (PHED, 1992). Furthermore, databases have been developed that consider consecutive mixing, loading and application by the same person.

PRINCIPLES OF OPERATOR EXPOSURE MODELLING

It is clear that for operators the application rate of the pesticide, relevant meteorological conditions, liquid pressure at the nozzle, geometry of crop and application equipment are very important variables (van Hemmen, 1992a). Furthermore, work methods and hygienic measures taken by the operator (e.g. wearing of protective clothing) also affect exposure.

The databases should include exposure data from a large set of field studies in order to form an appropriate basis for predictive extrapolation. The better the delineation of the exposure or use scenario, then the more exact will be the range of predicted exposure. However, with the present availability of field studies for these databases, a further differentiation in the scenarios, beyond that described above, is not viable, given the decreasing number of exposure data and studies involved, and thus the quality of the database.

Databases have been developed by the following: Crome (1985); the governments of the USA and Canada, in conjunction with the National Agricultural Chemicals Association (NACA) (PHED 1992; Nielsen *et al*., 1995); government and industry in the UK (JMP, 1986; Martin, 1990; POEM, 1992); industry and government in Germany (Lundehn *et al*., 1992); government and industry in the Netherlands (van Hemmen, 1992a; van Golstein Brouwers *et al*., 1996; Snippe *et al*., 2002); an expert group for the European Commission (EUROPOEM, 1996). Such databases contain field studies and exposure data extracted from those field studies in several formats (Kangas and Sihvonen, 1996). These studies are all different and most of them are not publicly available or critically reviewed in respect to documented criteria (van Hemmen, 1993).

The most important independent databases in use for risk assessment purposes in formal pesticide registration processes are PHED, the German model, UK-POEM, the Dutch model and EUROPOEM. These databases, also called *predictive exposure models*, will be discussed in detail in this chapter. Emphasis will be put on the quality of data, available scenarios, type of formulations considered, exposure reduction measures and current developments for updating and performing statistics. The databases/models will be assessed with respect to their usability and how they compare with the other models. In addition to this, a proposed approach, which uses biological monitoring data in a generic database, will be presented. This generic approach to the use of biological monitoring will be considered separately, because it is not contained in the already mentioned predictive exposure databases.

Only very recently, a critical appraisal of these databases was made at an international ILSI workshop on probabilistic assessment of operator exposures in Brussels (November 2003). The final report of this meeting is still under preparation (it will be made available at www.rsi.ilsi.org/publications). The workshop considered both EUROPOEM and PHED databases. Some of the results are discussed at appropriate sections in this chapter.

PHED: PESTICIDE HANDLERS EXPOSURE DATABASE

GENERAL DESCRIPTION

The Pesticide Handlers Exposure Database, Version 1.1 (PHED, 1992) is a software tool designed to predict pesticide exposures during mixing/loading, application and flagging. PHED was designed by a task force consisting of representatives from the United States Environmental Protection Agency (USEPA), Health Canada's Pest Management Regulatory Agency (PMRA) and the American Crop Protection Association (ACPA, previously known as the National Agricultural Chemicals Association). PHED is a generic database containing exposure data (submitted on a voluntary basis) describing workers mixing/loading and/or applying pesticides in the field. PHED contains data for over 1700 monitored exposure events. The assumption is made that exposure while handling

pesticides can be estimated generically, because exposure is a function of the physical parameters (e.g. application method, packaging type, clothing scenario and formulation) of the handling and application process.

The standard exposure values are based on the 'best-fit' values calculated by PHED. The model calculates 'best-fit' exposure values by assessing data distributions for replicates representing each body part, and then by calculating a composite exposure value (the entire body consists of the following different sections: head, neck-front, neck-back, upper arms, chest, back, forearms, thighs, lower legs, feet and hands) by summing the appropriate measure of central tendency (i.e. geometric mean, median or arithmetic mean). The quality grade of the data which is assigned separately to inhalation, hand and dermal (excluding hand) exposure data must be considered for the records in the selected subset. The grading criteria for the studies are based on laboratory recovery, storage stability and field recovery.

Based on the PHED, the USEPA has prepared a surrogate exposure table (PHED, 1998) containing a series of standard unit exposure values for a number of occupational exposure scenarios. This surrogate guide is designed to ensure consistency in exposure assessment and clearly describes a (limited) number of scenarios. In addition, the surrogate guide is more user-friendly than the PHED, which requires considerable in-depth knowledge of the operation of the model to ensure relevant exposure calculations.

QUALITY OF DATA

Data are assigned to one of five classes, A through E, based on the results of experiments to determine the recovery of the analyte from fortified samples. Data from the three kinds of recovery experiments mentioned previously (laboratory recovery, storage stability and field recovery) are used to classify the exposure data. This is described in Table 5.1 (PHED, 1992).

FORMULATIONS AND USE SCENARIOS

The formulations covered in the PHED are as follows: liquids, including emulsifiable concentrates, aqueous suspensions, microencapsulated systems, solutions, liquids (undiluted) and solids, including dry-flowable materials, dusts, wettable-powders and granules.

The various application scenarios handled include airblast, groundboom tractor, groundboom truck, aerosol can, aerial fixed-wing and aerial rotary-wing, low-pressure hand wand, paint brush, backpack, airless sprayer, 'rights-of-way' sprayer, 'rights-of-way' (cannon type/rail) car, high-pressure hand wand (greenhouse and ornamentals) and high-pressure hand wand (chem-lawn type).

The number of data sets and the quality of the data sets available per scenario varies greatly. The PHED Surrogate Exposure Guide (1998) characterizes the data set for each scenario from low to high confidence, based on data quality and quantity.

Table 5.1 Data grading criteria

Data grade	Laboratory recovery (%)	CV for laboratory recovery[a]	Field recovery (%)	Storage stability (%)	Data corrected for[b]
A	90–110	≤ 15	70–120	–[c]	Field recovery
B	80–110	≤ 25	50–120	–[c]	Field recovery
C	70–120	≤ 33	30–120	–[c]	Field recovery
				or	
	70–120	≤ 33	Missing	50–120	Storage stability
D	60–120	≤ 33	–[c]	–[c]	Field recovery, if available; if not, then storage stability; if not, then laboratory recovery
E	Does not meet above criteria				

[a] CV, coefficient of variation.
[b] If a recovery of 90 % or greater *is* obtained, no correction (based on field recovery) of the data is necessary.
[c] Does not matter if available or missing.

USE IN RISK ASSESSMENT

This model only estimates exposure and gives no indication how these data should be used in risk assessment.

EXPOSURE REDUCTION MEASURES

Unit exposure values are derived from actual exposure studies where the same formulation types, equipment and methods were employed. In addition, the data can be 'subset' to represent various clothing scenarios. The following scenarios are available:

- long pants, short sleeves, no gloves
- long pants, short sleeves, gloves
- long pants, long sleeves, no gloves
- long pants, long sleeves, gloves
- protective overall over long pants, short sleeves, no gloves
- protective overall over long pants, short sleeves, gloves
- protective overall over long pants, long sleeves, no gloves
- protective overall over long pants, long sleeves, gloves
- Protective overall over no clothing, no gloves
- protective overall over no clothing, gloves

For inhalation, no subsets for exposure reduction measures are available.

PHED also allows for subsetting dermal and inhalation data for engineering controls such as closed mixing loading systems and closed cabs. North American

regulatory agencies may also apply default exposure reduction factors to the PHED data to account for the protection afforded by clothing and equipment, as some of the above-noted clothing scenarios do not contain sufficient data.

MODEL UPDATES

It is possible to add data from more recent studies to the database. Some of the data included in the PHED are fairly old. Proprietary data can be included in the database, although only for use by the owner of the data. An update to the PHED, with inclusion of new data and a new windows-based platform, was planned in the late 1990s. At this time, no further work on the PHED is planned since a new activity is underway.

In North America, a new industry task force, with the USEPA and Health Canada's Pesticide Management Regulatory Agency (PMRA) participation and oversight, has been recently established to develop a new exposure database to replace the PHED. At this time, the Agricultural Handler Exposure Task Force (AHETF) has screened available exposure studies against established acceptability criteria, including study design, sampling techniques and quality control. The ACPA has a large number of recent high-quality studies that have not been entered into the PHED. Once further data gaps have been identified, additional studies will be conducted. Studies must be representative of current North American use scenarios (e.g. modern formulations and application equipment) and unlike the PHED, must measure whole-body dermal exposure. To handle these new exposure data, a new software model, the Agricultural Handlers Exposure Database (AHED), is being developed and is almost finalized.[1] Population of the database will commence shortly with finalization likely to take another year, particularly since the European Crop Protection Agency (ECPA) is considering entering data into the AHED as well. The ECPA also has studies recently carried out which have not been entered into EUROPOEM. The new database will be able to handle probabilistic assessments and will provide percentiles, means and distributions of exposure. The objective of the new database is to rectify the deficiencies of the current PHED and EUROPOEM. The number of scenarios covered will also be increased significantly. Further details will be presented in the 'Conclusions and Recommendations' section of this chapter.

COMMENTS ON THE MODEL

PHED composite point-estimates are based on assumptions of central tendency values for each body part from replicate data. There is typically a high variability among replicates in exposure studies, and most studies in PHED do not have exposure data for all body parts. The PHED exposure data are presented per body part, including a description of the distribution of the body-part exposure data. The description is limited to log–normal, normal, etc.

[1]As of 2004.

The model is not simple to use. A good knowledge of the selection criteria and their effect on the exposure estimate is fundamental to generating representative exposure estimates with the PHED model. The latter has a large database, composed of data submitted in a standardized form (exposure survey forms) and graded exclusively on analytical quality assurance. The data are not graded on the basis of study design. Some studies could be considered incomplete, but emphasis is placed on the quality of individual data points. Therefore, no information is available on study design. The database provides the possibility of refining exposure estimates by subsetting for a number of variables, such as area treated per day, clothing type, equipment type, etc. However as further refinements are made to the subset, the amount of data per subset decreases. For this reason, North American regulatory agencies use standard PHED surrogate tables (PHED, 1998) which provide subsets for a limited number of variables (e.g. for mixer/loaders, formulation type, clothing, open versus closed system, etc.).

When using different scenarios with respect to protective clothing, it should be clear that the underlying database subsets might be completely different.

GERMAN MODEL

GENERAL DESCRIPTION

The German model was developed with a goal to determine the nature of any special risks and safety precautions for the protection of workers handling pesticides as required by Council Directive 91/414/EEC. To comply with this Directive, exposure estimates must be compared to tolerable (acceptable) exposures for the relevant use scenarios and the active substance (active ingredient) under consideration.

Exposures, D(ermal), I(nhalation) and O(ral) are expressed as mg/person × kg of active substance. The amount handled is calculated from the use rate (application rate) (R) in kg of active substance (a.s.)/ha and the area treated (A) per day in ha, leading to the equation for the three relevant routes of uptake, as follows:

$$\text{Dermal } (D) = D^* \times R \times A \tag{5.1a}$$

$$\text{Inhalation } (I) = I^* \times R \times A \tag{5.1b}$$

$$\text{Oral } (O) = O^* \times R \times A \tag{5.1c}$$

in which D^*, I^* and O^* are the experimentally determined specific exposures related to handling 1 kg of a.s.

A further differentiation is made for hands (H), head (C) and body (B) for the operator, who is supposed to be moderately dressed with half of the upper arms, forearms, thighs and lower legs unprotected. For the mixer/loader operations, it is assumed that exposure is almost exclusively to the hands. Because oral exposure is stated to be experimentally accounted for by inhalation exposure, oral exposure data are not considered. However, in situations where there is a

significant contribution of non-respirable particles, oral and inhalation exposure should be differentiated. This has not been carried out in the published edition of the model (Lundehn *et al*., 1992). Because the evaluation of the exposure data was said to reveal logarithmic–normal distributions of exposures, the geometric mean was used to calculate the means of specific exposures. Such calculated exposures are shown in the tables for mixing/loading (Table 5.2) and application (Table 5.3). The default values for the area treated per day are given in Table 5.4.

FORMULATIONS AND USE SCENARIOS

As can be seen from Tables 5.2 and 5.3, the formulations included for mixing/loading are liquids, powders and granules and the various scenarios for

Table 5.2 Specific exposures (mg for 1 kg a.s. handled)[a] during mixing/loading (M)

Exposure[b]	Liquid		Solid			
	Tractor-mounted	Hand-held	Wettable powder		Wettable granule	
			Tractor-mounted	Hand-held	Tractor-mounted	Hand-held
I (M)[c]	0.0006	0.05	0.07	0.8	0.008	0.02
D (M_H)[c]	2.4	205	6.0	50	2.0	21

[a] Active substance (active ingredient).
[b] H, hand.
[c] Provisional value.

Table 5.3 Specific exposures (mg for 1 kg a.s. handled)[a] during application (A)

Exposure[b]	High crop		Field crop
	Tractor-mounted	Hand-held	
I^*(A)	0.018	0.3	0.001
$D^*(A_c)$	1.2	4.8	0.06
$D^*(A_H)$	0.7	10.6	0.38
$D^*(A_B)$	9.6	25.0	1.6

[a] Active substance (active ingredient).
[b] C, head; H, hand; B, body.

Table 5.4 Treated area (ha) per day

Scenario	High crop		Field crop
	Tractor-mounted	Hand-held	
A	8	1	20

application are downwards- and upwards-spraying with tractor-mounted equipment and hand-held equipment.

The underlying database of exposures is presented in Lundehn *et al*. (1992). The size of the database varies, and is relatively small ($n < 15$) for mixing/loading of wettable powders (WPs) and wettable granules (WGs). The database for downward spraying with tractor-mounted equipment is also rather small ($n < 20$). The studies in the database were carried out by industry for registration purposes.

USE IN RISK ASSESSMENT

Within this model, attention is given to the use of the data in risk assessment. The approach is very simple for compounds that show (1) no cumulative toxicity, (2) no evidence of reproductive toxicity, mutagenicity or oncogenicity, and have (3) neither sensitizing nor primary irritating effects, even at diluted concentrations.

The risk assessment is based on the No Observable Effect Level (NOEL) for the relevant route of administration, a safety factor of 25 and an average worker body weight of 70 kg. In the case of dermal exposure, an oral semi-chronic NOEL may be used and corrected for the dermal absorption. When unknown, a default dermal absorption of 10 % is assumed. If the NOEL for inhalation is not available, the NOEL from a semi-chronic oral study may be used.

EXPOSURE REDUCTION MEASURES

The exposure reduction through various measures is also taken into account, as indicated in Table 5.5. The basis of this table is not given in Lundehn *et al*. (1992).

MODEL UPDATES

This model can easily be updated with new exposure or other information, but so far no such updates have been published.[2]

Table 5.5 Reduction coefficients for exposure

Protective gear	Reduction coefficient	
	Dermal	Inhalation
Universal protective gloves (plant protection)	0.01	—
Standard protection garment (plant protection) and sturdy footwear	0.05	—
Protective clothing against chemicals (type 3)	0	—
Broad-brimmed headgear of sturdy fabric	0.5	—
Hood and visor	0.05	—
Particle filtering half-mask FF2-SL or half-mask with particle filter P2	0.8	0.05
Half-mask with combination filter A1P2	0.8	0.02

[2]As of 2004.

COMMENTS ON THE MODEL

This model has a straightforward structure and is simple to use. It is based on exposure studies carried out for registration purposes. In addition, it has relatively small databases for two out of three formulations and for downward applications with tractor-mounted equipment. It covers the full range of the risk assessment process, i.e. dermal absorption and a comparison of estimated exposure and tolerable exposure. Exposure reduction coefficients are presented for several important exposure reduction measures.

Not all of the required underlying information, however, is provided in sufficient detail. The exposure database is only described at the database level, and *not* at the level of the studies. The choice of the statistics is solely based on the fact that for log–normal distributions, the geometric mean is the central tendency value. How this relates to the risk assessment is not discussed.

In the risk assessment, some steps are not well described. For example, subchronic toxicity studies and *not* chronic toxicity studies are used in the risk assessment. Exposure duration and frequency considerations are not discussed. Route-to-route extrapolation is considered acceptable implicitly, without further evaluation of the various issues involved. The rationale for using a dermal absorption default of 10 %, in the absence of data is also not discussed.

UK-POEM: UK PREDICTIVE OPERATOR EXPOSURE MODEL

GENERAL DESCRIPTION

The UK-POEM database is based on a review of the data available on the exposure of pesticide spray operators (in the UK). The review indicated that several factors determined the dose absorbed by a spray operator. These included the following: the volume of external contamination, the extent to which this external contamination penetrated clothing to reach the skin and the rate at which the chemical came into direct contact with the skin surface and was absorbed (JMP, 1986; Martin, 1990). These various independent factors were assumed, with the exception of dermal absorption, to be of a sufficient generic nature to be suitable for extrapolation purposes. Two major work activities were differentiated: mixing/loading and application. An update of the default values in UK-POEM has been presented (POEM, 1992).

FORMULATIONS AND USE SCENARIOS

For mixing/loading, two formulation types are considered, namely liquids and powders. The database is largest for liquids and the level of exposure is shown to be largely dependent on the container size and the neck aperture. In Table 5.6, the level of contamination/exposure is given as a function of the container design and neck aperture. A default value for the 75th percentile was based on test data on pouring. The original data are not presented, but can be obtained on request.

Table 5.6 Exposure levels and container size and neck aperture

Container size (L)	Potential dermal exposure (mL/operation)
1 (unspecific design)	0.01
2 (unspecific design)	0.01
5 (unspecific design)	0.20
5 (wide neck, 45 or 63 mm)	0.01
10 (unspecific design)	0.50
10 (wide neck, 45 mm)	0.10
10 (wide neck, 63 mm)	0.05
20 (unspecific design)	0.50

No values for exposure to dusts, supported with experimental data, are presented and in the absence of such data, estimates are used. For small packs (around 100 g), 0.01 g per operation and for larger packs (around 1 kg), 0.1 g per operation are used as defaults for the potential dermal exposure. Inhalation exposure is not taken into account for mixing/loading.

For penetration of gloves, 10 % is used for emulsion concentrates (ECs), 5 % for suspension concentrates (SCs) and 1 % for solid formulations.

For applications, a distinction is made between downward and upward spraying. Nominal values for potential exposure are taken as the upper limit of the class containing the 75th percentile of the available database.

The work rates typically used for a risk assessment are 50 ha/d for downward spraying and 30 ha/d for upward spraying. For hand-held spraying, 1 ha/d is used as the default or 400 l spray/d.

In Table 5.7, an overview is given of the exposure data for the various application techniques that are considered.

USE IN RISK ASSESSMENT

For absorption, two approaches were considered, i.e. the absorption rate and the percentage absorbed. Both are described and illustrated with examples. For practical purposes, pesticides are categorized as fast, medium or slow penetrants with nominal absorption values of 100, 10 or 1 %, respectively. A 10 % dermal absorption is assumed in the risk assessment, where there are no specific data. The no-effect level for evaluation of risk with the estimated systemic absorption is said to be determined by sub-chronic oral toxicology tests, although repeated dermal testing is said to be of greater value. This assumes that a large proportion of toxicity is due to dermal exposure. Inhalation exposure is, however, also considered in detail in the model that was developed based on the available exposure data collected by industry and by the government in the UK.

Table 5.7 Distribution and exposure levels for spray applications

Vehicle-mounted (with cab) and hydraulic nozzles; volume of surface contamination, 10 mL/h; inhalation exposure, 0.01 mL/h			
Distribution (%)	Hands, 65	Trunk, 10	Legs, 25
Clothing	None	Permeable	Permeable
Clothing penetration (%)	100	5	15
Dermal exposure (mL/h)	6.5	0.05	0.375
Vehicle-mounted (with cab) and rotary disc atomizers; volume of surface contamination, 2 mL/h; inhalation exposure, 0.005 mL/h			
Distribution (%)	Hands, 75	Trunk, 15	Legs, 10
Clothing	None	Permeable	Permeable
Clothing penetration (%)	100	5	5
Dermal exposure (mL/h)	1.5	0.015	0.010
Vehicle-mounted (without cab) and air assisted with application volume of 500 L/ha; volume of surface contamination, 400 mL/h; inhalation exposure, 0.05 mL/h			
Distribution (%)	Hands, 10	Trunk, 65	Legs, 25
Clothing	None	Permeable	Permeable
Clothing penetration (%)	100	2	5
Dermal exposure (mL/h)	10	5.2	5
Vehicle-mounted (without cab) and air assisted with application volume of 100 L/ha; volume of surface contamination, 50 mL/h; inhalation exposure, 0.02 mL/h			
Distribution (%)	Hands, 10	Trunk, 65	Legs, 25
Clothing	None	Permeable	Permeable
Clothing penetration (%)	100	15	20
Dermal exposure (mL/h)	5	4.875	2.5
Vehicle-mounted (without cab), air assisted and rotary discs, with application volume of 50 L/ha; volume of surface contamination, 20 mL/h; inhalation exposure, 0.02 mL/h			
Distribution (%)	Hands, 10	Trunk, 65	Legs, 25
Clothing	None	Permeable	Permeable
Clothing penetration (%)	100	20	15
Dermal exposure (mL/h)	2	2.6	0.75
Hand-held outdoors hydraulic nozzles with low-level application; volume of surface contamination, 50 mL/h; inhalation exposure, 0.02 mL/h			
Distribution (%)	Hands, 25	Trunk, 25	Legs, 50
Clothing	None	Permeable	Permeable
Clothing penetration (%)	100	20	18
Dermal exposure (mL/h)	10	2.5	4.5

(*continued overleaf*)

Table 5.7 (*continued*)

Hand-held outdoors rotary discs atomizers with low-level application; volume of surface contamination, 20 mL/h; inhalation exposure, 0.01 mL/h			
Distribution (%)	Hands, 10	Trunk, 5	Legs, 85
Clothing	None	Permeable	Permeable
Clothing penetration (%)	100	5	20
Dermal exposure (mL/h)	2	0.05	3.4
Hand-held outdoors rotary discs atomizers with high-level application; volume of surface contamination, 50 mL/h; inhalation exposure, 0.01 mL/h			
Distribution (%)	Hands, 10	Trunk, 65	Legs, 25
Clothing	None	Permeable	Permeable
Clothing penetration (%)	100	15	20
Dermal exposure (mL/h)	5	4.875	2.5

EXPOSURE REDUCTION MEASURES

As can be seen from Table 5.7, exposure reduction is partly considered in the exposure assessment. Additional reduction measures are not considered.

MODEL UPDATES

The present description is based on a first update of the database. Further updates are possible, but have not yet been published. In fact, the PSD decided not to update the database, expecting EUROPOEM to be accepted for use in Europe by the European Commission (P.Y. Hamey, personal communication).

COMMENTS ON THE MODEL

This model has a straightforward structure and is simple to use. It is based on studies carried out in part for the specific purpose of model development. However, not all of the required information is publicly available. The databases are not described at the study level; the exposure data are only available in classes, although more detailed information is available on request. The choice of the statistics is not discussed. In the risk-assessment approach, some steps are not clearly presented. Sub-chronic toxicity studies, and *not* chronic toxicity studies, are used in the risk assessment. Exposure duration and frequency considerations are not discussed. Route-to-route extrapolation is considered acceptable implicitly, without further evaluation of the various issues involved. The rationale for using a dermal absorption default of 10 %, in the absence of data, is not discussed.

DUTCH MODEL

GENERAL DESCRIPTION

The Dutch model was developed in the early 1990s, because of the lack of operator exposure studies in The Netherlands. Attempts to obtain sufficient information about the studies underlying UK-POEM and the German model by the Dutch government were not successful, due to the confidential nature of the information and/or the fact that the studies were not described in a way that was suitable for information transfer. It was concluded that a predictive exposure model had to be developed based on available exposure information in the published literature (van Hemmen, 1992b). A detailed assessment of the exposure data on mixing/loading (van Hemmen, 1992c) and application (van Hemmen, 1992d) was prepared and published by the Ministry of Social Affairs and Employment in The Netherlands. A review of this evaluation was published elsewhere (van Hemmen, 1992a). An overview of already existing databases has been given by van Hemmen (1992b).

The exposure data were categorized according to formulation type and application technique and presented in graphs, in order to obtain a comprehensive overview of the large spread in exposure data per literature source and formulation type (for mixing/loading) and per application technique (for application).

FORMULATIONS AND USE SCENARIOS

Attempts were made to find exposure data for mixing/loading of powder, granular and liquid formulations. Hardly any information was found on exposure to granular formulations. From limited databases, a default value was chosen at around the 90th percentile of potential exposure. The main reasons for this were the relatively small size of the databases, the large spread in the exposure data and the need to protect the large majority of the workers, given their sometimes inadequate personal hygiene with respect to personal protective equipment (PPE).

Furthermore, evidence from available Dutch field studies indicated that in repeated measurements some persons frequently had high exposures, and others frequently had low exposures, indicating that exposure is not homogeneous. The chosen parameter of exposure was largely determined by the data presented in the published literature. The parameter of choice (amount of exposure per amount handled) could not be used, because for most exposure data it could not be calculated from the published information. Therefore, since the amount of pesticide handled was not available, it was decided to use the amount of exposure per unit of time. The default values in the Dutch model for the various formulations and type of exposure are presented in Table 5.8.

Table 5.8 Indicative levels of exposure (90th percentile) for mixing/loading

Formulation	Inhalation exposure (mg formulated product/h)	Potential dermal exposure (g formulated product/h)
Liquid	0.02	0.3
Powder	15.0	2.0

Table 5.9 Indicative levels of exposure (90th percentile) for application

Application	Inhalation exposure (μL spray/h)	Potential dermal exposure (mL spray/h)
Downward spraying outdoors (tractor-mounted)	25	10
Downward spraying outdoors (aerial equipment)	5	10
Soil fumigation	—	—
Application of granules	—	—
Upward spraying outdoors (tractor-mounted)	1000	250
Spraying indoors (upwards and downwards)	200	200
Ultra-low-volume spraying (indoors)	—	—
Soil fumigation indoors (under plastic)	—	—
Dusting (indoors)	—	—
Disinfection of seeds and bulbs	—	—
Spraying of animals	—	—
Dipping of animals	—	—

For an application scenario, a list of possible application techniques was prepared and an attempt was made to find relevant exposure data. It was observed, however, that only limited data were publicly available for several scenarios. In those cases, no default values were proposed. This can be seen in Table 5.9, where the chosen format is volume of spray per unit of time.

In recent years, a lot of work has been carried out in The Netherlands to generate exposure data, which has led to the extension of the Dutch model (van Golstein Brouwers *et al*., 1996; Snippe *et al*., 2002), also including re-entry exposure assessment and incorporation of the other European models, specifically EUROPOEM.

USE IN RISK ASSESSMENT

The Dutch model only provides exposure data. No direct application to risk assessment is indicated.

EXPOSURE REDUCTION MEASURES

This model describes potential exposures, which may then be modified with exposure reduction factors. The model contains no data on reduction factors. In the Dutch risk assessment for registration purposes, a factor of 10 may be proposed to account for personal protective measures for each relevant body part, or for inhalation. This presumes adequate personal behaviour and hygiene on the part of the worker.

MODEL UPDATES

Model updates can easily be made, and this has been done (van Golstein Brouwers *et al*., 1996; Snippe *et al*., 2002). Further updates are unlikely, because The Netherlands is now using EUROPOEM as the central database for their assessments.

COMMENTS ON THE MODEL

This model is rather conservative in view of the choice for the 90th percentile. It is based on literature data that are almost completely taken from surveillance studies and not from studies carried out for registration purposes. This may be a second factor that increases the obtained levels of exposure. This database is interesting, as it describes exposure levels as they occur in actual practice as farmers may not always take the precautions prescribed on the label.

EUROPOEM DATABASE

GENERAL DESCRIPTION

Exposure studies relevant to exposure estimations under European conditions should be collected from all available sources. This has proved difficult, because many studies are proprietary (owned by industry) and are therefore not freely available. This may bias any database to an unknown degree.

Criteria for selection of studies to be included in the database have been developed by the EUROPOEM expert group. However, it must be stated that recent studies are frequently carried out by using much better exposure assessment methodology than in the past. Consequently, a very strict use of high-quality criteria would lead to an almost empty database. Therefore some criteria need a more or less ‘flexible’ approach. The major quality criteria are as follows: (1) good documentation, describing in detail study design, participants and results; (2) representativeness of the study for European situations; (3) adequate sampling methodology applied to different workers under varying conditions of equipment and climate for a large part of the work shift (this excludes at least in part the sampling of single workers for many times); (4) adequate chemical analyses, with appropriate quality controls. The EUROPOEM group has requested

studies from industry, academia and governments and agreed to maintain a high-level confidentiality for the studies. This was accomplished by having these studies summarized by experts who, by their position in industry and government, were entitled to read the complete reports. The summaries were then further considered in detail by a group of experts with appreciable field experience in exposure studies – using the selection criteria. This has led to a positive list of studies which contain exposure data that could be included in the database. Inhalation data for compounds having a vapor pressure above 10–100 mPa at ambient temperature were excluded from the database. For such compounds, the database does not therefore indicate appropriate inhalation exposure levels.

For several subsets, measurements of the potential exposure for only specific body parts were also taken into account. For dermal exposure, a further study was made into the observed average distribution of the contamination over the body. This distribution was calculated for each relevant body part per subset and rounded to whole figures (EUROPOEM, 1996). These data may provide an appropriate basis for selection of protective clothing and gloves.

FORMULATIONS AND USE SCENARIOS

In order to conduct a risk assessment, both the exposure levels to workers and the toxicity for the compound under consideration must be known. As relevant exposure data may be difficult to obtain, it is proposed by the EUROPOEM expert group to use surrogate values for exposure. Choosing surrogate values for registration purposes is difficult, because it is not a purely scientific process.

For the EUROPOEM database, the following reasoning has been considered very important. For instance, when only about 15 data points are available from three different studies carried out in various parts of Europe, it must be recognized that in view of the large spread in exposure data, as observed in the literature of the last 40 years, such data may only give a very rough estimate of other exposures with similar mixing/loading scenarios and comparable application techniques. This indicates that the statistics to be used for surrogate exposure should be chosen to account for a sufficient degree of uncertainty. This has been operationalized in such a way that for a first estimate of exposure (surrogate value), the choice must vary from the maximum value for 15–20 data points from a few studies, up to about the 75th percentile for 50–100 data points or more from at least 10 studies with a wide range of active substances, agricultural uses and climatic conditions. For intermediate cases, the 90th percentile may be more appropriate. This also reflects that the databases are not homogeneous, so that calculation of average values and confidence intervals is inappropriate. In the case of a large database and use of exposure data for risk assessments in registration procedures, the 75th percentile is generally a reasonable statistic for exposures occurring throughout a season or a year and throughout a working life. The reason for the choice of the 75th percentile, and not the 50th percentile or a different ‘central tendency’ value, is that it is generally

not known which variables contribute most to the spread in the exposure data; it may depend to a large extent on the size of the equipment, the behaviour and hygiene of the operators in various parts of Europe, and may also depend on specific crop conditions. The 75th percentile may therefore be a somewhat conservative estimate of typical exposure, not accounting for 'within-worker' variability.

The first version of the EUROPOEM database contains about 40 studies covering a range of exposure scenarios, including mixing and loading of liquids, wettable granules and wettable powders, and applications using vehicle and hand-held methods, such as boom and pistol spraying (upwards and downwards, indoors and outdoors). In a number of studies, exposures during combined mixing, loading and application scenarios were measured. The studies cover a total of about 750 data points, i.e. exposure was measured for 750 replicates, some of which are measured more than once for a single worker. Some replicates for single workers were not used, in view of the criteria indicated above, which led either to the exclusion of the study or specific exposure data from the study in the final database. The original database contained over 200 mixer/loader exposures, about 450 applicator exposures and about 80 mixer/loader/applicator exposures.

For each scenario that contained exposure data, the database was analysed in detail and a full description of the data points was made. The data are presented in graphs, combined per study to give a good view of the spread in the data 'within-studies' and 'between-studies'. It can be concluded from the surrogate values presented in Tables 5.10, 5.11 and 5.12 that there are still appreciable gaps in the subsets.

Since the development of the EUROPOEM database (now called EUROPOEM I), the expert group has continued its work in EUROPOEM II. The group developed the following: (1) an update of the database for operator exposure; (2) a database and approach for assessment of re-entry (post-application) exposure; (3) a database and a practical approach for assessment of bystander exposure; (4) an approach for assessing mitigation measures. The databases and approaches have been presented to the European Commission and are available through the Commission Services. The operator database is also accessible through the website (www.europoem.csl.gov.uk). Reports on the work of the expert group are available through Commission Services and BIBRA, Carshalton, UK, as well as from the PSD, York, UK and TNO, Zeist, The Netherlands.

The databases are not yet in use, since user guidance is being prepared and acceptance by the Commission and Member States in Europe is still to be discussed.

Furthermore, the already mentioned international ILSI workshop in Brussels has led to some new insights which do affect the further acceptance and use of the current versions of EUROPOEM I and II. This will be discussed in more detail in the 'Conclusions and Recommendations' section below.

Table 5.10 Surrogate values for mixing/loading

Formulation type	Application equipment	Route of exposure	Potential exposure (mg/kg a.s.)[a]
Wettable powder (WP)	Vehicle-mounted (all types)	Hands	100 (indicative)
		Dermal (body and hands)	100 (indicative)
		Inhalation	1 (indicative)
	Hand-held (all types)	Hands	No good data
		Dermal (body and hands)	No data
		Inhalation	No good data
Wettable granule (WG)	Vehicle-mounted (all types)	Hands	1 (indicative)
		Dermal (body and hands)	2 (indicative)
		Inhalation	0.1 (indicative)
	Hand-held (all types)	Hands	No good data
		Dermal (body and hands)	No good data
		Inhalation	0.1 (indicative)
Liquid	Vehicle-mounted (all types)	Hands	20
		Dermal (body and hands)	20
		Inhalation	0.005
	Hand-held (all types)	Hands	120
		Dermal (body and hands)	130
		Inhalation	0.1 (indicative)

[a] a.s., active substance (active ingredient); 'indicative' – represents a 'low-confidence' value.

USE IN RISK ASSESSMENT

Several values are called 'indicative', indicating that the present subsets are too limited and need further data. In these cases, the statistic of choice is either a high percentile or the highest observed value; therefore using these values in risk assessment may lead to relatively small 'margins of safety'. In such cases, it may be useful to research whether other databases/models will give additional information. The Dutch model has, in the case of mixer/loader/applicators with hand-held equipment (indoors) for any formulation, a 90th percentile surrogate value of 200 mg/kg active ingredient (a.i.) for potential dermal exposure, whereas EUROPOEM has an indicative surrogate value of 1370 mg/kg a.i. (maximum value) (see Table 5.12). The reason for the difference is that several studies that are used for estimating the Dutch surrogate value were not available for the current EUROPOEM model. It also strongly indicates the need for model updates, based on additional studies. Presently, EUROPOEM only uses point-estimates as surrogate values. Ross and Dong (1997) have indicated the usefulness of probabilistic modelling for refining exposure assessments. This will be discussed in more detail in the final section ('Conclusions and Recommendations').

Table 5.11 Surrogate values for application

Spray direction	Application equipment	Route of exposure	Potential exposure (mg/kg a.s.)[a]	Potential exposure (mL spray/h)
Downwards	Vehicle-mounted (groundboom)	Hands	2	2
		Body (no hands)	0.6	0.7
		Dermal (body and hands)	3	2
		Inhalation	0.008	0.01
Upwards	Vehicle-mounted (air-assisted broadcast)	Hands	11	2 to 17[b]
		Body (no hands)	63	15 to 70[b]
		Dermal (body and hands)	76	19 to 90[b]
		Inhalation	0.03	0.01 to 0.04[b]
Downwards	Hand-held (all types)	Hands	100	6
		Body (no hands)	250	24
		Dermal (body and hands)	300	24
		Inhalation	0.01	0.0004
Upwards	Hand-held (all types)	Hands	65[c]	No good data
		Body (no hands)	1100[c]	No good data
		Dermal (body and hands)	1200[c]	No good data
		Inhalation	1[c]	No good data

[a] a.s., active substance (active ingredient); 'indicative' – represents a 'low-confidence' value.
[b] A differentiation has been made for volume rates. The lower value is for volume rates less than 400 L/ha, while the upper value is for volume rates more than 400 L/ha.
[c] Indicative value.

Table 5.12 Surrogate values for mixing/loading/application – formulation type, liquid

Application equipment	Route of exposure	Potential exposure (mg/kg a.s.)[a]
Vehicle-mounted (groundboom)	Hands	10
	Body (no hands)	15
	Dermal (body and hands)	30
	Inhalation	0.02
Hand-held (indoors)	Hands	1350[b]
	Body (no hands)	130[b]
	Dermal (body and hands)	1370[b]
	Inhalation	0.3[b]

[a] a.s., active substance (active ingredient).
[b] indicative, i.e. represents a 'low-confidence' value.

EXPOSURE REDUCTION MEASURES

Several studies are available on the protective capacity of normal clothing and of specially designed protective clothing. In view of the large differences in work practice, climatic conditions and the large variation in clothing, it is difficult to derive default values which can be used for a general degree of protection for a predictive assessment of actual exposure. In addition, the exposure reduction values used are not necessarily the most appropriate. Major drawbacks are the small number of actual field data on which the values are based, the nature of the contamination (solid or liquid) and the increase in penetration of (textile) clothing or gloves caused by moisture due to, for instance, spraying.

The EUROPOEM expert group intended to extend the analysis on default values in the near future, taking account of the experimental evidence for protective efficiency in field studies. For the time being, a reduction factor of 10 is used for each body part and inhalation in case of appropriate hygienic behavior. The recent developments will be discussed in the final section, ('Conclusions and Recommendations').

MODEL UPDATES

Model updates are easily handled and are foreseen by the EUROPOEM expert group on a regular basis (see also the final section, 'Conclusions and Recommendations').

COMMENTS ON THE MODEL

The model is straightforward to use, providing point-estimates of exposure. Some databases, especially for mixing/loading of wettable powders and wettable granules, are rather small and lead to surrogate values that are probably very conservative. An excellent feature of the EUROPOEM model is the fact that it has clearly defined the criteria for selection of studies and exposure data. Such studies have been described in a summary format, because some have a proprietary nature. All data are considered relevant for at least some European conditions and techniques.

COMPARISON OF DATABASES/MODELS AND THEIR USE IN RISK ASSESSMENT WITH A TIERED APPROACH

COMPARISON OF DATABASES/MODELS

The described models each use a different set of input variables for calculating exposure levels. The format of study data and the procedure for estimating the exposure levels vary for each model. The German and the UK models have used only local and mainly unpublished studies. The PHED is largely based on studies

carried out in North America, with a minimal number of replicates (<10 %) from studies carried out in Australia, or The Netherlands. The Dutch model utilizes data from published studies. The EUROPOEM group has requested data from industry, academia and governments. Studies accepted for inclusion in EUROPOEM are specifically relevant to the European agricultural practices. In EUROPOEM, data are included from studies carried out in Europe (90 %) and outside of Europe (10 %). The fact that the models are based on data from studies carried out in different regions is a major obstacle for comparison. Agricultural and climatic conditions, as well as equipment used in different parts of the world, may affect exposure. It is not possible to account for regional differences in the German or UK models (non-public data). The PHED, as well as EUROPOEM, allow for the selection of a representative region. The Dutch model, as well as EUROPOEM, is geared towards the European agricultural practice, but this model does not allow for selection of a representative region. There is a limited amount of information available on the data included in the different models. This limitation includes the format of the data. This makes it difficult to transfer data sets between the models. In addition, some of the models take a very different approach to estimating exposure. For example, in the UK model, exposure depends on the volume sprayed per unit area. The estimation of exposure during mixing and loading is based on studies that are not available to the public, and this makes it difficult to transfer the data for inclusion in another model. The PHED model provides a lot of detail on the study data (e.g. humidity, temperature, application method and location), while all other models describe their data only in basic terms.

The percentile used for exposure estimates varies with each model. The German model provides a geometric mean estimate, the UK model uses the 75th percentile (or higher depending on the class-width containing the 75th percentile), the Dutch model is based on the 90th percentile, the PHED model on the central tendency (50th percentile, geometric mean, arithmetic mean or median, depending on the data distribution) and EUROPOEM on the 75th percentile (when a large data set is available). Differences in exposure estimates due to the percentile utilized can be significant; for example, the ratio for the German model for geometric mean versus 90th percentile is 2–30 for inhalation exposure and 3–20 for dermal exposure (van Hemmen, 1993). It should be noted that data derived from the PHED can reflect almost any number, depending on what data are selected for inclusion, but an effort can be made to reflect data that would be comparable to the European models. For example, only data of A, B and C quality (as described in Table 5.1) should be included and data based on protected skin can be excluded from the data sets. In addition, to reflect mixing/loading for the identified application, the exposure data can be normalized to reflect total kg of active ingredient handled in a typical workday.

For risk-assessment purposes, actual dermal exposure needs to be estimated. Procedures to obtain these values differ. In the PHED, they are based on values

of actually observed data. The use of actual exposure data observed in field studies may be biased, because in the studies, workers may have been observed wearing new protective gloves versus gloves that were in long-term use by the worker. This could bias the exposure estimates and if not accounted for makes comparison of data impossible. The fact that gloves can be put on and taken of again during such a study does not affect the potential exposure, but does affect the actual exposure. The other models are based on potential exposure (German model, UK model, Dutch model and EUROPOEM), and the distribution of the contamination over the body is used to estimate actual dermal exposure. Data on maintenance, repair and cleaning while mixing/loading and/or applying is not available, although this can contribute significantly to exposure.

A quick glance through the presented default values/surrogate values shows indeed that comparison of the data is not simple. This may further indicate the need for a data set that can be specified for agricultural (machinery, plot sizes, etc.), climatological (temperature and wind) and geographical conditions, as well as crop. The PHED provides such data, although for some scenarios the number of replicates is limited. EUROPOEM utilizes a similar format. Other attempts to compare the outcome of databases have been published, such as van Hemmen (1993) and Lunchick and Hamey (1998). The general conclusion is that for comparable scenarios, the databases are also more comparable than when considering different use scenarios.

CASE STUDIES: A LIMITED COMPARISON

To illustrate previous comments, an attempt was made to compare estimated exposure levels of the different databases using one scenario, i.e. the downward groundboom application of a wettable powder (WP) formulation. In order to compare the outputs, specific input data must be selected. The input data presented in Table 5.13 for the identified scenario are considered to be a reasonable representation for all European databases.

The method of data selection for the North American model (PHED) is quite different. Given the complexity of the PHED model, USEPA surrogate exposure values (PHED, 1998) were used. The USEPA specifications for the selection of

Table 5.13 Input data for European models – technique, vehicle-mounted spray technique (downwards)

Mixing/loading, solid formulation (wettable powder), 25 % (a.i.)[a]
Container size, 10 kg
Application rate, 0.125–0.5 kg a.i./ha[a]
Area to be treated, 20–50 ha
Dilution rate, 200–600 L/ha
Spray concentration, 0.2–2.5 g/L
Work time, 1 h mixing/loading and 6 h application

[a] a.i., active ingredient (active substance).

Table 5.14 Specifications for the PHED, taken from the USEPA surrogate tables (PHED, 1998). Unit exposure values were extrapolated to a comparable scenario (2.5–25 kg a.i. handled, based on an application rate of 0.125–0.5 kg a.i./ha and area to be treated of 20–50 ha)[a]

Mixing/loading
• Wettable powder, open mixing • No protective clothes, no gloves, no respirator • Dermal and inhalation data grades A, B and C
Application
• Groundboom, liquid • No protective clothes, no gloves, no respirator • Dermal and inhalation data grades A and B

[a] a.i., active ingredient (active substance).

the PHED data and the assumptions used to extrapolate to a comparable scenario are given in Table 5.14.

The results for estimated potential exposure are presented in Table 5.15 for the five models, using the standard values as described earlier. As different statistics were used in the various models, only a rough comparison can be made.

For mixing and loading application (Table 5.15), the highest values for inhalation exposure were calculated by using the Dutch model. The latter also derived the

Table 5.15 Comparison of estimated potential exposure levels based on selected data, as used in five different models (see text for details)

Application model[a]	Inhalation (mg a.i./d)[b]	Dermal (mg a.i./d)[b]
Mixing/loading of wettable powder		
UK-POEM	No data	25–250
German model	0.18–1.75	15–150
PHED (North American model)	0.24–2.4	37–369
Dutch model	3.8	500
EUROPOEM	No data	No data
Groundboom		
UK-POEM	0.012–0.15	8.3–104
German model	< 0.01–0.03	5.1–51
PHED (North American model)	0.004–0.04	0.25–2.53
Dutch model	0.03–0.375	6–75
EUROPOEM	0.02–0.2	7.5–75

[a] UK-POEM, 75th percentile; German model, geometric mean; PHED, geometric mean; Dutch model, 90th percentile; EUROPOEM, 75th percentile.

[b] a.i., active ingredient (active substance).

highest values for dermal exposure. Inhalation exposure values, calculated by using the PHED and German models, were the lowest. However, overall the inhalation and dermal exposure values from all of the models are similar.

For groundboom application (Table 5.15), the highest values for inhalation exposure were calculated with the Dutch model. Higher values for dermal exposure were calculated with the European models than with the PHED model where application exposure was lower by approximately a factor of 10. Differences in local practices, farm sizes and statistics used could contribute to the range of values but cannot be confirmed because a study design of the PHED studies has not been published.

The data on which the estimated levels of exposure are based vary greatly. Some of the differences in these calculated exposure levels might be explained by the use of different statistics, differences between pre-registration studies (UK model, German model and PHED) and surveillance (post-registration studies), but it is likely that some other (local) factors contribute substantially to the variance.

A TIERED APPROACH FOR RISK ASSESSMENT

The tiered approach was presented at a workshop on 'Risk Assessment for Worker Exposure to Agricultural Pesticides' held in The Hague (Henderson *et al*., 1993) and further formalized within the EUROPOEM expert group (EUROPOEM, 1996). This approach is presented in Figure 5.1.

For an assessment of exposure for a specific use scenario, the relevant subset in the database of a predictive model is considered and the surrogate value for inhalation and dermal exposure for that subset is taken as a first tier. This exposure estimate is then compared to the relevant risk value, generally the Acceptable Operator Exposure Level (AOEL), as required under European legislation. The AOEL is derived from the No Observed Adverse Effect Level (NOAEL), from the most relevant toxicity study divided by the appropriate safety or uncertainty factor. In North America, the term Reference Dose (RfD) is used synonymously with AOEL and its derivation is described in the introduction to this book. When the ratio of exposure to AOEL is below 1, the compound in the use scenario considered is acceptable. When the ratio is above 1, a second-tier assessment is appropriate. In the second tier, some more refined assumptions should be made on the basis of experimental evidence for dermal absorption. Further (validated) assumptions may be made on the efficiency of protective measures, leading to more appropriate and less conservative data for the compound under consideration. The result is that the *potential* exposure data are now transformed into more realistic *actual* exposure data. Again, a comparison of exposure and AOEL may lead to a ratio below or above 1. When the ratio is still above 1, a well-designed field study should form the final and third tier. In most cases, biological monitoring based on a full knowledge of the human pharmacokinetics is the ultimate way to determine whether the proposed use scenario leads to acceptable exposure

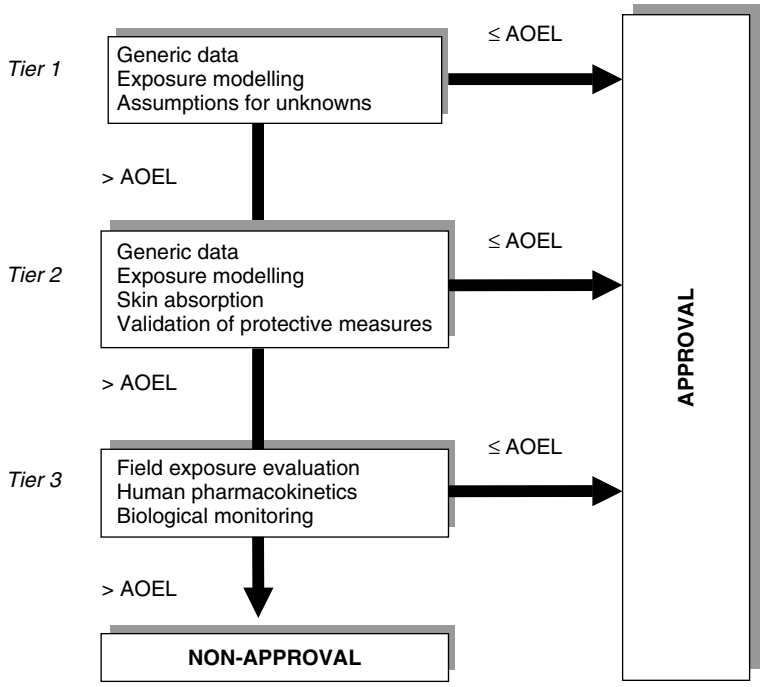

Figure 5.1 Tiered data requirements for estimating operator exposure for use in risk assessment and regulation of pesticides (AOEL, acceptable operator exposure level)

levels. The biological monitoring study may be carried out in the field by using the protective measures that are proposed for the label of the formulation.

In the actual practice of exposure assessment for registration purposes, one would like to start with a representative well-designed field study with the compound under consideration for the requested use scenario. When such a study is not available, one might look for a reference study carried out with another compound for the relevant use scenario. Such a reference study may be more appropriate than predictive models, considering that a model contains all types of studies, which by themselves may be less comparable with the considered use scenario. The reference study must also be well designed and of appreciable size to be appropriate. Such a reference study will preferably be a biological monitoring study (EUROPOEM, 1996).

GENERIC USE OF BIOLOGICAL MONITORING DATA

In the tiered approach, the ultimate basis for acceptability of an active substance or formulation is a field study using biological monitoring, interpreted on

the basis of sound pharmacokinetics, preferably with humans (Woollen, 1993). Extrapolation from such a study for a comparable use scenario with another compound would therefore be very efficient and effective. Such an approach is possible by using the concept of the rate of absorption (Chester, 1988).

The advantage of the experimental passive dosimetry studies described in this present chapter is that the routes of uptake for a compound in the body are differentiated (inhalation and dermal) and quantified as generic external potential or actual measures, which may be quantified as internal dose with appropriate knowledge of absorption per route of uptake. The use of biological monitoring is clearly specific for the compound, since the pharmacokinetics of absorption and excretion are unique to the chemical. The possibility of using biological monitoring data generically is thus clearly dependent on specific conditions, which have to be defined.

It has been frequently shown that the absorbed dose (by dermal penetration) depends on the rate of percutaneous absorption, the duration of skin contact and the area of skin contact as the major determinants. This has led to an approach which can be used for any compound and method of application for which the respiratory exposure is negligible. This is essential because the model is based on the premise that percutaneous absorption is the primary, if not the only, determinant of systemic uptake of the pesticide. Assuming an appropriate reference biological monitoring study for a certain use scenario (with a similar formulation type and a similar application technique, and workers using comparable protective measures, i.e. comparable clothing), and assuming appropriate knowledge on the rates of absorption for both compounds, it is possible to extrapolate from the reference study to the absorbed dose for the compound under consideration, since the ratio of the absorbed doses are equal to the absorption rates, and can thus be calculated. If the absorption rates are not known for humans, it is assumed that the absorption rates obtained with *in vivo* animal experiments have the same ratio as for humans. This approach is accepted by the EUROPOEM expert group, although the experience with this approach is not extensive.

CONCLUSIONS AND RECOMMENDATIONS

USE OF PREDICTIVE EXPOSURE MODELS IN RISK ASSESSMENT

For risk-assessment purposes, the best choice is a field study which is carried out for the specific purpose of obtaining exposure values under representative conditions for the use scenario and active substance that are being considered. In view of the possible range of exposure due to the large number of potential variables, it is absolutely required that the study include between about 10 and 30 replicates spread over a reasonable time period accounting for variation in climatic conditions and the relevant application technique. The number of replicates per person should be as small as reasonably possible. Workers should be monitored during whole work shifts while using the relevant and/or required personal protection

equipment (PPE). It should be noted, however, that to gain knowledge on inter- and intra-worker variability another design may be required. The most appropriate study uses biological monitoring based on a sound knowledge of human pharmacokinetics. When such a study is not available for the compound under consideration, one might consider as a surrogate, a biological monitoring study with another compound for the same or a very similar use scenario. If this is not possible, one could consider a field study not including biological monitoring for the compound under consideration or a fully representative study with another active substance for the same or a very similar use scenario. If these possibilities are not available, one might use a surrogate value from the most appropriate predictive model, preferably from a large representative subset of the model for the same or a very similar use scenario.

Since, in general, the most common use of the exposure data is to estimate risk of systemic long-term exposure, the statistic for choosing the surrogate value is the arithmetic mean (AM) of the exposure distribution and not the geometric mean (GM). The reason for this is that, although the exposure distributions are generally not normal but log–normal and thus the central tendency for exposure is the GM, the relevant average exposure for producing the toxicological effect is the AM. For not too large a geometric standard deviation (GSD) in the data distribution, the 75th percentile as a typical exposure value for risk assessment purposes is very close to the nominal value of the AM. The robustness of this value can be indicated by confidence limits based on sample size and GSD.

In the case of a relatively small database, one should err on the safe side and take a higher percentile of the distribution, such as the 90th percentile. For assessing risk for an acute toxicological effect, the 90th percentile is considered to be a better choice. In general, one should consider the whole relevant exposure database, as well as the whole toxicological database for the compound. This is a major reason for using a probabilistic approach, considering the full distributions of relevant data; this holds for the exposure assessment as well as for the hazard assessment, and thus the risk assessment (Vermeire *et al*., 1998).

PROBABILISTIC APPROACH

Point-estimates can overestimate exposure significantly. In general, the potential for overestimating exposure increases with the number of parameters and the range of values for the parameters (Ross and Dong, 1997; Lunchick, 1999). In contrast to deterministic techniques, probabilistic risk assessments more fully consider ranges of input values to estimate potential exposure. In addition, probabilistic risk assessment weighs possible values by their probability of occurrence. Instead of utilizing individual input values to generate a point-estimate, the latter is replaced where possible by a distribution reflecting a range of potential values. A computer simulation then repeatedly selects individual values randomly from each distribution to generate a range and frequency of potential exposures. The outcome is a distribution of estimated possible exposures based

on the distributions of the variables, from which exposures at any given percentile can be determined.

In May 1997, the USEPA issued a policy on the use of probabilistic techniques in characterizing uncertainty and variability. This policy recognizes that probabilistic analysis tools such as Monte Carlo analysis are acceptable, provided that risk assessors present adequate supporting data and credible assumptions (USEPA, 1998).

In 2000 in The Netherlands, a workshop was held on innovative elements in the exposure assessment for pesticide operators. This also covered the use of probabilistic exposure assessment (van Hemmen and van der Jagt, 2001).

In order to illustrate the effect of a probabilistic exposure estimate versus a point estimate, a case study has been put together in which a German model point-estimate is compared to the German model probabilistic estimate when using a probability distribution generator (DistGen).

The following assumptions were used as input for the German model: tractor-mounted high crop, dermal absorption of 15 %, inhalation absorption of 100 %, operator body weight of 78.1 kg (USEPA, 1999), acreage of 8 ha and application rate of 3.5 kg a.s./ha. This resulted in an absorbed dose estimate of 7.7 mg/person/d. Because this number is based on the central tendency, there is a 50 % chance that the actual exposure is at or below the mean, assuming a normal distribution. The predicted exposure is considered a reasonable 'worst-case' estimate. However, multiplying 'worst-case' single point-estimates will almost always overestimate exposure and risk. The predicted exposure will often be representative of the 99.9th percentile exposure rather than 50th, or even 90th, percentile exposure (Finley *et al*., 1994). In this example, 'worst-case' estimates are used for acreage and application rate, and therefore the German model does not truly represent a geometric mean, but rather something between the 50th, or even the 90th, percentile. Subsequently, the same operator exposure assessment was run by using DistGen and adding in distributions for body weight (USEPA 1998), application rate (from the label) and orchard size (National Agricultural Statistics Survey (USDA), as cited in Lunchick (1999)). The median for this exposure output is 1.9 mg/person/d (25 % of the original exposure estimate). The probabilistic approach minimizes the effect of multiple assumptions, utilizing a broader range of data. Therefore, the probabilistic estimate is assumed to reflect a more meaningful exposure estimate. The question remains on what exposure percentile to regulate (Lunchick, 1999).

At an international ILSI workshop held in Brussels (November 2003), experts in occupational exposure assessment and experts in statistics discussed the present possibilities to use probabilistic assessments for regulatory purposes when using datasets (taken from the PHED and EUROPOEM) and use information (taken from the California PUR reports and use surveys in the UK). It was concluded that the algorithms used at present for assessing exposure are not quite as sound as they should be and need improvement. For this and other reasons, specifically lack of data, it was concluded that the databases for exposures and use information

should be improved first before probabilistic assessments could become common practice in regulatory settings. The final report on this workshop is currently (August 2004) still under preparation.

OTHER IMPROVEMENTS AND INTERNATIONAL HARMONIZATION

The advantages of the various models with respect to platform, quality control of the data, and most importantly, the 'user-friendliness' of the models, could be and should be enhanced and adopted by each model. In Europe, the EUROPOEM model was meant to become the standard and the other European models would lose their value to users, and therefore the models will not be adapted except for specific local reasons. EUROPOEM, as it is available now, has been developed by an expert group and was extended and improved with money made available by the European Union by adding relevant studies made available to the expert group. Regular updates are important if EUROPOEM is to remain relevant. This specifically holds for the quality of the studies in the database, most of which are not very recent. Industry (the European Crop Protection Agency (ECPA)) holds some 30 studies which have been carried out recently but they have not been added to the current EUROPOEM database.

While there are no plans for improvements of the platform for the PHED model, some of its features are highly acclaimed, since a representative subset, possibly large enough, to cover the basic needs for the required extrapolation may be selected from the database. This can now be done by computer for EUROPOEM. On the other hand, the quality assessment of the studies from which exposure data are taken is much more science-based in EUROPOEM than for the PHED, where selection only depends on the analytical quality. This latter deficiency should be rectified in the new Agricultural Handlers Exposure Database (AHED) described earlier.

There is a strong need for improvements to both the North American and European databases. Currently, the most appropriate approach would be that industry and regulatory authorities from both Europe and North America come together and use the recently developed and fully innovated database software (AHED) for the purpose of entering only data from studies which fit some strict criteria, as indicated earlier. If this is accomplished, there will be an appropriate set of data for a thorough data analysis, hence leading to the best possible algorithms to be used in the exposure and risk assessment for regulatory purposes, in either a deterministic or probabilistic approach. Both models (PHED and EUROPOEM) should then be exchanged for the new database with perhaps separate sets of quality-assessed data for North America and Europe, in view of differences in agricultural characteristics, but using the same general software platform as provided for by AHED.

Given the current interest of regulators in harmonization, this database integration and harmonization could be carried out under the auspices of the Organization for Economic Co-operation and Development (OECD) where all relevant

countries from Europe and North America, as well as many other countries, such as Australia, are organized within the Working Group on Pesticides. The approach for integration and harmonization could be prepared by a suitable expert group, and the organizational structures of the OECD are well suited for carrying this out. This would also promote harmonization of pesticide-use scenarios throughout the world to the extent required.

MODERN FORMULATIONS AND APPLICATION TECHNIQUES

Environmental considerations and regulatory pressures are causing formulators and manufacturers to redefine their formulation and adjuvant strategy. The trend towards the use of water-based suspensions or emulsions and water-dispersible granules, thereby reducing exposure to organic solvents which are potentially more toxic to workers and the environment, has lead to considerable research on the interaction between surfactants and solid particles or emulsion droplets in terms of dispersion and stabilization. Adjuvants were originally used as the 'wetter' or as an aid to improve droplet adhesion. In recent years, they have been used in high concentrations to enhance the performance and efficacy of pesticides by increasing uptake into the target (Rogiers, 1995). Surfactants currently used in agrochemicals serve as wetting agents, and improve dispersion, emulsification, solubilization and/or bioenhancement (Knowles, 1995). New adjuvant strategies to increase uniform target coverage and increase pesticide efficacy at reduced application rates stimulate the use of adjuvants in order for generic formulations to work better and optimize the activity of all newly developed pesticides. A well-designed adjuvant system is included in the concentrate as part of a formulation package, so that the end-user receives full instruction without having to use other additives. The advantages of adjuvant incorporation in the concentrate will include increased spreader sticker activity, penetration, translocation where needed, reduced leaching, reduced drift and biodegradability of the inert system (Nayayanan, 1996).

A move to microencapsulation is stimulated by its beneficial properties. Microencapsulation reduces leaching to groundwater, improves biological efficacy and lowers the acute toxicity of organic compounds. An additional advantage of microencapsulation is converting liquid organic compounds to a high-concentration dry solid form. Dry solid formulations offer storage stability and packaging advantages over liquid products (Beestman, 1996). A disadvantage is the slower degradation in the field. An active agent inside a shell wall is protected from chemical, photochemical and microbial degradation processes. (Stern and Becher, 1996). With the increasing demand for environmentally safe products, this can be a concern. The encapsulated formulae (capsulated soluble, microencapsulated, etc.) are designed to improve the toxicity profile for registration purposes. Encapsulation only offers an additional advantage for registration purposes of formulations that are not too highly concentrated.

Pressure to reduce the use of broad-spectrum chemical insecticides has increased the development of biological control products. In most countries, it is necessary to demonstrate the safety of microbial pest control agents (MPCAs) to public health and the environment through safety testing and product registration (Richards and Rodgers, 1990). In addition, the USEPA includes biochemical pesticides (e.g. pheromones) in the separate registration of biologicals (Mendelsohn *et al*., 1995).

In order to reduce exposure during pesticide use, there is a move away from wettable powders to a new type of granule, such as the 'non-dust granule'. More products come 'pre-measured' in water-soluble packages or in ready-to-use formulations. Worker exposure is reduced, and there is less waste and potential damage due to inaccurate measuring and mixing. In addition, use rates have fallen greatly. Higher concentrations of active ingredients and less filler go into each package.

Low-volume and covered-boom sprayers in general increase efficiency and are therefore more environmentally safe. Low-volume sprayers come as 'pull-behind' or 'out-front' models and apply the proper amount of active ingredient, using less water and chemical.

Covered-boom sprayers look similar to a large, 'bat-wing-type' reel mower. Spray nozzles are enclosed so that spray is directed with little drift. In addition, many sprayers today are computerized. Computers control the amount of output depending on ground speed, sprayer height, wind speed and flow rate pressure. Computers also can perform such functions as tracking the number of hectares treated, the amount of product used and the day and time it was applied. The possibilities are many, but they all may not be practical or affordable (Walker, 1997).

It is clear that the possible exposure reduction potential of these newer technologies is not yet considered in the databases. The current databases may even overestimate exposure when using particularly older studies carried out with classic techniques for classic formulations. This further underlines the need for using well-designed field studies representative of these new developments.

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6 Predictive Residential Models

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INTRODUCTION

Quantification of residential exposure is challenging because exposure assessment involves specifying contact with pesticides and determining concentration–time profiles for each means of contact during and after use of the product. These exposure concentrations can be determined empirically, giving an accurate picture of a single experimental event or predicted by mathematical models. The advantage of models is that they yield predicted concentrations with specified uncertainty and can be applied to a range of exposure situations by adjusting for variables, such as different amounts of pesticide, different ventilation volumes, diversity in types of residential pesticide products, means of application and types of users. Ideally, empirical measurements and model predictions are combined to provide the most useful information for exposure assessments. Measurements of exposure concentrations are used to validate and check models, while measurements of exposure factors, such as the applied amount and room ventilation, are used to provide parameter values to models to fit them to specific circumstances.

Because data on non-professional exposure is scarce but exposure assessments are necessary, models have become a main tool in assessing residential exposure. It appears to be easier to obtain good quality data on exposure factors (room sizes, typical amounts used, etc.), which can be used as parameters in models, than to obtain direct exposure measurements. Critics of the modeling process say that the information generated through models is suspect because of the inherent simplifications involved. This criticism may be valid if risk assessors who utilize models do not make the appropriate selections that are needed in their application. They need to ask the following: which model should be used?; which data should be fed into the model?; why do these two (three) models produce different results, and are the differences significant for risk assessment?; which data are necessary

for a full picture of exposure? Credible skepticism will lead to useful methods to assess risks of pesticides.

In this present chapter, the role that models can play in the risk assessment of pesticides used in the residential setting and the currently available models are described. In particular, the ways in which residential exposure models are constructed, validated and used are explored.

STATUS OF RESIDENTIAL MODELS

Compared with the occupational exposure of applicators and workers following pesticide application in the field, post-application residential exposure to pesticides used in and around the home is lower in level, but encompasses a wider variety of scenarios, such as age distribution, activity patterns and product use. Typically, few data are available on residential exposure, while a large body of data does exist for occupational exposures. Residential exposure assessment and modeling may benefit from the new data requirements under the United States Food Quality Protection Act of 1996 (Lewis *et al*., 1994; Hill *et al*., 1995; Lu and Fenske, 1998; USEPA, 1990; Whitmore *et al*., 1994). In occupational exposure assessment, a database approach is favored, while in residential exposure assessment a mechanistic and statistical modeling approach is dominant.

Simple models have been developed to screen for consequences of 'worst-case' exposures (van de Meent *et al*., 1995; USEPA, 1997b). For example, these models calculate 'worst-case' exposure by dividing the amount of active ingredient by the room size. When better estimates of exposure are needed, simple models are advanced based on mechanistic processes or statistical relations, in conjunction with experiments aimed at quantifying exposure factors (Jayjock, 1994; Matoba *et al*., 1998a,c; van Veen, 1996) (see the model overview below). These models describe the mechanisms of exposure and include key factors that influence exposure, such as ventilation rates of rooms and vapor pressures of chemicals. In addition, they provide a more precise temporal and spatial scale of exposure and dose. These scales enable identification and exposure assessment of persons at various distances from the application and of persons having various time-intervals of contact with the pesticide.

An approach to extrapolate data beyond the actual circumstances encountered during monitoring is to use statistical relationships. These statistical models are also based on previously measured data but add an empirical relationship with, for instance, molecular properties. The fact that the relationship is empirical, rather than mechanistic, distinguishes these models from the mechanistic ones. A transfer-coefficient approach to estimate dermal post-application exposure can be seen as an application of a statistical relationship. The dermal transfer coefficients are derived from measurements of dislodgeable residues and measured dermal exposures (USEPA, 1997a) and are used to estimate dermal exposure in general cases, in fact, extrapolating from underlying measured data. By using this method, Ross *et al*. (1990, 1991) derived transfer coefficients for post-application

residential exposure after using foggers, by setting the 'Jazzercise exercises'. The dislodgeable ratio of a chemical to the concentration of the residue on room materials, which is derived from this approach, can be incorporated into a model for estimating dermal exposure (Matoba *et al*., 1998c). There is a detailed discussion of this in Chapter 4.

EXPOSURE PHASES IN RESIDENTIAL EXPOSURE

Residential exposures are no different from occupational exposures in terms of the phases of exposure. Generally, exposure can be divided into the following three phases (EC, 1998).

MIXING AND LOADING PHASE

Mixing and loading includes the handling of the can, container or bag containing the concentrate or dilution of the pesticide to be used with water or another suitable fluid. Exposures during the mixing and loading phase are of significant importance because contact with undiluted product may occur, hence resulting in a potential exposure which is much higher than would be the case through contact with the same amount of diluted product. This exposure may also have local effects on the skin or eyes, or cause a high-peaked dose in the body. Published descriptions of a few cases of residential use of pesticide (Weegels, 1997) show that users may ignore precautions on the label and dilute the pesticide using their bare hands to handle materials on the kitchen countertop. Bottles may have residues of undiluted pesticide on the outside, so resulting in dermal contact.

Unfortunately, there are no mechanistic models to predict mixing and loading exposures, and few measurement data regarding exposure in residential scenarios (van Hemmen, 1992). Mixing and loading exposure have received considerable attention in the field of occupational hygiene, and data are reported in the literature. Occupational exposure is typically concerned with large amounts of pesticide, and exposures are often expressed in milligrams of pesticide exposure per kilogram of active ingredient used. This format enables a rough extrapolation of residential exposure by adjusting for the amount of pesticide handled. The United States Environmental Protection Agency (USEPA) (1997b) estimates exposure for the mixing and loading phase in the residential environment by using the agricultural data in the Pesticide Handlers Exposure Database (PHED). Reliance on the latter is decreasing as the Residential Exposure model (REx), developed by the Outdoor Residential Exposure Task Force (ORETF), becomes available. REx contains several hundred replications of outdoor residential exposure data.

APPLICATION PHASE

This includes the actual application of concentrate or the diluted product in a large variety of ways, with or without special equipment. Exposures during the

application phase mostly concern the user, although bystanders who are present may also be exposed. The user is close to the application and is expected to experience a higher exposure than a bystander. The user and bystander are expected to be exposed through multiple routes, due to airborne pesticide (inhalation) and dispersion of pesticide near the body (dermal). Bystander exposure is generally much lower than that of the user (Stevens and Davis, 1981; Solomon *et al*., 1993; Ganzelmeier *et al*., 1995; Lloyd *et al*., 1995).

Pesticides are used in residential settings by professional and non-professional users, who differ in a number of aspects. First, professionals are assumed to be skilled and healthy adults, while non-professionals may include the young and the old, the careless and the careful. For professionals, it is appropriate to assume that personal protective equipment is used; however, such an assumption cannot be made for non-professionals, even when such precautions are recommended. Secondly, use frequencies and use duration will generally be larger for professionals when compared to non-professionals. Thirdly, as a consequence of their intensity of contact, professionals are expected to use higher amounts of pesticides than non-professionals.

Most models use the application phase as the starting point for exposure modeling. In CONSumer EXPOsure models (CONSEXPO), the use duration refers to the application phase and exposure for post-application takes place during the remainder of the total contact duration. The Multi-Chamber Concentration and Exposure Model (MCCEM), Version 2.4, Total Human Exposure Risk DataBase and Advanced Simulation Environment (THERdbASE) and INdoor PESTticide (InPest) start with the application phase which gradually becomes post-application exposure. The European Union System for the Evaluation of Substances (EUSES) and Uniform System for the Evaluation of Substances (USES), Models 1 and 2, are based on the life cycle of the product, thereby starting exposure assessment with the production of the chemical and not with its use. Overviews of the above models are described later in this chapter. The non-professional's exposure itself can also estimated by the PHED database, selecting from experimental or monitoring circumstances which are considered similar to the actual intended use (USEPA, 1997b). REx contains data for professional lawn applications and non-professional lawn, garden and tree applications. The UK Predictive Operator Exposure Model (POEM) has a home garden sprayer option and is available on the UK PSD homepage (http://www.pesticides.gov.uk/applicant/aahip/aahl0316.htm).

POST-APPLICATION PHASE

This phase includes contact with the pesticide after application, e.g. by contact with contaminated equipment and surfaces, or contact with treated surfaces and materials, or by entering treated environments. Anyone remaining in the treated area may be subject to exposure long after the application has been completed from residues remaining in the air, residues on surfaces such as the floor or

walls, ingestion through food or water, and secondary exposures caused by use of treated materials. For example, sawing treated wood may release high concentrations of impregnated wood dust in air during work. Various workers (Rapp *et al*., 1997; Byrne *et al*., 1998; Gurunathan *et al*., 1998) have detected elevated air concentrations of chlorpyrifos for at least two weeks following a 10 min use period. This is probably due to evaporation from settled sources. All residential exposure models describe post-application exposure as a direct result of the application phase.

Of special interest is post-application exposure of toddlers and children, who tend to play on the floor and show extensive 'mouthing' behavior (Davis and Ahmed, 1998; Groot *et al*., 1998). Toddlers and children contact residues which have settled on the floor by wiping the floor and stirring up dust. Semivolatile and volatile pesticides evaporate and absorb onto various surfaces, including babies' toys, which have extensive contact with children (Gurunathan *et al*., 1998). In addition, the low body weight compared to adults is a risk factor for toddlers and children.

MODEL CONCEPTS: FRAMEWORKS

To simulate behavior of pesticides, most models are based on the following conceptual frameworks.

MASS-BALANCED AIR QUALITY MODEL

A mass-balanced air quality model, such as is used in CONSEXPO and MCCEM, is the most widely accepted indoor air quality model. This focuses only on the air in the room environment, assuming that concentration in a room is uniform. Interactions of pollutant gain and loss are most often described through a differential equation that is applied to a defined indoor volume, as follows:

$$V\frac{\mathrm{d}C}{\mathrm{d}t} = G - VLC \tag{6.1}$$

where V is the room size (m^3), C the indoor pollutant concentration (g/m^3), t the time (s), G the rate of pollutant gain (g/s) and L the rate of pollutant loss (s^{-1}). According to the type of application, the source term G can take different forms. For example, it contains, for spraying, a term that describes formation of aerosol droplets and evaporation from the droplets. For painting activities, it contains an evaporation term from the painted materials. The rate of pollutant loss, L, includes transport out of the room, and degradation of pollutant in the air, as well as adherence of pollutant to the room materials, as follows:

$$L = Q_{i0}/V + k + d \tag{6.2}$$

where Q_{i0} is the airflow rate from room i to outdoors (0) (m^3/s), k the rate constant of degradation (s^{-1}) and d the rate constant of adhering loss (s^{-1}). For multiple rooms, a mass balance equation is formulated for each room i as follows:

$$V_i \frac{dC_i}{dt} = G_i - V_i L_i C_i + \sum Q_{ji}(C_j - C_i) \tag{6.3}$$

where the summation takes place over all adjacent rooms j, Q_{ji} (m^3/s) is the airflow between room j and i, and the other parameters have been defined in the above without room specificity.

FUGACITY MODEL

To describe a chemical's partitioning, transport and transformation processes, Mackay (1979) developed a modeling approach which has proved to be particularly convenient in this context. This approach employs the concept of *fugacity*, which means an 'escaping tendency'. Fugacity has the units of pressure and can be viewed as the partial pressure which a chemical exerts when it attempts to escape from one medium or compartment and migrates to another. The relationship between fugacity (f) (Pa), concentration (C) (mol/m^3), amount of chemical (N) (mol) and compartment volume (V) (m^3) is simply stated as follows: $C = N/V = Zf$. Thus, if V is constant, $VZdf/dt = dN/dt$, where Z is the fugacity capacity with units of mol/m^3 Pa and quantifies the capacity of each compartment for fugacity. In the case of an air compartment, it can be shown that Z is $1/RT$ where R is the gas constant (Pa m^3/mol K) and T the absolute temperature (K), as defined by the ideal gas law.

After treatment, chemicals are subject to degradation reactions such as photolysis and oxidation, as well as to a dispersal movement due to ventilation, as expressed in the following equation for the air compartment:

$$\frac{dN_{air}}{dt} = -C_{air}[Q_{i0} + (k + d)V] \tag{6.4}$$

where N_{air} is the chemical amount in the air (mol), C_{air} the aerial concentration (mol/m^3), Q_{i0} the air flow rate (m^3/s), k the rate constant of degradation (s^{-1}) and d the rate constant of adhering loss (s^{-1}). A diffusive transfer rate of a chemical between air and floor compartments can be written as follows:

$$\frac{dN_{air}}{dt} = -D_{air,floor}(f_{air} - f_{floor}) = -\frac{f_{air} - f_{floor}}{1/(\nu_{air} A Z_{air}) + 1/(\nu_{floor} A Z_{floor})} \tag{6.5}$$

where $D_{air,floor}$ (mol/s Pa) is a transfer parameter, f_{air} and f_{floor} (Pa) the fugacities of the chemical in the air and floor compartments, respectively, ν_{air} and ν_{floor} (m/s) the phase mass transfer coefficients in the compartments, and A (m^2) the transfer area (connecting area) between the compartments. The variables ν_{air} and ν_{floor}

should be regarded as piston velocities with which the solute moves through each phase to and from the interface.

Therefore, the general differential equation of the chemical in the air compartment for a single room with room materials j, such as floor, walls and ceiling, is expressed as follows:

$$V_{\text{air}} Z_{\text{air}} \frac{\mathrm{d}f_{\text{air}}}{\mathrm{d}t} = G_{\text{air}} - C_{\text{air}}[Q_{i0} + (k + d)V] - \sum D_{\text{air},j}(f_{\text{air}} - f_j) \qquad (6.6)$$

where G_{air} represents the emission rate (mol/s). Using this fugacity concept, InPest has been developed to simulate the indoor behavior of pesticides in the room environment.

FLUID DYNAMICS MODEL

Development of more powerful digital computers in the last decade has made possible fairly rigorous analysis of a wide range of flow phenomena by using a model of fluid dynamics. The flow phenomenon is simulated by solving the basic equations of mass, momentum, energy and chemical species conservation. By using fluid dynamics, Matoba *et al.* (1994a) simulated the indoor behavior of a pesticide being released with an electric vaporizer settled in a room, and the results were incorporated into InPest for electric vaporizing modeling (Matoba *et al.*, 1994b).

MODEL CONCEPTS: SOURCES AND SINKS

Each model developed by using the above frameworks contains source and/or sink terms. The source terms add the pesticide to the residential environment, while the sink terms remove it from the environment. Here, details regarding a number of important source and sink terms, specifically, evaporation, aerosol droplets, material sinks and degradation in indoor air, are provided.

SOURCE: EVAPORATION OF PESTICIDES

The following estimations are commonly incorporated into the models to describe the pesticide evaporation. In addition, simple evaporation terms, including exponential decay (Clausen *et al.*, 1993) and double-exponential or second-order decay (Guo, 1993) describe emission characteristics regardless of the room concentration.

Vapor-Pressure-Driven Evaporation

Evaporation can be modeled by the back-pressure approach advocated by Jayjock (1994) where the evaporation rate G (g/min) is driven by the difference between

the equilibrium (P_{eq}) (mmHg) and the actual (P_{act}) (mmHg) vapor pressures of a compound, as derived from (Tibodeaux, 1979):

$$G = 21AM^{2/3}(P_{eq} - P_{act})/T_{air} \tag{6.7}$$

where A is the evaporation area (m^2), M the molecular weight (g/mol) and T_{air} the temperature (K). The actual vapor pressure of the compound in air (i.e. back-pressure) is calculated from the air concentration (C) (g/m^3) by the following:

$$P_{act} = 0.0623CT_{air}/M \tag{6.8}$$

The estimation can be used by both CONSEXPO and MCCEM.

Chinn Evaporation

Chinn (1981) focused on the capacity of air and manipulated the ideal gas law to determine the volatility of a compound. He then found that the logarithm of the volatility E (mg/m^3) correlates linearly with the logarithm of the time required for 90 % evaporation of pure chemicals, as determined by using a Shell thin film evaporometer at 25 °C and 0 % relative humidity for 40 chemicals, as follows:

$$\log_{10} t = 7.3698 - 0.9546 \log_{10} E \tag{6.9}$$

where t (s) is the time required for 90 % evaporation. This leads to the following equation when the room humidity is 0 % and t_{90} (min) is the time required for 90 % evaporation:

$$t_{90} = X/[(PM)^{0.9546}] \tag{6.10}$$

where P is the vapor pressure (mmHg), M the molecular weight (g/mol) and X is 8416, 8555, 8695 and 8834 at 15, 20, 25 and 30 °C, respectively. Using this time t_{90}, THERdbASE and SCIES, as well as the USEPA's Standard Operating Procedure (SOP) (USEPA, 1997b) simply calculate the emission rate (G) (g/min) of the compound as $G = N/t_{90}$, where N is the total amount of the applied compound (g).

SOURCE AND SINK: BEHAVIOR OF AEROSOL DROPLETS

When an aerosol canister containing an oil- or water-based formulation is sprayed in a room environment, the size of the aerosol droplets containing pesticides decreases with time due to evaporation of the dominant solvent, such as oil or water. The diameter (d) (m) of the droplets at time t (s) is determined by the rate of evaporation at which vapor can diffuse away from the aerosol droplets (Hinds, 1982), as follows:

$$d = \sqrt{d_0^2 - 2\alpha t} \tag{6.11}$$

where d_0 (m) is the droplet diameter immediately after application and α (m^2/s) the diameter coefficient:

$$\alpha = \frac{4 D_d M_d}{R \rho_d} \left[\frac{P_d}{T_d} - \frac{P_\infty}{T_\infty} \right] \tag{6.12}$$

where D_d is the diffusion coefficient of the dominant solvent in air (m^2/s), M_d the molecular weight of the dominant solvent (g/mol), R the gas constant (8.315 Pa m^3/K mol), ρ_d the specific gravity of the dominant solvent (g/m^3), P_d the vapor pressure of the dominant solvent on the surface of the droplet (Pa), P_∞ the vapor pressure of the dominant solvent far from the droplet (Pa), T_d the temperature at the surface of the droplet (K) and T_∞ the temperature of the room (K). In their study, Matoba *et al*. (1993) assumed that the dominant solvent of the aerosol droplet was *n*-tridecane, taking into account the content of an aerosol canister, and the diameter coefficient (α) was estimated to be 1.5×10^{-11} m^2/s at a room temperature of 25 °C. In the case of a water-based aerosol released into a room at 25 °C, α had values of 2.33×10^{-10} m^2/s in the room at 60 % relative humidity, 3.49×10^{-10} m^2/s for 40 % relative humidity or 1.19×10^{-10} m^2/s for 80 % relative humidity.

The motion of aerosol droplets following space spraying is governed by gravity and the resistance of air particle motion. Droplet settlement depends on the size of the droplet. The droplet settling velocity (v_i) (m/s) is given by Stokes' law (Hinds, 1982):

$$v_i = \frac{\rho_d g d^2}{18 \eta} \left[1 + \frac{12.64 + 4.02 \exp\ (-8.322 \times 10^6 d)}{7.6 \times 10^7 d} \right] \tag{6.13}$$

where g is the acceleration gravity (9.81 m/s^2) and η the air viscosity (25 °C, 1.85×10^{-2} g/m s).

The number (n) of aerosol droplets floating in the air decreases with time because of loss through ventilation and adherence to materials in the room. The rate of change of n is given by the following:

$$\frac{dn}{dt} = -n \left[\frac{v_i}{H_s} + \frac{Q}{V} \right] \tag{6.14}$$

where H_s is the height of sprayed zone derived from application (m), Q the ventilation rate (m^3/s) and V the room volume (m^3). These parameters have been incorporated into InPest.

SINK: DEGRADATION OF PESTICIDES IN INDOOR AIR

Degradation of airborne pesticides is caused by absorption of light (direct photolysis), as well as by reaction with OH-radicals and ozone in air (indirect photolysis).

Direct photolysis in a room environment occurs by artificial light from a room lamp, sunlight through the room's closed windows, or sunlight when the windows are open. The degree of direct photolysis from these kinds of light depends on absorption of light by the pesticide itself, i.e. the overlap between the light emission spectrum under room conditions and the light absorption spectrum of the pesticide. For example, typical pyrethroids such as *d*-tetramethrin, *d*-resmethrin and *d*-phenothrin have an absorption peak at a wavelength of 222 nm, 208 nm and less than 200 nm, respectively (Matoba *et al.*, 1998a); the light absorption spectra of the three pyrethroids do not overlap any of the spectra of the three kinds of light mentioned above. Thus, direct photolysis would be negligible for pyrethroid pesticides in the room environment.

Indirect photolysis of a pesticide in the air occurs mainly by reaction with OH-radicals or ozone. The degradation rate with OH-radicals and ozone of a pesticide in a room can be estimated by multiplying the rate constant (k_{OH}, k_{O_3}) (cm^3/molecule/s), predicted from the pesticide chemical structure, by concentration of OH-radicals and/or O_3 in the air (Atkinson, 1985; Atkinson and Carter, 1984). The computer program, 'Atmospheric Oxidation Program' (Meylan and Howard, 1993, 1994), which is recommended by the Organization for Economic Co-operation and Development (OECD) (1993) and the USEPA (1999), makes it possible to estimate the rate constants. In this context, the most appropriate average concentrations of the OH-radical [OH·] and ozone [O_3] seems to be 7×10^5 and 4.9×10^{11} molecule/cm^3, respectively, in a room environment at an air-exchange rate of 1 h^{-1} based on findings by Weschler and Shields (1994, 1996, 1997). Therefore, the rate constant (k) (s) of the pesticide in the indoor air due to indirect photolysis is estimated by $k = k_{OH}[HO\cdot] + k_{O_3}[O_3]$. For example, the half-lives due to indirect photolysis are calculated to be 30, 28 and 39 min for *d*-tetramethrin, *d*-resmethrin and *d*-phenothrin, respectively. The degradation rate can be easily applied to CONSEXPO and InPest.

SINK: DIFFUSION OF PESTICIDES INTO ROOM MATERIALS

When airborne pesticides, or aerosol droplets including pesticides, adhere to room materials such as the floor, walls and ceiling, the pesticide will permeate into the materials. A diffusion depth (e) (m) of an organic compound in a polymer has been shown to follow a linear relationship with the square root of time (t) (s) and the diffusion constant of the compound (D_c) (m^2/s) (Lapcik *et al.*, 1976), according to the following:

$$e = 2\sqrt{D_c t} \tag{6.15}$$

A carpet consists of a polymer textile which is typically laid on a wooden floor which is usually coated by a polymeric material such as polyurethane resin. For the Japanese-style floor, tatami, made of rush, the latter is composed of 46 % crude fibrous lipid and gummy material (Hirai *et al.*, 1984) with properties considered to be similar to those of a polymer. Wallpaper on the ceiling and walls is

usually made of a poly(vinyl chloride) material. Thus, the velocity of pesticide in the room material (v_c) (m/s) can be expressed by the following:

$$v_c = \sqrt{D_c/t} \tag{6.16}$$

The diffusion constant (D_c) in poly(vinyl chloride) was reported by Lapcik *et al.* (1976) as 2.67×10^{-15} m^2/s for methyl red and 5.25×10^{-15} m^2/s for methyl palmitate. In contrast, the method of Wike and Lee (William and Nelken, 1982) gives a diffusion coefficient (D_{air}) in air of 4.27×10^{-6} m^2/s for methyl red and 4.54×10^{-6} m^2/s for methyl palmitate. Since the D_c/D_{air} ratio is almost 10^{-9}, Matoba *et al.* (1995a) proposed that the D_c of the pesticide in room materials is 10^9 times lower than the D_{air} estimated by the method of Wike and Lee. The diffusion of pesticides in room materials is modeled by InPest.

MODEL VALIDATION

Model validation can be divided into two parts, a conceptual part including exposure validation, and a numerical part including pesticide movement.

CONCEPTUAL VALIDATION

Conceptual validation addresses the question of whether the model contains all relevant processes underlying exposure in accordance with the present body of knowledge. Conceptual validation also applies to cases in which models aim at a reasonable 'worst-case' prediction of exposure; it should be validated whether the scenario as described by the model actually is a reasonable 'worst-case'. In order to model exposure to a pesticide, all relevant routes of exposure should be included; a first conceptual check of the model is to determine if the model contains all of these routes. If not, only part of the possible exposures will be modeled. The model can further be checked against physico-chemical laws and mass balances. For example, if the model describes inhalation exposure over a range of temperatures, they must be included in the model since temperature affects evaporation (Schenk *et al.*, 1997).

The SCIES and MCCEM models give only inhalation exposure, but the simulated results can be incorporated into a whole-risk assessment in the residential space such as the USEPA SOP framework (USEPA, 1997b) which estimates multiple exposure levels via all routes (i.e. inhalation, dermal and oral). THERdbASE is capable of estimating inhalation and dermal exposures based on the simulated airborne concentration and the film-thickness theory, and InPest estimates all exposures, including oral routes, based on the simulated concentration in the air and amounts on the room materials (Matoba *et al.*, 1998c).

CONSEXPO, EUSES and USES each provide multiple exposure levels via all routes with various options in line with the package of the EU Technical Guidance Document (EC, 1996). Of these models, CONSEXPO and MCCEM provide a

probabilistic distribution of exposure levels, and this approach is expected to be a useful tool to show realistic exposures by using tendencies in exposure factors instead of a single value.

NUMERICAL VALIDATION

Numerical validation for pesticide movement addresses the question of whether the results generated from the model predict actual experimental values. A few models have been validated by correlating the estimated airborne pesticides and/or the amount on room materials with actual measurements in certain specific cases. van Veen *et al*. (1999) reported an experiment to validate a 'painting' model of CONSEXPO which describes concentrations of a volatile solvent in room air both during and after the application. The concentrations depended on evaporation, initial concentration of solvent in two layers of paint, volume of paint and removal of solvent by ventilation from the room. Model parameters were either measured from the room before the experiment (ventilation rate, room size, physico-chemical parameters, etc.) from the act of painting (surface painted and amount of paint used), or fixed in advanced (relative size of the two layers of paint, transfer rate between the layers, etc.). The model predicted room concentrations that were within 80 % of the actual measured concentrations (Figure 6.1). Important with respect to the evaporation term is that peak concentrations could be predicted very well, so indicating that the source term is appropriate.

In order to assess the accuracy of the developed InPest, the unsteady state behavior of pesticides was simulated by the model, and the predicted concentration in the air and residue amounts on the room materials were compared with measurements by Matoba *et al*. (1993, 1994b, 1995a, 1998a,b,c). The

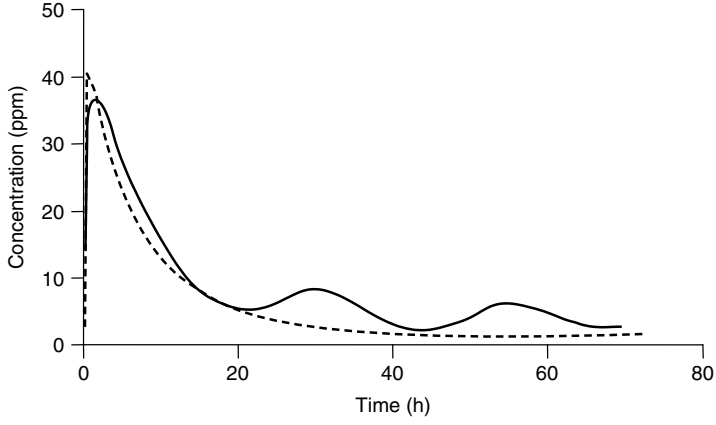

Figure 6.1 *n*-Alkane concentrations resulting from painting 1 m^2 of wood with a paint based on organic solvents in a closed office room (after van Veen *et al*., 1999): (–) experimental; (- - -) model

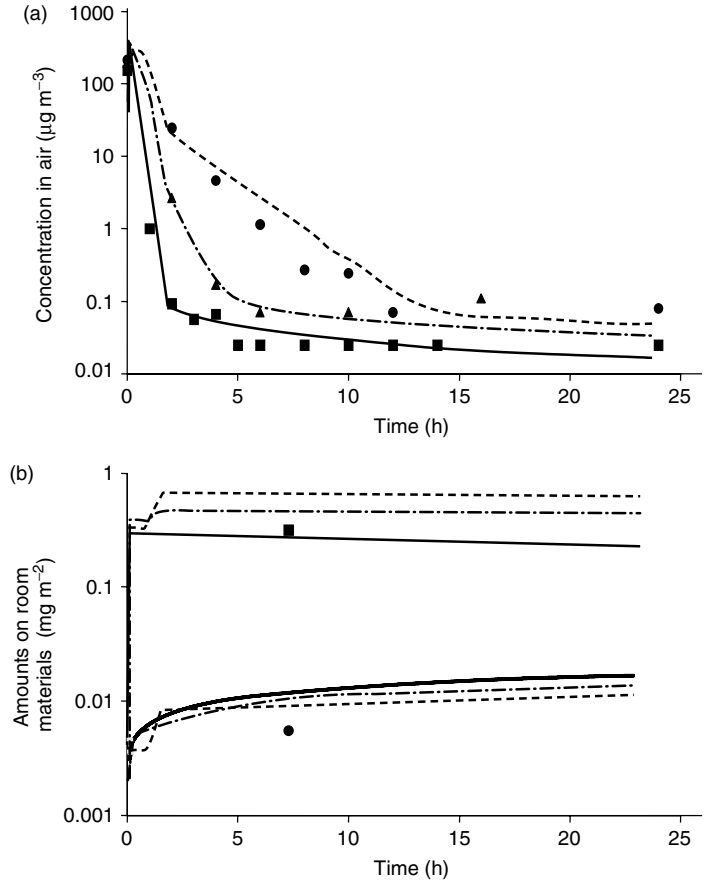

Figure 6.2 (a) Time-dependent concentrations of *d*-tetramethrin in the air following a space spraying in a room at three different air-exchange rates, as predicted by InPest (lines) and from actual measurements (filled symbols): ● (– – –), 0.5 h^{-1}; ▲ (–·–·–), 1.6 h^{-1}; ■ (———), 4.1 h^{-1}. (b) Time-dependent amounts of *d*-tetramethrin on the floor (upper plots) and on the ceiling (lower plots), as derived by InPest: (– – –), 0.5 h^{-1}; (–·–·–), 1.6 h^{-1}; (———) 4.1 h^{-1}: ■ and ●, measured values at a rate of 1.6 h^{-1} (Matoba *et al.*, 1998c). Reproduced by permission of the Air & Waste Management Association from Y. Matoba, J. Yoshimura, J. Ohnishi, N. Mikami and M. Matsuo, *J. Air Waste Management Assoc.*, **48**, 969–978 (1998)

comparison results obtained for space spraying using both pyrethroid (Figure 6.2) and organophosphorous pesticides (Figure 6.3(a)) show that the estimated values obtained accurately correlated with actual measurements examined at one or several air-exchange rates. In the same manner, InPest models for an electric vaporizing (Figure 6.3(b)), as well as for broadcast (Figure 6.3(c,d)) and direct sprayings (Figure 6.3(e,f)), show that the predicted time-dependent concentrations

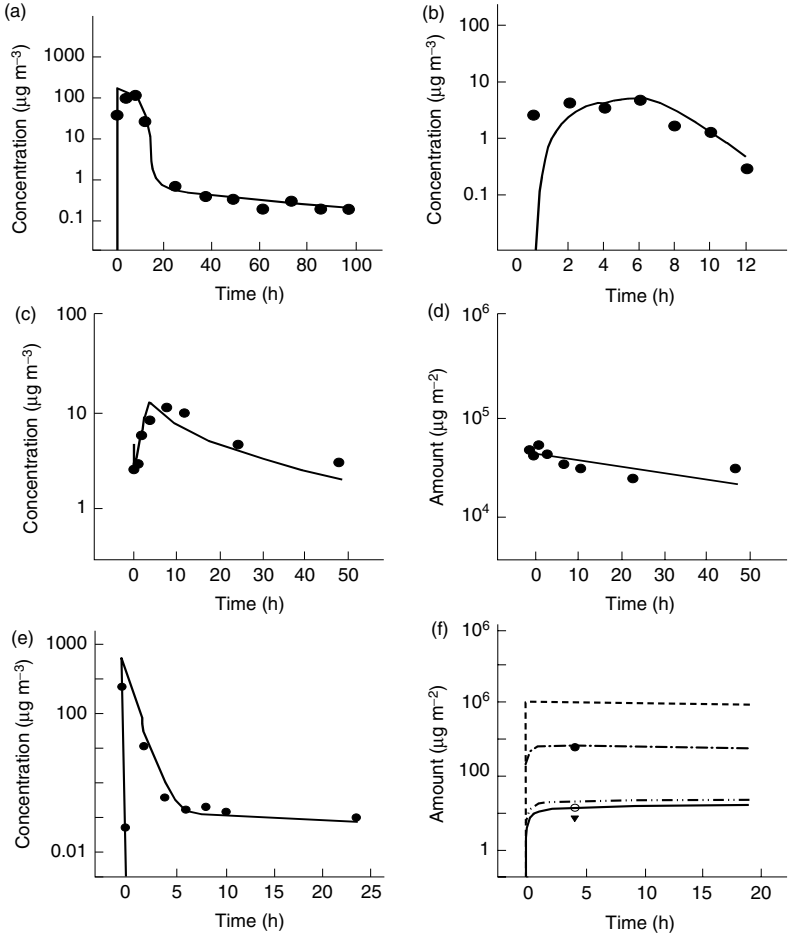

Figure 6.3 Comparison between measured (symbols) and estimated concentrations in the air and/or amounts on room materials by using InPest (lines). (a) Time-dependent concentrations of fenitrothion in the air, as derived from a space-spraying simulation when the windows are kept closed (Matoba *et al*., 1993). Reprinted from *Chemosphere*, **26**, Y. Matoba, J. Ohnishi and M. Matsuo, 'A simulation of insecticides in indoor aerosol space spraying', pp. 1167–1186, Copyright (1993), with permission from Elsevier. (b) Time-dependent concentrations of *d*-allethrin in the air, as also derived by a simulation describing the use of an electric vaporizer, which heats and releases *d*-allethrin in a vaporizer liquid, continuously for 6 h (Matoba *et al*., 1994b). Reprinted from *Chemosphere*, **28**, Y. Matoba, J. Ohnishi and M. Matsuo, 'Indoor simulation of insecticides supplied with an electric vaporizer by the fugacity model', pp. 767–786, Copyright (1994), with permission from Elsevier. (c) Time-dependent concentrations of chlorpyrifos in the air and (d) the amounts on the applied carpet, as calculated by a broadcast spraying simulation where a water-based emulsion containing chlorpyrifos is uniformly applied on a carpet floor (Matoba *et al*., 1995a). Reprinted from *Chemosphere*, **30**, Y. Matoba, J. Ohnishi and M. Matsuo, 'Indoor simulation of insecticides in broadcast spraying', pp. 345–365, Copyright (1995), with permission from Elsevier.

Figure 6.3 (*continued*)
(e) Time-dependent concentrations of phenothrin in the air and (f) the amounts on room materials, as calculated by a residual spraying simulation where a residual aerosol is sprayed in the four corners of a room for a total of 2.5 min: (– – –), sprayed area; ● (–·–·–), floor; ○ (–··–··–), wall; ▼ (———), ceiling (Matoba *et al*., 1998b). Reproduced by permission of the American Industrial Hygiene Association from Y. Matoba, Y. Takimoto and T. Katuo, *Am. Ind. Hyg. Assoc. J.*, **59**, 181–190 (1998)

of pesticide in the air (Figure 6.3(b,c,e)) and/or the amounts on the room materials (Figure 6.3(d,f)) are in good accordance with the actual measured values.

By using the MCCEM model, the indoor behavior of a pyrethroid pesticide in the air was predicted and compared with actual measurements (Matoba *et al*., 1998a) under conditions in which an aerosol canister containing *d*-tetramethrin was sprayed in the air of a room for 10 s. The results (Figure 6.4) show that the concentrations in air predicted by MCCEM (continuous line) were lower than the actual measurements (symbols) after 7 h post-application. This indicates that the indoor behavior of pesticides includes occurrence, advection transference and degradation, although the MCCEM and SCIES models, as well as the THERdbASE and CONSEXPO models, consider only advection (and degradation, if specified by the user). In contrast, with InPest, which is designed to take these movements into consideration, the predicted values (Figure 6.4, dashed line) were in good agreement with the actual measurements (symbols). Nonetheless, it must be emphasized that the airborne concentration estimated by the former simple models (MCCEM, SCIES, THERdbASE and CONSEXPO) can correlate with a higher part of the profile after application.

Many current models treat ventilation loss based on the assumption of a 'well-mixed' space. Furtaw *et al*. (1996) conducted experiments with pre-set ventilation rates and constant source strengths. These authors showed that rooms with high ventilation rates behave as well-mixed spaces, and that the ventilation rate accurately accounts for steady-state levels and ventilation loss when the source is turned off. At lower ventilation rates, mixing is not uniform and concentrations near the source deviate from those further away. However, once the source is turned off, the ventilation rate accurately accounts for the observed decrease in air concentration. The assumption of a well-mixed room is questionable in the case in which there are few activities and no mixing of air currents. In such cases, diffusion and multiple-zone models can be used to more realistically capture spatial heterogeneity (Furtaw *et al*., 1996; Nicas, 1996, 1998). Another approach for estimation is a fluid dynamics model utilizing a supercomputer (Matoba *et al*., 1994a).

Room temperature may be a key factor in estimations and thus the temperature should be included in the model, since it can have a considerable effect on evaporation (Schenk *et al*., 1997). Matoba *et al*. (1995b) have shown the dependency of room temperature and humidity of indoor movement of pesticides by

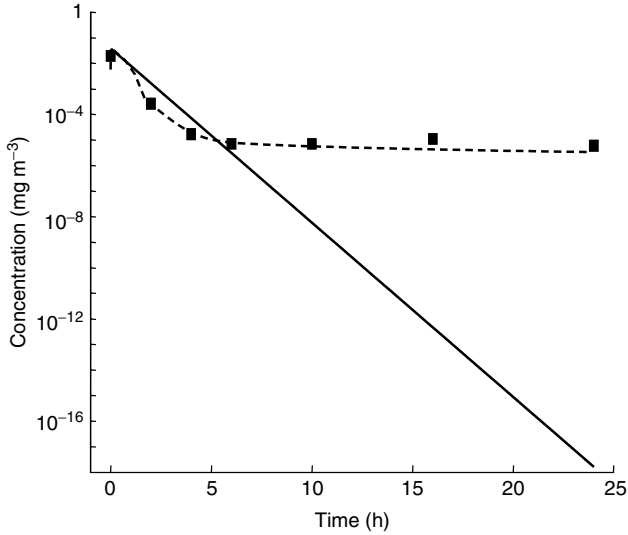

Figure 6.4 Comparison between measured and estimated values for a pyrethroid pesticide in the air. A space aerosol product containing 0.45 g of *d*-tetramethrin was uniformly sprayed for a total of 10 s in a room (*l*, 3.6 m; *w*, 2.7 m; *h*, 2.4 m) at an air-exchange rate of 1.55 h^{-1}. The concentrations of *d*-tetramethrin in the air after spraying were measured (symbols) (Matoba *et al.*, 1998a) and compared with those simulated by the MCCEM (———) and InPest models (– – –)

using the InPest model and the fugacity approach. In conclusion, InPest and, in some respects, CONSEXPO, have been shown to provide well-validated data for pesticide movement in a room environment. MCCEM, SCIES, THERdbASE and portions of CONSEXPO are each based on very simple operational theories, but can roughly simulate the higher concentrations in the air after application.

SOFTWARE OVERVIEW

Many simulation models can be used to estimate residential exposures, but the following models are considered to be typical and specialized residential simulation models currently in use.

EUSES AND USES

Features

In the European Union, Directive 92/32/EC and EC Council Regulation 793/93 require risk assessment for new and existing substances, respectively. Principles for this risk assessment have been established, supported by a detailed package

of EU Technical Guidance Documents (EC, 1996). The European Union System for the Evaluation of Substances (EUSES) is an update of the Uniform System for the Evaluation of Substances (USES 1), and is fully in line with the package of Technical Guidance Documents. EUSES is the result of a co-ordinated effort of EU Member States, the European Commission and the European Chemical Industry. USES 2 (RIVM, 1998) is an update of both USES 1 and EUSES, and comprises risk-assessment methods for biocides and plant-protection products, in addition to those for new and existing substances. The risk-assessment methods for biocides and plant-protection products are in accordance with the relevant European national legislative statutes and, as much as possible, with the relevant EC regulations. In USES 2, the risk assessment methods for new and existing substances are fully equivalent to EUSES.

- EUSES and USES facilitate the quantitative assessment of the risks of chemicals to humans and the environment. Risks to humans pertain to consumers, workers and humans exposed through the environment. Protection goals in the environment include sewage-treatment plant populations of microorganisms, aquatic, terrestrial and sediment ecosystems, and the populations of predators.
- EUSES and USES can be used to carry out tiered risk assessments of increasing complexity, each more advanced tier requiring additional data. By using the OECD terminology, they can specifically be used in the initial (or screening), intermediate and more precise stages of assessment. The programs can be applied to intermediate or more precise assessments by allowing the entering (replacement) of default values, estimated parameter values or intermediate results using more accurately estimated values or by measured data.
- Exposure assessments in EUSES cover the whole life-cycle of substances, as well as their outcomes in all environmental compartments on three spatial scales: the personal scale for consumers and workers, the local scale for human and ecosystems near point-sources, and the regional scale for human and ecosystems exposed as a result of all releases in a large region. Pesticides are assessed for application at a local scale. Both short- and long-term time-scales are considered, where appropriate.
- USES is not specifically designed for site-specific assessments, but adjustment of parameters may allow for insight into specific local or regional situations.

Theoretical

The endpoint of both EUSES and USES is a quantitative comparison per substance of the results of the effects and the exposure assessment. The latter aims at providing ‘reasonable-worst-case’ results by applying unfavorable, but not unrealistic, standard exposure scenarios. The risk assessment is carried out in a stepwise procedure, starting with data input and estimation, and further involving estimation of emissions, prediction of environmental distribution, calculation of human and environmental exposure, derivation of no-effect levels and risk

characterization. The resulting risk characterization ratios (RCRs) can be regarded as indicators for the likelihood of occurrence of adverse effects.

Remarks

The assessment is transparent: EUSES is well documented and is a currently available, 'user-friendly' computer program. EUSES is designed to facilitate the risk assessment of a broad range of substances according to the EU Technical Guidance Documents. In order to effectively apply the program, the user needs sufficient expertise to be able to appreciate the advantages, such as quick calculations and a good overview, and the disadvantages, such as the screening-level approach and average concentrations, of the Technical Guidance Documents and the system. Expertise is also needed to evaluate the quality of the input data, to make a proper data selection and to understand the assumptions made, as well as the inherent limitations of the estimation methods, and, finally, to correctly interpret the results.

CONSEXPO

Features

The CONSumer EXPOsure models (CONSEXPO) program is being developed at the Dutch National Institute of Public Health and the Environment (RIVM) to provide estimation routines to assess exposure to consumer products including pesticides (van Veen, 1995, 1997, 2001). CONSEXPO contains both simple screening models based on the European Union Technical Guidance Document, accompanying new and existing substances legislation (EC, 1996) and advanced models to describe indoor exposure caused by consumer products.

- Total exposure is defined from the combination of contact, exposure and uptake scenarios for each route of entry, and dose measures are calculated. These dose measures contain concentration estimates and short- and long-term average doses in terms of milligram of chemical per day per kilogram of body weight. The program allows for stochastic parameters and each parameter can attain a normal, log–normal or uniform distribution, or an empirical distribution defined by data. Exposure and dose distributions reflect stochastic parameters and these distributions can be depicted and percentiles can be quantified.
- The program provides sensitivity analyses for each stochastic parameter, in which mean exposures or doses as a function of the value of a selected stochastic parameter are depicted and analyzed.

Theoretical

This program's operation is based on a modeling framework containing a contact, an exposure and an uptake component (Figure 6.5). The contact component

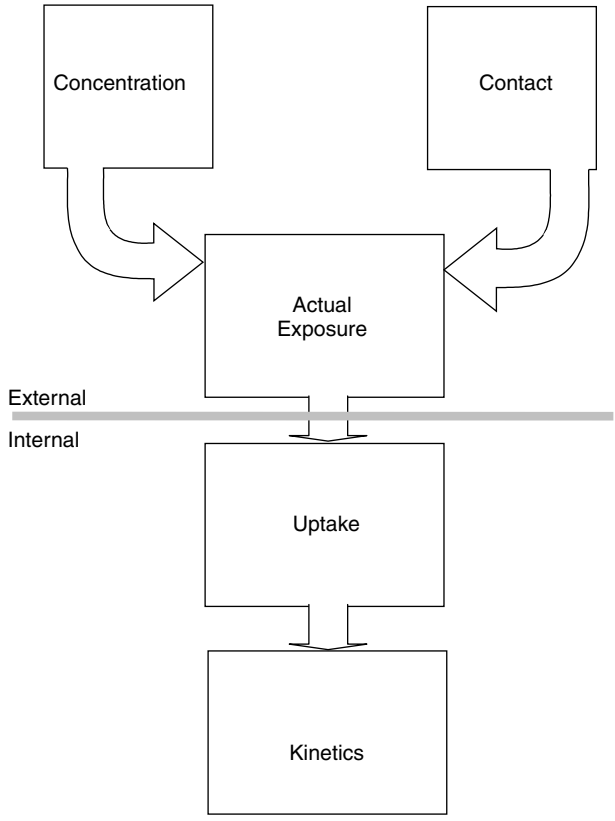

Figure 6.5 The elements of concentration, contact and uptake underlying exposure to a chemical compound in CONSEXPO

defines how long and how often contact is made with the chemical, and the exposure component defines what the concentration of the chemical is, while the uptake component defines how much is taken up by the body. For each of these, the user selects a model and provides its parameters. The contact component is not a model but specifies duration of actual use, duration of contact with the product and frequency of use. The duration of actual use and the duration of contact might differ if actual usage is short, as when using a spray, but compounds from the product fill the air around a person, hence causing a prolonged exposure.

The exposure component contains multiple models to estimate the concentration of compound in the medium which directly contacts the human body. These estimation models range from simple screening models to advanced models describing specific exposures. Exposure includes the respiratory, dermal and oral

routes, and the software provides a function of modeling exposure through multiple routes. For the respiratory route, the advanced models include painting, evaporation, exhaust gas production and a continuous source. For the dermal route, the models include transfer factors, contact rates and a fixed volume of product. For the oral route, the models include ingestion, leaching from materials into food, leaching from materials into the mouth and hand–mouth contact.

The uptake component estimates the amount absorbed through the skin, the lungs or the gastrointestinal wall. This denotes the amount that reaches systemic circulation. If information on the fraction absorbed is available, this can be specified. Otherwise, simple diffusion models can be used to estimate the fraction taken up. As an alternative, uptake can be set to 100 %, in which case potential doses are calculated by the program.

Remarks

In CONSEXPO, the user has to select appropriate models and provide parameter values. The translation from product type, e.g. spray can, to appropriate exposure model, e.g. source and ventilation model, is therefore the responsibility of the user. Currently, a defaults database for CONSEXPO is being developed. This database will refer to product types and assign default models and default parameter values to the product type. These types will include 'ready-to-use' spray cans, spraying after dilution of a concentrate, dusting, evaporation from a matrix, etc. Factsheets for CONSEXPO and the defaults database have been developed for room size, ventilation rates and body parameters (Bremmer and van Veen, 2000), children's toys (Bremmer and van Veen, 2002), cosmetics (Bremmer *et al*., 2002a) and pest control products (Bremmer *et al*., 2002b). CONSEXPO 3 can be obtained from the RIVM, Bilthoven, The Netherlands (van Veen, 2001).

SCIES

Features

The Screening Consumer Inhalation Exposure Software (SCIES) has been developed by Versar, Inc. to assist the Exposure Evaluation Division of the Office of Toxic Substances of the USEPA (Versar, Inc., 1992). This is designed to perform screening-level assessments of potential dose rates resulting from inhalation of new and existing chemicals in consumer products. It has the following features:

- The SCIES model allows screening-level estimates of average individual inhalation potential dose rates to components of consumer products, which can be classified into 11 different product categories.

- The model estimates potential dose rates for both actively exposed users of the product and passively exposed non-users (i.e. individuals present in the residence who are not actively using the product), taking into account these individual activity patterns.
- This model combines the results of an effort to measure ventilation flows within residences via a perfluorocarbon tracer method (Versar, Inc., 1989) with a two-zone mass balance model to allow estimation of potential dose rates to users and non-users.
- The following chemical properties are needed for conducting the SCIES estimation: molecular weight of the chemical in question, vapor pressure of the chemical and weight fraction of the chemical within the product being used.

Theoretical

Within SCIES, a generic house with a volume of 293 m^3 is used for modeling purposes. Two modeling scenarios related to the room designated for product use are employed: kitchen (volume of 20 m^3) versus the rest of the house, and bedroom (volume of 40 m^3) versus the rest of the house. Airflow rates between the indoors and outdoors are assumed to be equal. The common default value in SCIES is an air-exchange rate of 0.2/h, which is in the 10th percentile of values for all entries in phase one of the PFT database (D'Ottavio, 1998).

The SCIES program uses three different approaches to determine the source term. The first is that the rate at which the film is applied and the change in mass of a chemical substance released from the surface are taken into account. The second assumes a constant release of source from a surface where the amount of chemical substance remaining on the surface is the same throughout the evaporation time. For this scenario, the SCIES program uses the approach developed by Chinn (1981) to estimate the evaporation time. After a concentration is calculated by using this method at the end of each minute, the concentration is compared to the saturation concentration. If the calculated concentration exceeds the saturation concentration, the concentration will be recalculated to equal the saturation concentration by using a new source term. The excess source is returned to the surface area for evaporation at a later time. The third approach is a constant release of source in the form of aerosol spray. This continuous aerosol method is similar to the above continuous method, with some exceptions. One is that in the continuous aerosol method, SCIES bypasses Chinn's calculation and sets the evaporation time equal to the duration of use. Another difference is that the aerosol method ignores the saturation concentration comparisons, which means that no correction will be made for surpassing saturation concentration.

Remarks

There are some limitations to the SCIES model. It is intended for use as a screening-level tool and is designed to employ very limited data to generate

'high-end' exposure estimates. Even if values calculated by SCIES exceed the saturation concentration, they are used in the exposure-assessment process. In addition, the Chinn relationship is based on the evaporation of pure substances under artificial conditions and may overestimate the emissions expected from substances in mixtures. The USEPA (1997b) recognizes that these assumptions are valid to calculate 'high-end' estimates based on observations from similar field studies.

The SCIES model has been upgraded. The new version is called the Consumer Exposure Module (CEM). Some of the default values have been changed. Additionally, the emission term for paints has been revised, and is presented in the Wall Paint Exposure Model (WPEM). Information on CEM and WPEM can be obtained from the Exposure Assessment Branch of the USEPA.

MCCEM

Features

The Multi-Chamber Concentration and Exposure Model (MCCEM), Version 2.4, was developed by GEOMET Technologies, Inc., for the USEPA Office of Pollution Prevention and Toxics. It has been designed to estimate indoor concentrations for chemicals released in residences (GEOMET, 1995). It has the following features:

- MCCEM requires time-varying emission rates for a chemical in each zone of the residence and outdoor concentrations. The emission rates of pollutants can be entered into the model either as numbers or as formulae.
- Inhalation exposure levels are calculated from the estimated concentration if the user specifies the zone where an individual is located in a spreadsheet environment.
- MCCEM has data sets containing infiltration and interzonal airflow rates for different types of residences in various geographic areas. The user can select from the data sets or can input zone descriptions, volumes and airflow rates.
- Concentrations can be modeled in as many as four zones (chambers) of a residence.
- The program is capable of performing Monte Carlo simulation on several input parameters (i.e. infiltration rate, emission rate, decay rate and outdoor concentration) for developing a range of estimates for zone-specific concentrations or inhalation exposure.
- The program has an option to adjust sensitivity of the model results in response to change(s) in one or more of the input parameters.
- The percentage of cases for which modeled contaminant concentrations are at or above a user-specified level of possible concern or interest is determined.

Theoretical

This multi-chamber mass-balance model has been developed by using air infiltration rates and corresponding interzonal air flows for a user-selected residence or a user-defined residence. The model provides a spreadsheet environment to the user in which time service data for emission rates in one or more zones, the zone of exposure and concentration values of the contaminant outdoors can be entered.

Information assembled by the Brookhaven National Laboratory concerning measured infiltration/exfiltration airflow, interzonal airflow and the volume and description of each zone for different types of structures in various geographic areas has been incorporated in the software for access by users. Two generic houses represent average volume (408 m^3) and flow information in summer or fall/spring. The house data has been compiled from a large number of residences (Koontz and Rector, 1995). One generic house has a bedroom and the remainder, while the other has a kitchen and the remainder. The air-exchange rates for the generic houses are 0.18/h in summer and 0.45/h in fall or spring.

Remarks

Guidelines for the user, which list good examples, make it possible for risk assessors to easily handle all items within MCCEM. In addition, MCCEM contains a database of various default house data which are needed to complete each calculation. These include, for example, air-exchange rates, geographically based inter-room air flows, and house/room volumes. However, such a potentially rich database might cause confusion to risk assessors who aim to evaluate the risk tendency of pesticides for a typical population at the first-tier approach. Therefore, it seems reasonable that the user's guide suggest that a two-storey residence be chosen by using the defaults, and the USEPA (1997b) recommends a fixed storey using the above generic house in summer to estimate a 'high-end' assessment. The MCCEM model (Version 1.2, February 2001), for use in a Windows'95 operating environment, is available on the USEPA homepage (http://www.epa.gov/opptintr/exposure/docs/mccemdl.htm).

THERdbASE

Features

The Total Human Exposure Risk DataBase and Advanced Simulation Environment (THERdbASE) is a data/model management system which contains total human exposure information. THERdbASE is a USEPA-sponsored modeling platform which is being developed and upgraded by the Exposure Modeling and Software Engineering Division of InfoScientific, Inc. (Butler and Engelman, 1998).

Theoretical

THERdbASE contains two major modules, namely a Database Module and a Model Base Module. The Database Module relates information from exposure, dose and risk-related data files, and contains information about the following: population distributions, location/activity patterns, food-consumption patterns, agent properties, agent sources (use patterns), environmental agent concentrations, food contamination, physiological parameters, risk parameters and miscellaneous data files. The Model Base Module provides access to exposure dose and risk-related models. The specific models included with the software are as follows: Model 101, subsetting activity pattern data; Model 102, location patterns (simulated); Model 103, source (time application); Model 104, source (instantaneous application); Model 105, indoor air (two zones); Model 106, indoor air (*n* zones); Model 107, inhalation exposure (BEAM); Model 108, inhalation exposure (multiple chemicals); Model 109, dermal dose (film thickness); Model 110, dose scenario (inhalation/dermal); Model 201, soil exposure (dose assessment).

Model 101 allows the creation of smaller subsets of activity pattern data from larger sets. These subsets are based on selected demographic variables and estimate summaries of duration by location and by activity. Model 102 generates simulated location patterns (e.g. location distribution and duration) for any number of people, based on actual location patterns obtained from field studies, since the sample sizes for field studies are usually restricted by economic and logistic constraints. Outputs from Model 101 can be used as input to Model 102, and the simulated location patterns can be used as input by the two inhalation-exposure-related Models 107 and 108.

Models 103 and 104 generate release parameters of chemicals, such as the evaporation time estimated by the Chinn evaporation method, to run Model 105. These are characterized by two zones (as with the SCIES model) or Model 106, characterized by *n* zones, where *n* is up to four (such as for the MCCEM model).

Both Models 107 for benzene and 108 for multiple chemicals are based on the Benzene Exposure Assessment Model (BEAM) (Behar *et al*., 1993) to generate benzene or chemical inhalation exposure profiles for different human subgroups. For an estimation of dermal dose, Model 109 is a simple 'film-thickness'-based model like DERMAL (Versar, Inc., 1995). Model 110 estimates multiple pathways exposure (i.e. inhalation and dermal doses) to multiple chemicals from the use of consumer products.

Model 201 is independent of the other models, and the source of contamination considered in this model is contaminated soil in the outdoor vicinity of a residence. The exposure routes considered are dermal, ingestion and inhalation. Human physiological parameters, such as dermal exposed surface area, soil ingestion rate, inhalation rate and body weight, allow estimation of the dose for different age groups.

Remarks

THERdbASE has a 'user-friendly' interface and a large database of exposure-related information. However, this software does not include a function which would make it possible to link with any user-specified external models. The user is thus required to use only the limited models provided with the software. When trying an evaluation of true risk in a real situation, a risk assessor may feel thwarted at the imbalance between the abundant database and the very simple models provided in this software.

InPest

Features

INdoor PESTticide (InPest) was developed by Matoba *et al*. (1993, 1994b, 1995a,b, 1998a,b,c) based on the 'Fugacity Model' to simulate pesticide behavior applied in a room environment. It has the following features:

- InPest can simulate pesticide behavior in four popular spraying procedures: (1) space spraying with a water- or oil-based aerosol containing pesticides toward flies and/or mosquitoes; (2) electric vaporizing with an electric vaporizer, which is a new delivery system for mosquito control; (3) broadcast spraying to the surface area of a carpet where the pests habitat; (4) direct spraying toward room materials such as the floor, i.e. residential or 'crack-and-crevice' treatment by which the pest touches the sprayed pesticide remaining on the room surface or by which the pests on the surface are directly sprayed.
- The room environment to be simulated can be changed, i.e. room size, room temperature and humidity, air-exchange rate and floor materials (i.e. tatami made of rush, wooden floor or carpet).
- Description on the time-dependent behavior of pesticide includes concentration on the floor, wall and ceiling, as well as in the air.
- Input of physico-chemical properties of the pesticide realize a more precise prediction of indoor behavior, and the necessary data are easily available properties, such as molecular weight, vapor pressure, water solubility and octanol/water partition coefficient.
- Usage and specification of the pesticide product is able to reflect the movement of the pesticide.

Theoretical

InPest for space spraying has been developed to simulate pesticide behavior when an aerosol canister containing an oil- or water-based formulation is sprayed into the air of a room. Settlement of the sprayed droplets depends on aerosol size, which becomes smaller with time because of evaporation. The number of droplets decreases with time due to ventilation and adherence to the room materials. Any

pesticide adhering to the room materials will permeate into the materials. The pesticide in each medium is not only degraded by photolysis or oxidation but is also transferred to other media or discharged by ventilation. These phenomena are incorporated into the 'fugacity equation'. The time-dependent concentrations of a pesticide are simulated by solving the differential fugacity equations as to all relevant media, such as the droplet, room air, floor, wall and ceiling.

The behavior of a pesticide supplied continuously by an electric vaporizer can be simulated by using a fluid-dynamics model and a 'supercomputer'. By incorporating the results of the above fluid-dynamics model, InPest for electric vaporizing has been developed by using the 'Fugacity Model'. InPest for broadcast spraying was developed for conditions in which a water-based emulsion is uniformly applied on a carpet floor. Some of the emulsion adheres to the carpet and the rest floats as airborne droplets. The water on the carpet and the floating droplets decrease in volume due to evaporation. Moreover, the fugacity capacity of the sprayed emulsion changes over time with evaporation of organic solvent (xylene in an emulsifiable concentrate) from the diluted emulsion, hence making it capable of accepting the pesticide. The fugacity concept has been applied to InPest by incorporating the above factors. In the same manner, InPest for direct spraying has been developed in which an aerosol is sprayed on a corner of the floor and/or wall where insects are found.

Remarks

The InPest software is not available to the public at present.[1] In comparison to other programs, the concept of InPest, which considers all movements of indoor pesticides, enables risk assessors to perform a more realistic evaluation for the safety of room occupants in regards to the applied pesticide. The advantages of this fugacity approach are that the complex behaviors, such as movement between two connecting media, are more easily compiled and manipulated, so expediting correct interpretation of environmental monitoring data. The disadvantage is that a risk assessor must acquire understanding of the new concept of fugacity, which may be unfamiliar, and with two related quantities, fugacity capacities and transport-rate parameters.

OTHER PROGRAMS

Since the promulgation of the Food Quality and Protection Act in the USA, several new programs have been developed to assist in the derivation of aggregate and cumulative exposures. These programs, i.e. SHEDS, CARES and Lifeline are discussed in further detail in Chapters 4 and 8.

[1]As of 2004.

CONCLUSIONS AND RECOMMENDATIONS

TIERED APPROACH CONCEPT

By taking a sequential or tiered approach to risk assessment, all available information is used and then necessary exposure data are generated to conduct a risk assessment. A higher tier requires increasingly sophisticated approaches and information sets. When predicted exposures give adequate margins when compared to appropriate toxicological endpoints, assessments do not need to be pursued further. In the light of other definitions (EC, 1998) the following tiers are recognized.

Tier 1

Risk notification accompanied by generic reasonable 'worst-case' exposure with a default value of dermal absorption rate, which is a specific percentage penetration value via the dermal route. This screening tier should be quite simple, checking for the kinds of users and product use. Exposure estimates are retrieved from 'high-end' indicative values (from databases or models) or from reasoned cases. Models suited to aid the process are EUSES/USES, SCIES/MCCEM, THERdbASE and the simple models in CONSEXPO and InPest with reasonable 'worst-values'.

Tier 2

Risk evaluation accompanied by generic exposure data (modeled or actual), with consideration of the patterns of use and the mitigating effects of control measures (including personal protective equipment). In this tier, the risk assessor needs to be aware of the full exposure ranges and have exposure estimates for all of the relevant tasks and exposure routes. The exposure estimates should be based on expected actual use of the product, including the mixing and loading, plus the application and post-application phases of exposure. Models suited to aid the process are CONSEXPO, THERdbASE, MCCEM and InPest.

Tier 3

Risk certification accompanied by data requirements, such as individual product operator exposure studies, dermal absorption data and/or the range of results from biological monitoring of those exposed. This tier recognizes that where the best available knowledge used in the second tier still indicates risks, then exposure measurements for the actual product will be necessary. Exposure surveys need to be of adequate size, sufficiently reported and representative in order to be convincing. Exposure surveys may gather data that can be used for statistical relations, such as transfer coefficients, which may be used for other products in the lower tiers.

EXPOSURE ESTIMATION CONCEPT

The basic concept underlying residential exposure assessment is that exposure levels for an individual vary greatly through a combination of many factors. Such factors include uses of the pesticide product (product packaging, amounts used, application method, frequency of use of the product, etc.), exposure time (duration and season), place of exposure (type of home, room size, ventilation rate, temperature, etc.) and characteristics of the exposed individual (activity patterns and body weight – whether actual applicator or not). Taking into account these exposure criteria, individual doses in each population (adult, toddler and child, and/or pregnant women if the pesticide shows reproductive toxicity) is recommended to be calculated for each route (inhalation, dermal and oral exposures) and duration (short, medium or long exposures). Exposure doses should then be compared with relevant toxicological doses of the pesticide. To predict systemic effects, routes should be aggregated appropriately and compared to relevant toxicological data (duration and toxicological effects). For local effects, routes can be considered on their own in comparison with relevant information regarding local toxicological effects.

Residential exposure should be estimated by taking into account distributions of exposure factors. Methods to assess distributions are through the deterministic or probabilistic approach (Figure 6.6). The former is often taken in preventive risk assessment in which each default value is determined from each distribution as a reasonable 'worst-case'. The estimated exposures for the deterministic approach are expected to occur in the upper range. For actual risk assessments, the probabilistic approach directly uses the parameter distributions instead of single values to calculate distributions of exposure. To characterize exposure, an

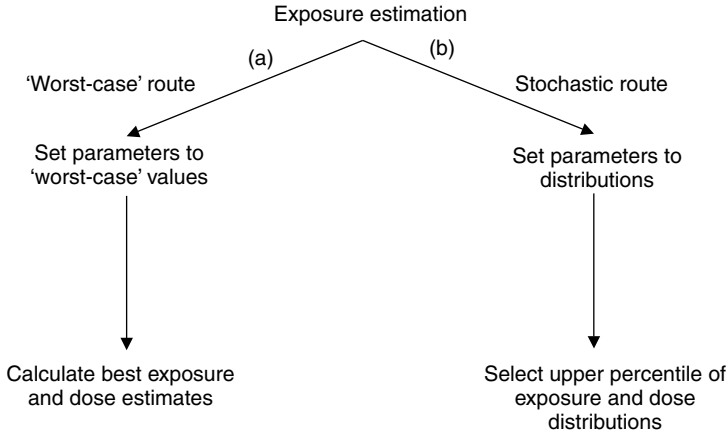

Figure 6.6 Routes for implementing exposure assessment, where (a) implements a deterministic 'worst-case', while (b) implements a probabilistic route

upper percentile from the exposure distribution is taken. There is currently no consensus over which percentiles obtained from the probabilistic approach are best used for risk analysis.

Both the deterministic and probabilistic approaches assume good data to quantify parameters. Data inherently introduce natural variability and uncertainty in the numerical values of the parameters. Both causes of variance occur and the resulting exposure distributions require careful interpretation. In the case that no data are available, exposure assessment can either be postponed until more data become available or explored by using reasoned cases. The latter combine known parameter values and assumptions on others derived from expert judgment to find the order of magnitude of exposure by using simple screening calculations. Examples of reasoned cases are presented by the USEPA (1997b), the Biocides Steering Group (EC, 1998) and the European Commission (EC, 2002). CONSEXPO (EUSES/USES), MCCEM and SCIES (THERdbASE) and InPest can all incorporate reasoned cases and then realize reasonable estimations of residential exposures.

MODEL UTILITY CONCEPT

The basic concept is that estimated results for pesticide movements and exposure levels vary greatly with the model types and modeling philosophy. Before conducting a model exercise, a conceptual check of the model is needed to ascertain if the model contains all relevant routes of exposure. A simple model, such as SCIES, is based on 'worst-case' assumptions, and may be sufficient for inhalation risk assessment. More complicated simulation models, such as CONSEXPO and InPest, provide information on the amounts of pesticides on the room materials, as well as the airborne concentration, and they are appropriate for risk assessment via all routes. Even in complicated models, each mechanistic model contains assumptions to simplify the process description of the pesticide movement in the 'real world'. The underlying assumptions for each of the models, and the relevant processes they implicate, are criteria to consider when selecting an appropriate model. Therefore, the validity of the assumptions used for the assessment should be considered before using the model, and they should be well documented. A simple phrase such as, 'we used model *xx* to estimate an exposure level of *yy*', is inadequate for documentation purposes.

In addition, once a particular model has been chosen, input values must be assigned to parameters with appropriate certifications in the documentation, since there are infinite possibilities for quantifying parameters for the model. Documentation should not only contain the parameter values used in the assessment, but also their relevance with respect to the aim of the assessment ('worst-case' versus actual) and country- or site-specific characteristics (e.g. mechanical versus natural ventilation traditions). For instance, a 'worst-case' assessment of indoor use would employ small room sizes and ventilation volumes, while an assessment for an actual case would employ the values as valid for that particular case. To

summarize, model and parameter documentation should enable reproduction of the exposure estimation by independent persons who have access to the models, as well as by the original risk assessor after the passage of time.

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Section Three

Epidemiology

7 Exposure Assessment for Pesticides in Epidemiological Studies

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INTRODUCTION

Epidemiology is the science that involves the study of the distribution and determinants of disease. With regard to pesticide exposure, to workers through

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occupational use or to people in their homes through direct or indirect exposure, the research considers the role of pesticides in the etiology of a number of diseases, ranging from acute poisoning and neurological effects to cancers and reproductive outcomes. The results of epidemiological studies can be used for development of preventive strategies as part of public or occupational health programs, especially when quantitative exposure information has been used and exposure–response relationships have been evaluated.

This chapter will focus mainly on the derivation of occupational exposure values and the special challenges it poses to epidemiologists studying the health effects of workers exposed to pesticides. Despite the fact that occupational exposures are our focus, the issues introduced in this chapter are also relevant to studies of environmental health risks from pesticides, to farmers' family members, although studies among this category of exposed individuals are still relatively exceptional. Exposure of family members during low-exposure tasks is likely to occur (De Cock *et al*., 1998a,b; Arbuckle *et al*., 2004a; Hogenkamp *et al*., 2004). In addition, domestic exposure to detectable residues of pesticides in homes of farmers is an area of concern (Loewenhertz *et al*., 1997).

First, this chapter will describe a conceptual framework to illustrate the special challenges posed because exposures assessed for epidemiologic studies must be relevant to the health outcome under investigation. Secondly, some of the most commonly applied epidemiological study designs will be introduced, with special emphasis on exposure assessment issues associated with the design. Thirdly, some widely applied exposure assessment approaches will be introduced, ranging from qualitative classifications of exposure to quantitative exposure assessment of pesticide concentrations. The influence of measurement error on measures of association between exposure and disease, such as the slopes of exposure–response relationships and risk or odds ratios, will be briefly reviewed. Finally, exposure proxies used in case-control studies of chronic effects of pesticide exposure will be reviewed and the concepts introduced earlier will be applied.

EXPOSURES RELEVANT TO HEALTH: THE CONCEPTUAL FRAMEWORK

Considering pesticide exposure in the context of epidemiological investigations involves the evaluation of exposures that are relevant to health. Exposure is usually defined as contact with an agent and can be contrasted with absorbed dose, the amount that enters or interacts with the organism. The concept of health-relevant exposure implies that not all exposures lead to, or are associated with, a certain health risk.

CONSIDERATIONS OF EXPOSURE TIMING

An important dimension of health-relevant exposure is the time axis. For instance, when studying cancer risks, current exposures to pesticides are usually not relevant, but exposures in the past may be important. Although exposure might

be ongoing, the more recent exposures might be omitted in an epidemiological study of carcinogenic effects of pesticide exposure. The terminology for this phenomenon is the health-relevant 'time-window' of exposure. The time-window differs for different health endpoints. For instance, evaluation of the effects of pesticide exposure on the semen quality of sprayers involves a considerably shorter time-window, perhaps as short as one cycle in spermatogenesis.

The combination of the health-relevant time-window and the toxicokinetic properties of the agent of interest determine the optimal exposure assessment strategy. Dioxin, a contaminant of chlorophenoxy herbicides and fungicides, has a relatively long biological half-life, estimated at about seven years and is measurable in serum. Serum measurements of dioxin are therefore relatively stable, and simple first-order kinetics have been used to 'back-estimate' serum dioxin levels on the basis of an occupational history. Such exposure data have been used quite successfully in epidemiological analyses of cohorts of pesticide producers (Hooiveld *et al*., 1998).

Nowadays, in Western countries in particular, pesticides with shorter biological half-lives are being used. Captan is an example of a well-known fungicide with a half-life in the environment of 10 to 17 days. The half-life in the body is shorter; most captan is metabolized and excreted within 48 h. Therefore, measurements in urine are only representative of exposure for a short period after exposures during application or re-entry activities. In addition, exposure during re-entry only occurs in the first few weeks after fungicide application since captan is also not persistent in the environment. An epidemiological study in which the exposure assessment is based on evaluating the level of tetrahydrophthalimide (THPI), an easily measurable metabolite of captan, will involve complex logistics and will in most cases be impractical, since timing of the measurements need to be closely related to the activities of the farmers. Moreover, a single measurement of THPI is likely to be a poor predictor of the long-term average captan exposure because of the short half-life, and thus of little use when chronic effects are of interest.

CONSIDERATIONS OF EXPOSURE ROUTE

The route of exposure is another aspect of exposure in which health-relevance must be considered. In Section One of this book, there is a detailed discussion of exposure assessment methodologies, including the importance of identification of the most prevalent route of exposure (dermal, inhalation or oral) and the necessity of knowing the absorption of the pesticide to allow calculation of the absorbed dose for risk assessment. For epidemiological purposes, exposure-assessment studies are usually limited to assessing contact exposure levels. Since dermal absorption is not known for many pesticides or complex mixtures, uptake through the dermal route can often not be estimated and contact exposure data are a poor proxy of internal exposure (absorbed dose) (Schneider *et al*., 1999).

These factors illustrate the complexity of exposure assessment for epidemiology. The need to consider both the health-relevant time window and the biological

aspects of exposure and dose may lead to complex logistics and creative methods to estimate internal dose. In diseases with long induction and latency periods, the opportunity to quantitatively measure relevant exposures may simply have passed before epidemiological studies are initiated.

PRACTICAL CONTEXT OF PESTICIDE EXPOSURE

Most agricultural workers use numerous pesticides over a growing season. Depending on the crop, some pesticides are applied in combinations (tank mixes) or are applied at different times during the season. As a result, epidemiological studies on the health effects of occupational pesticide exposure evaluate the effects of these mixtures. Attribution of health effects to any single pesticide is difficult, if not impossible. Few studies among pesticide workers establish the effect of exposure to one or a mixture consisting of a limited number of pesticides.

EPIDEMIOLOGICAL STUDY DESIGNS AND EXPOSURE ASSESSMENT

It is conceptually easiest to introduce all epidemiological study designs by starting with the cohort study design.

PROSPECTIVE COHORT STUDIES

In a prospective cohort study, disease-free exposed and unexposed individuals are selected and followed concurrently over time to determine whether or not they develop the disease(s) of interest. This type of study requires enumeration and follow-up of the workers involved. The risk of developing the disease (i.e. disease incidence) is usually calculated as the number of individuals who develop the disease during follow-up, divided either by the number of individuals at baseline (the source population), or the accumulated number of 'person-years' at follow-up (Figure 7.1). The latter measure is preferred since it is less sensitive to differential loss to follow-up in diseased and disease-free subjects, but also compensates for a potentially different disease incidence in the exposed and unexposed due to other external factors than the exposure under study. The background incidence of the disease of interest is based on observations among unexposed controls. The difference in incidence between exposed and unexposed is usually expressed as a ratio, the 'risk ratio' or 'relative risk' (RR), although other expressions can be used. Since a sufficient number of disease cases will only be accumulated after a reasonable follow-up time, prospective cohort studies are relatively expensive and time-consuming. The advantage, on the other hand, is that all exposure assessment options are available; investigators can decide to assess the exposure to any agent of potential relevance in a quantitative way, and repeated over time if desired.

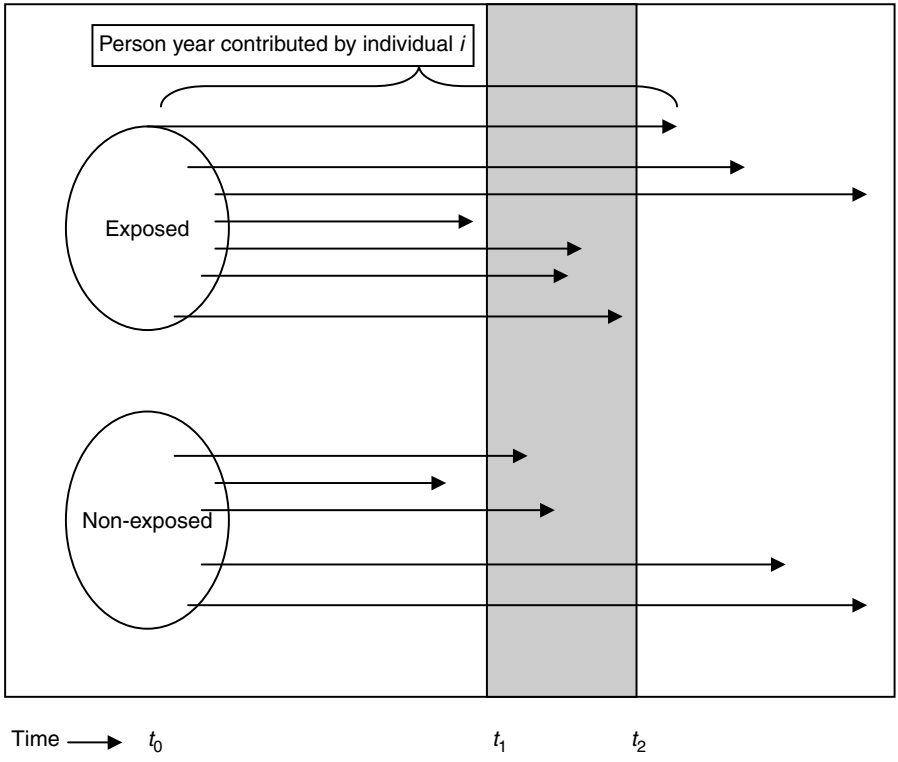

Figure 7.1 The design of a cohort study and its relationship with case-control study designs. Individuals who died during follow-up in the shaded area are eligible for inclusion in a case-control study including incident cases between t_1 and t_2. The controls in the case-control study are individuals who did not have the disease of interest at the time of involvement. Arrows indicate end of follow-up, either because of (a) loss to follow-up, (b) mortality due to cause of interest, or (c) other causes of death. The risk ratio, or relative risk (RR) = (# died cause of interest in exposed/Σ person years)/(# died cause of interest controls/Σ person years)

RETROSPECTIVE COHORT STUDIES

A more efficient form of the cohort study is the retrospective cohort design. The study population must be identified through personnel files or other available historical information. Depending on the information available, individuals exposed and even deceased decades ago may be enrolled in the study. A long follow-up period allows evaluation of excess risks even for diseases with a relatively low incidence. Morbidity or mortality outcomes must be established through disease registries or national mortality statistics, as they are for prospective cohort designs. A retrospective study, including identification of the cohort and completion of the disease follow-up can be completed in one or a few

years, depending on the local data sources. The disadvantage is that data about past exposures are usually not available, and so exposure estimates have to be based on often poorly described measurement series, expert opinions, worker reports, or sometimes even reconstructions of exposure processes. In many retrospective cohort studies, only qualitative information related to exposure is available through knowledge of the job titles or departments in which the person worked. In rare instances, the agent under study may be persistent in the body and can be measured in serum or another body fluid, as in the dioxin example described above.

CASE-CONTROL STUDIES

The case-control design is different from the cohort design, but clearly related. Cases arising during follow-up can be randomly matched to controls from the same cohort, but without the disease of interest at the time the case occurs. Figure 7.2 shows the basic elements of a case-control design. The goal of the investigation is then to identify whether the pesticide exposure histories of cases differ from those of the controls. The most important aspect of this approach is that no information about the source population is needed to derive an estimate of the relative risk, called the 'odds ratio'. The relative risk is estimated by the ratio of the odds of exposure in cases divided by the odds of exposure in controls. Mantel–Haenszel or logistic regression methods can be used to calculate odds ratios while adjusting for potential confounding factors. The design described here, a case-control study within a cohort, is usually referred to as a *nested* case-control study. This approach is used because the design is more efficient than a cohort study. More effort can be used to evaluate historical exposures in a very detailed way in a small number of study subjects, and the estimated risk ratios will be similar.

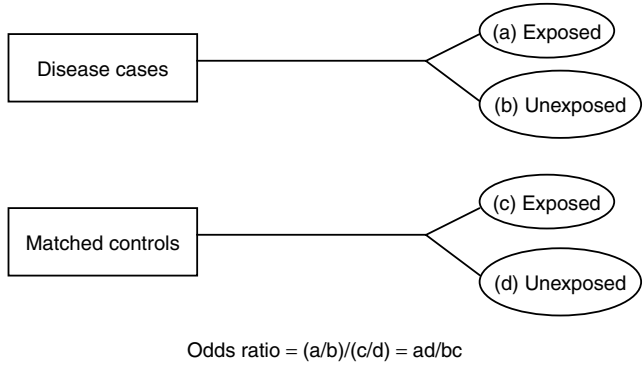

Figure 7.2 Schematic of the design and analysis of a case-control study

The most interesting aspect of the case-control design study is that participants do not necessarily need to be enrolled through a cohort study. Participants can also be identified through disease registries or medical records. Controls representing the population from which the cases arose are selected at random, with matching on criteria such as age and sex, which may affect disease distribution independently of the exposure of interest. This type of case-control study, referred to as 'population-based', is especially efficient when relatively rare events are being studied.

An advantage of case-control studies is their relatively low cost when compared to cohort studies, especially when investigating rare diseases, since only a sample of the population of interest is enrolled as controls, rather than the entire cohort, which generated the cases. For exposures such as pesticides, which may occur in widely dispersed segments of the population, including manufacturers, farmers, crop harvesters, food packers and processors, pesticide applicators, florists, landscaping personnel, silviculture workers and others, a population-based case-control design theoretically allows examination of a broad range of exposure levels and should be logistically simpler than assembling a cohort when the exposed individuals are scattered in small work groups. Case-control studies will have the greatest power to examine the effects of pesticides when they are based in locations such as agricultural communities where the proportion of the population exposed is high. They also offer the opportunity to enumerate multiple exposures, including both occupational and residential exposures, as well as medical and lifestyle factors that may be confounders of the pesticide–disease association.

Despite the advantages of case-control studies, exposure assessment remains the most problematic element. Recent reviews of pesticide studies indicate that exposure data are usually gathered by interviewer-administered questionnaires, or occasionally from mailed questionnaires or medical records (Maroni and Fait, 1993; Bohnen and Kurland, 1995; Daniels *et al*., 1997). Exposures enumerated from these sources are not quantitative measurements, but subject- or proxy-reported job histories, tasks, residence locations, or recalled exposures to pesticides (Bohnen and Kurland, 1995; Daniels *et al*., 1997; Zahm and Ward, 1998). More sophisticated techniques for assessing exposures in case-control studies are available, but to date only rarely employed. The validity and reliability of recall is therefore an essential question in considering the results. In a study in which the level of the herbicide 2,4-D was known, the sensitivity of self-reported use was only 56.7 % with a specificity of 86.4 %; it was much higher (sensitivity 91.6 % and specificity 67.4, respectively) for another herbicide, MCPA (Arbuckle *et al*., 2002). However, the relevant question to ask is not only what the accuracy is of a certain exposure characterization methodology, but also what the effect of imperfect accuracy is on measures of association in epidemiological studies. This has been an area of major development over the last decades and is described in the following sections.

CROSS-SECTIONAL STUDIES

Another common design used in pesticide epidemiology is the cross-sectional study. As implied by the name, these studies evaluate exposures and disease status simultaneously at one point in time, usually at the work site of interest. This design is used for investigating diseases which are not routinely reported, and therefore require measurements to allow cases to be identified. An example is respiratory disease that involves lung function measurements. Relative risks can be estimated by comparing the disease prevalence in subjects with differing levels of exposure (note: prevalence is the number of existing disease cases, and is not the same as disease incidence). A major flaw of this study type is its inability to identify the temporal relationship between the exposure and the disease, i.e. did the exposure take place prior to disease development or not? Related to this issue is the concern that individuals who are most susceptible to an exposure may leave the workforce early, and therefore may not be present to be enrolled in the study. An advantage of cross-sectional studies is that quantitative exposure measurements can be made at the work site during the study period. However, investigators must be conscious of whether these measurements adequately estimate exposures in the health-relevant time-window.

Additional details on the design and analysis of epidemiological studies can be found in standards texts such as Checkoway *et al*. (2004) and Rothman and Greenland (1998).

EXPOSURE ASSESSMENT STRATEGIES

As indicated by some of the examples described earlier, epidemiological studies can use a wide range of approaches for characterizing exposure to chemical agents such as pesticides (Table 7.1).

Qualitative information on exposure can be obtained from study subjects using questionnaires or interviews. Experts such as occupational hygienists can evaluate the exposure by ‘walk-through’ surveys, detailed workplace investigations using validated checklists or judgements based on their experience.

Quantitative exposure assessment is possible by measuring the external exposure in air or on skin, or by measurements of biological markers in serum, urine, fat or other relevant body fluids.

Quantitative exposure data can be used in different ways, as follows:

- to confirm that exposure has occurred (absorbed);
- to directly estimate the exposure of study subjects;
- to validate qualitative or semiquantitative exposure estimates;
- to predict exposures on the basis of empirical modeling.

Direct exposure assessment using quantitative exposure estimates can involve different strategies, ranging from assessing the exposure for each participant by using repeated measurements over time to grouping strategies that categorize

Table 7.1 Exposure assessment methods in different epidemiological study designs

Exposure assessment	Prospective cohort studies	Retrospective cohort studies	Nested case-control studies	Population-based case-control studies	Cross-sectional study
Qualitative					
Job title, department, industry	Common	Common	Common	Common	Common
Generic job-exposure matrix (JEM)	Not usually needed, but study-specific JEM may be created	Not usually needed, but study-specific JEM may be created	Not usually needed, but study-specific JEM may be created	Common	Not usually needed, but study-specific JEM may be created
Subject-reported exposure	Common	Very difficult	Very difficult	Common	Common
Estimates by occupational hygienists, experienced workers or other experts	Not usually needed	Common	Common	Common	Not usually needed
Quantitative					
Studies to validate qualitative measures	Not usually needed	Common	Common	Rare, but possible	Not usually needed
Exposure databases	Not usually needed	Common	Common	Rare, but possible	Not usually needed
Empirical modeling of determinants of exposure	Rare, but possible	Common	Common	Rare, but possible	Rare, but possible
Direct measurements of study subjects	Common	Very difficult	Very difficult	Very difficult	Common

workers into homogeneous exposure categories (Rappaport, 1991). Some examples of validation studies exist (de Cock *et al*., 1998a,b; London and Myers, 1998) but there is a need for more. Empirical modeling studies show that information on determinants of exposure, such as contamination of foliage or time since the last spraying of an orchard, can be quantitatively associated with dermal exposure and might be used to group workers into high- and low-exposure categories (Brouwer *et al*., 1994; Tielemans *et al*., 1999b). However, few examples exist of application of these principles in epidemiological studies. De Cock *et al*. (1994) grouped fruit growers in different exposure categories based on information regarding type of spray, use of a vehicle cab during spraying, size of the orchard, etc., in a study on time to pregnancy and pesticide exposure. Their grouping was validated by detailed exposure measurements of the pesticide in the air or on the skin of the worker.

Before examining each of these exposure assessment methods in more detail, it is important to consider the consequences of imprecise or biased exposure assessment on the risk estimates made in an epidemiological study.

INFLUENCE OF THE ACCURACY OF EXPOSURE PROXIES ON MEASURES OF ASSOCIATION

The issue of measurement errors has received considerable attention in the field of epidemiology. This is because measurement errors influence the estimates of association between exposure and disease and can obscure or inflate the true exposure–response relationship. Therefore, the accuracy of exposure assessment should be an integral element of any etiological epidemiological study and needs to be reviewed before final conclusions can be drawn.

The accuracy of exposure assessment is determined by systematic and random errors in the assessment. For quantitative exposure assessments, important sources of error include measurement errors (i.e. from laboratory and field monitoring techniques), as well as variations in exposure over time and space. For qualitative exposure proxies (e.g. self-reported past exposures, occupational histories or expert evaluations), the most important sources of error are recall bias (systematic differences in exposure recall between cases and controls) and random error, expressed in terms of intra- and inter-rater agreement. Although systematic errors can result in serious misinterpretations of the data, especially due to scaling problems, random errors have received more attention in epidemiology because this type of error is pervasive, and its effect is usually to diminish estimates of association between exposure and disease. The magnitude of random errors can be considerable in epidemiological field studies.

ERRORS IN QUALITATIVE PROXIES

Although it is difficult to generalize, the validity of qualitative proxies of exposure can be very poor in some cases. Tielemans *et al*. (1999a) recently compared

qualitative exposure proxies obtained by self-reports, expert judgements, simple checklists and job–exposure matrices to measurements of solvent and metal exposures in a general population study. The sensitivity to identify truly exposed individuals by using the qualitative approaches ranged from only 21 to 85 %, while the specificity to identify truly unexposed individuals ranged from 34 to 94 %. These results corroborate with observations made specifically for the pesticides cited earlier, by Arbuckle *et al*. (2002). Errors of this magnitude, if random, can lead to considerable error in the estimation of the true exposure–response relationships (Stewart, 1999). In a study on herbicide exposure to farm children, the sensitivity and specificity of a simple questionnaire item on use were 47 and 72 %, respectively, for 2,4-D, and 91 and 30 % for MCPA, by using urinary biomonitoring data as the 'gold standard' (Arbuckle *et al*., 2004a). If the child was outside during any of the herbicide handling activities, the figures for sensitivity dropped, but specificity improved.

Other factors influence the magnitude of the effect of exposure misclassification on estimates of association between exposures and disease. The effect depends not only on the extent of exposure misclassification, but also on the prevalence of exposure in the population studied. Since pesticide exposure prevalence may differ in different populations and is certainly different in general population studies when compared to studies in farming communities, the performance of exposure assessment techniques will vary according to the study context. The specificity determines the bias in risk-ratio situations with a low exposure prevalence. Thus, a poor sensitivity, for instance, the one reported by Arbuckle *et al*. (2002) for 2,4-dichlorophenoxyacetic acid (2,4-D), may not be problematic in a general population or case-control study, as long as the specificity is sufficiently high.

Exposure misclassification may not be random, but may differ for individuals with and without the disease of interest (differential exposure misclassification). This further complicates the impact of exposure misclassification and may make it impossible to predict the effects without more detailed information about the structure of the errors.

Other special cases of relevance for pesticide exposure exist. Some studies suggest that residential pesticide exposure of farmers and family members may be as high as exposures experienced during re-entry activities. When such a relevant background exposure is present and correlated to the measured exposure, and not dealt with in an epidemiological study, as usually happens, this may result in nondifferential misclassification of the occupational exposure under study. This can lead to over- or underestimation of the association between exposure and disease, depending on the magnitude of the error and the detailed error structure (Loomis and Savitz, 1994).

ERRORS IN QUANTITATIVE ASSESSMENTS VERSUS VARIABILITY

With regard to quantitative exposure assessment, many investigators focus their efforts on ensuring that errors due to laboratory and field sampling methods

are minimized. Typical precision of measurement methods range from ± 5 to ± 35 %. In contrast, natural variation of the exposure over time and space may be considerably larger. Pesticide applications (i.e. agricultural) that take place outdoors result in larger variability in exposure than those done indoors (i.e. residential, greenhouses, etc.). Day-to-day differences in exposure levels, due to meteorological conditions, ventilation, production volume and other potential determinants, may be as large as 10- to 1000-fold. As an example, in a large study of fruit growers, exposure to captan during application (mixing, loading and spraying) varied by as much as a factor of 750 for respiratory exposures, 300 for dermal exposure of the arms, and 540 for dermal exposure of the wrists (de Cock *et al*., 1994, 1998b). These wide variations were made up of day-to-day variability in each worker's exposure, as well as variability between workers. Exposure variation during re-entry to the orchards was smaller and could be attributed mainly to day-to-day variability. Interestingly, between-worker differences tended to be larger for dermal exposure than for inhalation exposure, hence suggesting that work style and possibly personal hygiene have a greater effect on dermal exposures. There is a more detailed discussion of variability, and the steps taken into consideration when the data are being used in risk assessment, in Chapter 1.

Data from a large exposure study in fruit growers provide a clear illustration that day-to-day variability is usually larger than the measurement error, including both sampling and analytical errors. In Table 7.2, a breakdown is given of the total variability in exposure (log (dermal captan concentration)) into variance components for different dermal patch areas. Interestingly, the interlocation variability in dermal exposure seems only relevant when the head, sternal area, wrists and arm are taken together. The variance component of 4.5 suggests systematic differences between these patches. A variance component of 1 for interlocation

Table 7.2 Interworker, intertask and intra- and interlocation variability in dermal exposure to captan assessed through hand-rinsing and using dermal patches, in a large population of fruit growers (from De Cock *et al*., 1998a,b)

Area	Method	N^a	k^b	Interworker[c]	Intertask[c]	Interlocation[c]	Intralocation[c]
Head, sternal area, wrists (average), arm	Patches	677	126	1.0	1.4	4.5	2.8
Forehead, sternal area	Patches	339	126	2.0	1.0	1.0	2.8
Arm[d]	Patches	292	126	1.0	3.5	1.0	2.7
Hands (left, right)	Hand-rinse	348	126	2.5	2.6	1.0	3.1
Wrists (left, right)	Patches	167	126	1.6	3.6	1.0	3.0

[a] Number of observations.
[b] Number of farm workers.
[c] Variance components expressed as standard deviations of log-transformed exposure data.
[d] Two patches on same arm.

in the rest of the table suggests that no differences in exposure exist between the forehead, sternal area, arms, hands and wrists, respectively. This also suggest that differences in distribution of the exposure over similar body parts (left versus right hands, wrists, etc.) or the same body part (two patches on the same arm) do not seem to be present, or at least do not contribute in a relevant way with this number of samples taken in a large population study. Since these variance components have been obtained by taking repeated samples for each individual, the intralocation components can be interpreted as day-to-day variability and sampling and analytical error in exposure on the patch. This variance component is relatively large.

Such tremendous variabilities illustrate that a single measurement, or even a limited number of repeated measurements, are most likely poor predictors of long-term average exposure. If few measurements have been taken, some individuals' true average exposure will be underestimated, while for others it will be overestimated. This type of error will usually lead to a loss of study power and underestimation of the relationship between exposure and disease. Formulae exist to allow epidemiologists to reduce this bias in the exposure–response relationship to an acceptable level by calculating the number of repeated measurements required per individual, given a certain ratio of the intra- and interindividual variability in exposure. Interestingly, the underestimation is not determined by the absolute magnitude of the day-to-day exposure variability, but by the ratio (λ) of the day-to-day variability to the variability in exposure between individuals. This ratio can be regarded as a noise-to-signal ratio, as follows:

$$b = \beta(1 + \lambda/k)^{-1} \tag{7.1}$$

where b is the observed value of the empirical regression coefficient for the relationship between a health outcome (Y) given an exposure (X), when X is measured with error, β is the true value of the regression coefficient of Y on X, λ is equal to ${}_{w}s_i{}^2/{}_{b}s_i{}^2$ (in which ${}_{w}s_i{}^2$ is the estimate of intraindividual (day-to-day) variance in exposure and ${}_{b}s_i{}^2$ is the estimate of interindividual variance in exposure), and k is the number of repeated measurements per individual.

As an example, consider the data on day-to-day and interindividual variability of fruit growers' respiratory and dermal exposure to captan shown in Table 7.3 (de Cock *et al*., 1998a). The ratio of the 97.5th percentile to the 2.5th percentile of the exposure distribution (R_{95}) is usually larger for the intraindividual or day-to-day variability, when compared to the interindividual variability. The variance ratio, λ, can be calculated from the R_{95} values, since the standard deviation of each exposure distribution is equal to $\ln R_{95}/3.92$, and the square of the standard deviation gives the variance. For the respiratory exposure, this results in a variance ratio λ of 32.8, whereas for dermal exposure of the wrist the variance ratio is considerably lower, approximately 3.0. What are the implications of these variance ratios for the number of measurements per study subject? For a bias of less than 10 % (or $b/\beta \geq 0.90$), the number of repeated measurements per subject

Table 7.3 Intra- and interindividual variability in exposure to captan, expressed as R_{95} (ratio of the 97.5th percentile to the 2.5th percentile of the exposure distribution) in a large population of fruit growers (from De Cock *et al*., 1996)

Captan in/on	N^a	k^b	R_5, interindividual	R_{95}, intraindividual
Inhalable dust	154	108	3.1	541
Wrist	188	133	17.3	143
Arm	176	127	14.2	80.8
Sternal area	184	131	7.1	12.9

[a] Number of observations.
[b] Number of farm workers.

required to obtain a good estimate of the average respiratory exposure is 295, and of the dermal exposure 27. Needless to say, this is an unrealistic measurement effort that cannot be realized in most practical contexts (Heederik and Attfield, 2000). However, it is not surprising that this measurement effort is required. The day-to-day variability is especially large in these agricultural workers, compared to many other occupational groups, and could be attributed to variable meteorological conditions or differences in work activities such as the number of tank fills, etc. On the other hand, differences between the fruit growers are relatively small, likely because they all perform more or less the same tasks by using a limited range of different technologies. The study design could be optimized by including other workers with captan exposures, but with considerably higher or lower exposure levels. This would increase the interindividual variance, so that the number of repeated measurements per subject could be reduced considerably. Details regarding such design considerations can be found in the literature (Boleij *et al*., 1995; Heederik and Attfield, 2000).

Variance ratios obtained from studies of many occupational groups and different chemical exposures suggest that individual exposure assessment is rarely efficient (Kromhout *et al*., 1993). Because of this, another strategy is often used; workers are grouped into homogeneous exposure categories and exposure data are gathered to estimate the group average exposure. This average exposure level is then applied to all members of that group. Remarkably, in most cases, grouping workers will lead to reasonably unbiased estimates of the exposure–response relationship, because the systematic overestimation or underestimation of exposure of some of the group members leads to an error of the 'Berkson' type (Tielemans *et al*., 1998).

Theoretically, a grouping strategy is optimal, if each exposure category is as homogeneous as possible with regard to the exposure, if as much contrast as possible exists between categories, and if sufficient measurements per category have been taken so that the estimate of the average exposure in each category is sufficiently precise. This will be accomplished by minimizing the interindividual variability within an exposure category (intragroup variability), maximizing the contrast between groups (intergroup variability) and minimizing the standard error

of the mean in each exposure category. These requirements may be conflicting because there are always only a limited number of measurements available. Making categories as homogeneous as possible will generally lead to a large number of small categories of workers with similar occupations or tasks. In the extreme case, the grouping strategy becomes an individual exposure assessment strategy when each individual is in a separate category. This, in turn, reduces the number of measurements per exposure category and thus the precision of the estimate of the average exposure. This apparent conflict between several requirements can only be solved by using quantitative expressions for calculating optimum grouping strategies, as already exist for individual-based exposure assessment strategies. Some formulae have recently been published for balanced data sets assuming a constant variance over and within exposure categories (Tielemans *et al*., 1998). Expressions applicable to a broader range of conditions are not yet available.

Some of the above-described problems with quantitative exposure assessment, combined with the logistical difficulties that are introduced when one wants to apply quantitative assessments to populations of agricultural workers (especially difficult for distant past exposures), probably explain why so few epidemiological studies use measurement data. In addition, differences between workers in the agricultural sector might be somewhat less when compared to the industry because often similar tasks are performed with relatively comparable technology. This implies that one is interested in exposure contrasts with a relatively homogeneous exposed population. It is unfortunate that so few quantitative exposure data are available, because as a result, epidemiological studies can often not be used in risk assessment or to set exposure standards. When only simple qualitative proxies of exposure, such as job title or agricultural activity, have been used, inferences about the levels of exposure responsible for adverse health effects are difficult or even impossible.

EXPERIENCE WITH EXPOSURE ASSESSMENT IN CASE-CONTROL STUDIES

Maroni and Fait (1993) reviewed the literature on the chronic health effects of pesticides over the period from 1975 to 1991, and found that case-control studies were the most common design, representing about 47 % of epidemiological studies. A search of the 'Medline' bibliographic database from 1992 to 1999 showed that the proportion of case-control studies remains equally high. The large majority of these studies use a population-based, rather than nested, case-control design. This is likely because the health effects that have dominated pesticide research, in particular adult and childhood cancers and reproductive outcomes, including birth defects (Maroni and Fait, 1993), are rare events that are more easily examined by using this study type.

As mentioned earlier, population-based case-control studies have many advantages; however, exposure assessment is generally considered a fundamental

weakness of these designs. Quantitative exposure assessment methods are rarely used, and only in recent years have the reliability and validity of typical qualitative assessment methods been examined. Because of the unusual nature of the 'exposure assessment' methods used in case-control studies, it is worthwhile to consider their strengths and limitations here. The following sections will consider in more detail these methods: occupational histories, exposure matrices, self-reported exposures, expert-reviewed exposures, determinants of exposure studies, exposure databases and direct exposure measurement. As indicated in Table 7.1, most of these methods may also be used in other types of epidemiological studies.

OCCUPATIONAL HISTORIES

In the initial exploratory work examining potential associations between an exposure and disease, analyses comparing the relative risks across occupations or industries may point to exposures requiring further study. Data on job and industry in case-control studies, whether from medical records or questionnaires, are usually derived from self-reports or, when a subject is dead or in some way incapable, reports by next-of-kin. A great advantage of using occupation and/or industry as the 'exposure' is that there is consistent evidence in comparisons with company, pension and union records with earlier self-reports that occupational histories are well recalled by study subjects (levels of agreement from 70 to 90 %), although there is a tendency to recall more recent and usual jobs more accurately than past or short-term jobs (Baumgarten *et al*., 1983; Rosenberg *et al*., 1987; Stewart *et al*., 1987; Bond *et al*., 1988; Bourbonnais *et al*., 1988; Rona and Mosbech, 1989; Brisson *et al*., 1991; Wärneryd *et al*., 1991; Brower and Attfield, 1998)

In open-ended questioning, next-of-kin report occupational histories somewhat less well, reporting fewer jobs, especially omitting those early in a subject's working life (Pershagen and Axelson, 1982; Pickle *et al*., 1983; Lerchen and Samet, 1986; Rocca *et al*., 1986; Boyle *et al*., 1992; Schnitzer *et al*., 1995). If there are more next-of-kin interviews (proxies) for cases than controls, it is possible that risk estimates will be underestimated for jobs early in cases' lives. Several studies have specifically examined proxy reporting of agricultural jobs (Johnson *et al*., 1993; Wang *et al*., 1994) and found 85 to 93 % agreement between next-of-kin and subjects on prompted questions about 'ever farmed', 'agricultural work' and 'field crop farming'. The level of agreement did not differ between cases and controls, hence suggesting little likelihood of recall bias arising from prompted reports of occupation by next-of-kin.

The difficulty with analyses by occupation and industry is that they do not identify specific agents as risk factors. For example, farmers may be exposed to pesticides, but they also have potential for exposures to other agents, including fuels, solvents, welding fumes, wood dust, silica, crop dust, animal danders, zoonoses and endotoxins. In addition, although some farmers use pesticides, many others do not (Blair and Zahm, 1993). An elevated risk in a job can only be suggestive of particular exposure risks.

EXPOSURE MATRICES: USING JOB OR CROP TO INFER EXPOSURE

In an effort to utilize the accurate recall of occupational information, but overcome its indirect connection to exposures, there was a movement in occupational epidemiology in the 1980s to develop job–exposure matrices (JEMs). The latter list a wide range of jobs on one axis and a wide range of exposures on the other, while the cells of the matrix indicate the intensity, frequency and/or probability of a specific exposure in a specific job. A number of generic JEMs, made publicly available, were created by using either expert judgement, often aided by published literature (Hoar *et al*., 1980; Pannett *et al*., 1985), or 'walkthrough' surveys of a representative sample of work sites (Sieber *et al*., 1991). Studies comparing exposure assessments between these JEMs have found poor agreement (Linet *et al*., 1987; Kromhout *et al*., 1992; Hawkes and Wilkins, 1997) as have studies examining the comparability of JEMs and self-reports (Kromhout *et al*., 1992; Roeleveld *et al*., 1993; Rybicki *et al*., 1997) or JEMs and study-specific expert assessments (Bouyer *et al*., 1995; McNamee, 1996; Rybicki *et al*., 1997). The problem seems to stem from the often very poor sensitivity of generic JEMs, understandable given the number of cells which need to be evaluated, and the sometimes unpredictable circumstances in which chemicals may be used.

Most JEMs do not include pesticide exposures or agricultural work in the matrix. Recently, a number of investigators have developed exposure matrices directly applicable to agricultural work (Duares *et al*., 1993; Miligi *et al*., 1993; Nanni *et al*., 1993; London and Meyers, 1998). A unique feature of these matrices it that experts from the agricultural industry and occupational hygienists have used not only job, but also crop and other information as the basis for assigning exposures. In addition, these matrices are more study-specific, and have attempted to assign a limited number of agricultural chemical exposures to a limited set of jobs or crops, therefore increasing the likelihood that the experts are knowledgeable about the factors they are rating. The crop–exposure matrix of Miligi *et al*. (1993) had sensitivities ranging from 0.83 to 1.0 and specificities ranging from 0.66 to 0.96 when compared to self-reports – a substantial improvement over the results from generic JEMs. However, organophosphate exposure estimates derived by the London and Meyers (1998) matrix explained only 5% of the variability in erythrocyte cholinesterase levels in a small sample of their study population. More validity and reliability data are required to evaluate the utility of such matrices.

SELF-REPORTED EXPOSURES

Questionnaires used in case-control studies now commonly ask about more than a subject's occupational history, querying use of pesticides as a group, classes of compounds or specific-tradename products or active ingredients. Investigations of environmental risks from pesticides most often use questionnaire self-reports of pesticide use in gardens, on pets and in homes, as well as potential exposures from drinking water, contaminated food, agricultural drift or contaminated clothing.

Studies examining the ability of subjects to accurately report their exposures indicate that the quality of responses is directly linked to the type of questioning. Improvements occur with prompted over open-ended questioning, with chemical names used in the work site over the names of chemical constituents, and with compounds that can be sensed over those which are odorless and invisible (Ahlborg, 1990; Joffe, 1992; Blair and Zahm, 1993; Teschke *et al*. 1994; Nieuwenhuijsen *et al*., 1997).

Blair and Zahm (1993) postulated that farmers may be more likely than others to recall the use of specific pesticides and their active ingredients, because their use is such a critical component of the success of farming operations. In their study comparing farmers' self-reported use of 'herbicides' and 'insecticides' to suppliers' records, the level of agreement was about 60 %. Agreement about years of pesticide use ranged from 38 to 68 %. The suppliers' records were not considered a 'gold standard', and therefore the validity of the self-reported information was expected to be greater than suggested by these results. The levels of agreement were similar for cases and controls, thus suggesting recall bias is unlikely. In a similar study of structural fumigation workers, Calvert *et al*. (1997) found Pearson correlation coefficients of 0.97 for years of employment in the company, and 0.66 to 0.88 for percentage of jobs using two specific fumigants, but lower for days worked. Population-based studies (Eskenazi and Pearson, 1988; van der Gulden *et al*., 1993) showed 82 % agreement in repeated self-reports of exposure to the broad category 'pesticides'. In populations less involved with pesticide application, such as migrant farmworkers or those living in residences which have been treated, there is evidence that few know the names of specific pesticides to which they have been exposed (Zahm and Blair, 1993).

Evidence about next-of-kin reports of subjects' exposures is mixed. Some studies of farmers and their wives querying the use of specific pesticides (Blair and Zahm, 1993), as well as population-based samples querying pesticide use in general (Boyle *et al*., 1992), indicated that next-of-kin under-reported exposures. Other studies have reported rather good concordance between subjects and next-of-kin, with agreements of 70 to 95 % for use of 'pesticides', 'herbicides', 'insecticides' or 'fungicides' (Johnson *et al*., 1993; Wang *et al*., 1994). In most studies, pesticides that were less frequently used were less well known by next-of-kin, as were details about frequency of use, or specific pesticides. Studies which examined the next-of-kin's recall separately for cases and controls found once again that there was little difference in recall patterns by case status (Johnson *et al*., 1993; Wang *et al*., 1994).

EXPERT-REVIEWED EXPOSURES

It is difficult for subjects reporting their own exposures to consider their exposures in relation to those of other subjects in the study (Teschke *et al*., 1989). For example, office workers whose building was sprayed with insecticides might consider themselves exposed, but might not give the same answer if asked to

compare their exposure to that of a pesticide applicator. As a mechanism for overcoming this problem, it is now a common feature of case-control studies to include a review of self-reported information by occupational hygienists or other experts.

Studies examining agreement between experts' ratings of pesticide exposures have shown good concordance. An overall weighted kappa of 0.76 was measured for two agricultural chemists ranking exposure to phenoxy herbicides, based on subject-reported jobs, farm locations, crops and pesticide handling (Ciccone and Vineis, 1988). A kappa of 0.75 was found for repeated assessments of exposure to 'agricultural chemicals' by four industrial hygienists, based on subject-reported occupational histories (McGuire *et al*., 1997). Intraclass correlations of 0.88 to 1.0 were reported for eight agronomists rating exposures to 'fungicides' and 'insecticides' in vine growing, based on subject-reported job title and pesticide exposures (Segnan *et al*., 1996). These excellent results were not sustainable for specific pesticides unless the experts were supplied with product lists from the farms. Somewhat lower levels of agreement were observed in a study examining pairs of hygienists' ratings of sawmill fungicide exposure based on job-title information (intraclass correlations of 0.40 to 0.68) (Teschke *et al*., 1989), and a study of groups of five experts' assessments of captan exposure based on task, equipment and weather information (intraclass correlations of 0.53 to 0.81) (de Cock *et al*., 1996). One study examined the agreement between subject-reported and hygienist-assessed exposure to 'pesticides' (Rodvall *et al*., 1996). The kappa was 0.88 for cases and 0.46 for controls, in one of the few studies suggesting a basis for concern about recall bias. Controls were more likely to report pesticide exposure when the hygienist assessed none.

The validity of experts' ratings has also been examined. Segnan *et al*. (1996) found that experts' attribution of 'fungicide' exposure had high sensitivities (0.99) when compared against farm records of pesticide use. The sensitivities for 'insecticides' were lower (0.54 to 0.61), but the specificities improved when the experts used additional information on pesticide use from study subjects (from 0.60 to 0.99). The validities of specific pesticide ratings were very poor, such that risk estimates could be reversed because sensitivities and specificities added to less than 1.0 (Flegal *et al*., 1986). In studies using exposure measurements as the 'gold standard', the Pearson correlation coefficients ranged from 0.28 to 0.51 when comparing hygienists' ratings to urinary chlorophenol measurements (Teschke *et al*., 1989), while the Spearman correlation coefficients for experts' rankings of captan exposure levels ranged from −0.25 to 0.9 (de Cock *et al*., 1996). These studies highlight the need to consider the accuracy of 'experts'. All of the validity studies considered exposures within narrow occupational settings, unlikely to mimic the range of jobs being assessed in case-control studies. Determining the validity of both self-reported exposures and experts' assessments in the typical population-based setting of case-control studies remains a difficult problem, without study-based exposure measurements, as discussed below.

DETERMINANTS OF EXPOSURE STUDIES

A method which holds promise for improving the validity of exposures assessed by questionnaires is to guide the formulation of questions and interpretation of their answers with studies which evaluate the factors affecting pesticide concentrations (Blair and Zahm, 1990). Determinants of exposure studies include experimental and observational studies, which measure exposures and concurrently document work or residence characteristics which may increase or reduce exposure levels (Burstyn and Teschke, 1999). There is a large and growing literature on pesticide exposures, in the mixer, loader and applicator population which is routinely examined for pesticide registration purposes, but also in populations exposed in other environments, including harvesting, residences, silviculture and elsewhere (van Hemmen, 1992; Stewart, 1999). Factors which have been examined as determinants of pesticide exposure are extremely varied, for example, method of application, surface area treated, weather conditions, ventilation, tractor enclosure, tasks, crops, region, protective clothing, time since application, cleaning and laundry facilities, pesticide storage, proximity of residences to mixing and spraying operations, and work practices. One particular study evaluated the effectiveness of personal protective equipment in an observational study (Arbuckle *et al.*, 2004b). However, the exposure–determinant exposure studies conducted so far suggest that the known determinants explain the variability in exposure only to a limited extent. More studies and more developmental work are needed to optimize this approach and make it applicable in an epidemiological context.

Moreover, translating these data into questions useful to assess exposures in case-control studies is not a simple process. Given that data on exposure determinants are likely not to have been collected in the worksites or residences of the study subjects, it would be necessary to consider the transferability of the information. Where studies show consistent patterns and greater variability between the determinants of interest than between sites, useful questions might be developed to distinguish exposure levels. Questions about exposure determinants would have to be answerable by study subjects, suggesting that determinants such as tasks may be much more useful than technical ones such as air-flow rates of greenhouse ventilation systems. Where insufficient information is available in the literature, researchers might consider designing their own determinants of exposure studies prior to embarking on the epidemiological investigation. Tailor-made determinants studies, underpinned by studies testing the validity of subjects' questionnaire responses, would be the ideal method to optimize exposure estimates. Some interesting examples exist of studies which have measured exposures in large numbers of worksites to create predictive models for use in epidemiological studies (Preller *et al.*, 1995; Burstyn and Teschke, 1999).

EXPOSURE DATABASES

Another method to help quantify pesticide exposures is the use of exposure databases. The exposures measured for pesticide applicator studies are now

routinely included in the Pesticide Handlers Exposure Database (PHED) database in North America (Leighton and Nielsen, 1995) and POEM and others in Europe (see Chapter 5). They contain data on the dermal and respiratory exposures of mixers, loaders, applicators and flaggers required for pesticide registration, but not of other occupations. In addition, they do not identify the data by the specific chemical name but do indicate the class of pesticide (i.e. herbicide, insecticide, etc.) and the formulation type. A major limitation of several of the above-mentioned databases is that the data are collected for pesticide registration and describe exposure under relatively ideal circumstances and a limited number of exposure scenarios. Data from observational studies that measure exposure under 'real-life' conditions are not included, and therefore exposure estimates based on these databases may underestimate both exposure levels and variability.

Other data sets, with a broader coverage of jobs throughout the population, are likely to be needed for estimation of pesticide exposures in case-control studies. For example, Stewart and co-workers (Stewart and Stewart, 1994; Stewart *et al*., 1998) have used detailed occupational questionnaires with job-specific modules, together with data from the US Occupational Safety and Health Administration (OSHA) Integrated Management Information System to aid in assigning study subjects' exposures to multiple chemicals, including pesticides.

The basis for assignment of exposures is limited by the supplementary information included in the database. The OSHA data set, for example, contains information on job and industry but not tasks or other determinants. Proposals for broadening the data contained in these administrative databases could make them useful for determinants of exposure studies, with the promise and caveats stated above (Rajan *et al*., 1997).

EXPOSURE MEASUREMENTS

An avenue for both occupational and environmental exposure assessment which has only rarely been used in case-control studies is direct exposure measurements of the study subjects. For pesticides with long biological half-lives, and whose concentrations are unlikely to be affected by the disease, biological measures of exposure can be made. For example, Caldwell *et al*. (1981) and Scheele *et al*. (1992, 1996) measured pesticide levels in bone marrow and serum in adult and childhood cancer cases and controls.

For outcomes with short induction and latency periods, measurements of current exposures may serve as reasonable surrogates of exposure in the induction period. Floderus *et al*. (1993), in a case-control study of brain cancer and leukemia, made 924 measurements of magnetic fields in 169 jobs held longest in the workplaces of study subjects. Similar comparisons have been made for exposure to solvents and heavy metals in a study on reproductive outcomes (Tielemans *et al*., 1999a; Stewart, 1999). Given advances in occupational hygiene monitoring equipment over the last two decades, it is reasonable to consider mailing simple sampling equipment, such as passive dosimeters or electronic data loggers,

to study subjects for exposure assessment. If these avenues of exposure assessment are adopted in case-control studies, the issues involved will be similar to those faced by researchers using quantitative measures, as discussed earlier in this chapter.

CONCLUSIONS AND RECOMMENDATIONS

A wide range of exposure assessment approaches is available and the guiding concepts can be found in the epidemiological and occupational and environmental hygiene literature. However, exposure assessment of pesticides in epidemiological studies is still in its infancy, as shown by a review of the literature on exposure assessment in case-control studies. Most exposure proxies are, at their best, qualitative, and discriminate only between exposed and unexposed subjects. There is a clear need for validation of questionnaire self-reports and expert-based proxies of exposure using quantitative data gathered under 'real-life' conditions and describing the variability in exposure over time and space. Quantitative pesticide exposure studies have seldom been applied in epidemiology – another opportunity for improvement. A complication in this field is that the exposures of interest must be relevant to health. This requires consideration of the time-windows when damage occurs, as well as the routes of exposure, which contribute most to absorbed dose. The dermal route is an important, if not the most important, route of entry. Dermal exposure assessment techniques have been standardized and most regulatory agencies within the Organization for Economic Co-operation and Development (OECD) require whole-body dosimetric methods to be used. This may be useful for registration purposes, although this is not always relevant for epidemiological studies since the scientific basis for measuring whole-body dosimetry for a specific health effect is absent.

As a result, to date epidemiological studies of pesticide exposures have only been indicative of the presence of elevated health risks. Quantitative studies contributing to evidence on exposure–response relationships which could be used for quantitative risk assessment purposes are not widely available. This implies that the epidemiological potential has not been explored to its limits, as has been done for certain other agents such as asbestos and lead, for which present legislation has been based, to a large extent, on quantitative evidence of health risks in humans obtained from epidemiological studies.

It is often mentioned that observational epidemiological studies have many disadvantages, among which weaknesses in exposure assessment, and sensitivity to different forms of bias such as selection, information and confounding bias, are the major drawbacks (Nelson, 1988). Toxicological studies in animals with their greater control over the experimental design are sometimes considered superior. However, when available, good epidemiological studies are to be preferred when chemicals need to be classified or when quantitative risk assessments have to be performed. Why so few good epidemiological studies are available for pesticides

is a matter of speculation. The fact that exposure assessment in epidemiology is a complex area, not always completely understood by epidemiologists, contributes to the explanation. Other factors might be the absence of technologies to evaluate the exposure to pesticides on a large scale in epidemiology studies, especially the absence of accurate techniques to evaluate dermal exposure and absence of insight in the most recent methodological developments. The principles of exposure assessment strategies for registration of pesticides and epidemiological studies differ. This seems not to have been completely understood by all researchers and so adds to the confusion. The fact that epidemiological studies on pesticides often have to be conducted in agricultural regions with the population spread over large areas, introducing logistic problems for quantitative exposure assessment strategies, contributes to the explanation for the absence of quantitative studies as well. However, even good or perfect epidemiological studies will not be able to answer all questions that need to be answered before risk assessments are possible. Epidemiological studies in agriculture, and even in pesticide-producing industries, may involve populations with exposure to mixtures of different pesticides. The conclusions that can be drawn from these studies are limited by this and usually do not allow specific conclusions about the particular risk associated with the use of one pesticide. Toxicological information will always be needed to complete the picture and give information about biological plausibility, and risk from individual agents. On the other hand, positive epidemiological findings from well-conducted studies, in the presence of negative toxicological findings, are usually a trigger for further studies. In addition, quantitative studies of exposures in occupationally and environmentally exposed populations are the only way to ascertain human exposure levels. This discussion illustrates that neither of the two scientific methods, epidemiology nor toxicology, give the complete answer.

Despite the fact that few epidemiological studies with quantitative exposure assessment data are available for pesticide exposure, more insight is now present on how the optimal exposure assessment strategy might look. In particular, the use of determinants of exposure studies, as reviewed recently, and their application in health-based exposure estimation, seems a promising approach that can solve many of the problems associated with pesticide exposure assessment in agriculture. This approach will be of use in both occupational and domestic epidemiological studies on this topic.

In summary, few epidemiological studies are currently available that have explored the limits with regard to quantitative exposure assessment to pesticides. It is also clear that exposure assessment in epidemiology is a complex process, but can be optimized by the application of existing principles and concepts. This will help improve the quality of epidemiological studies and allow the use of study results in quantitative risk assessment. A new generation of epidemiological pesticide studies is emerging. Such studies should help us develop a much more sophisticated understanding of the effects of pesticides in humans when proper exposure assessment strategies have been included.

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Section Four

Advances in Data Interpretation

8 Probabilistic Approaches to Aggregate and Cumulative Risk Assessment

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INTRODUCTION

This chapter describes and illustrates probabilistic approaches to aggregate and cumulative assessments of exposure, dose and risk. Aggregate assessments account for multiple sources (e.g. food, water, residence and occupation) and multiple routes (ingestion, dermal and inhalation) of exposure for a single pesticide. Cumulative assessments combine exposures for chemicals that share a

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common mechanism of toxicity. Regulatory agencies in North America do not normally include occupational exposure in aggregate and cumulative assessments.

Probabilistic risk assessment methods are used to incorporate uncertainty and variability into both aggregate and cumulative risk assessments. Herein, *uncertainty* refers to lack of knowledge or the limitations in the current state of knowledge. For example, the dermal permeability of a pesticide may not be known with certainty. *Variability*, on the other hand, refers to a value that differs from one individual to another individual in a population or from one instance to another. For example, the number of applications of a residential pesticide in a year may vary from one individual to another. Probabilistic methods use probability distributions to incorporate uncertainty and variability into both aggregate and cumulative risk assessments.

A fairly detailed case study illustrating a probabilistic approach to both aggregate and cumulative assessments is described in the first part of this chapter. This case study focuses on chronic exposure (that is, a person's long-term average dose). The case study was prepared as part of a submission to the US Environmental Protection Agency (USEPA) in 1996.

The methodology in the case study for chronic exposure, as well as several recent advances in probabilistic assessment methodology for acute exposure (e.g. a person's exposure on a single day), are being incorporated into computer models that facilitate exposure and risk assessment such as the Cumulative and Aggregate Risk Evaluation System (CARES), which begun in 2000 and is being further developed under the auspices of the International Life Sciences Institute (ILSI) in 2004. Some of the major advances being incorporated into CARES and other computer software are discussed at the end of this chapter.

OVERVIEW OF AGGREGATE AND CUMULATIVE RISK ASSESSMENT

Until recently, most risk assessments focused on a single pesticide, considered each route separately, and evaluated each separately. Aggregate assessments consider a single pesticide but combine multiple routes and multiple sources of exposure. Cumulative assessments combine exposure assessments for chemicals that share a common mechanism of toxicity.

Aggregate and cumulative assessments are performed separately for each exposure duration of concern such as acute (a day), short (a week), intermediate (a month) and chronic (a year or a lifetime). The term 'exposure duration' is used herein with the understanding that the exposure level may not be greater than zero throughout the time-period.

In addition to performing aggregate and cumulative assessments for each exposure duration of concern, aggregate and cumulative assessments are performed separately for each toxicity endpoint of concern. For a specified exposure duration, if a pesticide is associated with endpoint (1) and endpoint (2), then the aggregate assessment for endpoint (1) and for endpoint (2) is performed separately.

The cumulative assessment for endpoint (1) combines only those chemicals and routes that are associated with endpoint (1) via a common mechanism and incorporates only those No Observed Adverse Effect Levels (NOAELs), benchmark doses, uncertainty factors, etc. associated with endpoint (1). A similar cumulative assessment would be carried out for endpoint (2). Guidance on aggregate exposure and cumulative risk assessment has been recently published (USEPA, 2003).

CHARACTERIZING DOSE AND RISK IN A CUMULATIVE ASSESSMENT

Risk characterization is a combination of two components: (1) a toxicological characterization of each pesticide having a common mechanism for the given toxicity endpoint and exposure duration, and (2) the exposure characterization for a specified population. Exposure characterization is illustrated in the case study and is also discussed later in this chapter. The methodology for combining the exposure characterization with the toxicological information to form the dose and risk characterizations is discussed in the remainder of this section.

As discussed in the 'Introduction and Overview' Chapter, the NOAEL determined from the toxicity tests divided by the appropriate safety and/or uncertainty factors is called a Reference Dose (RfD). This term can also be called the Acceptable Operator Exposure Level (AOEL) when assessing worker risk. This approach is used in Europe and if the exposure (dose) is lower than the AOEL, the pesticide is considered to pose no unacceptable risks. Another way of expressing acceptability is to divide the NOAEL (or another benchmark dose such as the Effective Dose_{10} (ED_{10})) by the expected exposure value to derive a Margin of Exposure (MOE). In North America, occupational exposure assessments are conducted by using the MOE approach. If the MOE is greater than the target MOE, which is a value based on the required safety and/or uncertainty factors, the pesticide is considered to pose no unacceptable risk

A major issue in aggregate and cumulative risk assessments is determining a risk metric to be used in conjunction with aggregate and cumulative exposures. The appropriate risk metric depends on whether the biological endpoints and the target MOE are the same across all routes of exposure. This topic is the subject of continuing study. The following paragraphs in this section describe the total margin of exposure (Total MOE) which is the risk metric that makes the most statistical and toxicological sense. However, it can only be used when the target MOE is common across exposure routes and the pesticides being assessed.

Although the Total MOE is usually defined by using the following equation:

$$\text{Total MOE} = 1/\{[1/\text{MOE}(1)] + [1/\text{MOE}(2)] + [1/\text{MOE}(3)] + \cdots\}$$

its toxicological relevance is more readily apparent if the margin of exposure MOE(I) for the Ith chemical/route combination ($I = 1, 2, \ldots$) is replaced by its

definition, namely:

$$\text{MOE}(I) = \text{BMD}(I)/\text{dose}(I)$$

where:

$$\begin{aligned}\text{BMD}(I) &= \text{Benchmark Dose}(I)\\ &= \text{NOAEL, ED}_{10}, \text{ etc. for the } I\text{th chemical/route combination}\end{aligned}$$

and:

$$\text{dose}(I) = \text{dose from exposure to the } I\text{th chemical/route combination.}$$

Following these replacements and a little algebra, we obtain the following:

$$\begin{aligned}\text{Total MOE} = \text{BMD}(1)/\{&\text{dose}(1) + [\text{BMD}(1)/\text{BMD}(2)] \times \text{dose}(2)\\ &+ [\text{BMD}(1)/\text{BMD}(3)] \times \text{dose}(3) + \cdots\}\end{aligned}$$

In this equation, BMD(1)/BMD(I) is a toxic equivalence factor (TEF(I)) indicating the relative toxicity of the Ith chemical/route combination compared to the '1th' chemical/route combination. For example, if the BMD is the ED_{10}, then:

$$\text{TEF}(I) = \text{ED}_{10}(1)/\text{ED}_{10}(I)$$

Thus:

$$\begin{aligned}\text{Total MOE} = \text{BMD}(1)/[&\text{dose}(1) + \text{TEF}(2) \times \text{dose}(2) + \text{TEF}(3)\\ &\times \text{dose}(3) + \cdots]\end{aligned}$$

or, equivalently:

$$\text{Total MOE} = \text{BMD}(1)/\text{Total TED}$$

where the toxic equivalent dose (Total TED) is the sum of the chemical and route-specific toxic equivalent doses (TED(i) = TEF(i) × dose(i)), namely:

$$\begin{aligned}\text{Total TED} &= [\text{dose}(1) + \text{TEF}(2) \times \text{dose}(2) + \text{TEF}(3) \times \text{dose}(3) + \cdots]\\ &= [\text{TED}(1) + \text{TED}(2) + \text{TED}(3) + \cdots]\end{aligned}$$

From this equation, it is apparent that the Total MOE is a dose (BMD(1)) with known toxicological characteristics divided by the total toxic equivalent dose (Total TED). Thus, despite the non-transparent form of the usual equation for

the Total MOE, the latter is a logical comparison of two doses and a true margin of exposure.

Several features of the Total MOE and its calculation are notable. First, the Total MOE is based on the Total TED and the corresponding BMD (that is, the BMD for the '1th' combination of chemical and route). Secondly, the numerical value of the Total MOE is the same regardless of which combination of chemical and route is assigned to be the '1th' combination of chemical and route. Thirdly, the doses for different chemicals and routes are scaled to toxic equivalent doses (TEDs) before they are summed in the Total TED. Fourthly, the toxic equivalence factors (TEFs) are specific to the toxic endpoint being evaluated. Fifthly, the doses (BMD(i) and dose(i), $i = 1, 2, \ldots$) must all be calculated in common units (e.g. mg/kg/d). Sixthly, the dose from each chemical and route should be calculated on the most biologically relevant dose-scale available. (The absorbed dose is preferable to the chemical intake, while the delivered dose to the target tissue is preferable to the absorbed dose.) Finally, if a biologically effective dose is available which reflects not only the delivered dose but also the net biologically relevant activity occurring at the target site, then the biologically effective dose scale is preferred over other scales.

Because the Total MOE is a straightforward comparison of a benchmark dose to the Total TED, the Total MOE is superior to the alternative approaches, such as those based on reference doses (RfDs), that obscure interpretation by interspersing multiple different chemical- and route-specific uncertainty factors and conservatisms throughout the risk assessment process and fail to separate science from policy (Sielken, 2000). After the Total MOE has been calculated for each individual and the distribution of the Total MOE in the population determined, then uncertainty factors and conservatisms may be used to determine an 'acceptable' Total MOE from a risk management perspective. Subsequent to the case study presented in this chapter, a more complicated cumulative risk assessment has been conducted on the 32 organophosphate pesticides registered in the USA (USEPA, 2002a). One of the biggest challenges has been how to deal with the variable completeness of the databases for the pesticides included in the risk assessment where critical data for some routes of exposure and NOAELs are missing.

When the Total MOE approach is used and toxic equivalent factors and doses computed, the BMDs should be comparable. Comparability is increased if all of the BMDs are for the same endpoint (or endpoints related to the common mechanism of action and of comparable severity). Comparability is also increased if the BMDs are all $ED_{\#}$s (with the same #) as opposed to all NOAELs or all Lowest Observed Adverse Effect Levels (LOAELs), because the NOAELs and LOAELs are influenced by differences in experimental designs. Comparability is also increased if the BMDs all refer to the same species.

The toxicological characterizations (ED_{10}, BMD, TEF and TED), the calculation of the doses from exposures, and the risk characterization (Total MOE) are illustrated in the case study that follows.

CASE STUDY

This case study is based on US data, involves two triazine herbicides (atrazine and simazine) and includes exposures during herbicide mixing/loading and application, as well as exposures from food and tap water in the USA. The case study focuses on chronic exposure (that is, an exposure duration of a year or more and a person's long-term average dose). It should be pointed out that North American regulatory authorities do not use a long-term average (*amortized*) dose unless the pesticide is considered to be a carcinogen.

Although this risk assessment does include some qualitative discussion of the uncertainties associated with the quantitative characterization of the risk, it does not include important qualitative discussions of the available toxicological data, the assumption that adverse health effects observed in animals will necessarily be observed in humans, the absence of observed adverse health effects in humans, etc.

The results presented in this case study were developed by the author and were submitted to the USEPA in 1996. The case study is for illustrative purposes only and data from more recent atrazine reviews by the USEPA (2002b) and PMRA (2003) are not included.

The reader is also referred to a cumulative risk assessment for the organophosphate compounds (USEPA, 2002a) for an additional case study.

CASE STUDY: DEFINING RISK

The risk of an adverse health effect is the likelihood that an individual will develop the effect as a result of that individual's exposure to atrazine and/or simazine. The risk assessment is quantitative because it characterizes the likelihood in numerical terms.

The likelihood that an individual will develop a specified adverse health effect depends on the dose the individual receives as a result of exposure. The dose of atrazine and/or simazine is measured herein as the intake in milligrams of herbicide per kilogram of body weight per day (mg/kg/d).

The way in which the likelihood that an individual will develop a specified adverse health effect at low doses is characterized depends upon the dose–response relationship which is defined and discussed in the next section.

CASE STUDY: THE DOSE–RESPONSE RELATIONSHIP

The manner in which the proportion of subjects developing an adverse effect (a response) changes as the dose level changes is the dose–response relationship. If the proportion decreases in parallel with decreasing dose (e.g. halving the dose halves the proportion), then the dose–response relationship is linear. However, if the proportion decreases faster than linearly (e.g. halving the dose results in

either one-fourth of the proportion or no occurrences of the adverse effect), then the dose–response relationship is sublinear (one type of nonlinearity).

In some types of experimental animals and at some high dose levels of atrazine or simazine, there are adverse health effects for which the observed proportion of animals developing the adverse health effect increased relative to the proportion in unexposed or control animals (Rinde, 1989; USEPA, 1989; Breckenridge, 1996a,b). Among these adverse healths effects, the observed incidence of mammary tumors in female Sprague–Dawley rats increased at smaller doses than any other adverse health effect. Thus, for both atrazine and simazine, the incidence of mammary tumors in female Sprague–Dawley rats is the most sensitive adverse health effect in the most sensitive sex, strain and species tested (Breckenridge, 1996a,b). In June 2001, after this case study was developed, the Federal Insecticide, Fungicide and Rodenticide Agency Scientific Advisory Panel of the USEPA determined that the mechanism by which atrazine and simazine cause mammary tumors in female Sprague–Dawley rats is not relevant to humans and that these tumors should not be used as a basis for human risk characterization.

The proportion of female Sprague–Dawley rats developing mammary tumors decreases very rapidly as the dose decreases (American Biogenics Corporation, 1986; McCormick, 1988; Thakur, 1991, 1992). The observed dose–response relationship is sublinear. Furthermore, the biological mechanism by which atrazine and simazine cause this response is most likely a threshold mechanism; thus, the sublinear dose–response relationship contains a range of positive doses for which the frequency of the response is not increased above the background frequency at zero dose (Andersen *et al.*, 1998; Connor *et al.*, 1998; Eldridge *et al.*, 1998; Simpkins *et al.*, 1998).

CASE STUDY: USING THE MARGIN OF EXPOSURE TO CHARACTERIZE THE RISK

If a chemical has a linear cancer dose–response relationship, then the likelihood that an individual will develop a specified carcinogenic response at a specific dose is usually characterized in terms of the increased probability of the carcinogenic response occurring (increase above the background probability). However, for sublinear cancer dose–response relationships, it is frequently very difficult to accurately estimate either the shape of the dose–response relationship at low doses or the location of any thresholds and, hence, very difficult to quantify the increase (if any) in the cancer probability at low doses. Hence, in its 1996 proposed guidelines for carcinogen risk assessment, the USEPA proposed an alternative method of characterizing the likelihood that an individual will develop a specified carcinogenic response. This alternative method of characterizing cancer risk is based on the margin of exposure.

Based on the mechanistic data for mammary tumors in female Sprague–Dawley rats, two panels of independent scientists (Lamb, 1995; Simpkins, 1996) have

concluded that exposure assessment should be based on a margin of safety or a margin of exposure approach.

The margin of exposure (MOE) is defined as a benchmark dose divided by the dose from exposure. As the latter becomes smaller, the MOE becomes larger and the likelihood of any adverse health effect as a result of the exposure becomes smaller, or even zero. The larger the MOE, then the more confidence there is that no adverse health effect will be observed as a result of the exposure.

The MOE does not quantify risk (the increased probability of an adverse health effect). Instead, the MOE indicates how far the dose from exposure is below the benchmark dose. If the MOE is sufficiently large and exceeds the target MOE, then the increased probability of an adverse health effect is either zero (because the dose is below a threshold for the adverse health effect) or *de minimis* (without appreciable risk or practical certainty of no harm) and, hence, acceptable or safe.

In 1954, Lehman and Fitzhugh of the US Food and Drug Administration proposed the use of a '100-fold margin of safety' based on species extrapolation (10) and intraspecies sensitivity (10). Additional safety factors may be used, dependent upon the severity of the toxicological endpoint and uncertainty factors when there are data gaps. These factors are route- and study-specific. Factors of 10, 100, and 1000 are used by the Drinking Water and Health Committee of the National Research Council (NRC, 1977). Typically, for environmental exposures (e.g. from drinking water and food), the minimum acceptable target MOE is in the range from 10 to 1000 (Lu and Sielken, 1991; Dourson *et al*., 1996). For environmental exposures, margins of exposure in excess of 1000 provide an ample margin of safety and an acceptably small likelihood of an adverse health effect. For occupational exposures, the margins of exposure greater than 100 are generally considered to be sufficiently large for US regulators. This is not the case in some other countries where the MOE for workers is not less than warranted by the toxicological endpoint.

CASE STUDY: BENCHMARK DOSES

Traditionally, the benchmark dose for noncancer endpoints has been the No Observed Adverse Effect Level (NOAEL), or the Lowest Observed Adverse Effect Level (LOAEL) when the NOAEL is not quantifiable. The NOAEL is the highest dose of a substance at which there are neither statistically nor biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Because the NOAEL is limited to one of the experimental dose levels and is sensitive to the sample size in the experiment, the effective dose (ED_{10}, ED_{05}, etc.) is increasingly being used as the benchmark dose (USEPA, 1996). For example, the ED_{10} is the dose corresponding to an increase of 0.10 in the probability of an adverse health effect above the background probability at dose zero. The ED_{10} corresponds to a well-defined increased risk, is usually in or near the range of the experimental doses, and its estimated value is usually relatively insensitive to the type of

dose–response model fit to the observed experimental data. Use of the ED_{10} as the benchmark dose in a margin-of-exposure characterization of cancer risk for sublinear dose–response relationships is consistent with USEPA's 1996 proposed guidelines for carcinogen risk assessment (USEPA, 1996).

The benchmark dose used in this margin of exposure-based risk characterization for atrazine and simazine is the ED_{10} for the mammary tumor response observed in female Sprague–Dawley rats in carcinogenicity studies (Sielken *et al.*, 1996). Although the doses given to male Sprague–Dawley rats and both sexes of Fischer 344 rats and CD-1 mice are large enough that there should have been an observed increment in their tumor response if they are as sensitive as the female Sprague–Dawley rats, atrazine and simazine did not increase the incidence of mammary tumors in Fischer rats or in mice, did not increase the incidence of other tumor types in either Fischer or Sprague–Dawley rats or in mice, and did not increase the incidence of any adverse noncancer effects at doses as low as those increasing the incidence of mammary tumors in female Sprague–Dawley rats (Breckenridge, 1996a). Thus, the ED_{10} for this tumor response is the ED_{10} for the most sensitive adverse health effect observed in the most sensitive sex, strain and species studied in animal chronic bioassays.

For atrazine, an ED_{10} was calculated for each of the 24 possible combinations of four dose–response modeling factors (Sielken *et al.*, 1996). The two alternatives for the first factor were the two chronic bioassays involving female Sprague–Dawley rats. For the first bioassay, the three alternatives for the second factor were using all five doses, only the lowest four doses, or only the lowest three doses. For the second bioassay, the three alternatives for the second factor were the oncogenicity study, the hormone study, or both studies combined. The two alternatives for the third factor were the multistage model which excludes time-to-response information and the multistage-Weibull model which includes time-to-response information. The two alternatives for the fourth factor were two different ways of fitting the dose–response models to the tumor data (one way is with the model forced to be linearly increasing at low doses and the other way is without the requirement to increase as soon as the dose increases above zero). The range of the 24 corresponding ED_{10}s is from 1.4 to 26.3 mg/kg/d. Although treating each of these 24 calculated ED_{10}s as equally likely and using the corresponding distribution to characterize the ED_{10} would have been a better reflection of the uncertainty in the dose–response characterization, the smallest of these 24 calculated ED_{10}s (approximately the 5th percentile in the distribution of estimated ED_{10}s) is the value used for the ED_{10} for atrazine herein. A similar lower bound (95 % lower confidence limit) is used for the ED_{10} for simazine. The range of the eight calculated ED_{10}s for simazine is from 2.6 to 13.1 mg/kg/d. The lower bounds on the ED_{10}s are conservative (in the sense of minimizing the MOE and maximizing protection of human health), 'worst-case' estimates of the smallest dose that causes a 10 % increase in tumor incidence in the carcinogenicity studies on atrazine and simazine. These conservative values for the ED_{10}s for

atrazine and simazine in animals are 1.4 and 2.6 mg/kg/d, respectively (Sielken *et al*., 1996).

In this example, the distributions of ED_{10}s were derived for atrazine and simazine. The 5th percentiles in these distributions have a straightforward interpretation. However, this would not be the case if lower bounds (LED_{10}s) based on the linearized multistage model were used instead of ED_{10}s. In addition, the use of multiple lower bounds introduces an unknown amount of compounded conservatism which is not readily interpretable and is potentially very misleading in a regulatory setting.

CASE STUDY: MARGINS OF EXPOSURE

The doses of atrazine and simazine received by individual humans through either environmental (drinking water ingestion and food) or occupational (herbicide handling) exposures are much smaller than the doses required to observe adverse health effects in the most sensitive sex, strain and species of experimental animals. Thus, the margins of exposure for individuals exposed to atrazine and simazine are quite large, hence implying a considerable margin of safety. Quantifying the magnitude of these margins of exposure is the main subject in the rest of this case study.

CASE STUDY: PROBABILISTIC CHARACTERIZATIONS OF THE DOSES FROM EXPOSURE

The doses from exposure are characterized by distributions that quantify the probability of an individual in a specified population or subpopulation receiving different dose levels as a result of exposure to atrazine and simazine through drinking water ingestion, dietary consumption, herbicide handling, or a combination of these potential exposure routes. Lifetime average daily dose (LADD) is the traditional (default) dose metric for lifetime exposures and chronic toxic endpoints, including cancer. Distributions of LADDs have been determined, and the corresponding distributions of the margins of exposure are presented herein.

Human health risk assessment has often been dominated by the use of default assumptions and 'worst-case' analyses based on the use of upper bounds on the dose estimated from the exposure instead of distributional characterizations of the dose. There are severe limitations associated with the use of default assumptions and upper bounds instead of distributions when detailed exposure and/or dose–response data are available. The US National Academy of Sciences, the USEPA and many others have recognized the need for new risk assessment methodology (NRC, 1983, 1993, 1994; USEPA, 1992; CRARM 1997; van Hemmen and van der Jagt, 2001). This need has promoted the development of quantitative risk assessment methods that use probabilistic techniques such as Monte Carlo simulations for distributional characterizations of exposure, the

dose–response relationship and risk. For these reasons, this paper uses a probabilistic approach. An indication of some of these new methods and the type of results they produce are given in this case study.

CASE STUDY: EXPOSURE CHARACTERIZATION

The object of the exposure assessment described herein is to characterize the water, diet and occupational exposure pathways for atrazine and simazine (Sielken *et al*., 1996, 1998). For each exposure pathway, the chemical-specific doses (mg/kg/d) from each relevant route (ingestion, inhalation and dermal) are summed. The total chemical-specific dose for each exposure pathway is characterized separately, and then these doses are aggregated by summing over the multiple exposure pathways. The pathway-specific and aggregate assessments are performed separately for atrazine and simazine. In addition, because atrazine and simazine are assumed to have a common mechanism of toxicity, a cumulative exposure assessment combining the doses of atrazine and simazine is performed.

The aggregate and cumulative assessments required by the 1996 Food Quality Protection Act (FQPA) (US Congress, 1996) when sufficient data are available combine the water, diet and non-dietary pathways (e.g. residential users) but exclude occupational pathways. The aggregate and cumulative assessments in this chapter include not only residential users but also occupational herbicide handling by growers and commercial operators. Thus, the corresponding aggregate and cumulative assessments for atrazine and simazine in this chapter indicate more exaggerated doses and risks than would be observed through application of the requirements of the FQPA.

The exposure analyses are based on data provided by Syngenta Crop Protection, Inc. to the USEPA on March 23, 1995, and updated on October 31, 1996. These data include several up-to-the-minute studies to add to the current state of knowledge in 1996 about the potential human exposure to atrazine and simazine through drinking water (Clarkson, 1996), diet (Bray, 1996a,b,c) and as a result of herbicide handling (Selman, 1996a,b,c).

The distribution of the dose from exposure is characterized separately for the US population, four regional subpopulations, several states and several different subpopulations of herbicide handlers that reflect different herbicide uses, formulations and tasks. These distributions reflect the variability in the dose from individual to individual within the population (or subpopulation). Rather than focusing on an average dose in a population, the distribution describes the relative frequency of each dose value. This means that these distributions indicate the dose that is most likely to occur, the range of doses expected in the population, and the relative likelihood of the different doses in that range. Each of the individual doses in the distribution is the best estimate of that individual dose and not an upper or lower bound on that dose.

There is only enough space in this chapter to provide an overview of the exposure, dose and risk assessments for atrazine and simazine. The underlying

databases and detailed algorithms needed to reproduce the numerical results presented herein have been presented to the USEPA in a three-volume submission of over a thousand pages (Sielken *et al*., 1996).

CASE STUDY: THE ROLE OF MONTE CARLO SIMULATION

The exposure from each of the routes of exposure (drinking water ingestion, dietary consumption and herbicide handling by workers) is described by an equation in the atrazine and simazine assessment. Some of the components of these equations have values that are variable (e.g. from individual to individual, from one year to the next, from one serving of a specific food to another serving, and from one handling of a herbicide to another handling). These variable components of the exposure equations are described by probability distributions that reflect the relative frequency of the different values for the variable.

The outcome of the exposure equation is a dose. This dose varies because of the variability of the components in the equation. The probability distribution of the dose is generally quite difficult to calculate analytically but can be fairly readily approximated by using a straightforward technique known as Monte Carlo simulation. Such a simulation consists of numerous iterations. In an iteration, a single value for each component in the exposure equation is randomly sampled from its corresponding distribution. These component values are then substituted into the exposure equation and the outcome (exposure) is explicitly calculated. The frequency distribution of the calculated values from numerous iterations is the simulated exposure distribution. The exposure equations and the probability distributions of the components are treated as known in the distributional results presented in this chapter. Thus, the simulated exposure distributions reflect exposure variability but not the uncertainty about these equations, the distributions of the components, and related assumptions. This uncertainty and its quantitative impact on the simulated exposure distribution are presented in Sielken *et al*. (1996).

In the Monte Carlo approach, there are no inherent limitations on the complexity of the exposure equation, the number of component variables, the probability distributions for the variable components, or the number of iterations. This freedom from limitations is especially useful in simulating the distributions of a lifetime average daily dose (LADD) for the different exposure scenarios considered herein. As its name suggests, a LADD is the average over all of the days in an individual's lifetime of the dose of a chemical (e.g. atrazine, simazine, or both) received by that individual in those days as a result of his or her exposure from one or more exposure pathways (e.g. water, diet and herbicide handling). Because the exposure equation can explicitly consider each day individually, the values of the equation's variable components can vary from day to day and have different distributions for different ages. The length of an individual's lifetime can also vary from individual to individual.

Another powerful feature of the Monte Carlo approach is that it can reflect dependencies among the components in an exposure calculation. For example,

when determining a person's dose from drinking water ingestion in a region containing several states, the computer software used herein allowed each Monte Carlo iteration to first randomly select the person's state and then randomly select the concentration of atrazine or simazine in the individual's drinking water from the distribution of drinking water concentrations in the community water systems within the selected state. This capability of conditioning the distribution of one variable (e.g. the concentration in the drinking water) on the value of another variable (e.g. the state) helps advanced Monte Carlo implementations better reflect reality.

The Monte Carlo exposure calculations described in this chapter are carried out with a flexible computer software package known as DistGEN (Sielken, Inc., 1995). This package allows the exposure equations to be specified in the general computer language called FORTRAN, so they can have practically any form. Furthermore, the user-specified distributions for the components of the exposure equations can be selected from a wide variety of classical statistical distributions (normal, log–normal, etc., with user-specified parameter values) or be sample data (either the sample values themselves, frequency histograms, etc.). Each Monte Carlo simulation described herein is based on 10 000 iterations (10 000 evaluations of the exposure equations for individuals).

CASE STUDY: MARGIN OF EXPOSURE

The margin of exposure is defined herein as follows:

$$\text{Margin of Exposure (MOE)} = \text{ED}_{10}\text{ (from toxicity studies)}/\text{Dose (estimated exposure)}$$

The dose from exposure is the LADD. The equations for calculating the daily doses going into the LADD are indicated for drinking water ingestion, dietary consumption and herbicide handling in the next three sections, respectively, and the corresponding distributions of the MOE displayed. Aggregate exposure is characterized separately for atrazine and simazine by the distribution of the MOEs aggregated across these pathways. Cumulative exposure is characterized by the distribution of the MOEs cumulated over atrazine and simazine and all pathways.

CASE STUDY: DRINKING WATER INGESTION

The LADD (mg/kg/d) from drinking water ingestion for an individual is calculated herein by using the following equation:

$$\begin{aligned}\text{LADD} = &(\text{Concentration of Herbicide in Drinking Water (mg/L)}) \\ &\times (\text{Amount of Drinking Water Ingested per Day (L/d)}/ \\ &\text{Body Weight (kg)}) \end{aligned} \quad (8.1)$$

The probability distributions for the LADD in the 18 states that use the most atrazine and simazine every year (approximately 90 % of the total) are determined. In these 'major-use' states, the concentration of herbicide in the drinking water varies too much from individual to individual to be accurately characterized by a single number. Instead, the database of observed individual concentrations collected by the states for local community water supplies and the number of people served by each community water supply are used in the Monte Carlo evaluations of Equation (8.1) and the corresponding LADD distributions. In determining the latter, the objective is to make the person whose drinking water herbicide concentration is used in Equation (8.1) equally likely to be each person served by community water supplies. For example, if the population of interest is a state, then the LADD distribution in that state is determined by randomly selecting a large number of individuals from that state and randomly selecting each individual's drinking water concentration from the database of drinking water concentrations for that individual's community water supply system. In order for the resulting distribution to correspond to the state's distribution, the selection process is carried out in a way that makes each person in the state equally likely to be selected and makes the likelihood of a community water supply being selected equal to its relative size within the state (i.e. the number of individuals served by the community water supply system divided by the number of individuals in the state). If the population of interest includes more than one state, then individuals are selected so that each individual in the population is equally likely to be selected and the likelihood of the each state is proportional to the relative size of the state within the total population.

Because the variability in the amount of drinking water ingested per day per kilogram of body weight is much smaller than the variability of the atrazine and simazine concentrations in the drinking water, Equation (8.1) is evaluated by assuming a default upper bound value of 2 L/d and a default adult body weight of 70 kg. Regulators would use more refined values for intake and body weight related to age and gender in their risk assessments.

The distributional analysis of the dose from exposure using Equation (8.1) indicates that for atrazine at least 95 % of the estimated LADDs from drinking water ingestion have an MOE of at least 50 000 in the 18 'major-use' states combined for atrazine (Figure 8.1(a)). This figure shows a histogram of the MOE for atrazine in the 18 'major-use' states combined. The horizontal axis indicates intervals of possible MOE values, while the vertical axis shows the proportion of individuals in the 18 'major-use' states that are estimated to have MOEs in that interval. For example, the smallest MOEs in the population are in the interval from 1000 to 5000; the proportion in this interval is only 0.0013 (0.13 % of the population). The proportion of the population with MOEs below 50 000 is approximately 0.05 ($0.0013 + 0.0065 + 0.0443 = 0.0521$), so that approximately

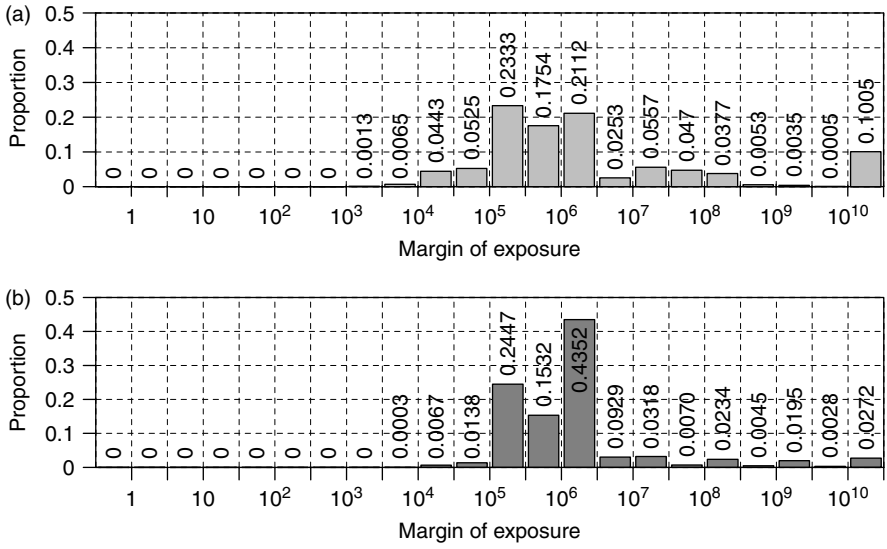

Figure 8.1 The distributions of the margins of exposure associated with (a) atrazine and (b) simazine and drinking water ingestion in the 18 major 'major-use' states combined

95 % of the MOEs in the population are greater than 50 000. Figure 8.1(a) indicates not only the 95 % lower bound on the MOE but also the entire distribution of the MOE. This distribution covers a range from 10^3 to more than 10^{10}, which indicates that the MOE in the population is quite variable and that most of the population have MOEs considerably above the 95 % lower bound. For simazine (Figure 8.1(b)), at least 95 % of the MOEs are greater than 200 000 in the 18 'major-use' states combined.

Figures 8.2 and 8.3 show the same type of histogram as shown in Figure 8.1 for atrazine, except that these figures combined show the MOEs for the 18 individual 'major-use' states separately. The entire histograms in these figures are not all easily seen, but what is important is that these 'major-use' states have hardly any MOEs below 5000 and that most of the people in every state have much larger MOEs.

The ample margins of safety suggested by the MOEs in Figures 8.1–8.3 are even more ample when the exposure evaluation is expanded to include the following alternatives:

- a drinking water consumption distribution and body weight distribution;
- age-dependent drinking water consumption and body weight distributions;

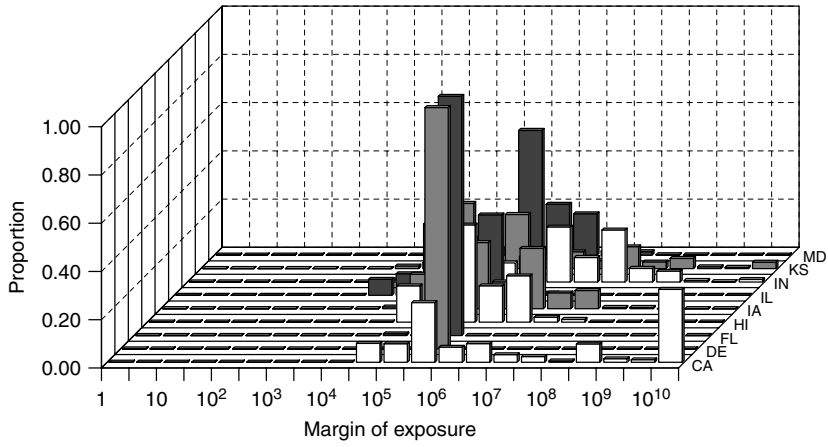

Figure 8.2 The distributions of the margins of exposure associated with atrazine and drinking water ingestion in 9 of 18 'major-atrazine-use' states: CA, California; DE, Delaware; FL, Florida; HI, Hawaii; IA, Iowa; IL, Illinois; IN, Indiana; KS, Kansas; MD, Maryland

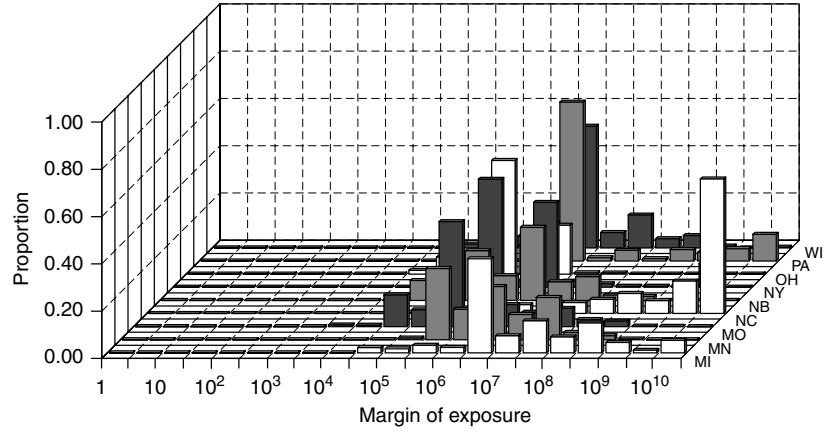

Figure 8.3 The distributions of the margins of exposure associated with atrazine and drinking water ingestion in 9 of 18 'major-atrazine-use' states: MI, Michigan; MN, Minnesota; MO, Missouri; NC, North Carolina; NB, Nebraska; NY, New York; OH, Ohio; PA, Pennsylvania; WI, Wisconsin

- year-to-year variability, as opposed to the same concentration and consumption for 70 years;
- exposure duration distributions corresponding to residential durations, as opposed to 70 years.

CASE STUDY: DIETARY CONSUMPTION

The LADD (mg/kg/d) from dietary exposure can be calculated for an individual in a specified population or sub-population, which in this case is an adult male, by using the following equation:

$$\begin{aligned}\text{LADD} &= \text{Sum of the Dose from Each Food} \\ &= \sum_{i=1}^{\#\text{ of Foods}} [\text{Amount (mg) of Food}_i \text{ Consumed in a Day/} \\ &\quad \text{Body Weight (kg)} \\ &\quad \times (\text{Residue Concentration in Raw Agricultural Commodity} \\ &\quad \text{Contributing to Food}_i \text{ (mg herbicide/mg food))} \\ &\quad \times (\text{Adjustment Factor 1 for Food}_i) \\ &\quad \times (\text{Adjustment Factor 2 for Food}_i)] \end{aligned} \tag{8.2}$$

In this equation, the amount of food consumed of each type in a day per unit body weight of the consumer is assumed to be a constant equal to the corresponding food consumption value in the USEPA's database in their computer software system for Dietary Risk Exposure Assessments (DRES) which is an average chronic consumption value (USDA, 1983). For most consumed foods, the food originates as a raw agricultural commodity. The fraction of the weight of the raw agricultural commodity that is the chemical of interest (e.g. atrazine or simazine) is the 'residue concentration'. The latter in the raw agricultural commodity is not necessarily the same as the chemical's concentration in the food as it is consumed. For example, the concentration of atrazine in an ear of corn when it is harvested in the field and the concentration in an ear of corn after it has been cleaned and cooked may be different. This difference is accounted for by 'Adjustment Factor 1'. The values for this adjustment factor are the default constant values in DRES. Now, regulatory agencies are using the Dietary Exposure Evaluation Model (DEEM™) and DEEM™ + Food Commodity Intake Database (FCID). During an individual's lifetime, some of the raw agricultural commodity in his or her consumed food may come from crops treated with the chemical of interest, while some may come from untreated crops. An individual's lifetime average proportion coming from treated crops is assumed to equal the proportion of acres treated with the chemical. This proportion is reflected in Equation (8.2) as 'Adjustment Factor 2'. The constant values for this adjustment factor are the latest market share (percentage of crop treated) data available (1993, communication from Maritz Marketing Research Inc., St. Louis County, MO, USA, and Doane Marketing Research Inc., St. Louis, MO, USA to Ciba Plant Protection). In sensitivity analyses, Adjustment Factor 2 can be set to 1.0 to correspond to an individual's food

being all locally produced and treated instead of having residue concentrations corresponding to the national average.

Macadamia nuts, guava, refined sugar and molasses are the only raw agricultural commodities treated with atrazine that are consumed as foods. There are no known residue concentrations of atrazine or its chloro-metabolites above their analytical limits of detection (LODs) for any of these four foods. In evaluating Equation (8.2), the residue concentration in each of these four foods is assumed to be equally likely to be any value between zero and its LOD (i.e. uniformly distributed between zero and the LOD).

For meat, milk and eggs, the 'Residue Concentration in Raw Agricultural Commodity Contributing to $Food_i$' in Equation (8.2) is the concentration of the chemical of interest in meat, milk and eggs that results from some of the raw agricultural commodities in the diets of cattle and poultry being treated with that chemical. While the observed residue concentrations in meat, milk and eggs are below their LODs, the concentrations of atrazine in the raw agricultural commodities used as feed for cows and poultry are sometimes quantifiable. Thus, the probability distributions on the anticipated residue concentrations of atrazine and its chloro-metabolites in meat, milk and eggs are based on observed residue concentration distributions in feed items for cows and poultry. The anticipated residue distributions also incorporate the estimated composition of the animal's diet (specifically, how much of the diet is represented by each feed item). Only animal diets that provided adequate nutrition to poultry and lactating dairy cattle were considered. Animal diets are also restricted to those that maximized the amount of feed items treated with atrazine. Finally, the anticipated residues in meat, milk, and eggs are proportions of the residues in the feed consumed by the animals. The proportions are estimated from experimental data relating high experimental concentrations in feed to resulting concentrations in meat, milk and eggs (Sielken *et al.*, 1996).

Using Equation (8.2), the distributional analysis of dietary exposure to atrazine and its chloro-metabolites in the USA and the four regions (North East, North Central, Southern or Western) indicates that at least 95 % of the estimated LADDs from dietary consumption have an MOE of at least 300 000 in each of the four regions and 330 000 in the USA as a whole (Figure 8.4).

Unlike the drinking water and occupational exposure pathways, the dietary pathway could conceivably involve exposure to the chloro-metabolites of atrazine. Hence, the atrazine chloro-metabolites have been combined with atrazine in Figure 8.4. Atrazine chloro-metabolites have been assumed to have the same toxicity as atrazine in calculating the MOEs in this figure.

There is not much variability in the distributions in Figure 8.4 because all of the components in Equation (8.2) have been assumed to be their lifetime average values, except for the residue concentrations. Thus, the only really important characteristic of the distributions in Figure 8.4 is that the MOEs in the distributions are quite large.

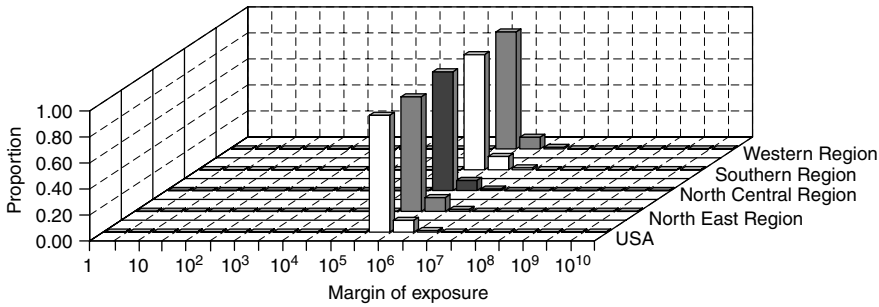

Figure 8.4 Distributions of the margins of exposure in the USA for atrazine plus its chloro-metabolites from dietary consumption

For simazine, the residue concentrations in Equation (8.2) are constants (averages or upper bounds), determined directly from the most recent residue data on the commodities themselves or, for meat, milk and eggs, determined indirectly from the diets of cattle and poultry. The corresponding MOE is at least 1 750 000 for each of the four regions and at least 2 000 000 for the USA as a whole.

While the following two observations are not critical in the distributional characterization of the intake of atrazine and simazine from dietary consumption, such observations can be important in other situations. First, making the assumption that the residue concentration in an individual's food is the same concentration every time that food is consumed (as is done in Equation (8.2)) exaggerates the variability in the intake distribution. Without this assumption, both the low and high percentiles of the intake distribution would be closer to the median intake, and the 95 % lower bound on the MOE would increase. Secondly, when a sum is being characterized (such as the sum of intakes in Equation (8.2)), it is important to determine explicitly the probability distribution of the entire sum and not attempt to infer the characteristics of the distribution of the sum indirectly from the distributions of its components. For example, the 95th percentile of a sum may be much smaller than the sum of the 95th percentiles of its components.

CASE STUDY: HERBICIDE HANDLING BY WORKERS

The LADD (mg/kg/d) from dermal absorption and inhalation due to herbicide handling exposure can be calculated for an individual in a specified population or sub-population by using the following:

$$\text{Dose} = \{[(\text{Pounds of Active Ingredient Applied per Acre (lb a.i./acre)}) \times (\text{Number of Acres Treated in a Year (acres/year)})$$

$$\times \text{(Number of Years in which Treatments Occur (years))/}$$
$$[(70 \text{ years}) \times (365.25 \text{ days/year}) \times \text{(Body Weight (kg))}]\}$$
$$\times \left[\sum_{k=1}^{12} \text{(Fraction Absorbed for the } k\text{th Body Part)}\right.$$
$$\left.\times \text{ (Amount of Exposure for the } k\text{th Body Part (mg/lb a.i.))}\right] \quad (8.3)$$

In the above equation, the overall assumption is that the dose is proportional to the amount of herbicide applied and the fraction of that amount that the body is exposed to and absorbs. The application rate per acre is in terms of the pounds of active ingredient (here, atrazine or simazine) as opposed to the pounds of whatever mixture containing atrazine or simazine is actually applied to the acres. The application rate per acre multiplied by the number of acres treated per year is the total amount of active ingredient applied per year. This total amount applied per year is multiplied by the number of treatment years in a lifetime and divided by 70 years, 365.25 days per year, and body weight (kg) in order to convert to the lifetime average pounds of active ingredient applied per kg of body weight per day. The dose from exposures is calculated by multiplying the amount of active ingredient by the sum of the fraction absorbed and the amount of exposure for each of 12 body parts in which the human body is partitioned.

An individual's absorbed dose is assumed to be proportional to the amount of active ingredient applied. In this paper, that proportion (mg per pound of active ingredient applied) is derived from the exposure information in the Pesticide Handlers Exposure Database (PHED, 1992) and herbicide-specific dermal absorption data. The PHED provides exposure information on the twelve parts of the body as opposed to the body as a whole. For each body part, the PHED provides data on the amount of active ingredient that comes into contact with that body part per pound of active ingredient applied (amount inhaled or amount of dermal contact per pound applied). The PHED data used herein assume that the individual is wearing normal clothing and gloves but not additional protective devices such as aprons or respirators. Based on atrazine- and simazine-specific studies conducted by Syngenta, the fraction of atrazine and simazine absorbed as a result of dermal contact is 0.056 when the exposure is less than or equal to $8\,\mu g/cm^2$, 0.012 for exposures greater than or equal to $80\,\mu g/cm^2$, and a linear interpolated value for intermediate exposures. The fraction of the inhaled atrazine or simazine that is assumed to be absorbed is 1.

In applying Equation (8.3), the pounds of active ingredient applied per acre is assumed to be a use-specific constant, and the number of acres treated in a year is assumed to be a use-and-user-specific distribution. Use refers to crop (e.g. corn, sorghum, North American sugar cane or Hawaiian sugar cane), vegetation management, sod or lawn care, while user refers to either a commercial operator

or a grower or homeowner, as well as the method of herbicide mixing, loading and application. The number of years in which treatments occur is assumed to be 10 years for commercial lawn care operators and 35 years for all other uses and users.

The distribution of body weights is assumed to be a normal distribution, with a mean of 70 kg and a 20 % coefficient of variation (i.e. a standard deviation equal to 14 kg).

The amount of exposure for a body part is a PHED-based distribution depending on the body part and the type of user, as well as the type of herbicide formulation used. The latter can be granule formulations (used only by homeowners using atrazine for residential lawn care), flowable formulations (FFs) (which are among the formulations classified as emulsifiable concentrates (ECs) in PHED) and water-dispersible granules (WDGs).

By using Equation (8.3), the distributions of exposure indicate that at least 95 % of the estimated LADDs associated with herbicide handling exposure have an MOE of at least between 500 and 11 000 for atrazine, and between 10 000 and 20 000 for simazine, depending on the herbicide use (e.g. corn, sod, etc.) (Figures 8.5–8.7).

Even though the smallest MOEs in Figures 8.5–8.7 are relatively large, their true values are probably even larger. In statistical terms, this probable underestimation of the smaller MOEs occurs because the variance of an average of several variable events is less than the variance when every event is assumed to have the same value. Thus, the lower percentiles in the distribution for an average of several events are larger than the lower percentiles in the distribution when every event is assumed to be the same. (For the same reason, the upper

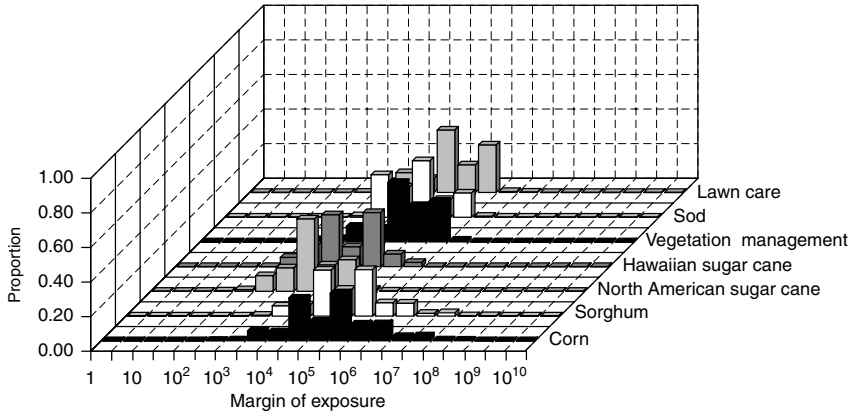

Figure 8.5 Distributions of the margins of exposure for atrazine from herbicide handling with flowable formulations for 'different-use' populations in the USA

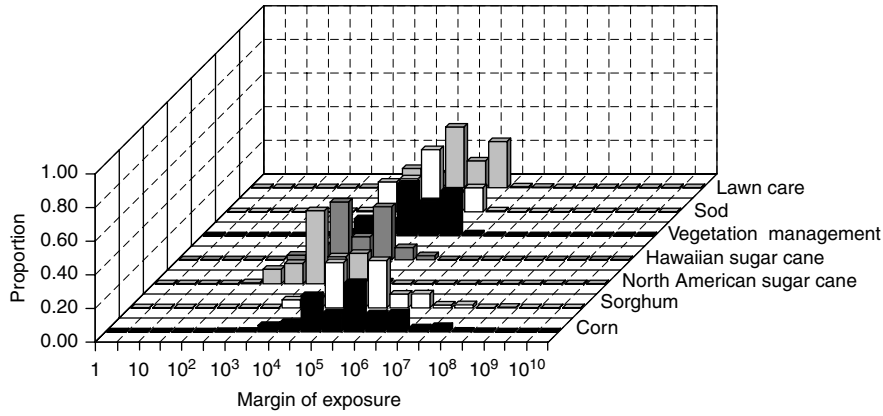

Figure 8.6 Distributions of the margins of exposure for atrazine from herbicide handling with water-dispersible-granule formulations for 'different-use' populations in the USA

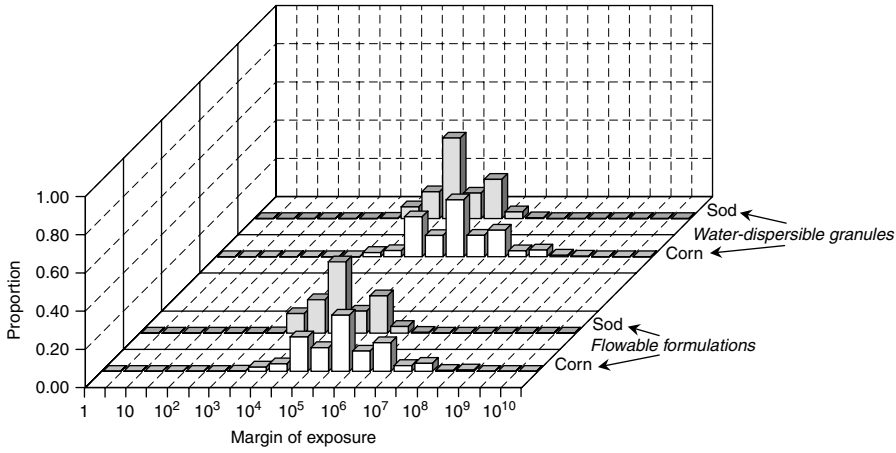

Figure 8.7 Distributions of the margins of exposure for simazine from herbicide handling with flowable and water-dispersible-granule formulations for corn and sod use populations in the USA

percentiles in the distribution for an average of several events are smaller than the upper percentiles in the distribution when every event is assumed to be same. However, the smaller MOEs are of primary interest herein.) In simpler terms, the lifetime average daily dose is almost always the average of a large number of different daily doses corresponding to different exposure events and not the result of the same daily dose and the same exposure event repeated over and over again throughout the lifetime. However, Equation (8.3) implicitly assumes that all of

the daily doses and exposure events are the same. For example, the pounds of active ingredient applied per acre is implicitly assumed in these equations to be the same for every year in which treatments occur. The number of acres treated in a year is assumed to be the same for every year. The fraction of the amount of herbicide applied, that the body is exposed to and absorbs, is assumed to be the same for every year in which treatments occur. If these factors are allowed to vary within the lifetime of an individual, then the 95 % lower bounds on the MOEs shown in Figures 8.5–8.7 would be larger.

For each herbicide use, the whole population of herbicide handlers and each of several subpopulations of potential interest are explicitly evaluated. For example, for crops, the following subpopulations are explicitly evaluated:

(1) all growers;
(2) growers who carry out mixing/loading;
(3) growers who carry out applications;
(4) growers who carry out both mixing/loading and application;
(5) all commercial herbicide handlers;
(6) commercial herbicide handlers who use the herbicides for ground application;
(7) commercial ground mixer/loaders;
(8) commercial ground applicators;
(9) commercial herbicide handlers who use the herbicides in aerial applications;
(10) commercial aerial mixer/loaders;
(11) commercial aerial applicators (pilots).

These subpopulations are also further subdivided as follows:

(a) herbicide formulation (flowable formulations (FFs) and water-dispersible granules (WDGs));
(b) type of mixing/loading operation;
(c) type of application.

Monte Carlo techniques allow the exposure characterizations for the different subpopulations to be properly aggregated into a population characterization which reflects the relative subpopulation sizes and the different exposure distributions in each subpopulation without having to assume the ‘worst-case’ for the population or a specific subpopulation. For example, Figure 8.8 shows how the population of herbicide handlers involved in the production of corn crops is related to its component subpopulations. The Monte Carlo simulation for the population of herbicide handlers involved in the production of corn crops can be carried out in such a way that 97 % of the iterations in the simulation are expected to be for ‘Grower’ and 3 % for ‘Commercial’, and among the iterations for ‘Grower’ one-third are expected to be for ‘Mixer/Loader’, etc. Thus, a Monte Carlo simulation correctly characterizes a population by sampling its

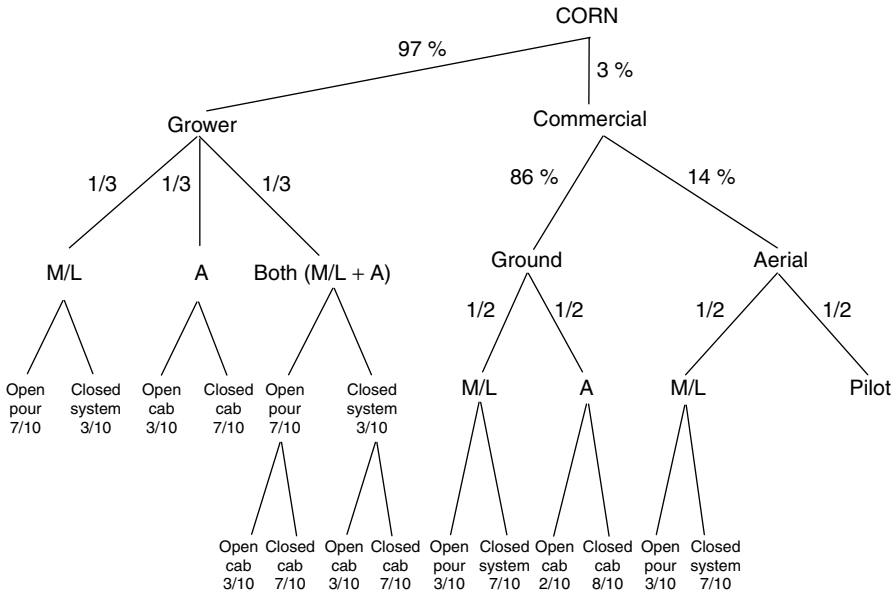

Figure 8.8 The composition of the USA population of all herbicide handlers using atrazine in association with corn production in terms of its component subpopulations and the relative number of herbicide handlers in each subpopulation: M/L, mixer/loader; A, applicator

subpopulations with the appropriate frequencies, rather than incorrectly characterizing a population solely in terms of its most-exposed subpopulation or incorrectly characterizing an individual's exposure as the weighted average of exposures from different subpopulations.

Figures 8.9 and 8.10 indicate the distributions of the MOEs in the atrazine handling population involved in corn production and each of its subpopulations for the flowable and water-dispersible-granule formulations, respectively.

CASE STUDY: AGGREGATE EXPOSURE

Monte Carlo techniques allow the distributions of the LADDs for the combined exposure pathways for atrazine or simazine to be appropriately determined. It has been assumed herein that it is appropriate to add the absorbed doses from each route (ingestion, inhalation and dermal) and each pathway (drinking water, diet and herbicide handling) together. Thus, the LADD distribution is the distribution among individuals of the lifetime average of the sum of the individual's daily doses from the different exposure pathways and routes. The individual's lifetime average daily doses from the different pathways and routes are summed, and then the distribution of these sums in a population or subpopulation is determined.

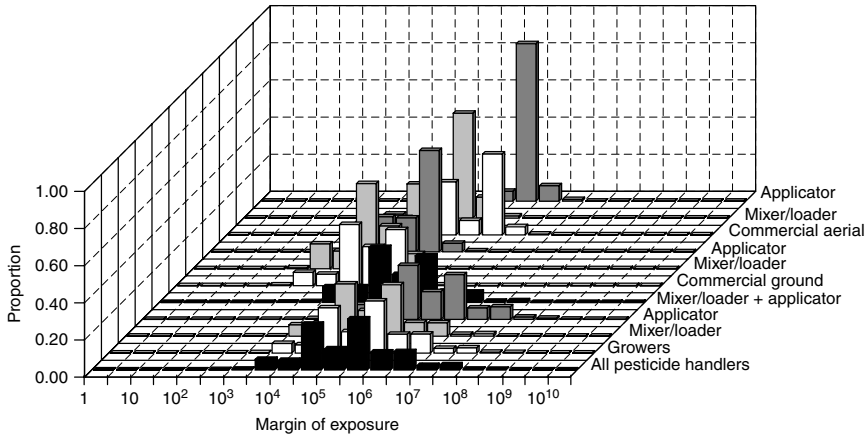

Figure 8.9 Distributions of the margins of exposure for atrazine from herbicide handling with flowable formulations in association with corn production for the entire USA population of such herbicide handlers and its component subpopulations

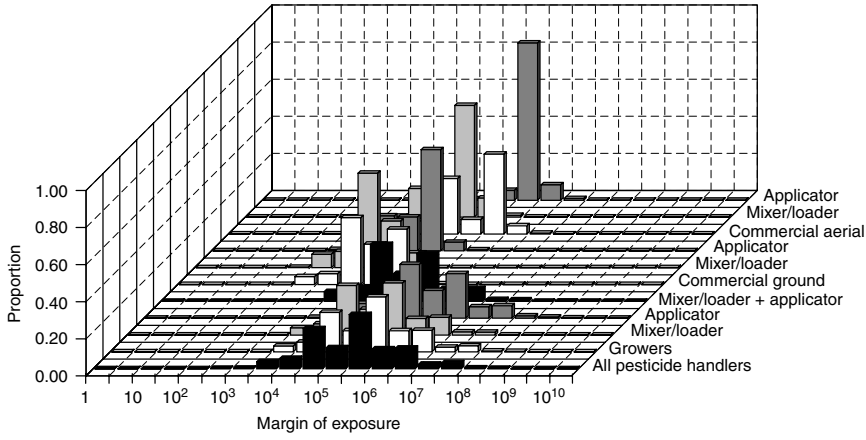

Figure 8.10 Distributions of the margins of exposure for atrazine from herbicide handling with water-dispersible-granule formulations in association with corn production for the entire USA population of such herbicide handlers and its component subpopulations

For example, this approach combines an individual's dose from drinking water ingestion with that same individual's dose from dietary consumption. This avoids combining one person's dose from drinking water ingestion with a different person's dose from dietary consumption. Similarly, the 95th percentile for the combined pathway exposure is not determined by summing the 95th percentiles for the different pathways.

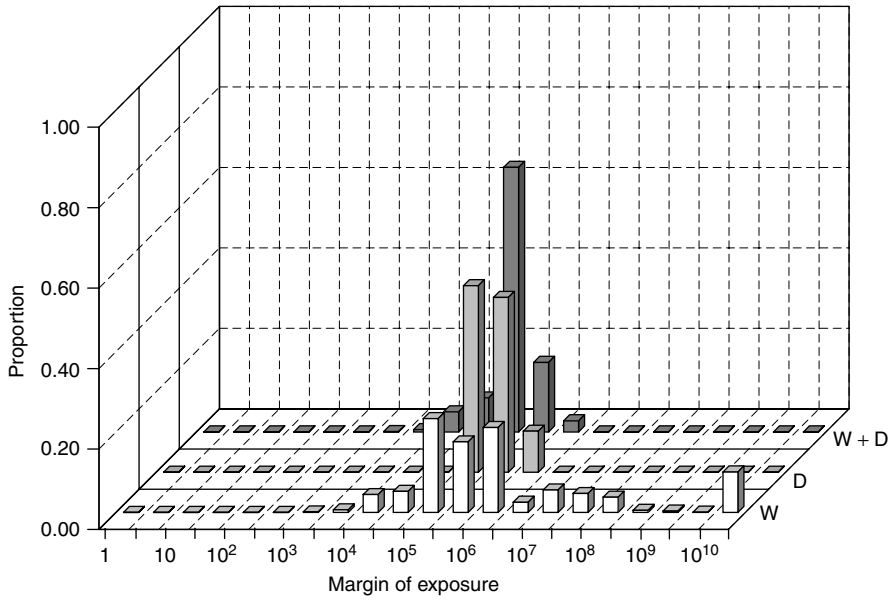

Figure 8.11 Distributions of the margins of exposure for atrazine in the USA from drinking water ingestion (W), dietary consumption (D) and both exposure pathways combined (W + D)

The distributions of the LADDs for atrazine or simazine contain only very small values for water, diet and the combination of water and dietary exposures; hence, the corresponding margins of exposure are quite large even when the water and dietary pathways are combined (Figures 8.11 and 8.12).

The LADD distributions for herbicide handlers contain slightly larger values for flowable formulations than for water-dispersible granules, and both distributions contain considerably larger values than the distributions for water, diet, and the combination of drinking water ingestion and dietary consumption. Finally, the values in the LADD distributions for herbicide handlers are not substantially increased by the addition of drinking water and dietary exposure pathways. Thus, the large MOEs for herbicide handlers remain large even when their doses from drinking water and dietary consumption are added to their doses from herbicide handling (Figures 8.13 and 8.14).

CASE STUDY: CUMULATIVE EXPOSURE

'Margin-of-exposure' distributions for atrazine and simazine combined contain only very large margins of exposure for water, diet, and the combination of water and dietary exposures (Figure 8.15). Distributions for herbicide handlers who apply either atrazine or simazine and who are also exposed to atrazine and

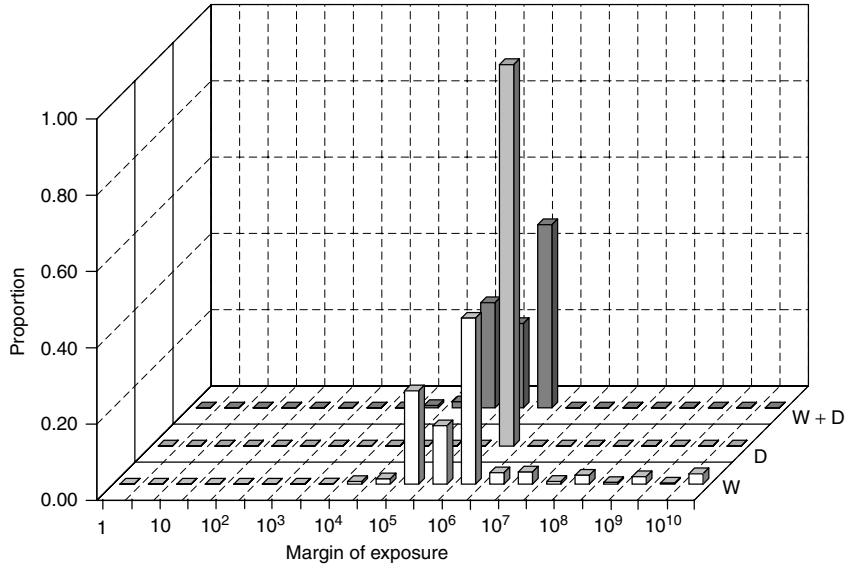

Figure 8.12 Distributions of the margins of exposure for simazine in the USA from drinking water ingestion (W), dietary consumption (D) and both exposure pathways combined (W + D)

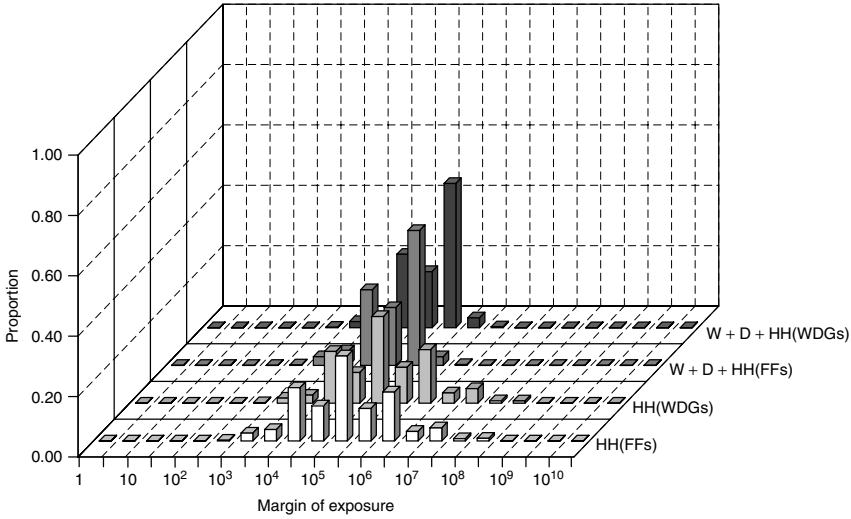

Figure 8.13 Distributions of the margins of exposure for atrazine herbicide handlers involved in corn production in the USA from their use of flowable formulations or water-dispersible granules and from their herbicide handling combined with both drinking water ingestion and dietary consumption: FFs, flowable formulations; WDGs, water-dispersible granules; W, drinking water ingestion; D, dietary consumption; HH, herbicide handler

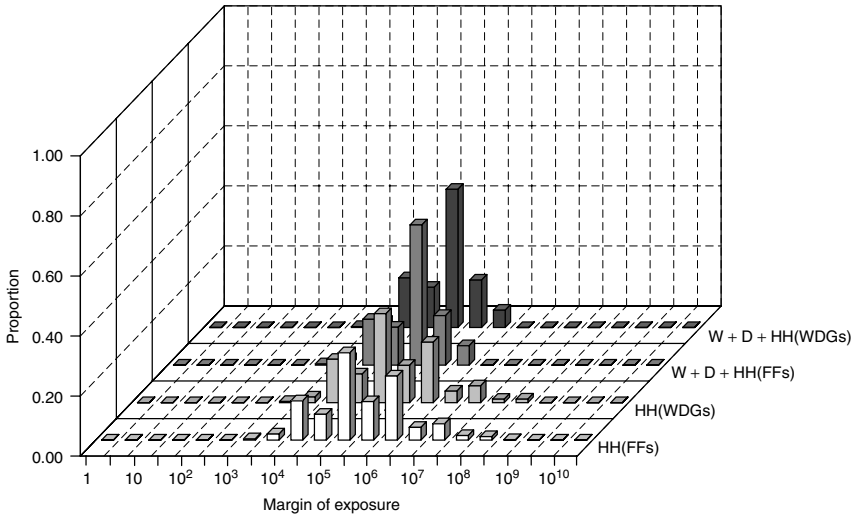

Figure 8.14 Distributions of the margins of exposure for simazine herbicide handlers involved in corn production in the USA from their use of flowable formulations or water-dispersible granules and from their herbicide handling combined with both drinking water ingestion and dietary consumption: FFs, flowable formulations; WDGs, water-dispersible granules; W, drinking water ingestion; D, dietary consumption; HH, herbicide handler

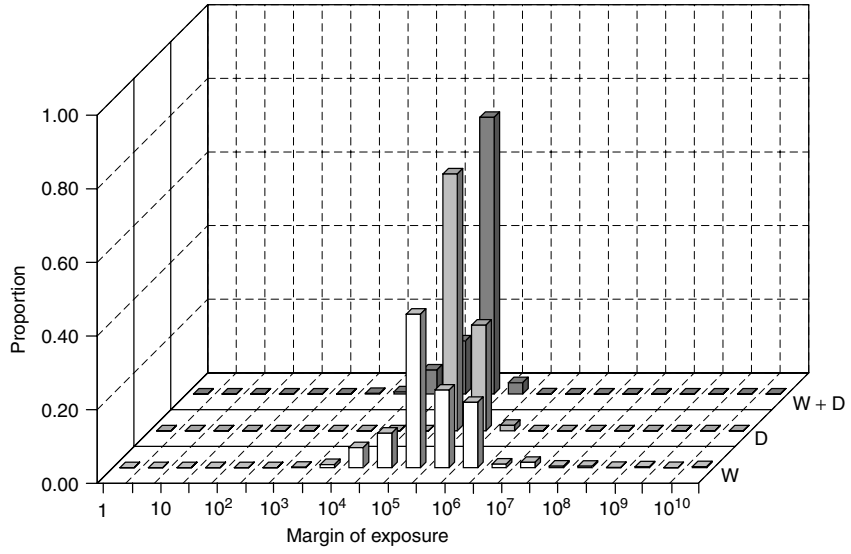

Figure 8.15 Distributions of the margins of exposure in the USA for atrazine and simazine combined from drinking water ingestion (W), dietary consumption (D) and both exposure pathways combined (W + D)

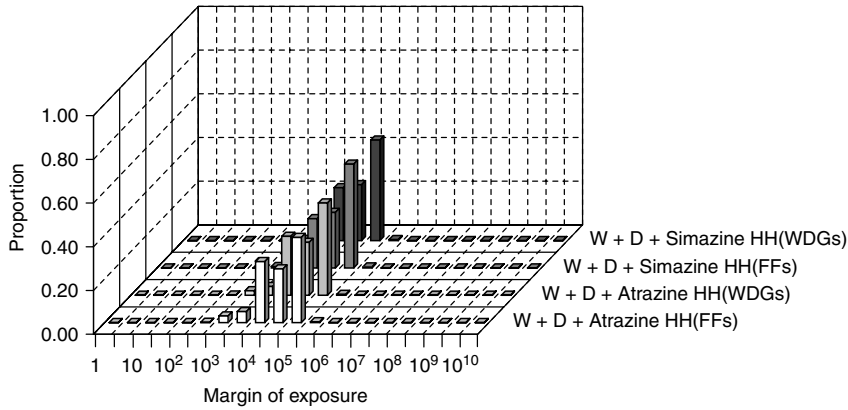

Figure 8.16 Distributions of the margins of exposure for US herbicide handlers who apply either atrazine or simazine and who are also possibly exposed to both atrazine and simazine via the water and dietary pathways: FFs, flowable formulations; WDGs, water-dispersible granules; W, drinking water ingestion; D, dietary consumption; HH, herbicide handler

simazine via the water and dietary pathways are almost the same as the distributions corresponding to the herbicide handling component alone (Figure 8.16). (This is because the effects of atrazine and simazine on weeds are similar, and that herbicide handlers generally use either atrazine or simazine, but *not* both.)

The cumulative margin of exposure (MOE) for atrazine and simazine is calculated by using the following equation:

$$\mathrm{MOE}_{\text{Atrazine and Simazine}} = 1/[(1/\mathrm{MOE}_{\text{Atrazine}}) + (1/\mathrm{MOE}_{\text{Simazine}})] \tag{8.4}$$

Because Equation (8.4) is mathematically equivalent to either of the following equations:

$$\mathrm{MOE}_{\text{Atrazine and Simazine}} = \mathrm{ED}_{10,\text{Atrazine}}/[1 \times (\mathrm{Dose}_{\text{Atrazine}}) + (\mathrm{ED}_{10,\text{Atrazine}}/\mathrm{ED}_{10,\text{Simazine}}) \times (\mathrm{Dose}_{\text{Simazine}})] \tag{8.5}$$

or:

$$\mathrm{MOE}_{\text{Atrazine and Simazine}} = \mathrm{ED}_{10,\text{Simazine}}/[(\mathrm{ED}_{10,\text{Simazine}}/\mathrm{ED}_{10,\text{Atrazine}}) \times (\mathrm{Dose}_{\text{Atrazine}}) + 1 \times (\mathrm{Dose}_{\text{Simazine}})] \tag{8.6}$$

the formula for $\mathrm{MOE}_{\text{Atrazine and Simazine}}$ in Equation (8.4) is of the proper form, namely, a benchmark dose corresponding to a known amount of toxicity divided by a cumulative dose from exposure which reflects the relative toxicity of the

cumulated chemicals. For example, in Equation (8.5) the multiplier of the dose due to simazine exposure ($\text{Dose}_{\text{Simazine}}$) is the toxic equivalency factor:

$$(\text{ED}_{10,\text{Atrazine}}/\text{ED}_{10,\text{Simazine}}) = (1.4\,\text{mg/kg/d}/2.6\ \text{mg/kg/d}) = 0.5385$$

which implies that a dose from simazine is only approximately half as toxic as the same dose from atrazine.

These equations are appropriate for atrazine and simazine because these herbicides appear to have a common mechanism of action and the toxicological endpoints for the ED_{10}s are the same. The toxicological endpoint is the incidence of mammary tumors in female Sprague–Dawley rats in similar experiments. The common mechanism of action appears to be an accelerated suppression of the luteinizing hormone surge leading to increased days in estrous. Thus, both the toxicological endpoint and the mechanism of action are very specific.

In addition, these equations do make the implicit assumption that the atrazine and simazine doses are additive and that the relative impacts of atrazine and simazine at low doses is the same as it is at the ED_{10}s. That is, whatever the shapes of the dose–response relationships are for atrazine and simazine in the low-dose region, a low dose from simazine has only approximately half the impact as the same dose from atrazine.

CASE STUDY: CONCLUSION

The conclusion in the case study is that neither occupational exposure nor environmental exposure to atrazine and simazine is likely to produce adverse health consequences in the United States population. This conclusion is based on a quantitative risk assessment which estimated that human intakes of atrazine and simazine are much smaller than the intakes required to produce adverse health effects in animal experiments.

In the human health risk assessments in this case study, the margin of exposure (MOE) is defined as the amount of a substance required to produce adverse health effects in animal experiments, divided by the amount that a human receives. The larger the MOE, then the lower the risk from exposure. The MOEs for atrazine and simazine are very large for both cancer and noncancer effects and suggest an ample margin of safety (Tables 8.1 and 8.2).

At the time this analysis was carried out, there was some debate as to whether atrazine and simazine should be considered to be carcinogens. It has been concluded that since the cancer rate was increased at only one site in one strain of rat, but not in other rat strains or mice, that they are *not* carcinogens. However, this analysis shows how a positive carcinogen could be handled. The MOEs reported herein are based on a lower bound on the lifetime average daily intake that produced an increase of 0.10 in the cancer probability in the most sensitive tissue in the most sensitive animal species and sex.

Table 8.1 Margin-of-exposure assessment for US herbicide handlers using flowable or water-dispersible-granule formulations of atrazine or simazine and including drinking water and dietary exposures to atrazine and simazine combined[a]

Herbicide and use	Distribution of margin of exposure			
	Flowable		Granular	
	50th percentile	5th percentile	50th percentile	5th percentile
Atrazine formulations				
Residential lawn care	44 000	5 000	44 000	5 000
Sorghum	68 000	8 000	71 000	8 000
Corn	76 000	7 000	83 000	8 000
Sod	21 000	4 000	25 000	5 000
Vegetation management	48 000	3 000	51 000	4 000
Hawaiian sugar cane	10 000	970	11 000	1 200
North American sugar cane	5 000	530	5 000	650
Simazine formulations				
Corn	96 000	11 000	92 000	12 000
Sod	33 000	6 000	39 000	8 000

[a]Lower bounds on atrazine $ED_{10} = 1.4$ mg/kg/d and simazine $ED_{10} = 2.6$ mg/kg/d.

Table 8.2 Margin-of-exposure assessment for atrazine and simazine from water and diet separately and combined[a]

Herbicide	Distribution of margin of exposure		
	50th percentile	25th percentile	5th percentile
Atrazine			
Water[b]	980 000	240 000	48 000
Diet[c]	520 000	410 000	320 000
Water and diet[b, c]	320 000	170 000	44 000
Simazine			
Water[b]	1 800 000	450 000	180 000
Diet[c]	2 000 000	2 000 000	2 000 000
Water and diet[b, c]	980 000	370 000	170 000
Atrazine/simazine combined[d]			
Water[b]	380 000	150 000	38 000
Diet[c]	420 000	350 000	280 000
Water and diet[b, c]	190 000	110 000	34 000

[a]Lower bounds on atrazine $ED_{10} = 1.4$ mg/kg/d and simazine $ED_{10} = 2.6$ mg/kg/d.
[b]Using concentration data for the combination of 18 'major-use' states.
[c]Dietary consumption on a national basis.
[d]Margin of Exposure $= 1/[(1/MOE_{Atrazine}) + (1/MOE_{Simazine})] = 1/[(\text{Total Atrazine Dose/Atrazine } ED_{10}) + (\text{Total Simazine Dose/Simazine } ED_{10})]$.

Probabilistic techniques (including Monte Carlo methods) are used to incorporate the variation in individual human exposures and resulting intakes. The frequency distribution of individual intakes and MOEs in a population are estimated

from the number of individuals in each of the population's component subpopulations and their corresponding intake distributions.

Distributions of the MOEs have been presented for individual exposure pathways (drinking water ingestion, dietary consumption and herbicide handling), for the combined exposure pathways, and for atrazine and simazine, both separately and combined.

Even when an individual's atrazine and simazine intakes from drinking water ingestion (water) and food consumption (diet) are combined, 95 % of the MOEs exceeded 30 000. The minimum acceptable MOE for human environmental exposure to noncarcinogens is usually in the range between 100 and 1000; thus, MOEs in excess of 30 000 provide an ample safety margin. For atrazine and simazine combined, 95 % of the MOEs are in excess of 38 000 for water alone and in excess of 280 000 for diet alone.

The MOEs are also calculated for herbicide handlers by using atrazine in conjunction with crop production (corn, sorghum, sugar cane or sod), vegetation management or residential lawn care and for herbicide handlers using simazine in crop production (corn or sod) and both flowable and granular herbicide formulations. These MOEs included the combined atrazine and simazine intakes from occupational exposure, water and diet. These MOEs exceeded 3000 in at least 95 % of the calculations for each use except sugar cane, where nevertheless the MOE exceeded 500. In comparison to a minimum acceptable MOE for occupational exposure in the USA (generally, 100), the calculated MOEs (including both occupational and environmental exposures) for atrazine and simazine provide an ample safety margin.

The MOEs for each herbicide use are calculated not only for the population of all such herbicide handlers, but also for several subpopulations (growers, commercial operators, mixer/loaders, applicators, etc.). The calculation of the frequency distribution of triazine herbicide intake from herbicide handling included data on the size of the different herbicide handler subpopulations, the frequency distribution of pounds of herbicide (active ingredient) applied, the frequency distribution of the amount of exposure inside normal clothing per pound of active ingredient applied (for each body part, herbicide formulation, method of mixing/loading and method of application) and the frequency distribution of adult body weight.

The MOEs for water are calculated for each 'major-use' state and all 'major-use' states combined. The calculation of the frequency distribution of triazine herbicide intake from water included the number of people using each community water supply system in each 'major-use' state and the corresponding concentrations of the herbicide in the drinking water in these community water supply systems in each of the four seasons.

The MOEs for diet are calculated for different regions and for all regions combined. The calculation of the frequency distribution of herbicide intake from diet included all food potentially exposed to the herbicide, the average amount of each of these foods consumed per day in a lifetime, and the frequency distribution

of the residue concentration (triazine herbicide and chloro-metabolites) in each of these foods.

Probabilistic techniques and distributions are used in the triazine quantitative risk assessment to incorporate more of the available data and to more accurately reflect the variability associated with the components of the risk assessment (e.g. drinking water concentrations, food residue concentrations, and herbicide handling exposures associated with different user subpopulations, crops, herbicide formulations and techniques of mixing/loading and application). Specifically, these probabilistic techniques allow the variables in the exposure equations to be described in terms of databased distributions reflecting the relative likelihood of the different possible variable values rather than restricting the characterization of these variables to a single summary value. Furthermore, Monte Carlo techniques make it possible to more realistically combine exposures from multiple exposure pathways, multiple chemicals and multiple subpopulations, without having to assume the 'worst-case' for each component. Thus, probabilistic techniques, including Monte Carlo simulation, help the risk assessor avoid the pitfalls of compounding multiple conservatisms and decrease the exaggeration of the magnitude of exposure and risk in human health risk assessments. Probabilistic techniques also facilitate risk characterizations that reflect and explicitly quantify the relative likelihood of different risk values in the overall population, as well as its component subpopulations. These Monte-Carlo-based distributional characterizations of risk provide greater information to risk managers than single-number summaries or bounds and, hence, should lead to better risk management decisions.

BENEFITS OF USING PROBABILISTIC TECHNIQUES INSTEAD OF DEFAULT CONSTANTS

Risk assessments conducted by many federal and state agencies have generally relied on the use of 'default' constants (i.e. the use of a single value for an unknown or uncertain component of the risk assessment). Each of these single values is generally selected to fulfil the goal of being 'health-protective', that is, selected to be reasonably certain that risk is not underestimated and to err on the side of overestimating the risk. The use of these default constants has several shortcomings that can be largely overcome by having good quality exposure data and using probability distributions and probabilistic techniques.

In contrast to the use of a single (default) value for a risk parameter, a probability distribution can reflect the relative likelihood of the different possible values of the parameter. Thus, a probability distribution can reflect not only the largest and smallest possible values of a parameter but also the probability of the occurrence of each of the values in its range.

If conservative default constants are used for each of several different parameters in the risk assessment, then the conservatism in the individual components is compounded when the components are combined in the risk characterization. Furthermore, the extent of the overestimation cannot be readily quantified, and thus

the magnitude of the overestimation of the average risk is not identified. However, distributional techniques make it possible to more realistically combine exposures from multiple years, subpopulations, exposure pathways and chemicals without having to assume the 'worst-case' for each component. By carrying all of the information on each component of the risk assessment through to the end of the entire risk characterization instead of requiring interim single-number characterizations at different stages in the risk assessment, probabilistic techniques help avoid the compounding of multiple conservatisms.

An estimated lower bound on the margin of exposure obtained by combining default constants provides no indication of the relative likelihood or frequency of that MOE or any other MOE greater than the exaggerated lower bound. On the other hand, the characterization of the MOE obtained by using probability distributions and probabilistic techniques provides a quantitative assessment of the relative likelihood of each of the different possible values for the MOE.

Furthermore, default constants and assumptions do not explicitly address the uncertainty and variability that are an inherent part of human risk; however, probability distributions can explicitly include both uncertainty and variability.

Finally, probability distribution characterizations can describe the entire population (all of the people in the exposed population) rather than a single hypothetical person or subpopulation.

PROBABILISTIC EXPOSURE CHARACTERIZATION

The chronic exposure assessment in the case study illustrates some of the important features of the probabilistic approach to aggregate and cumulative assessments. Specifically, it quantified the probability distribution of the dose from exposure and the margin of exposure for the individuals in the population. The dose that individuals in a population receive as a result of their exposure has a probability distribution resulting from both variability (e.g. the dose changes from individual to individual in the population) and uncertainty (e.g. an individual's dose is not known exactly or cannot be calculated or measured without the possibility of error). This probability distribution indicates the frequency or relative likelihood of each specific value of the dose in the population. The distribution of the dose in a population is frequently calculated by combining the distributions for subpopulations of individuals (e.g. infants, children and adults, or people living in the North East, Mid-West, South and West, or homeowners and nonhomeowners). The fundamental building block for both subpopulation and population dose distributions is the individual.

It is especially important to capture the temporal aspect of the exposures (e.g. which chemical and route-specific exposures occur together on the same day or in the same time-period). Therefore, an individual's exposure is characterized by a set of chemical and route-specific profiles. A profile is a sequence (time-series) of dose values with each value corresponding to a day (or other period) in a specified time-period. For example, CARES usually generates 365-day profiles

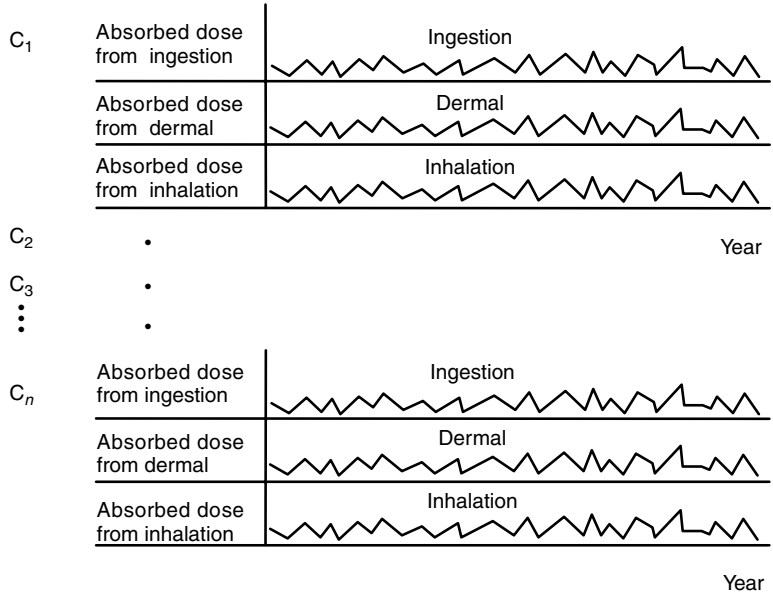

Figure 8.17 An example of the set of chemical- and route-specific dose profiles over a year for an individual

(one profile for each chemical and route). Figure 8.17 indicates an example of an individual's set of chemical and route-specific dose profiles. These profiles are scaled to profiles of toxic equivalent doses (TEDs) by using chemical and route-specific toxic equivalence factors (TEFs). The profiles of TEDs are combined across chemicals and routes to calculate a profile of the individual's Total TED (that is, a profile of the individual's dose from exposure). Profiles of individual doses from exposure are combined to yield probability distributions of acute, short-term and intermediate-term doses (TEDs).

For each individual and each chemical, the route-specific dose profiles are calculated by combining the doses from the different possible sources (food, water and non-dietary) (Figure 8.18). Only the doses occurring at the same time are combined. The dose profiles for the different sources depend on the individual's behavior over time.

An individual may have non-dietary exposure from multiple pesticide uses at different times of the year (Figure 8.19). A use may involve one or more chemicals, applicator exposure and post-application exposures on several days. The temporal occurrence of use events, the algorithms for calculating the time-dependent dose given that a use has occurred, and the individual's behavior generate chemical and route-specific dose profiles. These profiles are combined over the different uses to produce the chemical and route-specific dose profiles over time for the non-dietary sources.

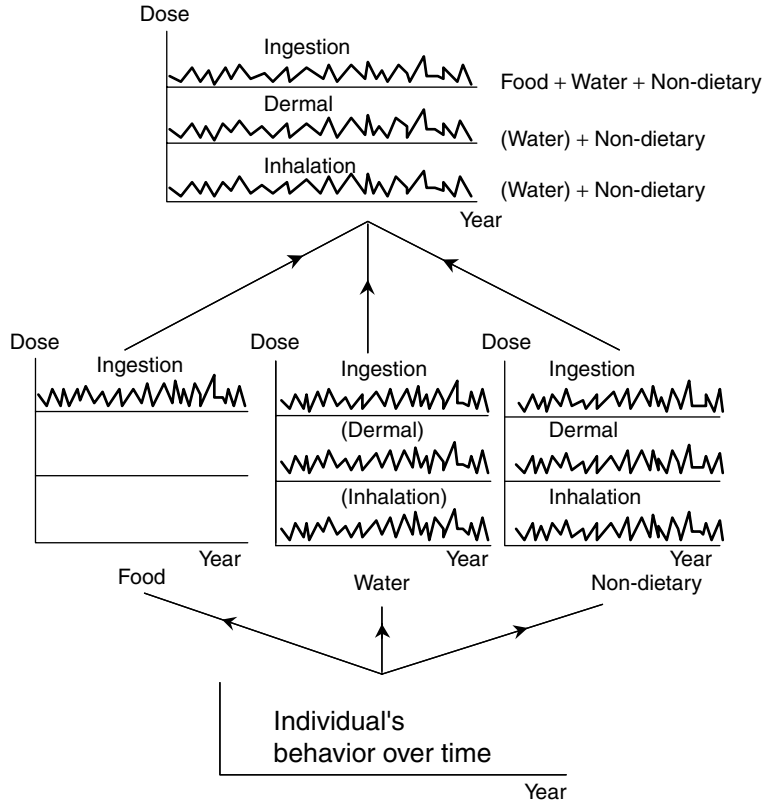

Figure 8.18 An example of the chemical-specific combination of route-specific dose profiles over a year from different sources for an individual

The calculation of an individual's chemical and route-specific dose profiles from water reflects the available information on the temporal pattern of the simultaneous concentrations of the chemicals in the individual's water as well as the individual's consumption or other uses of the water. The available temporal data may be only seasonal or longer-term average concentrations.

For food, the individual's chemical and route-specific dose profiles reflect the available information on the individual's food consumption and the residues on the food when it is consumed.

POPULATIONS OF INDIVIDUALS

Individuals are the building blocks for probabilistic characterizations of populations and subpopulations.

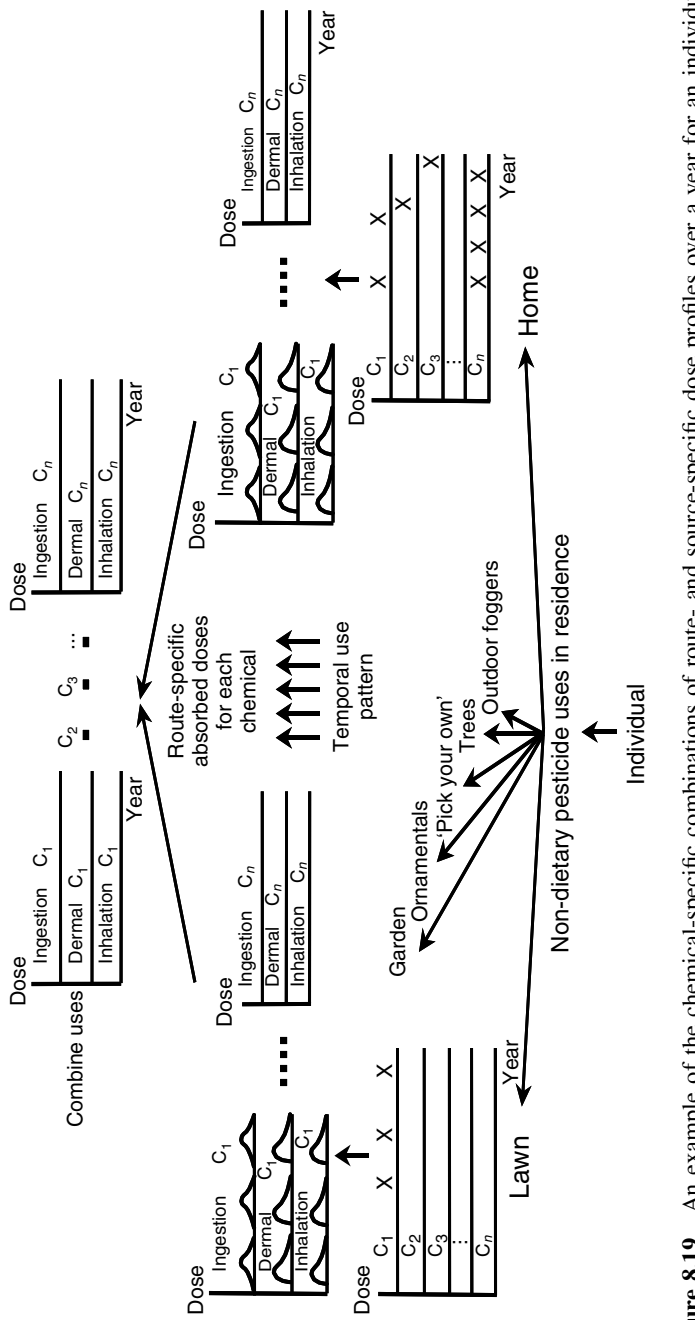

Figure 8.19 An example of the chemical-specific combinations of route- and source-specific dose profiles over a year for an individual

In the case study, the individuals are randomly generated from the distributions of their characteristics. The population of interest is the United States of America. Individuals are randomly assigned to a state, community water supply system, herbicide handling activity, etc. on the basis of the relative size of these subpopulations. The distribution of doses for these randomly generated individuals estimates the population distribution.

Another approach is to create a 'reference population' by randomly sampling individuals from a specified population. The dose from exposure is calculated for each person in the reference population, and the distribution of these doses estimates the population distribution. For example, CARES has created a reference population of 100 000 individuals from the US population. A stratified random sample based on the 1990 US Census has been used to sample real people of all ages, races, states, etc. A significant advantage of the reference-population approach is that, when an individual's dose from exposure is being calculated, the individual's characteristics (age, gender, type of residence, etc.) are known and can be used in the calculation. Furthermore, the joint distribution of the characteristics of these individuals is directly available in the census data, as opposed to having to assume that these characteristics are independent or that their joint distribution can be approximated in some simplistic way. Reference populations also facilitate comparisons between different exposure situations. Because the same reference population is used for all exposure situations, differences between distributions of dose and/or margins of exposure are due to the differences in the chemicals, exposure scenarios, etc. in the different situations and are not confounded by the differences in the individuals used in the analyses.

CONCLUSIONS AND RECOMMENDATIONS

This chapter illustrates probabilistic approaches to residential and occupational exposure assessment and their incorporation into aggregate and cumulative assessments of exposure, dose and risk.

Probabilistic risk assessment methods are described herein for determining a population's distribution of the dose from exposure and the combination of that exposure characterization with appropriate toxicological information to form aggregate and cumulative risk assessments. An individual's dose from exposure is characterized as a set of chemical- and route-specific dose profiles over time. Toxic equivalence factors (TEFs) that reflect the toxic endpoint and exposure duration of concern are used to scale chemical- and route-specific doses to toxic equivalent doses (TEDs). The latter are combined in a temporally consistent manner to form a profile over time of the Total TED. For each individual, a Total MOE is calculated by dividing a toxicologically relevant benchmark dose (e.g. an ED_{10}) by the individual's Total TED. The distribution of the Total MOE in a population provides important information for risk management decisions.

Exposure characterization is improved by the following factors:

- using the individual as the building block for calculating doses and for developing subpopulation and population characterizations;
- using calendar-based dose profiles whenever appropriate and possible;
- only combining doses across sources and uses in a temporally consistent manner;
- calculating the individual's dose from exposure for each chemical and route prior to combining doses in a risk characterization;
- using toxic equivalence factors to scale chemical- and route-specific doses into toxic equivalent doses;
- calculating a margin of exposure (Total MOE) by dividing a toxicologically relevant benchmark dose by the total toxic equivalent dose (TED);
- using probabilistic characterizations as opposed to deterministic default characteristics.

The conclusion of this chapter is that probabilistic approaches can be incorporated into source-specific exposure assessments as well as aggregate and cumulative assessments of exposure, dose and risk. The methodology exists now but is continuing to evolve.

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9 Dermal Absorption of Pesticides

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INTRODUCTION

The dermal route is the primary route of exposure for most pesticides both occupationally (Wolfe, 1976; Benford *et al*., 1999) and in residential settings (Ross *et al*., 1992). Despite the relatively high dermal exposure in occupational settings, regulation of pesticides, both in Europe and North America, has been more concerned in the past about the oral route of exposure (EEC, 1991; USEPA, 1993; EC, 1994). As a consequence, studies requested for registration purposes emphasized the oral route and low-level daily exposure (Krieger and Ross, 1993). This has changed over the past several years and since systemic toxicity is dependent on the internal dose (or more precisely, internal concentration profile) some means is required to relate the estimates of occupational dermal exposure to the No Observed Adverse Effect Level (NOAEL) in toxicity studies conducted via the oral route. This explains why in the United States, Canada and Europe dermal absorption studies are requested as part of the pesticide regulatory process (EEC, 1991; USEPA, 1993; EC, 1994).

Dermal absorption, the process by which a substance is transported across the skin and taken up into the living tissue of the body (USEPA, 1992), is a complex process. The skin is a multilayered biomembrane with particular absorption characteristics. It is a dynamic, living tissue and as such its absorption parameters are susceptible to constant changes. Upon contact with the skin, a portion of the substance can penetrate into the non-viable *stratum corneum* and may subsequently reach the viable epidermis, the dermis and, ultimately, the vascular network. During the absorption process, the compound may be subject to biotransformation (Noonan and Wester, 1989). The *stratum corneum* provides the skin its greatest barrier function against hydrophilic compounds, whereas the viable epidermis is most resistant to highly lipophilic compounds (Flynn, 1985).

Dermal absorption is influenced by several factors, e.g. the physico-chemical properties of the substance, vehicle, occlusion, concentration, exposure pattern and skin site of the body (ECETOC, 1993; Howes *et al*., 1996; Schaefer and Redelmeier, 1996). Despite the fact that guidance exists for the conduct of dermal absorption studies (USEPA, 1998, 2004; OECD, 2004a,b,c), there continues to be discussion on some experimental details. In order to harmonize the use of dermal absorption data in human risk assessment within the EU, a guidance document was prepared by the Commission (EC, 2002).

This present chapter focuses on some critical aspects influencing dermal absorption. This is followed by an overview of existing dermal absorption methodologies, including a discussion regarding the validation of these model systems. Some toxicokinetic considerations regarding the use of percentage of absorption in present risk assessment are presented. Finally, some considerations for improvement of dermal risk assessment, with special attention to dermal kinetic aspects, are provided.

FACTORS INFLUENCING DERMAL ABSORPTION

Skin absorption of pesticides is generally tested in studies according to methodologies described by international organizations (ECETOC, 1993; Howes *et al*., 1996; USEPA, 1998, 2004; SCCNFP, 2003; OECD 2004a,b,c). These documents provide a certain amount of standardization and thereby improve the comparison of data between studies. However, these guidelines only give a general description of the experimental design. Since many factors can influence the actual absorption of pesticides in field conditions as well as in experimental settings, a proper study protocol or guidance document (be it *in vivo* or *in vitro*) should take these into account.

Many factors have been shown to influence the dermal absorption of compounds (ECETOC, 1993; Howes *et al*., 1996; Schaefer and Redelmeier, 1996). Here, we evaluate the most important factors affecting the outcome of an *in vivo* or *in vitro* study for dermal absorption testing of pesticides.

FACTORS RELATED TO THE SKIN

Intraspecies Differences

In general, rat skin has been proven more permeable than human skin (ECETOC, 1993). This is likely to be caused by the different structure of the skin in both species (e.g. number of appendages, intercellular lipid composition of the *stratum corneum* and corneocyte surface area). It should be noted, however, that some cases have been reported where rat skin was found to be less permeable than human skin (Hotchkiss *et al*., 1992). Since the availability of human skin is limited, pig skin is often used. Because of its similar morphology and barrier function (Bronaugh *et al*., 1982), pig skin is often considered a good alternative to human skin.

Inter-individual Differences

Considerable differences in barrier function between human individuals have been reported. *In vivo* studies are often performed with inbred animal strains, thereby reducing the inter-individual differences. Studies with human volunteers, as well as *in vitro* studies, offer the possibility to include skin from various donors.

Skin Condition

The skin barrier can be severely impaired by diseases or mechanical damage. In general, this leads to an increased uptake of compounds via the skin (Wilhelm *et al*., 1991). Although it may be very well possible that pesticides come into

contact with damaged skin when used in the field, *in vivo* or *in vitro* studies are normally performed with healthy animals and preparations of healthy skin.

Anatomical Site

In animal studies, the test compound is most often applied to the dorsal skin, while in most *in vitro* studies human skin from the breast or abdomen is used. Workers are, however, mostly exposed to pesticides on their face, hands and arms. It is therefore important to realize that substantial regional differences exist with respect to dermal absorption (Maibach *et al*., 1971; Wester and Maibach, 1989; ECETOC, 1993). The most relevant regions are not easily examined in *in vivo* animal studies and human skin from these body areas is very rarely available for *in vitro* studies.

Skin Metabolism

It is commonly known that the skin contains a large range of enzymes capable of metabolizing topically applied compounds. For pesticides, esterase activity is among the most important (van de Sandt *et al*., 1993; Hewitt *et al*., 2000). Although the stratum corneum is generally accepted as the most important barrier in skin absorption, there are some indications that skin metabolism in other skin layers influences the percutaneous absorption of compounds (Potts *et al*., 1989). The interrelation between metabolism and absorption rate, however, has not been unequivocally established.

FACTORS RELATED TO THE EXPOSURE CONDITIONS

Dose

In general, several doses are tested that span the range of doses that can be expected to occur in field exposure conditions, within one person (distribution of the body) and within one use of a product (mixing, loading, re-entry and bystander exposure). In general, the percentage absorption decreases with increasing dose. Saturation of the absorption process may occur at higher doses (Zendzian, 2000; van Ravenzwaay and Leibold, 2004).

Formulation or Vehicle

Many of the formulations for plant protection are designed to help the active substance to penetrate the cuticle of plant leaves or insects. It is therefore not surprising that these formulations sometimes enhance the skin absorption in humans. To account for this in Europe, EC Directive 91/414 for pesticides requires testing of both the active substance and the formulated product (EEC, 1991). The United States Environmental Protection Agency (USEPA) requires that the vehicle system duplicates that used in the field (USEPA, 1998). Since many pesticides are

poorly soluble in water, acetone or ethanol are often used as vehicles for testing the pure active substance. Since the solvents can impair the barrier properties of the skin, the volume should best be kept minimal. For the testing of formulations, care must be given to the homogeneity of the formulation, especially when these are spiked with radiolabeled active substance.

Occlusion

Although percutaneous absorption of compounds can be clearly increased under occlusive conditions (Meuling *et al*., 1991; van de Sandt *et al*., 2000), it has been demonstrated that this is not always the case (Bucks *et al*., 1989). It should be noted that animal studies cannot be performed completely non-occlusively since a (gas-permeable) cover is necessary to protect the application site from coming into contact with the cage and to prevent animals from grooming. Moreover, in certain cases (semi)occlusion will be more representative for occupational exposure (e.g. exposure underneath clothing and protective gloves).

Temperature and Humidity

It is recognized that increased temperature of the skin may increase dermal absorption. Similarly, a high relative humidity has been associated with increased dermal absorption (Schaefer and Redelmeier, 1996).

Exposure Time

Studies should be tailored to the exposure scenario of concern and thus be performed in line with the use of the pesticide in the field. Therefore, the study needs to be designed to cover the expected duration and amount of exposure to a pesticide having a wide variety of uses. Generally, a 6–10-h exposure is considered a relevant ('worst-case') exposure duration for occupational settings, and this exposure time is therefore often used in dermal absorption studies. It should be realized, however, that many activities, such as mixing and loading, are generally performed within a much shorter time-span. On the other hand, poor personal hygiene practices may lead to a prolonged exposure time.

Duration of Sample Collection Time

It should be noted that dermal absorption generally continues after cessation of actual exposure. *In vivo* absorption should therefore preferably be assessed by repeated and continued sampling after cessation of the exposure until the test compound and/or its metabolites are no longer detectable in excreta in two serial samples (EC, 2002) or 10 urinary excretion 'half-lives' have passed (Thongsinthusak *et al*., 1999). *In vitro* studies may also be continued until a

plateau phase has been reached, but decreasing skin membrane quality generally prohibits studies longer than 48 h.

In addition to *in vivo* and *in vitro* experimentation, mathematical models and quantitative structure–permeability relationship (QSAR) methods have been used to predict skin absorption in humans. These models use the physico-chemical properties of the test compound (e.g. volatility, ionization, molecular weight, water/lipid partition, etc.) to predict skin absorption in humans (Moss *et al*., 2002). The models are particularly attractive because of the low cost and rapidity. However, because of the above-mentioned factors influencing dermal absorption, mathematical models are of limited use for risk assessment purposes. Since these models are currently not accepted by regulatory agencies involved in pesticide evaluations, they will not be further discussed in this chapter.

OVERVIEW OF CURRENT METHODOLOGIES

IN VITRO STUDIES

In vitro skin absorption studies can be performed in a variety of diffusion cell types. All cells consist of a donor and receptor compartment but may differ with respect to surface area, type of material and volume of receptor compartment. Furthermore, both static and 'flow-through' diffusion cells exist. The most well-known static cell is the Franz diffusion cell (Franz, 1975). In the flow-through cells, the receptor fluid is continuously pumped underneath the skin membrane and samples are collected automatically (Moody and Nadeau, 1993; Bronaugh, 1995). Despite the differences between the cell types, it appears that the data obtained are very similar (Bronaugh and Stewart, 1984; Clowes *et al*., 1994). In both static and flow-through cells, adequate removal of the absorbed test compound from the receptor compartment, ensuring 'sink' conditions, is of the utmost importance. This is especially significant when testing lipophilic compounds with low solubility in the receptor fluid.

The choice of receptor fluid can influence the outcome of the study considerably (Ramsey *et al*., 1994; Bronaugh, 1995). In order to avoid underestimation of skin absorption, the test compound should be soluble in the receptor fluid. On the other hand, the receptor fluid should not damage the barrier properties of the skin membrane. Various receptor fluids have been used, including saline (for hydrophilic test substances) and water/ethanol mixtures, or saline supplemented with bovine serum albumin or poly(ethylene glycol) 20 oleyl ether (for testing of lipophilic compounds). When performing studies with metabolically active skin preparations, the receptor fluid should support the viability of the skin. In these cases, a tissue culture medium is normally used.

Human skin membranes are usually prepared from abdominal or breast skin, while for animal skin membranes the commonly used sites are the flank and back (rat) or the flank and ear (pig). Three types of membranes can be prepared: epidermal membranes (thickness of approximately 0.1 mm, prepared by

heat separation, chemical or enzymatic separation), split-thickness skin (thickness of 0.2–0.5 mm prepared by using a dermatome) and full-thickness skin (thickness of 0.5–1.0 mm). Since the main barrier function of the skin is located in the stratum corneum, all three membrane types have been used for absorption studies. A possible disadvantage of full-thickness skin is that lipophilic compounds may be retained in the dermis instead of entering into the receptor fluid. On the other hand, epidermal membranes are more fragile and sometimes overestimate human *in vivo* skin absorption (van de Sandt *et al*., 2000).

To illustrate the differences between skin membrane types, Figure 9.1 shows a series of independent experiments with the lipophilic reference compound testosterone performed in our laboratory. The data demonstrate that epidermal membranes were approximately 3.5 times more permeable than full-thickness skin, based on the percentage of the applied compound reaching the receptor fluid during 24 h. Each experiment was performed with skin from a different donor, and the variation between the *in vitro* experiments was within the same range as reported for human volunteers *in vivo* (Schaefer and Redelmeier, 1996).

In order to check for possible leakage of skin membranes, it is recommended to test the integrity. Measurement of electrical resistance or permeability of tritiated water prior to application of the test compound is the most commonly used method (Lawrence, 1997). For practical reasons, skin is often stored at −20 °C prior to use. It has been reported that the barrier function does not alter when skin is appropriately stored and is not repeatedly thawed (Swarbrick *et al*., 1982).

In addition to the membrane types mentioned above, reconstituted human epidermis has been put forward to be used in skin absorption studies. Because of the limited and irregular availability of human skin for *in vitro* testing purposes and the inter-individual differences between donors, a standardized reconstituted epidermis with proper barrier properties would be of great value. Until now, however, the permeability of reconstituted epidermis has been shown to be far greater than that of normal human epidermis (Doucet *et al*., 1998). Therefore, reconstituted epidermis models are, at this stage of development, not suitable for the estimation of dermal absorption potential.

VALIDATION

No formal international validation study of the *in vitro* methodology has been performed. Importantly, the same applies however to the *in vivo* studies. Despite the publication of several well-conducted comparative studies (Franz, 1975; Yang *et al*., 1986a,b; Grissom *et al*., 1987; Scott and Ramsey, 1987; Hotchkiss *et al*., 1990, 1992; Scott *et al*., 1992; Ramsey *et al*., 1994; Roper *et al*., 1995; Dick *et al*., 1997a,b; Wester *et al*., 1998), the Organization for Economic Co-operation and Development (OECD) concluded in 2000 that evaluation of *in vitro* test methods by means of data available from the public literature is very difficult, because these studies, comparing *in vitro* and *in vivo* test results, contained too many variables (different species, thickness and types of the

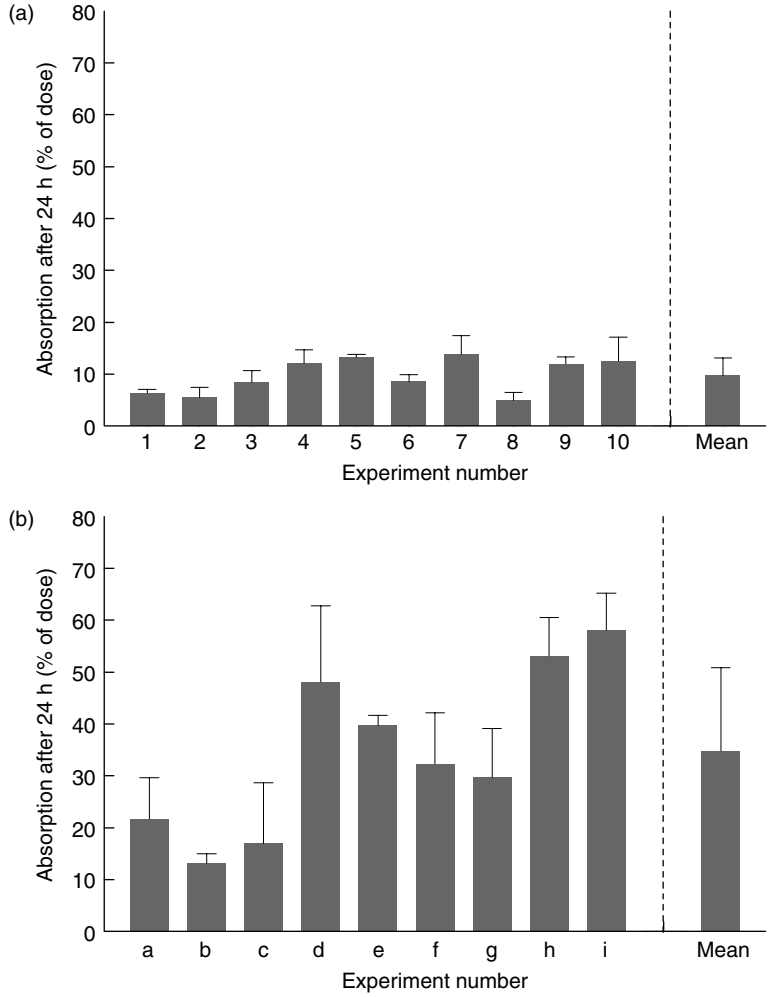

Figure 9.1 *In vitro* absorption of testosterone through (a) human 'full-thickness' skin membranes of approximately 1.00 mm thickness or (b) human epidermal membranes after 24 h exposure. Testosterone was applied at a dose of 15 $\mu g/cm^2$ and each independent experiment was performed with four to six membranes obtained from the abdominal skin of one donor

skin, exposure duration, vehicles, etc.) (OECD, 2000). However, several multi-center studies have been performed, assessing interlaboratory variation of the *in vitro* methodology (Beck *et al*., 1994, 2000; Benech-Kieffer *et al*., 2000), but these studies were limited in their approach with respect to the number of laboratories involved. In order to obtain proper data on the intra- and

interlaboratory reproducibility of the *in vitro* methodology, a European group of ten laboratories carried out a large-scale study, using the three chemicals that are recommended by the OECD as suitable reference compounds for regulatory studies, namely testosterone, caffeine and benzoic acid (van de Sandt *et al*., 2004). The experimental conditions (amount applied, exposure time, vehicle, receptor fluid, preparation of membranes, analysis, etc.) were standardized according to a detailed protocol that adopted many of the principles proposed by the OECD. This study demonstrated that the *in vitro* methodology for assessing skin absorption is relatively robust and that the variation observed may be largely attributed to human variability in dermal absorption and the skin source. In this study and during the OECD evaluation of public literature data, it was noted that an issue of concern in the *in vitro* procedure is the presence of some test substances in the skin membrane, which did not pass into the receptor fluid. By including the amount retained in the skin *in vitro*, at the end of the experiment, a more acceptable (but probably conservative) estimation of skin absorption can be obtained. Alternatively, this issue can be addressed by conducting longer-term experiments. It was noted that it is particularly difficult to examine very lipophilic substances *in vitro*. Water-soluble substances can be tested more accurately *in vitro* because they more readily diffuse into the receptor fluid (OECD, 2004c; van de Sandt *et al*., 2004). The studies on dermal absorption of the relatively hydrophilic pesticide propoxur (van de Sandt *et al*., 2000) and of the lipophilic pesticide *o*-phenylphenol (OPP) (Cnubben *et al*., 2002), were specifically aimed at *in vivo–in vitro* comparisons. For this reason, the *in vivo* and *in vitro* studies were carried out under identical conditions for all test systems. The results obtained indicated that the estimate of potentially absorbed dose *in vitro*, which in this case was obtained by measuring the applied dose minus the washed-off amount, appeared to be an effective estimate for the human *in vivo* situation.

IN VIVO STUDIES IN ANIMALS

In vivo skin absorption studies for risk assessment purposes are most often performed on laboratory rats. While the USEPA (1998) states that the rat is the only acceptable species, the OECD (2004b) mentions that also other animal species can be used when they have been proven to have more similar skin absorption rates to human. An advantage of the rat is that this is the species used in most toxicological and kinetic studies. On the other hand, it is known that data from rat studies generally overestimate human skin absorption (ECETOC, 1993; van de Sandt *et al*., 2000). As indicated before, and to the best of our knowledge, no extensive validation of the rat *in vivo* study has been performed in which reproducibility and the relationship to human skin absorption have been established.

In addition to the generally higher permeability of rat skin to that of human skin, the critical factor which is specific for animal studies is that the dosing site must be protected from grooming behavior (leading to oral intake of the

test compound), or from contact with the cage. This protection not only leads to discomfort of the animals, but also can increase the absorption of the compound due to occlusion of the skin. This may affect the outcome, particularly in those cases where no occlusion is anticipated in practice.

The present OECD and USEPA protocols typically focus on dermal uptake expressed as percentage of dose. In general, no information is provided on the rate of absorption (peak profile or sustained presence) and the metabolites formed, although some guidance on these issues exists (USEPA, 1998). This additional information on the behavior of the test substance could be very useful in (refinement of) the risk assessment. For instance, information on the metabolites formed after dermal exposure could be very helpful in addressing the question as to what extent oral toxicity studies could be used to assess the risk of the dermally exposed population. Information on the rate of absorption could be employed in a similar manner. This latter value can easily be obtained from *in vitro* studies.

STUDIES IN HUMAN VOLUNTEERS

There is no regulatory requirement for performing human volunteer studies addressing the dermal absorption of chemicals. However, the most reliable data for determining absorption through human skin are obtained from *in vivo* human volunteer studies performed under occupationally relevant test conditions (ECETOC, 1993). For technical and ethical reasons, however, the use of human volunteer studies is limited and the conduct of these studies is closely regulated (World Medical Assembly Declaration of Helsinki and ICH guidelines for Good Clinical Practice). The use of radiolabeled compounds for human studies is subject to yet further regulation (ECETOC, 1993). To estimate dermal absorption, the results from the dermal experiment (primarily urine analysis) have to be corrected for the proportion of chemical and/or metabolite(s) excreted in urine after oral or (preferably) intravenous (i.v.) or intramuscular (i.m.) administration. Alternatively, biological monitoring exposure studies with human volunteers may be conducted. In these studies, a good knowledge of the metabolism of the test substance is required.

Thus, despite the value of human volunteer studies, the technical and ethical constraints for studying dermal absorption of pesticides in human volunteers prevail. As a consequence, only limited data on the dermal absorption of chemicals are available from human volunteer studies. This is in contrast to pharmaceutical products, where the use of human volunteers is considered to be the only relevant approach to generate data of precise relevance to man.

DATA ANALYSIS CHALLENGES

As many studies submitted to pesticide regulatory jurisdictions use *in vivo* methodologies, but an increasing number of studies employ *in vitro* techniques, this section addresses data interpretation challenges with both study types. Discussion

is required at the international level to achieve consensus on the most appropriate approach with respect to the issues described below. Achieving a harmonized approach on these technical issues related to evaluation of dermal absorption studies, would facilitate work-sharing and joint-review endeavours.

INCOMPLETE RECOVERY

It is not uncommon for *in vivo* and *in vitro* dermal absorption studies to be compromised by lack of mass balance, e.g. recovery of $< 90\,\%$ of the radiolabel. The OECD Test Guidelines specify that adequate recovery is a mean of $100 \pm 10\,\%$ of the radioactivity, and that recoveries outside this range must be justified (OECD, 2004a,b). The following three approaches exist for addressing incomplete recovery, but there is no harmonized approach:

- Assume all of the missing radiolabel has been absorbed and include it in the calculation of the dermal absorption value. This is a 'worst-case' scenario.
- Normalize the percentage absorbed to reflect a 100 % recovery of the administered dose. This approach assumes a proportional loss of the administered dose across all analyzed moieties and is the approach typically taken with residue studies (e.g. dislodgeable residue studies).
- Assess the quality of the study and if the study is considered 'well-conducted', then use the data as is, and cite incomplete recovery as an uncertainty in the human health risk assessment using this value. This third approach is consistent with how other mammalian kinetic studies (e.g. metabolism studies) are evaluated.

SIGNIFICANT RESIDUES ASSOCIATED WITH PROTECTIVE DEVICE

When significant quantities of residue are associated with the protective device (i.e. cover, spacer, paper or gauze), it is not possible to determine whether the material was available for absorption, that is, was in contact with the skin. If the study is otherwise 'well-conducted' and reported, one approach is to assume that this residue was not available for absorption, and recalculate the applied dose accordingly.

SIGNIFICANT QUANTITY OF RESIDUES REMAINING BOUND TO THE SKIN

When significant quantities of residues remain at the skin site, the conventional approach is to include these residues in the percentage of absorbed dose. For instance, as part of the North American Free Trade Agreement (NAFTA) Technical Working Group on Pesticides, there was agreement that bound skin residues are considered absorbed when the bioavailability of residues cannot be determined (NAFTA, 2000). This approach is considered conservative as it is unlikely that all

skin-bound residues will be systemically absorbed (e.g. portions will be 'sloughed off'). However, the simplistic approach of including skin-bound residues in the estimate of dermal absorption can have repercussions on the risk assessment. As such, data analysis possibilities need to be considered. The fate of skin-bound residues has been examined in the literature from three different perspectives: (i) an examination of the excretion kinetics from a sufficiently rigorous *in vivo* study, (ii) skin stripping, and (iii) consideration of the physico-chemical properties of the test material.

First, a determination regarding the quantity of compound that remains bound to the skin can be based on the excretion curve – a decline of radioactivity in the excreta at the end of the study indicates that the dosed skin site may not become (completely) systemically available (Thongsinthusak *et al*., 1999). These authors validated this approach by comparing results with outcomes from studies where pesticides (twelve cases) were administered to humans. This approach provides a refined estimate of the percentage absorbed as skin-bound residues are not automatically included in the percentage absorbed; rather, the estimate is derived by extrapolating the excretion curve to the point of complete excretion. The authors used dermal absorption studies conducted in animals with five pesticides to demonstrate the utility of the model. Table 9.1 shows dermal absorption data calculated in two ways: (a) sum of % dose recovered from cage wash/cage wipe, carcass, feces, urine, 'bound' skin residues, blood and expired air, and (b) sum of % dose recovered from cage wash/cage wipe, carcass, blood, expired air and maximum excretion, as determined from the exponential saturation model. From Table 9.1, it is apparent that use of the exponential saturation model can provide refined estimates of dermal absorption. This model will not always be applicable because if excretion has not tapered off, the amount retained in the application site skin may eventually become systemically available. In such instances, the potentially absorbed dose (the amount systemically available plus the amount in the application site skin), either expressed as percentage dose or in absolute amounts, should be used as a value for dermal absorption, unless additional kinetic information demonstrates that this is a clear overestimate.

Secondly, it has been proposed that tape stripping is useful in characterizing the fate of skin-bound residues (Trebilcock *et al*., 1994). The OECD (2004a,b) discusses skin fractionation to further define the localization of the test chemical within the skin. Specifically, the OECD notes that tape stripping can be used to remove *stratum corneum* from skin (e.g. 15–25 strips of human skin); this method would normally be regarded as semiquantitative, but can be adequate to give a good indication of test chemical distribution, and hence its immediate bioavailability. Insufficient investigation into the role of tape stripping in characterizing the fate of skin-bound residues has taken place to date to provide a method to refine the estimates of dermal absorption. In fact, inappropriate timing of tape stripping (e.g. after skin wash, as opposed to at termination) can compromise, and complicate interpretation of *in vivo* dermal absorption studies.

Table 9.1 Comparison of the percentage of dermal absorption – with and without direct addition of 'bound' skin residues (from Thongsinthusak *et al*., 1999). Reprinted from *Reg. Toxicol. Pharmacol.*, **29**, T. Thongsinthusak, J.H. Ross, S.G. Saiz and R.I. Krieger, 'Estimation of dermal absorption using the exponential saturation model', pp. 37–43, Copyright (1999), with permission from Elsevier

Pesticide	Exposure/ sacrifice time (h)	Topical dose ($\mu g/cm^2$)	Percentage of administered dose								
			CW/CW[a]	Carcass	Feces	Urine	BSR[a]	Blood	Recovery	DA I[a,b]	DA II[a,c]
Tralomethrin	10/120	3.0	1.74	0.37	1.05	2.30	15.6	N/D[a]	94.6		
Corrected for % recovery[d]			1.84	0.39	1.11	2.43	16.5	N/D[a]	100.0	22.3	7.2
Metam sodium	10/72	8.6	0.10	0.00	0.01	1.05	2.79	1.28[e]	98.2		
Corrected for % recovery[d]			0.10	0.00	0.01	1.07	2.84	1.30[e]	100.0	5.3	2.5
Tribufos	10/168	1.93	2.89	2.49	3.05	36.0	2.82	0.02	91.8		
Corrected for % recovery[d]			3.15	2.71	3.32	39.3	3.07	0.02	100.0	51.5	47.5
Azinphos-methyl	10/168	0.93	3.65	1.87	9.8	26.2	15.8	0.08	97.4		
Corrected for % recovery[d]			3.75	1.92	10.1	26.9	16.2	0.08	100.0	59.0	44.2
Amitraz	10/120	10.0	1.41	0.24	2.30	8.69	0.48	0.02	94.2		
Corrected for % recovery[d]			1.50	0.25	2.44	9.23	0.51	0.02	100.0	14.0	13.8

[a] CW/CW, cage wash/cage wipe; BSR, 'bound' skin residue; DA, dermal absorption; N/D, no data available.
[b] Sum of % dose recovered from cage wash/cage wipe, carcass, feces, urine, BSR, blood and expired air (if there is any).
[c] Sum of % dose recovered from cage wash/cage wipe, carcass, blood and expired air (if there is any), and maximum excretion as determined from the exponential saturation model.
[d] Correction was made to reflect a 100% recovery of the administered dose.
[e] Expired air.

Finally, although compounds with a high K_{ow} (i.e. a high solubility in octanol relative to the solubility in water) may remain in the lipid layer of the skin (*stratum corneum*) and not become absorbed systemically, insufficient documentation exists to support exclusion of skin-bound residues from estimates of dermal absorption, based on the K_{ow} of the test material alone.

USE OF DATA

GENERAL CONSIDERATIONS

In order to assess risk to individuals following dermal exposure to a pesticide, dermal absorption data are often required to convert dermal deposition data to estimates of systemic exposure. These estimates of systemic exposure are then compared with the No Observed Adverse Effect Levels (NOAELs) from oral toxicity studies or limit values (for instance, Acceptable Operator Exposure Levels (AOELs)) derived from these oral data (Bos *et al*., 1998; Rennen *et al*., 1999). As noted in the introduction, oral studies are generally used because the toxicology database is typically focused on the oral route of exposure.

Although this method of using the oral toxicity data for risk assessment of dermal exposed populations ('route-to-route' extrapolation) appears straightforward, it may not be always applicable. If, for instance, fundamental differences in metabolism exist between the oral and dermal routes, excessive 'first-pass' effects occur and/or large differences in rate of absorption exist between the various routes of exposure, route-to-route extrapolation may not be feasible (Pepelko and Withey, 1985; Sharrat, 1988). When there is uncertainty about the relevance of route-to-route extrapolation, oral and dermal kinetic data may be useful, or conduction of pivotal toxicological studies (e.g. development, neurotoxicology, etc.) by the dermal route may be the most appropriate way forward.

When route-to-route extrapolation is deemed to be appropriate for the risk assessment, a tiered approach to selection of dermal absorption values, as outlined below, is recommended.

TIERED APPROACH

Tiered approaches to dermal exposure and risk assessment have been developed (OECD, 1997; de Heer *et al*., 1999; Hamey, 2000; EC, 2002). Although the number of tiers differ depending on the specific approach, common to all approaches is the sequential refinement of the value used for dermal absorption in the risk assessment. For example, in a Tier 1 risk assessment, a conservative value of 100 % dermal absorption is often used. If required, a more refined default may be justifiable, based on a number of considerations such as the physico-chemical properties of the substance and the toxicological database. Use of dermal absorption data would be the third tier. Biological monitoring data would be a potential fourth tier, if required.

Tier 1

In the first tier, an assumption of complete dermal absorption can be made, i.e. assume 100 % dermal absorption. Under the NAFTA Technical Working Group on Pesticides, it was agreed that in the absence of an acceptable *in vivo* dermal absorption study, dermal absorption and absorption via the oral route would be considered equivalent (i.e. up to 100 %). It is noteworthy that the California Department of Pesticide Research uses a Tier 1 default of 50 % for regulatory purposes. This default represents an upper-bound estimate of dermal absorption of 40 pesticides, which were obtained from studies in rats (Donahue, 1996).

Tier 2

If the results of a preliminary risk assessment, using a Tier 1 approach, do not generate acceptable risk levels, an examination of the physico-chemical properties of the substance, as well as the toxicological database of the product, may yield a justification for a lower dermal absorption default. A 'weight-of-evidence' approach should be used, e.g. both the physico-chemical information and the toxicological database should support the reduced default.

Several properties of a compound can influence its ability to penetrate the skin, including size (molecular weight), shape, charge, reactivity, solubility in polar and nonpolar solvents and physical state (solid or liquid) (ECETOC, 1993; EC, 2002). Unfortunately, clear cut-off values for negligible, low and/or high dermal absorption of chemicals cannot be derived from data presented in the open literature (Durkin *et al*., 1995). An example of the use of physico-chemical properties to refine dermal absorption defaults is provided by de Heer *et al*. (1999) who noted that based on theoretical considerations on skin permeation, it might be expected that there should be an optimum in log K_{ow}[1] and a maximum in molecular weight (MW) for facilitating percutaneous absorption. The following criteria were proposed by de Heer *et al*. (1999) to discriminate between chemicals with high and low dermal absorption:

- 10 % dermal absorption is used in cases where $MW > 500$ g/mol *and* log K_{ow} is smaller than -1 or higher than 4, or otherwise;
- 100 % dermal absorption is maintained.

The lower limit of 10 % was chosen because the data presented in the literature indicate the occurrence of dermal absorption for tested compounds even beyond the extremes of log K_{ow} and/or MW values. It was noted that, by expert judgment, a deviation from 100 % and 10 % dermal absorption can be chosen, on a case-by-case basis taking into account all data available (e.g. data on ionogenic state, 'molecular volume', oral absorption and dermal area dose in exposure situations in practice).

[1]Partition coefficient between octanol and water.

The toxicological database may also yield information which will assist in characterizing dermal absorption. For instance, in an analysis of dermal absorption studies, Zendzian concluded that severe dermal irritants did not show evidence of saturation of dermal absorption (Zendzian, 2000). As such, a reduced default for severely irritating or corrosive materials seems inappropriate.

An oral ADME (absorption, distribution, metabolism, excretion, following oral administration of the pesticide) study may also be of utility in refining the risk assessment. If a default value for dermal absorption of 100 % is applicable based on the physico-chemical properties of a substance and an appropriate oral ADME study is available, the results of this study may be used to refine the default value for dermal absorption. It is required that the oral absorption is determined at low dose levels in experimental animals, in order to obtain an accurate estimate of the oral absorption. Based on theoretical grounds and supported by a comparison of oral and dermal absorption data available for twelve pesticides, it is assumed that dermal absorption will not exceed oral absorption (Hakkert *et al*., unpublished data).

An estimate of dermal absorption cannot be deduced from the results of acute toxicity studies because differences in oral and dermal LD_{50} values are not necessarily a result of differences in absorption (EC, 2002). First, the result in a dermal LD_{50} study is dependent on the size of the exposed area and can be changed by altering this area. Secondly, differences in toxicity after oral and dermal exposure could be the result of 'first-pass' effects (i.e. substance is (in)activated in the liver). Furthermore, the toxicity of a substance is also influenced by the rate of absorption. Generally, and especially in acute (gavage) studies, oral absorption will be relatively fast, hence resulting in a peak concentration in the body, whereas the absorption after dermal exposure is generally more gradual. Finally, for setting LD_{50} values, usually high levels of test compound are given. Since absorption percentages are highly dependent on the applied dose, this may very well lead to underestimation of absorption percentages at (low) occupational exposure levels. Based on these considerations, it can be concluded that the results of acute toxicity studies can only be used to indicate high, but not a low, dermal absorption.

Tier 3

Tier 3 involves generation of experimental dermal absorption data. In order to ensure that data generated will be meaningful and relevant for risk assessments conducted by regulatory authorities, it is highly recommended that protocols be developed in consultation with these authorities.

Currently, for pesticide registration, there is an increasing consideration by regulatory jurisdictions of *in vitro* data as an alternative to *in vivo* dermal absorption data. At present, based on the OECD inventory and provided that levels of the pesticide remaining in the skin are included as absorbed, the results from *in vitro* methods seem to adequately reflect those from *in vivo* experiments, so supporting their use as a replacement test to measure percutaneous absorption (OECD, 2000; van de Sandt *et al*., 2004). This calculation, i.e. the inclusion of the amount

located in the skin as being absorbed, may result in a conservative estimate of the amount becoming systemically available *in vivo*. If refinement is needed, it should be convincingly demonstrated that the pesticide remaining in the skin does not become absorbed at a later stage.

In addition, *in vitro* studies can be used for semiquantitative comparison of absorption of chemicals between species, between compounds within one species, and between different vehicles within one species. In this regard, it is important to realize that *in vitro* studies give relative results, i.e. that they should primarily be compared with results generated within the same test system. Various calculations can be made on the basis of *in vitro* data, dependent on the dose applied (infinite versus finite dose). The maximum flux (derived from the linear part of the absorption versus time curve) may be used to semiquantitatively compare absorption between species, compounds or vehicles, based on finite dose experiments. In this case, attention should be paid to the differences in maximum flux values at relevant exposure levels. For example, if at 200 $\mu g/cm^2$ the flux through rat skin is ten times higher compared to human skin, but fluxes are comparable at the more relevant dose level of 20 $\mu g/cm^2$, there should be no correction for differences in skin permeability in health risk assessment.

If appropriate dermal penetration data are available for rats *in vivo* and for rat and human skin *in vitro*, the *in vivo* dermal absorption in rats may be adjusted in light of the relative absorption through rat and human skin *in vitro*. The latter adjustment may be carried out because the permeability of human skin is often lower than that of animal skin (McDougal *et al*., 1990; Sato *et al*., 1991; Barber *et al*., 1992; Howes *et al*., 1996). A generally applicable correction factor for extrapolation to man can, however, not be derived, because the extent of overestimation appears to be agent- and animal-specific (Bronaugh and Maibach, 1987; ECETOC, 1993).

CHALLENGES IN USE OF DATA

Application of *in vivo* and *in vitro* dermal absorption study results to a risk assessment for dermal exposure to a pesticide requires professional judgment as it is rare for a dermal absorption study to mimic the exposure scenario exactly. Some specific challenges are presented below. As noted in the previous section, achieving a harmonized approach on these challenges, and other technical issues related to application of dermal absorption studies to risk assessment, would facilitate work-sharing and joint-review endeavours.

Dose

Matching dose to anticipated field exposures is difficult as, even when the area dose levels are expected to bracket anticipated exposure levels, the nature of the exposure is different. In the experimental study, the full dose of the compound is applied at the beginning of the exposure period, whereas in the typical exposure scenario, the dose is received incrementally over the course of, for instance, the

work day (Ross *et al*., 2001). Ross *et al*. (2000) noted that a dermal dose acquired over the entire work day would produce peak plasma levels lower than the 'bolus-style' dermal dosing regime in a dermal absorption study. More investigation is required to explore the impact that these differing exposure regimes have on dermal absorption and risk levels.

Currently, for regulatory purposes, if the area dose levels applied in the *in vivo* study are at or below the area dose levels anticipated to occur in the scenarios under investigation, no underestimation of dermal absorption is expected. However, if the area doses are higher than the anticipated exposure levels, the percentage absorbed, as derived from the study, should not be used as it may underestimate dermal absorption, as in general, the percentage absorption decreases with increasing dose. If the values *are* used, the uncertainty associated with this decision should be documented in the risk assessment.

In addition, when considering the appropriateness of the area dose levels in the dermal absorption study to the subpopulations under consideration in the risk assessment, it is important to recognize that different area dose levels may be experienced depending on the scenario. For instance, with an agricultural worker, the mixer/loader may be exposed to the concentrated product, the applicator to the diluted spray mixture and the re-entry worker to dried residues on vegetation. As such, it is possible that different dermal absorption values have to be used for each work-function scenario.

Formulation and Vehicle

Dermal absorption is considered to be a chemical-specific phenomenon. However, even with the same pesticide, differences in formulations and vehicles can significantly influence absorption. If the dermal absorption study was conducted with a different formulation than the formulation being proposed for registration, the potential influence of formulant differences on absorption should be considered carefully before applying the data to a risk assessment. Some formulation components, such as solvent-based diluents found in emulsifiable concentrates, are associated with higher dermal absorption. In addition, it is not uncommon for a pesticide product to contain two pesticidal active ingredients with two separate dermal absorption studies for these two ingredients. The absence of a dermal absorption study on the 'co-formulated' product is a limitation, and the potential influence of one active ingredient on the absorption of the other should be considered carefully before using the data.

Furthermore, the exposure assessor should also recognize that vehicles are typically different for the mixer/loader versus the applicator versus re-entry workers or bystanders. Again, any uncertainties should be noted in the overall risk assessment.

Exposure Duration

It is recognized that the exposure period (i.e. time between when test material is applied and when the skin is washed) should mimic the length of anticipated

field exposures. In general, a 6–10 h exposure period is considered applicable to a pesticide handler or re-entry worker work day. The appropriate duration for residential scenarios, however, has been debated. As a wash event may not occur at the end of a day when exposure to a pesticide has been incidental (e.g. contacting treated turf during play), a dermal absorption value from a 24 h exposure period may be more appropriate.

Exposure Frequency

The dermal absorption studies requested for pesticide registration all refer to single exposures. Information on the effects of repeated exposure on dermal absorption is scarce, and no general conclusions can be drawn from these. Repeated exposures may increase dermal absorption (Roberts and Horlock, 1978; Wester *et al*., 1994) or may not affect the absorption characteristics (Bucks *et al*., 1985a; Tauber and Matthes, 1992). The experiments addressing repeated application further indicate that the results may be influenced by experimental conditions such as skin washing (Bucks *et al*., 1985b) and direct effects of the test compound on the skin (Roberts and Horlock, 1978). This is an area where further investigation is needed.

SUMMARY AND RECOMMENDATIONS

This chapter provides an overview of factors affecting dermal absorption. Factors influencing absorption are among others related to the skin (e.g. anatomical site, difference between species, metabolism, etc.) and the exposure conditions (e.g. area dose, vehicle, occlusion and exposure duration). In order to provide relevant information for the risk assessment of pesticides, dermal absorption studies should take these aspects into account. With respect to the methods being used nowadays for the assessment of dermal absorption, it is important to realize that neither *in vitro* nor *in vivo* animal studies have been formally validated. Available data from various *in vitro* studies, however, indicate that the use of the total absorbed dose (i.e. the amount of test substance in the receptor medium plus amount in the skin) could be used in a quantitative manner in risk assessment. Tape stripping of the skin can be adequate to give a good indication of test chemical distribution, and hence its immediate bioavailability.

An overview of a tiered approach for the use of dermal absorption data in dermal risk assessments is provided. Initial tiers utilize default assumptions, while higher tiers require results from *in vivo* and *in vitro* dermal absorption studies. For dermal absorption studies, challenges in data analysis, as well as in application of the data to risk assessment, are identified.

Although not of importance for the assessment of the dermal uptake as such, information on the metabolites formed after dermal and oral exposure is of the utmost importance for dermal risk assessment. This information, as well as information on the rate of dermal (and oral) uptake, will aid in the decision as to

whether oral toxicodynamic studies could be used in risk assessment of dermal exposure. Finally, an aspect that needs further attention, especially for the risk assessment of workers, i.e. the group that is often exposed various days in a row, is information on the effects of repeated exposure on dermal absorption.

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10 Occupational and Residential Exposure Assessment for Pesticides – Towards a Harmonized Regulatory Approach

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INTRODUCTION

A common goal of pesticide regulators worldwide is harmonization of the approaches and methods that they use. At its core, the concept of harmonization encompasses a willingness to work towards convergence of these approaches and methods, while recognizing that region-specific considerations will continue to play a role in some exposure assessments.

In recent years, there has been considerable activity in harmonizing occupational and residential exposure assessment approaches and methods, and the benefits of this are numerous. First, the regulatory community has access to a larger 'tool box' of approaches, methods and data sources. For jurisdictions with less experience in occupational and residential exposure assessment, this can be a significant benefit. Secondly, through careful scrutiny of available approaches and methods by the regulatory community as a whole, harmonization results in adoption of the best approaches and methods available. An additional benefit of this careful assessment of best approaches and methods is more focused research and development by both the pesticide manufacturers and the larger

research community. Thirdly, harmonization is a prerequisite to work sharing among governments – which reduces the burden of regulatory review. This, in turn, translates to consistent, transparent and efficient decision-making. Increased efficiencies allow regulatory agencies to allocate resources to exploration of alternative pest management strategies and increased re-examination of older pesticides; both activities enhance sustainable use of pesticides.

Harmonization initiatives can occur as a result of specific agreements between two or more countries, as in Europe (EU) through the European Commission (EC), in North America under the North American Free Trade Agreement (NAFTA) or more broadly under the umbrella of international nongovernmental organizations such as the Organization for Economic Co-operation and Development (OECD).

Under NAFTA, the Technical Working Group on Pesticides is committed to the harmonization of all aspects of pesticide regulation and one element of this Working Group was a recently completed project on *Harmonization of Occupational and Residential Exposure Assessment.* Key participants in this project were the United States Environmental Protection Agency (USEPA), Health Canada's Pest Management Regulatory Agency (PMRA), and the California Department of Pesticide Regulation. The goal of this project was to harmonize the assumptions, methodologies, data analysis and databases for occupational and residential exposure assessments so that pesticide exposure reviews and work could be shared among NAFTA countries.

In the area of occupational and residential exposure, a series of workshops designed to promote harmonization have been pivotal to the successes to date (Henderson *et al*., 1993; Curry *et al*., 1995; Bergeron *et al*., 1997; van Hemmen and van der Jagt, 2001).

Examination of the life-cycle of a pesticide submission from generation of the requisite data and compilation of the dossier by the manufacturer through the numerous steps leading to a regulatory decision by one or more jurisdictions, illustrates that there are numerous opportunities for improving the consistency, transparency and efficiency of occupational and residential exposure assessment through harmonization. Specific harmonization opportunities include the following:

- developing a framework for addressing data requirements;
- standardizing data requirements, and methodological guidance to generate these data;
- developing and using standardized databases and models;
- standardizing the reporting and formatting of data for regulatory submission;
- standardizing the evaluation of data by regulators;
- standardizing the use of data in occupational and residential exposure and risk assessments;
- establishing consistent recommendations for exposure mitigation.

In order to achieve harmonization in the area of occupational and residential exposure assessment, it is important that there be a common understanding of

the subpopulations which the assessments encompass. Occupational exposure can be defined as potential exposure to individuals who handle pesticides (e.g. mix, load and apply) or re-enter treated areas where pesticides are present in the ambient air or on treated surfaces such as foliage which the individuals contact as part of their work. Workers handling materials, such as textiles, treated with a pesticide also have post-application exposure potential. Residential exposure can be defined as potential exposure to homeowners who apply pesticides in and around the home, or to occupants who re-enter treated areas. In the EU, Directive 91/414/EEC identifies three subpopulations for which nondietary risk assessments must be conducted. These are operators (applicators), bystanders (those who may be incidentally exposed) and workers (those who may be exposed through re-entry activities) (Hamey, 2000). The scope of subpopulations included within the realm of occupational and residential exposure is not static. For example, in some countries residential exposures are expanding beyond the home and yard to include exposures in schools, recreational facilities and daycare centers.

The purpose of this present chapter is to outline the accomplishments in harmonization of occupational and residential exposure assessment of pesticides, to survey 'work-in-progress' and to identify and prioritize areas which are not currently harmonized and which present barriers to regulatory capacity gains.

TERMINOLOGY

A common understanding of the terminology used in occupational and residential exposure assessment is an important prerequisite to effective harmonization. For example, inconsistent use of terms such as exposure/dose and upper bound/'worst-case' is confusing and can be an impediment to effective harmonization.

Although some glossaries have been developed as an adjunct to guidance documents and guidelines, these are not considered comprehensive. International workshops on chemical exposure assessment methodology consistently identify terminology as an important first step in harmonization. Zartarian *et al.* (1997) also acknowledged this terminology challenge and provided a proposed framework.

Through the International Programme for Chemical Safety (IPCS), there is a joint collaborative project of the United Nations Environment Program (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO) on the *Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.* The Steering Committee of the IPCS recently supported expansion of this existing project, to include an activity to harmonize approaches to chemical exposure assessment (Sonich-Mullin *et al.*, 2000). The IPCS recognized that the use of diverse terminology in this field presents barriers to harmonization, and through its collaboration with other international partners, has developed a set of core terms and their definitions. Updates on this initiative

which is focusing on chemicals in general, are located on the IPCS Harmonization website (www.ipcsharmonize.org). The specific field of pesticide exposure assessment presents many unique terminology challenges (e.g. transfer factor versus transfer coefficient and dislodgeable versus transferable residues) and thus there is still a need for harmonized pesticide exposure assessment terminology.

FRAMEWORK FOR ASSESSING OCCUPATIONAL AND RESIDENTIAL EXPOSURE

Common to most regulatory jurisdictions is adherence to a tiered approach to occupational and residential exposure and risk assessment. This approach was presented, debated and refined at various international workshops throughout the 1990s and has gained wide acceptance. The tiered approach incorporates a sequential refinement of exposure assessments through the use or development of more specific data on an 'as-needed' basis (OECD, 1997). The approach, for workers involved in agricultural application, has been summarized schematically (OECD, 1997). The first tier compares NO Observed Adverse Effect Levels (NOAELs) from toxicology studies relevant to the use pattern to generic exposure data such as output from the Pesticide Handlers Exposure Database (PHED). If there is unacceptable risk or insufficient data, higher-tier data are required. Dermal absorption data is a common Tier 2 data element. If Tier 2 exposure estimates do not yield acceptable risk, Tier 3 data such as chemical-specific passive dosimetry or biological monitoring data are required in order to move the risk assessment process forward.

A proposal for a tiered approach to agricultural post-application exposure assessment was presented at an international workshop in Canada (Bergeron *et al*., 1997) and is also discussed in Hamey (2000) and Krebs *et al*. (2001). In the agricultural post-application scenario, Tier 1 data is comprised of upper-bound estimates of dislodgeable foliar residues, transferability and length of workday. Determination of dislodgeable foliar residues can be based on considerations such as application rate and surface area of crop foliage compared to the ground surface area (i.e. leaf area index). Generic transfer coefficients have been established for various crop–activity combinations and these are used in a Tier 1 post-application exposure assessment. In the absence of specific agricultural practice information, full workdays (8–10 h) are typically assumed. Higher-tier data include chemical-specific dislodgeable foliar residue data, dermal absorption data and/or passive dosimetry data. This approach, too, has gained some acceptance in the regulatory community. More effort, however, is required to reach consensus on specific inputs for this approach, including selection of 'day-zero' default residue values and generic transfer coefficients. However, these approaches do not currently address multiple applications in the basic algorithms and this needs to be incorporated into the approach. In addition, default dissipation kinetics merit discussion. Some jurisdictions have assumed 10 % dissipation

per day while others, in the absence of chemical-specific dissipation data, assume no dissipation of residues.

The USEPA has spearheaded a similar tiered approach for application and post-application in residential exposure scenarios. With the US Food Quality Protection Act (FQPA) as impetus, the USEPA has developed a series of algorithms which yield Tier 1 estimates for a broad range of residential application and post-application exposure scenarios. Approximately 40 unique scenarios are addressed in the USEPA's draft Standard Operating Procedure for Residential Exposure Assessment (USEPA, 1997c). Although some jurisdictions, including Canada, have adopted some of these algorithms, Tier 1 approaches for residential scenarios have not been the subject of substantial international discussion to date.

The tiered approach has also been recommended for the generation of use pattern information (Schipper, 2001). Tier 1 data would typically be comprised of general use pattern information culled from national census data or from experts in the area. Tier 2 data would typically be survey data using acceptable survey methodology, hence resulting in higher confidence inputs to the exposure assessment.

In some jurisdictions, Tier 1 assessments are conducted by the regulatory community, and the manufacturer of the pesticide is required to generate higher-tier data, as necessary. In other jurisdictions, the manufacturer is required to conduct an assessment as part of the submission and the onus is on the manufacturer to submit the appropriate level of data.

Integral to the tiered approach is the concept of 'negligible exposure'. Many jurisdictions will waive the requirement for a quantitative exposure and risk assessment, on a case-by-case basis, citing negligible exposure. Clear guidance on what constitutes negligible exposure is not available and a harmonized set of criteria for making this determination is required.

DATA REQUIREMENTS

CONVENTIONAL SYNTHETIC PESTICIDES

Although a comprehensive survey of occupational and residential exposure data requirements across all regulatory jurisdictions is beyond the scope of this chapter, it is evident that the majority of jurisdictions require an assessment of exposure for conventional pesticides if the proposed use pattern indicates potential handler exposure (either occupational and residential) or agricultural re-entry exposure. The extent to which exposure assessments are required/conducted for residential re-entry scenarios or bystanders, however, is less uniform. Although most jurisdictions require/conduct assessments for residential re-entry scenarios (e.g. treated turf, carpet, etc.), exposure assessment methodology for other types of bystander exposure scenarios (e.g. residential exposure in agricultural areas, direct exposure to drift, exposures from the use of pesticides in schools, daycare centers and other public places) is less mature and requires further collaboration.

The harmonization of the regulation of plant protection products throughout the EU has resulted in harmonized data requirements for occupational, bystander and worker exposure assessment. These requirements are outlined in Annex III of Council Directive 91/414/EEC. This annex lists product-related exposure data requirements and, consistent with the tiered approach outlined above, provides some advice as to when different data are required (Hamey, 2000). An estimation of operator exposure, using, where available, a suitable calculation model, must always be made and reported. Actual exposure data must be provided where the risk assessment indicates that a health-based value is exceeded or where no appropriate calculation model exists to estimate exposure.

In North America, a comparison of the USEPA and Health Canada's Pest Management Regulatory Agency (PMRA) occupational and residential exposure data requirements shows that the two countries are essentially harmonized with respect to data requirements. Using seed treatment chemicals as a case study, this has been documented in some detail (PMRA, 2003). Although there are some differences regarding specific triggers for exposure assessments, triggers for higher-tier chemical-specific data are similar. There is also agreement that recent advances such as aggregation and the requirement for comprehensive summaries increasingly require the assessment of exposure and characterization of risk, even in the absence of specific toxicology triggers.

Most regulatory jurisdictions will consider a science-based rationale to waive an occupational or residential exposure data requirement. For example, under NAFTA, the USEPA and Health Canada's PMRA have agreed upon guidance for considering a waiver for inhalation exposure data. Considerations are based on volatility, engineering considerations and particle size, and are outlined in Table 10.1.

For effective regulatory work sharing, it is important that waivers be assessed consistently across jurisdictions.

NON-CONVENTIONAL PESTICIDES

In general, harmonization is most advanced for conventional agricultural chemicals and less so for non-conventional chemicals such as biocides and biological pesticides.

Biocides

The term 'biocides' (referred to as *antimicrobials* in North America) is not defined consistently across all countries. In some regulatory jurisdictions, this term includes all non-agricultural uses associated with the control of a variety of pests, including microbes, insects, rodents, etc., which are found in industrial and residential settings. In certain jurisdictions, biocides can also include products regulated as public health products e.g. disinfectants. In other jurisdictions, biocides only include industrial and residential pesticides used to control

Table 10.1 Guidelines for considering a request to waive inhalation exposure data requirements (developed under the NAFTA Technical Working Group on Pesticides)

Volatility
Non-volatile products which are not readily aerosolized, and which are not heated, evaporated or diluted to an inhalable state during application. Non-volatile products are defined as those having vapor pressures less than 1×10^{-5} kPa (7.5×10^{-5} mmHg) for indoor uses, and less than 1×10^{-4} kPa (7.5×10^{-4} mmHg) for outdoor uses at 20–30 °C. Examples of formulations which may be good candidates for waivers based on volatility include viscous liquids, waxes, resins, lotions, tree injections, caulks, slow-release collars and ear tags.
Engineering considerations
Products handled using specific engineering controls that mitigate inhalation exposure. Examples of engineering controls which may allow a product to be a candidate for a waiver include formulations used in closed systems for the entire mix/load/application process.
Particle size
Formulations with proposed uses that yield a non-inhalable particle size (i.e. 99 % of the total mass of particles is greater than 100 μm in diameter). Examples of formulations which may be candidates for waivers based on particle size include microencapsulated formulations which are not biologically available for inhalation during mixing/loading or application, granular products placed in or on the soil, and baits applied by hand. In cases where solids are being proposed as candidates for inhalation exposure waivers, it will be further required that the solid be proven to be non-friable, as defined by the American Society for Testing and Materials (ASTM).

bacteria, fungi, viruses and fouling organisms (e.g. wood preservatives, material preservatives, antifouling coatings and industrial water treatment formulations).

The OECD Working Group on Pesticides has an active program on biocides. A goal of the Biocides Programme is to increase efficiency in regulating biocides through methods such as harmonization of data requirements, testing and risk assessment methods and by promoting the sharing of the work of government reviews. Results from a 1997–1998 Survey of OECD Member Countries' approaches to the regulation of biocides shows considerable variation in the way that OECD Member Countries regulate biocides. As a result of this survey, a workplan to increase harmonization in the biocide arena has been initiated. In the area of risk assessment, OECD countries have given high priority to developing guidance on how exposure assessments for biocides should be conducted. In view of the wide variety of exposure scenarios associated with biocide use, work to develop harmonized guidance has begun in a limited area, namely wood preservatives. The latter were selected since most countries have some regulatory experience with these materials. To identify what work on exposure

assessment was needed, a workshop on assessment of human exposure to wood preservatives took place in Ottawa, Canada, in June 2000 (OECD, 2000a). The workshop participants considered both primary and secondary exposure potential. Primary exposure was defined as that occurring to the person using the preservative and other persons involved in the mixing and loading, application or post-application phases, such as equipment maintenance, and handling of freshly treated wood. Secondary exposure was defined as post-application exposure via the environment, namely bystanders and consumers, including children, who may be inadvertently exposed to wood preservatives by inhalation, dermal contact or by ingestion, and have little or no control over this exposure. At this workshop, the data requirements to assess human exposure to wood preservatives were agreed to a large extent, and are summarized in Table 10.2. The workshop participants agreed that it was important to address secondary exposures in the risk assessment. However, it was recognized that secondary exposure scenario information was lacking, and recommended that the OECD should put effort into characterizing secondary exposure scenarios relevant to wood preservative use and corresponding data requirements to conduct exposure assessments.

As part of the NAFTA Technical Working Group on Pesticides, priority areas for development of biocide applicator data have been agreed upon. These include, in order of priority, high-pressure spray, low-pressure spray, painting (roller/brush), wipe/mop, place solids, aerosol spray, painting (airless), pour solid, pour liquid and pump liquid.

Table 10.2 Proposed data requirements for assessing primary exposure to wood preservatives (OECD, 2000a)

Data requirement
• The physical form of the product – how it is presented to the market
• The formulation – what substances are in the product and their concentrations
• What market is identified as the user – industrial, professional, non-professional
• What is the purpose of the preservative – preventative, curative
• Market – how many use sites/users are predicted
• How is the product to be used – product as supplied or diluted
• Where (in what environment) will the product be used
• How often will the user be exposed to the product
• How much product will be used pre-application and/or per unit area
• What are the tasks in preparing the preservative for use
• What are the tasks in using the preservative, plus equipment and application
• What are the post-application tasks, e.g. decontamination
• How long does each task take (or a range)
• What controls limit primary exposure, i.e. PPE[a] engineering controls
• What exposure data or models are proposed – inhalation and dermal exposure
• What decontamination methods are available

[a] Personal protective equipment (apparel and devices).

Rigorous exposure assessments have not typically been conducted for articles impregnated with biocides (e.g. textiles and cutting boards). The USEPA does provide Tier 1 approaches (e.g. generation of migration data) in their draft Standard Operating Procedure for Residential Exposure Assessment (USEPA, 1997c). However, as the marketing of these products increases, exposure potential (e.g. multiple exposures due to impregnation of an array of consumer products) increases, and this is an area requiring further attention.

Biological Pesticides

Harmonization of data requirements for this diverse group of compounds is being undertaken in a stepwise fashion.

Microbial pesticides are evaluated for toxicity and infectivity prior to making regulatory decisions. As traditional dose–response-based risk assessments are not considered appropriate for microbial pesticides, regulatory jurisdictions do not typically require occupational and bystander exposure data. However, a small number of studies have monitored airborne concentrations (colony forming units/m^3) of microbial pesticides following application (Teschke *et al*., 2001), and the utility of these data should be considered by the regulatory community.

As part of the OECD Working Group on Pesticides, a project was initiated to establish core data requirements for a specific class of biological pesticides, namely pheromones. *Semiochemicals*, which include pheromones, are inherently different from conventional pesticides in that they act by modifying the behavior of the pest rather than killing it, are more target-specific than conventional insecticides, are typically used at concentrations close to ambient background levels, and tend to dissipate rapidly. These factors were taken into consideration during discussions on data requirements for pheromones at recent Workshops in Wageningen, the Netherlands (OECD, 1999) and Ottawa, Canada (OECD, 2000b). For the occupational exposure data requirements, there was consensus among participants that a tiered approach should be implemented for pheromones (OECD, 1999, 2000b). Tier 1 data was identified as a core requirement and would typically be comprised of estimates of exposure based on available information (e.g. application method, application rate and physico-chemical properties). Higher-tier data is conditionally required if there is significant exposure potential and/or if Tier 1 toxicity tests indicate hazards which need to be addressed in a risk assessment. For illustrative purposes, the workshop documentation indicates that solid–matrix dispensers are unlikely to present significant exposure potential, although some spray applications may do so. The OECD guidance, based on these workshop proceedings, has been finalized (OECD, 2001).

METHODOLOGICAL GUIDANCE

Curry and Iyengar (1992) have reviewed and compared existing published and unpublished guidance for measuring exposure of individuals using pesticides or

exposed to pesticide residues in indoor and outdoor environments. Such guidance is used by study investigators to develop detailed study-specific protocols. The need for harmonization was recognized. It has been observed that although the toxicity testing of new pesticides is conducted according to internationally accepted guidelines, there is a lack of internationally accepted guidelines for conduct of studies that measure exposure (OECD, 1997). Various initiatives are underway to remedy this deficiency.

MIXER/LOADER/APPLICATOR

Over the course of several years, the OECD has facilitated international consultation necessary for the development of harmonized guidance for the measurement of occupational exposure to agricultural pesticides (i.e how the data should be generated.) The technical content of the OECD guidance document was determined over the course of two international workshops (Henderson *et al*., 1993; Curry *et al*., 1995) and a comprehensive international peer review process. The final document was published in 1997 (OECD, 1997). The focus of the guidance document is on the measurement of mixer/loader/applicator exposure during agricultural uses of pesticides. Although some of the methodology would apply to post-application occupational exposure and residential exposure, these scenarios were considered to be beyond the scope of the guidance document.

An important area of harmonization was defining the key parameters of a replicate, such as duration of monitoring, in passive dosimetry and biological monitoring studies. The OECD guidance document defines a replicate as a measurement of exposure to a worker during one typical workday, which includes all job functions related to pesticide use.

Availability of guidance does not preclude consultation with regulatory jurisdictions during study-specific protocol development. In order to ensure that the study is applicable to multiple jurisdictions, co-operative consultation should take place. In North America, for example, protocols for exposure studies were recently finalized for heavy-duty wood preservatives, with co-operative input from both the USEPA and PMRA of Health Canada. Selection of representative USA and Canadian sites ensured that the results would be applicable to both countries. Increased co-operative consultation at the protocol development phase will increase utility of data across multiple jurisdictions and will facilitate harmonization.

AGRICULTURAL AND RESIDENTIAL POST-APPLICATION

The USEPA, with input from the PMRA of Health Canada and the California Department of Pesticide Regulation (DPR), has substantially revised the USEPA Post-Application Exposure Monitoring Test Guidelines (USEPA, 1998a). This draft document has a broad scope and addresses passive dosimetry, biological monitoring, dislodgeable and transferable residue studies, soil residue studies and

non-dietary ingestion. This document was subject to a comprehensive critical review at an international workshop in 1997 (Bergeron *et al*., 1997). The technical content of the document also forms the basis of test guidelines in Canada (PMRA, 1998), ensuring harmonized guidance in North America for development of protocols for studies to measure post-application exposure.

As part of the OECD's Working Group on Pesticides, a Post-Application Exposure Steering Group has been struck to develop an OECD guidance document on methodology for conduct of post-application exposure studies in the agricultural setting. Using the USEPA draft guidance document as the basis, the Steering Group is currently preparing a guidance document which will undergo peer-review and be submitted to the OECD with the request that it be developed and published as an OECD Guidance Document. Guidance for conduct of post-application exposure studies in residential settings will be the subject of a future OECD endeavour.

Some agricultural re-entry scenarios involve contact with treated soil, rather than treated foliage (e.g. transplanting activities following a greenhouse soil drench). Although guidance is provided for soil dissipation studies, determination of transfer metrics for activities involving soil contact have not been established.

OTHER EXPOSURE SCENARIOS

Areas of emerging emphasis include measurement of exposure from scenarios such as children living with agricultural workers and/or in proximity to agricultural areas (Simcox *et al*., 1995; Loewenherz *et al*., 1997; Lu *et al*., 2000), direct exposure to drift, and exposures from the use of pesticides in schools, daycare centers and other public places. Methodological guidance is required in these areas. The USEPA has identified some preliminary approaches, such as using drift deposition estimates generated by the 'AgDrift' model. In the EU, existing bystander data are being collected as parted of EUROPOEM II, with the intention of developing a model to estimate potential bystander exposure (Hamey, 2000) A co-ordinated effort in this area would promote harmonization.

DERMAL ABSORPTION

An important aspect of a refined occupational or residential exposure assessment (Tier 2 assessment) is inclusion of a study to measure the dermal absorption of the pesticide which enables an estimate of systemic exposure (dose) to be derived from the measurement of dermal deposition. This step is necessary to allow comparison with the toxicity data which are generated primarily following oral exposure to the test animals.

In North America, as part of the NAFTA Technical Working Group on Pesticides, the USEPA and PMRA of Health Canada agreed to adhere to the USEPA-Series 870 Guidelines for conduct of *in vivo* rat dermal absorption studies. The experimental design and USEPA experience with the guidelines

has been documented (Zendzian, 2000). An OECD guideline for conduct of *in vivo* dermal absorption studies is also available (OECD, 2004a). Although both guidelines yield sufficient data to derive quantitative estimates of absorption, differences include duration of exposure and dose levels recommendations. In addition, the USEPA guidance provides more details regarding methodological details and modified study designs to address specific data needs (e.g. blood/plasma kinetics, fate of residues remaining on the washed skin, volatile compounds, infinite dose studies, etc.). Approaches for interpretation of residues remaining on the washed skin upon termination of *in vivo* dermal absorption studies have been proposed (Thongsinthusak *et al.*, 1999) and concurrence internationally on this issue would facilitate work sharing.

The utility of *in vitro* methodology to derive estimates of dermal absorption of pesticides for risk assessment purposes is currently being debated in the international community. An OECD Guideline for conduct of *in vitro* dermal absorption studies is available (OECD, 2004b). Acceptance of *in vitro* methodology is hindered by the absence of acceptable methodology validation studies. As part of the NAFTA Technical Working Group on Pesticides, the USEPA and Health Canada's PMRA agreed that *in vitro* data, alone, are not sufficiently validated for use in deriving estimates of systemic exposure, and there are currently no acceptable *in vitro* guidelines. Both countries support continuation of validation efforts. The EC has published a guidance document on dermal absorption (EC, 2004), presenting a tiered approach in which exposure assessment and dermal absorption are integrated. This document suggests that the EU may be prepared to go further in accepting *in vitro* studies, but the difficulty in validating *in vitro* data and the challenges presented by lipophilic pesticides are highlighted.

Dermal absorption studies have been conducted in 'non-human' primates (monkeys), but are infrequently used at this time for pesticides. Jurisdictions are not currently harmonized with respect to acceptability of dermal absorption studies conducted with human volunteers. Although formal guidance is not available, the methodology of Feldmann and Maibach (1974) and Wester and Maibach (1985) is generally recognized. The harmonization challenge, however, lies with the ethical considerations around studies conducted with human volunteers prior to registration of a pesticide. There are numerous jurisdictions assessing whether any studies should be conducted in humans, and if so, how.

PENETRATION THROUGH PROTECTIVE MATERIALS

Another option for refining exposure estimates is through generation of penetration/permeation data for protective materials. In the USA, the American Society for Testing and Materials (ASTM) has established a laboratory method for determining the resistance of protective clothing materials to permeation by liquids and gases (ASTM, 2003). However, it is uncertain how applicable the results from these laboratory tests are to pesticide use under field conditions (e.g. repeat use of protective materials, influence of external environmental conditions, and influence

of pressures and frictions due to repetitive nature of tasks). An appropriately designed passive dosimetry study (e.g. monitoring residues on inner and outer dosimeters) which can address these uncertainties and study design considerations has been outlined (OECD, 1997). Limited data from the analysis of inner and outer dermal dosimetry data in the Pesticide Handlers Exposure Database (PHED) indicate an inverse relationship between percentage clothing penetration/permeation and concentration of residues on the dosimeter ($\mu g/cm^2$). In order to assess whether material permeation/penetration data can be used generically, there is a need for investigation of the influence of factors such as formulation type, physico-chemical properties (e.g. viscosity of diluent) and residue loading on extent of permeation/penetration.

DEVELOPMENT AND UTILITY OF DATABASES AND MODELS

Exposure databases are considered as a compilation of empirical exposure data which can be subset for relevant characteristics. Models are mathematical algorithms that transform known inputs or conditions into an exposure estimate (i.e. output). Both have utility in occupational and residential exposure assessment.

MIXER/LOADER/APPLICATOR DATABASES

In North America, the Pesticides Handlers Exposure Database (PHED) was an early bilateral USA/Canada initiative, in conjunction with the National Agricultural Chemicals Association, to co-operatively generate a tool for deriving exposure estimates for agricultural mixer/loader/applicators. This database has been available since 1992, and plays an important role in registration and re-registration activities in the USA and Canada. The database also has some value as a research tool. Epidemiologists have used it for deriving exposure assessments for populations of interest.

The PHED was an element of the NAFTA project on *Harmonization of Occupational and Residential Exposure Assessment.* Under this project, guidelines for the use and reporting of the PHED were generated.

Use of the PHED is limited to a small number of traditional agricultural mixer, loader and applicator functions as it is replicates from these types of studies that populate the database. It is important that this database be updated with new data so that it reflects a broader range of mixer, loader and applicator functions and captures newer trends in agricultural application technology. This need has been recognized and preliminary meetings have taken place among pesticide manufacturers, the USEPA, PMRA, California Department of Pesticide Regulation and the US Department of Agriculture to discuss approaches for moving forward in this area.

The harmonization of the regulation of plant protection products within the European Community requires corresponding harmonization of approaches to occupational and residential exposure assessment. At this time, various national

models (UK, Germany and The Netherlands) are still used to estimate operator exposure. A single harmonized European predictive operator exposure model, i.e. EUROPOEM, has been produced as a first draft as a result of an EC Concerted Action. A second EC Concerted Action (EUROPOEM II) is currently updating EUROPOEM (Hamey, 2000). The EUROPOEM model is based on a database of relevant studies representative of European practices (Hamey, 2000)

Limited comparisons of exposure outputs from both the PHED and EUROPOEM models indicate some similarity (Lunchick *et al*., 1994). There is a more detailed discussion of these models and a newer generic database under development in North America in Chapter 5 of this text. It is generally considered that disparate results may reflect differences in European and North American agricultural practices, plus inherent variability in exposure potential, as well as other variables. For harmonized exposure assessments between North America and Europe, it is important to fully scope out the compatibility of these two databases. A combined database would facilitate harmonization and has been proposed. Region-specific considerations could be accommodated by additional subsetting options.

AGRICULTURAL AND RESIDENTIAL POST-APPLICATION DATABASES

The USEPA and Health Canada's PMRA are active participants in two initiatives to generate substantial proprietary agricultural and residential post-application exposure data. These initiatives were undertaken by pesticide manufacturers in 1994 in response to USEPA data 'call-ins'. The goal of the Outdoor Residential Exposure Task Force (ORETF) is to develop data to derive exposure estimates for homeowners and professional lawn care operators who mix, load and apply pesticides to turf, and for individuals who re-enter the turf following pesticide treatment. A significant accomplishment of the Outdoor Residential Exposure Task Force is development and validation of a transferable residue methodology for turf (Fuller *et al*., 2001; Klonne *et al*., 2001; Rosenheck *et al*., 2001). The goal of the Agricultural Re-Entry Exposure Task Force (ARTF) is to develop data to derive exposure estimates for agricultural workers re-entering treated areas to conduct activities such as harvesting. To ensure that the data generated will be acceptable to North American pesticide regulatory jurisdictions, both countries have membership in the regulatory advisory committees of these, and other, industry initiatives. Such initiatives will lead to databases for use by the regulatory community when evaluating submissions by ARTF and ORETF members.

The EUROPOEM II expert group is considering all published material in order to reach a similar goal to that of the ARTF.

MODELING INITIATIVES

Use of increasingly complex exposure algorithms has led to development of predictive models to estimate exposure. Key models in the field of pesticide exposure assessment are surveyed in Chapters 5 and 6 of this text. With the

plethora of modeling activities currently underway in the area of occupational and residential exposure assessment, development of overarching guidance is needed.

Under the NAFTA Technical Working Group on Pesticides, the USEPA and PMRA of Health Canada have reached agreement on general model validation criteria, good modeling practices and reporting criteria for model-based assessments, as set forth in draft USEPA-Series 875-Group B (USEPA, 1998a). At the Workshop on Post-Application Exposure Assessment, held in Toronto, Canada, in October 1997, a conclusion of the residential modeling session was that there is a need for a regulatory peer review mechanism of the numerous models under development (Bergeron *et al*., 1997). An activity of the International Programme for Chemical Safety (IPCS) Project on *Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals* is focusing on development of guidance on the utility of modeling in exposure assessment. Updates on this effort are located on the IPCS Harmonization website (www.ipcsharmonize.org).

REPORTING AND FORMATTING OF DATA FOR REGULATORY SUBMISSIONS

It is recognized that harmonized formats for data submissions are beneficial. Detailed guidance in this area will lead to a lower submission rejection rate by regulatory jurisdictions, will facilitate electronic submission, and will result in efficiency gains. There are several initiatives underway in this area.

As part of the OECD Working Group on Pesticides, guidelines and criteria for industry for the preparation and presentation of complete dossiers and of summary dossiers has been developed. As part of the NAFTA Technical Working Group on Pesticides, the USEPA and PMRA of Health Canada are working together to develop standardized format and content for each industry study report.

EVALUATION AND DATA ANALYSIS BY REGULATORY AUTHORITIES

Common approaches for evaluation of submitted data are important prerequisites to full harmonization. With agreement on the methodology for conduct of occupational and residential exposure assessments, harmonized approaches for regulatory interpretation of the data become important to review sharing.

EVALUATION TEMPLATES

Draft guidelines and criteria for the evaluation of dossiers prepared by applicants and for the preparation of reports prepared by regulatory authorities in OECD countries have been developed (*Guidelines and Criteria for the Evaluation of Dossiers and for the Preparation of Reports by Regulatory Authorities in OECD Countries Relating to the Evaluation of Active Substances, the Registration of*

Plant Protection Products, and the Establishment of Maximum Residue Limits and Import Tolerances).

At the data evaluation report level, as part of the NAFTA Technical Working Group on Pesticides, the USEPA and PMRA of Health Canada are working together to develop standard review templates for data elements, including occupational and residential data. Standard review templates have been developed for key data types, including passive dosimetry studies, biological monitoring studies, dislodgeable (transferable) residue studies and dermal absorption studies.

Canada is leading an initiative for the development of common review templates for OECD Member Countries. The occupational and residential exposure review templates developed under the NAFTA Technical Working Group on Pesticides are being proposed. These study review templates for occupational and residential exposure are currently being piloted by evaluators in the USA and Canada.

Challenges in establishing templates include reaching consensus on the level of detail in reporting, units, normalization approaches, conventions regarding technical adjustments, consistency regarding data-pooling approaches and agreement on statistical approaches.

EXPOSURE FACTORS

Exposure factors can be defined as the inputs used to translate unit exposure values (μg/kg active ingredient (a.i.) handled) to estimates of an individual's daily exposure (μg/kg body weight (b.w.)/d), which can then be compared to No Observed Adverse Effect Levels (NOAELs) in mammalian toxicology studies or Acceptable Operator Exposure Levels (AOELs). Exposure factors can be categorized as follows: physiological (inhalation rates, body weights, lifespan, etc.), pesticide usage (duration of activity and acreage treated per day) and lifestyle (activity patterns, co-occurrence information, etc.).

Physiological Factors

Physiological factors are key to deriving estimates of exposure. As part of the NAFTA Technical Working Group on Pesticides, the USEPA and Health Canada's PMRA have reached agreement on a number of physiological factors, including standard reference values for body weights, body surface areas, life expectancy, working lifetime and inhalation rates (Table 10.3). In addition, the NAFTA Technical Working Group on Pesticides has agreed to a default assumption that dermal absorption is equivalent to absorption via the gastrointestinal (GI) tract, with lower defaults supported with empirical data on a case-by-case basis.

Most regulatory jurisdictions assume complete retention and absorption of inspirable and respirable particulates and gases. In a route-specific risk assessment

Table 10.3 Adult physiological exposure factors developed by the NAFTA Technical Working Group

Scenario	Gender-specific			Comments
	Males	Females	Males and females[a]	
Body weight (kg)	76.9 (rounded to 77)	62.4 (rounded to 62)	69.7 (rounded to 70)	Median values (USEPA, 1996). Value for *males and females* represents the average of the *median* body weights for males and females (USEPA, 1996)
Surface area (cm^2)				Surface areas for individual body parts represent median values from USEPA (1996). *Male upper arms* represent the value for arms minus the value for forearms. *Female upper arms and forearms* are based on the data for arms, assuming the same ratio of upper arms to forearms as for males. *Totals* represent the sum of the median values for individual parts. Although it is not entirely correct to sum percentile values, it allows for consistency between the individual body parts data and the totals. Another appropriate method might be to use the median total surface areas, and the percentages of each body part to estimate surface areas for each part. This would also ensure consistency with total surface area. Values for males and females combined were calculated by averaging the data sets for the two groups
Head	1 300	1 110	1 205	
Trunk (including neck)	7 390	5 790	6 590	
Arms				
Upper arms	1 600	1 265	1 433	
Forearms	1 310	1 035	1 173	
Hands	990	817	904	
Thighs	3 820	3 260	3 540	
Lower legs	2 560	2 180	2 370	
Feet	1 310	1 140	1 225	
Total	20 280	16 597	18 440	
Life expectancy (years)	72.1	78.9	75	Average values, based on 1993 projections (USEPA, 1996, 1997)

Working lifetime (years)	—	—	40.0	Based on data from USEPA (1996, 1997) for the occupational group 'farming, forestry and fishing' that indicates a median tenure of 39.8 years for the 65+ age group
Chronic inhalation rate (m^3/d)	15.2	11.3	13.3	Based on the averages of three approaches for calculating inhalation rates (i.e. using average daily food energy equivalents, basal metabolic rates and energy expenditure based on activity level), as presented in USEPA (1997)
Short- and intermediate-term inhalation rate (m^3/h)				Based on the average of several studies presented in USEPA (1997). The activities correspond to the following: • *Rest* – lying down • *Sedentary* – sitting, pilot, driving a tractor • *Light* – flagger, mixer/loader (containers <50 lb), pneumatic reel sprayer, lawn treatment, most harvesters • *Moderate* – mixer/loader (containers >50 lb), backpack sprayer (greenhouse, hilly conditions, heavy brush), harvesters using ladders • *Heavy* – generally not applicable to occupational exposure to pesticides
Rest	—	—	0.4	
Sedentary activity	—	—	0.5 (8.3 LPM)	
Light activity	—	—	1.0 (17 LPM)	
Moderate activity	—	—	1.6 (27 LPM)	
Heavy activity	—	—	3.2 (53 LPM)	

[a] LPM, litres per minute.

comparing the inhalation exposure data to results from an inhalation toxicology study, it is assumed that the test animal and human subpopulation of interest have the same retention and absorption of pesticides via the inhalation route. When comparing the inhalation exposure estimate to a No Observed Adverse Effect Level from an oral toxicology study, this assumes that inhalation retention and absorption is equivalent to absorption through the GI tract. As retention and absorption might be expected to be greater following inhalation than from ingestion and uptake from the GI tract, this approach would not be considered conservative.

Pesticide Usage Factors

Pesticide usage factors include those factors needed to characterize the amount of pesticide an individual is potentially exposed to each day, as well as the duration, frequency and interval of potential exposures. For example, for mixer/loaders/applicators, this would include hectares typically treated per day, typical application rates, types of equipment used, and whether application is conducted by the farmer or a custom applicator.

As part of the NAFTA Technical Working Group on Pesticides, the USEPA and Health Canada's PMRA have established default values for hectares treated per day for agricultural scenarios (Table 10.4). These are considered as an approximation only to be used by evaluators to verify and supplement, rather than replace, crop-specific survey data.

It is recognized that regional differences in pesticide usage factors make it unlikely that such factors will become fully harmonized internationally. However, there is good consensus internationally on what the key usage factors are (Schipper, 2001).

Lifestyle Factors

Human activity data is a key element of higher-tiered exposure estimates and to modeling efforts. The USEPA has compiled a comprehensive Exposure Factors Handbook (USEPA, 1996, 1997a). Other jurisdictions have country-specific factors. Surveys (e.g. the National Human Activity Pattern Survey and the Canadian Human Activity Pattern Survey) are adding to the existing knowledge base. For effective harmonization, similarities, as well as country-specific differences, in exposure factors should be identified. For example, the Canadian Human Activity Pattern Survey showed that Canadians spent a similar amount of time indoors/outdoors to that of USA citizens, and therefore similar assumptions can be used in algorithms. A particular data need is detailed information quantifying the extent and types of surfaces and objects contacted by children.

To the extent possible, applicable defaults are being incorporated into evaluation templates. This will promote harmonization of these values.

Table 10.4 Average acres treated per full workday for various crops

Crop type	Application equipment	Dilution rate (USgal/acre)	Acres per workday	
			Grower	Custom applicator
Orchards–vineyards	Airblast	65	50	—
	Airblast	100–125	—	40
	Airblast	250	—	35
	Airblast	400–500	17	25
	Airblast	750	—	20
	Airblast	1000–1500	—	15
	Aerial fixed wing	20	—	220
	Aerial fixed wing	20	—	430[a]
Vegetables	Groundboom	25–35	80–100	—
	Groundboom	50	40–65	—
	Groundboom	75	—	30–60
	Groundboom	100	20	30–40
	Groundboom	>100–200	—	20
	Helicopter	5	—	175
	Helicopter	5	—	300[a]
	Helicopter	10	—	100
	Helicopter	10	—	170[a]
Field crops	Groundboom	37 749	350[b]	700–750[b]
	Groundboom	37 905	175–250[b]	540[b]
	Groundboom	30	—	320[b]
	Groundboom	35–40	100	200[b]
	Aerial fixed wing	37 654	—	1000
	Aerial fixed wing	5	—	500
	Aerial fixed wing	5	—	1000
	Aerial fixed wing	10	—	350
	Aerial fixed wing	10	—	700

[a] Assumes two airplanes are working together to treat the same sites with one worker doing the mixing/loading for both planes. For helicopters, the assumption was made that two mixer/loaders were servicing one helicopter.
[b] Assumes grower or employee of custom applicator is using a tractor equipped with latest application technology: 'closed' mixing/loading system, larger mix tanks, foam field marking system and extra wide sprayboom.

CURRENT DATA ANALYSIS CHALLENGES

Analysis and interpretation of data from occupational exposure studies present numerous challenges. In order to facilitate review sharing and consistent decision-making, it is important that consistent approaches to data analysis be adopted. Areas where there is currently divergence in approaches, or no clearly outlined approach, are noted below.

Mathematical Approach

First, individuals interpreting data must decide on whether to use a deterministic or a probabilistic approach to generate an exposure estimate for the analysis. The deterministic approach (point-estimate) is widespread and beginning with this approach is consistent with the tiered approach to exposure and risk assessment,

whereby less effort is spent on assessments which yield acceptable risk levels using straightforward assessment techniques. The topic of probabilistic exposure assessment is discussed in Chapter 8 of this text.

In recent years, some regulatory agencies have developed approaches and guidance for conduct of probabilistic assessments for exposure scenarios The USA is most advanced in this area, with draft guidance having been published (USEPA, 1997b, 1998b, 2000). For higher-tier assessments, this approach has much merit as it is capable of incorporating large data sets and the output yields much more information on exposure potential for a given subpopulation (e.g. characterizes variability, uncertainty and enables sensitivity analysis). In order to share outputs of a probabilistic data analysis, co-operative work on approaches and reporting format is needed. Mitchell and Campbell (2001) have identified issues for which harmonized detailed guidance are required These include the following:

- types of analyses for which probabilistic methodologies potentially add value;
- criteria for model validation;
- key considerations for fitting appropriate distributions to specific types of data;
- selection of appropriate output metrics;
- data-reporting formats;
- characterization of variability and uncertainty in input and output distributions;
- appropriate degree of formality for documenting distributions and assumptions based on expert judgment.

Interpretation of Residues Present Below the Limit of Detection

In passive dosimetry, biological monitoring and dislodgeable and transferable residue dissipation studies, it is not uncommon that, for a proportion of the data, no residues are detected on the matrix of interest at the analytical limit of detection and/or quantification. The limit of detection (LOD) is generally defined as the point at which a measured value becomes larger than the uncertainty associated with it, whereas the limit of quantification (LOQ) is generally defined as the lowest pesticide residue that can be accurately quantified in a reproducible fashion (USEPA, 1998a). The OECD recommends that for values below the limit of detection of the analytical technique, one-half of the limit of detection should be used in calculations (OECD, 1997). The USEPA (1998a,b) notes that historically the USEPA has used half of the limit of quantification to represent chemical concentrations in a matrix when the residue level in that matrix is at or below the LOQ. This guidance proposes that if values are above the limit of quantification, then use the value; if values are between the LOQ and the LOD, then use half of the LOQ, while if values are below the LOD, use half of the LOD. Additional approaches to quantifying ‘non-detect’ values have been proposed (Helsel, 1990; Ginevan, 1993) and such approaches need to be considered. For harmonization to be possible, there will have to be agreement on the approach

to be used or clear identification of what has been done to allow recalculation as necessary.

Corrections for Incomplete Field Recovery

Field recovery refers to data generated to determine the loss of analyte from sample-collection devices fortified in the field, when subjected to the same environmental conditions (e.g. temperature, light, relative humidity and wind) and duration as field-exposure samples (OECD, 1997). Interpretation of quality control and quality assurance components of field studies requires an examination of all aspects of a data set and it is difficult to provide prescriptive guidance regarding adjustments for field recovery. However, although established guidelines (OECD, 1997; USEPA, 1998a) do provide guidance, there is a divergence of approaches and more explicit guidance is needed.

The first challenge pertains to selection of the most relevant field recovery data for a given set of field measurements. Field recovery is generally characterized at three 'spike' levels, on each day of the study. The 'inter-spike' and 'inter-day' variabilities should be considered when selecting the most relevant field recovery corrections. For instance, if recovery is consistent across all spike levels there may be merit in generating an overall average field recovery for a given day. Similar considerations could be made for multi-day field recoveries which show little day-to-day variability. Guidance in the form of decision logic considerations for field recovery selection need to be developed.

The second challenge pertains to selection of the cut-off, above which no adjustment is merited. Although 90 % (USEPA, 1998a) or 95 % (OECD, 1997) are common conventions, other approaches are used. For example, although not an approach used by regulatory authorities, some study directors correct all data to 100 % recovery, including recoveries from field fortifications greater than 100 %. Harmonized guidance is required.

Characterization of Dissipation Kinetics

Transferable and dislodgeable residue studies are an important tool for characterizing post-application exposure potential. Analysis of these data requires characterization of dissipation kinetics. This raises a number of data analysis questions, including the following:

- Should each individual sample be used in the calculation of the dissipation curve or should the triplicate replicate samples collected on a given day be averaged in some manner?
- What procedure should be used for fitting dissipation curves to the residue data?
- How should data collected shortly after application (i.e. 'day zero') be handled in generating dissipation curves?

- How should data approaching the limit of detection or limit of quantification be handled in generating dissipation curves?

The approach taken to these issues can significantly influence post-application exposure assessments and lead to divergent outcomes by regulatory authorities. Harmonized approaches to analysis of dissipation kinetics are therefore needed.

Outliers and Atypical Observations

Inclusion or exclusion of outliers can significantly influence exposure assessments, and harmonized outlier rejection criteria are needed. The suitability of existing approaches (e.g. anything beyond three standard deviations is an outlier) to occupational exposure data sets, as well as the role of field study observations, needs to be considered.

METRIC SELECTION

Selection of the appropriate metric for use in the risk assessment can have a significant impact on the outcome of an assessment. Regardless of the mathematical approach used, it is important that harmonized guidance exists for metric selection. Guidance should be based on a number of considerations, including data quality, data quantity, distribution type, duration of exposure and nature of the toxicology endpoint. Based on personal experience with numerous deterministic exposure assessments, it is clear that regulatory authorities differ with respect to input and output metric selections.

Central Tendency Metric Selection

To evaluate the impact of central tendency metric selection on occupational risk assessment outcomes, Health Canada's PMRA conducted a small retrospective analysis of six recent occupational risk assessments for new active ingredients in which exposure estimates were based on 'best-fit' unit exposure values from the Pesticide Handlers Exposure Database (PHED), Version 1.1 (Table 10.5). The completed assessments were revisited to determine if use of the arithmetic mean rather than a best-fit measure of central tendency would have had a significant impact on risk-assessment outcome. For all six new active ingredients examined, the exposure estimates from the arithmetic mean were higher than those from the best-fit values and would have had a significant impact on one risk assessment. For 'Chemical E' in Table 10.5, use of the arithmetic mean would have triggered a requirement for a higher-tier chemical-specific exposure study or further investigation of exposure mitigation measures, such as lowering of the maximum application rate. In one additional case ('Chemical C' in Table 10.5),

Table 10.5 Analysis of impact of measure of central tendency selection on overall occupational risk assessment outcome

Chemical-scenario identifier	Scenario description[a]	Exposure estimate (mg/kg b.wt./d)		Toxicology endpoint selection		Risk assessment outcome (MOE)[c]		Comments regarding significance of measure of central tendency selection on risk assessment outcome
		'Best-fit'[b]	Arithmetic mean[b]	NOAEL (mg/kg b.wt./d)/ Q^*_1[c]	Target MOE[c]	'Best-fit'	Arithmetic mean	
Active ingredient A – 50 % dispersible granule proposed for airblast application to grapes (A-1), groundboom application to strawberries (A-2) and application to ornamentals using a hand-held wand (A-3); exposure duration, short-term								
A-1	M/L/A	0.13	0.53	1000	100	8 000	1 900	No impact on overall outcome due to use of short-term dermal toxicology study with NOAEL[c] of 1000 mg/kg b.wt./d
A-2	M/L/A	0.077	0.23	1000	100	13 000	4 300	
A-3	M/L/A	0.068	0.61	1000	100	15 000	1 600	
Active ingredient B – 80 % wettable granule (B-1, B-2, B-3, B-4); 25 % aqueous suspension (B-5, B-6, B-7, B-8); exposure duration, short-term to intermediate-term								
B-1	M/L/A–gb–custom applicator	0.23	0.7	1000	100	4 000	1 400	No impact on overall outcome due to use of short-term dermal toxicology study with NOAEL[c] of 1000 mg/kg b.wt./d
B-2	Aerial M/L	0.24	0.66	1000	100	4 000	1 500	
B-3	Pilot	0.015	0.1	1000	100	65 000	10 000	
B-4	M/L/A–airblast	0.053	0.223	1000	100	19 000	4 500	
B-5	M/L/A/–gb–custom applicator	0.15	2.2	1000	100	7 000	450	
B-6	Aerial M/L	0.14	2.6	1000	100	7 000	380	
B-7	Pilot	0.015	0.11	1000	100	65 000	9 000	
B-8	M/L/A–airblast	0.05	0.3	1000	100	20 000	3 300	

(*continued overleaf*)

Table 10.5 (*continued*)

Chemical-scenario identifier	Scenario description[a]	Exposure estimate (mg/kg b.wt./d)		Toxicology endpoint selection		Risk assessment outcome (MOE)[c]		Comments regarding significance of measure of central tendency selection on risk assessment outcome
		'Best-fit'[b]	Arithmetic mean[b]	NOAEL (mg/kg b.wt./d)/ Q^*_1[c]	Target MOE[c]	'Best-fit'	Arithmetic mean	
Active ingredient C – 50 % wettable granule; airblast application to apples; exposure duration, short-term								
C-1	M/L/A	0.065 (LADD = 0.0002)	0.27 (LADD = 0.0009)	1000 (Q^*_1 = 2.9×10^{-3})	100 (10^{-6})	15 000 (6×10^{-7})	3 700 (2×10^{-6})	No impact on non-cancer risk assessment. Cancer risk level of 2×10^{-6} may have triggered addition of coveralls to label
Active ingredient D – 75 % water-dispersible granule; groundboom application to corn; custom applicator; dermal absorption <10 %; exposure duration, intermediate-term								
D-1	M/L/A	0.024 (LADD = 0.000 04)	0.062 (LADD = 0.0001)	1000 (dermal) 5 (oral) 3 (oral) (Q^*_1 = 1.14×10^{-2})	100 300 100 (10^{-6})	41 000 1 350 1000 (5×10^{-7})	16 000 700 500 (10^{-6})	No impact on overall outcome

Active ingredient E – 55 % water-dispersible granule; groundboom application to soybean (E-1, E-2) and corn (E-3, E-4); farmer and custom applicator; dermal absorption <30 %; exposure duration, short-term for farmer and intermediate-term for custom applicator								
E-1	M/L/A–farmer	0.073	0.22	20 (dermal)	100 100	270 330	90 110	Use of arithmetic mean would have a significant impact on this risk assessment. As the exposure assessment is already based on two layers of clothing, further exposure reduction options are limited
E-2	M/L/A–custom applicator	0.16	0.47	20 (dermal) 7.3 (oral)	100 100	130 150	4 050	
E-3	M/L/A–farmer	0.11	0.31	20 (dermal)	100 100	190 230	6 080	
E-4	M/L/A–custom applicator	0.19	0.55	20 (dermal)	100 100	110 130	4 040	
Active ingredient F – 60 % dry flowable proposed for groundboom application to potatoes; farmer (F-1) and custom applicator (F-2); exposure duration, intermediate-term								
F-1	M/L/A	0.025	0.076	1000 (dermal)	300	40 000	13 000	No impact on overall outcome due to use of short-term dermal toxicology study with NOAEL[c] of 1000 mg/kg b.wt./d
F-2	M/L/A	0.15	0.47	1000 (dermal)	300	6 500	2 000	

[a] M, mixer; L, loader; A, applicator; gb, groundboom.
[b] LADD, lifetime average daily dose.
[c] NOAEL, No Observed Adverse Effect Level; Q^*_1, Unit of Risk Value; MOE, Margin of Exposure.

use of the arithmetic mean would have triggered additional personal protective clothing on the label. The remaining four active ingredients would not have been impacted. Albeit limited in scope, this analysis illustrates how differences in central tendency metric selection could have impacts on regulatory decisions and harmonization.

Recent consultations on central tendency selection for the Pesticide Handlers Exposure Database (PHED) resulted in general guidance (Ginevan, 1999) that may be applicable beyond the PHED. This consultation resulted in the following general guidance recommendations:

- ***For short-term exposures, the median is the appropriate measure of central tendency***. This guidance is based on the recognition that, for the two most prevalent distribution types (log–normal, and normal), the median approximates the mean (i.e. geometric mean for log–normal distribution and arithmetic mean for normal distribution).
- ***For longer-term exposures, the arithmetic mean is the appropriate measure of central tendency***. This is based on the recognition that the central limit theorem dictates that with multiple exposure events, the average of these events will converge to the arithmetic mean of the original distribution from which the events were drawn, and that the distribution of these averages will follow a normal distribution, regardless of the form of the original underlying distribution.
- ***For risk assessments addressing significant acute toxicity endpoints, the arithmetic mean or other reasonably high-end measure of exposure should be selected***.

Such guidance requires international debate and consensus as there can be differences between what regulatory authorities will utilize (e.g. geometric mean, arithmetic mean, median, etc.) and this can lead to divergence in country-specific assessments.

Metrics Other than Central Tendency

As for risk assessments addressing significant acute toxicity endpoints, the arithmetic mean or other reasonably high-end measure of exposure should be selected. Such high-end measures of exposure could include an upper percentile from a probabilistic output, or a maximum. Guidance is needed on what considerations should lead to the use of a high-end measure of exposure. Factors to be incorporated would need to include the nature of the toxicological endpoint, existing toxicologically based uncertainty or safety factors, and the confidence in the exposure estimates.

Daily Time-Weighted Average or Amortized Expressions of Exposure

Exposure estimates can be presented as estimates of exposure for a day, as estimates of an average daily exposure over a defined period of time (e.g. a season),

or as a lifetime-average daily exposure. Generation of a daily exposure estimate (e.g. μg/kg b.wt./d) is the most common approach. However, the toxicology database is the key determinate of the appropriate duration metric and there are instances where a time-weighted average expression of exposure, or a lifetime amortization expression of exposure, may be more appropriate.

Canada has generated time-weighted average exposures for occupational and residential post-application exposure scenarios where dislodgeable (transferable) foliar residue data have yielded dissipation curves which allow generation of daily exposure estimates on successive days following application. These estimates have potential utility in risk assessments not based on acute toxicological endpoints.

Amortization of daily exposure over the lifetime of an individual is another data analysis approach used by some jurisdictions. Although this value is not a true lifetime-average daily exposure estimate, and distorts the actual short-term exposure to higher values, the absence of a more accurate estimate has led the USA and Canada to use it by coupling with unit risk values for active ingredients considered as potential non-threshold carcinogens.

Guidance on the appropriate use of time-weighted average and amortized exposure estimates are required, as the selection of a daily versus time-weighted average versus a lifetime average daily exposure can lead to divergent risk assessment outcomes. Guidance in this area would be a function of several factors, including exposure duration, frequency and interval, the toxicology endpoint, mechanism of action considerations and documented sensitivities to specific subpopulations. Harmonized decision logic is required. An important aspect of such decision logic would also be addressing appropriate data analysis approaches for generating time-weighted average or lifetime average exposures across age categories, including juvenile categories.

RESEARCH NEEDS

Identification and prioritization of research needs at the international level would result in more focused and strategic research initiatives by both the pesticide manufacturers and the larger research community. For example, the USEPA National Exposure Research Laboratory has identified general areas of research needs in children's exposure assessments for environmental exposures (Cohen Hubal *et al.*, 2000). There is a requirement to develop harmonized priorities for research that would strengthen risk assessment methodologies for pesticides. This would need to be followed by an effective communication strategy so that funding bodies and the research community were informed about such priorities.

EXPOSURE MITIGATION

PROTECTION FACTORS

Potential exposure can be reduced through the use of protective clothing and gloves, respiratory protection and engineering controls. As Tier 1 exposure values

Table 10.6 Variability in default values for protection factors used in Canada, Germany, UK, USA and California

Factor	Range in % protection assumed
Clothing, gloves	
One layer of normal work clothing or regular coveralls	50–97
Chemical-resistant coveralls	90–95
Chemical-resistant gloves	90–99
Respiratory protection	
Supplied air respirator	> 99
Cartridge respirator	90–98
Dust mask (single-use)	50–80
Engineering controls	
Closed mixing and loading system	90–98
Enclosed cab	90
Enclosed cab with positive pressure and charcoal air-filtration unit	98

are generally based on typical clothing and engineering controls, these values can be refined through the application of protection factors.

In a cursory survey, Campbell (2000), has compiled available information on protection factors used in the UK, Germany, USA, California and Canada and found significant variability in the default factors used (Table 10.6). Harmonization regarding the degree of protection provided by personal protective apparel (clothing, gloves, etc.), equipment (respirators) and engineering controls should be feasible as region-specific considerations should be minor.

LABELING

An international mandate to pursue a globally harmonized system (GHS) for chemical classification and labeling was adopted at the United Nations Conference on Environment and Development (UNCED) in 1992. Specifically, Chapter 19 of Agenda 21 states that 'a globally harmonized classification and compatible labeling system, including material safety data sheets and easily understandable symbols, should be available, if feasible, by the year 2000'. It recommended that 'the new system should draw on current systems to the greatest extent possible, and should be developed in steps and should address the subject of compatibility with labels of various applications'. The technical work of harmonization is underway by different international organizations with specific expertise in the areas involved. Criteria for health and environmental hazards are being lead by the OECD and hazard communication by the International Labour Organization (ILO). Health criteria being developed to classify chemicals will be applied to pesticides, including end-use products. However, not all aspects of labeling will be applied in every instance. This reflects the current practice of classification and labeling pesticides based on identified acute hazards, while addressing identified reproduction hazards (for

example) through a risk assessment process (i.e. either acceptable or unacceptable risk for proposed use – no labeling).

RE-ENTRY INTERVALS

Re-entry intervals (also known as restricted entry intervals) provide a mechanism to reduce post-application exposure potential by preventing entry to treated areas until an established interval of time (e.g. 24 h) has expired.

It is generally recognized that re-entry intervals should be based on post-application exposure and risk assessments. In the absence of this type of assessment, some regulatory authorities have developed interim measures for deriving re-entry intervals. In the USA, EPA guidance is provided as part of the Worker Protection Standard. Re-entry intervals are based on the acute toxicity category of the active ingredient and are outlined in the USEPA's Label Review Manual (www.epa.gov/oppfead1/labeling/lrm). Options are either 12, 24 or 48 h, with a re-entry interval of 72 h reserved for products that are organophosphorous esters which inhibit cholinesterase and may be applied outdoors in an area where the average rainfall for the application site is less than 25 in/year.

Although climate-specific and cultivation-specific considerations may merit different re-entry intervals, approaches for deriving re-entry intervals should be harmonized as much as possible.

OCCUPATIONAL AND RESIDENTIAL RISK ASSESSMENT

AOELS VERSUS MOES

In the EU, Directive 91/414/EEC requires that for an active substance an Acceptable Operator Exposure Level (AOEL) should be considered. More than one AOEL may be appropriate for a given substance, depending on potential routes and durations of exposure (Hamey, 2000). Harmonized guidance on specific criteria and procedures to establish AOELs for pesticides in the EU is currently under development and a European Commission Working Document is currently used by some Member States as a draft reference guidance (Hamey, 2000). This documentation will be of value to the European Commission in its objective of achieving consensus within Europe on the procedure for AOEL setting.

In North America, similar approaches are used in the conduct of occupational and residential risk-assessment approaches. AOELs, *per se*, are not developed. Rather, appropriate toxicology endpoints are compared with exposure estimates and the resulting Margins of Exposure (MOEs) are compared with target margins of exposure.

Convergence to a common expression of risk (i.e. comparing exposure to an established AOEL or providing scenario-specific MOEs) is feasible and would promote harmonization.

ROUTE CONSIDERATIONS

Human health risk assessments can be either route-specific or combined routes. Dietary risk assessments, for instance, are straightforward from a route perspective as all intake is through ingestion. However, occupational and residential exposures virtually always involve contributions from more than one route (e.g. dermal, inhalation, non-dietary ingestion, etc.). As pivotal toxicology studies are frequently gavage or feeding studies, exposure assessors have traditionally summed exposures from these routes, incorporating absorption values, to derive a total systemic exposure. However, limitations to this approach have been identified. When the toxicology database indicates the need for route-specific assessments or when appropriate toxicology studies exist using the dominant route of exposure, route-specific approaches should be considered. Guidance is needed on when and when not to do this.

UNCERTAINTY AND SAFETY FACTOR SELECTION

Differences in approaches to application of uncertainty and safety factors can lead to divergent regulatory decisions.

In the EU, there is consensus on use of 10 to account for interspecies differences in toxic response to a chemical but there are different approaches in the intraspecies factor. These differences have not been fully resolved (Hamey, 2000).

In Canada and the USA, there is agreement on the use of a factor of 10 for interspecies differences and another factor of 10 for intraspecies differences. The US Food Quality Protection Act (FQPA) of 1996 and the Canadian Pest Control Products Act (PCPA) of 2002 require that when establishing food tolerances in the case of threshold effects, an additional tenfold safety factor for the pesticide chemical residue and other sources of exposure be applied to infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. A different safety factor for the pesticide chemical residue may be used only if, on the basis of reliable data, such a factor will be safe for infants and children.

There are differences as to how safety factors greater than 100 are applied to risk assessment for workers. Some regulatory authorities (e.g. Canada) apply additional uncertainty and safety factors when conducting occupational risk assessments. Other jurisdictions (e.g. the USA) do not. Such divergent approaches can lead to different risk assessment outcomes. Consistent approaches to application of uncertainty and safety factors would greatly facilitate harmonization.

AGGREGATION AND CUMULATIVE RISK ASSESSMENT

In the USA and Canada, aggregate exposure is defined as ‘the combined exposure of a target to a single pesticide via all relevant pathways and sources’.

Cumulative exposure is defined as 'the combined exposure of a target to two or more pesticides (with a common mechanism of action) via all relevant pathways and sources'. The US FQPA and the Canadian PCPA mandate the consideration of aggregation of pesticide chemical residues from dietary and residential exposures, and cumulative exposures of pesticide chemical residues with common mechanisms of action. This presents a formidable methodological challenge to exposure assessors.

To begin to tackle the methodological challenge, the International Life Sciences Institute (ILSI) organized workshops on aggregate exposure assessment (ILSI, 1998, 2000). An objective of these workshops was to develop an aggregate exposure assessment framework. Various private and public sector modeling initiatives are currently underway to develop approaches for aggregate and cumulative risk assessments. The USEPA has outlined general principles for performing aggregate exposure and risk assessments (USEPA, 2001).

Approaches for aggregating exposure for simple scenarios have been proposed in the literature (Shurdut *et al*., 1998; Zartarian *et al*., 2000). The USEPA's National Exposure Research Laboratory has developed the Stochastic Human Exposure and Dose Simulation (SHEDS) model for pesticides, which can be characterized as a first-generation aggregation model and the developers conclude that to refine and evaluate the model for use as a regulatory decision-making tool for residential scenarios, more robust data sets are needed for human activity patterns, surface residues for the most relevant surface types, and cohort-specific exposure factors (Zartarian *et al*., 2000). The SHEDS framework was used by the USEPA to conduct a probabilistic exposure assessment for the specific exposure scenario of children contacting chromated copper arsenate (CCA)-treated playsets and decks (Zartarian *et al*., 2003).

This increased complexity in exposure assessment will lead to improved regulatory decision-making. However, with increasing complexity comes increasing challenges from a harmonization perspective. In order to achieve harmonization on scientific approaches with complex underpinnings, it is critical that regulatory authorities be co-ordinated on these initiatives in the early stages.

CO-OPERATIVE REGULATORY ACTIVITIES

As part of the NAFTA Technical Working Group on Pesticides, the USEPA and Health Canada's PMRA have gained experience with respect to evaluation approaches through a parallel review of a product which was then assessed to determine whether the processes in each country were sufficiently similar to allow joint reviews to be undertaken. They were deemed to be so and progressively more new active ingredients and their associated end-use products are submitted jointly. In these joint assessments, the submission is divided up and one regulatory body is the primary reviewer for their agreed upon part of the submission, while the other regulatory body serves as the secondary or peer-reviewer.

In 1999, a co-operative international review team, comprised of Canada, the United States, Australia and the European Union (Ireland), participated in a pilot project that focused on exchange and utilization of each others' reviews. The pilot project confirmed that the new shared approach to review being taken by regulatory agencies worldwide leads to more efficient regulatory systems, while still allowing each country to uphold their own rigorous standards for health and environmental protection.

SUMMARY AND CONCLUSIONS

Significant progress has been made in the area of occupational and residential exposure assessment for pesticides. However, given the rapid evolution of this scientific discipline, continued progress is important. The following items, identified in this chapter, are considered priorities for harmonization.

TERMINOLOGY

1. Development of harmonized pesticide exposure assessment terminology.

FRAMEWORK

2. Agreement on elements of a tiered approach for post-application agricultural exposure assessment.
3. Development of a tiered approach for residential exposure assessment.

DATA REQUIREMENTS

4. Identification of subpopulations of bystanders which merit quantitative exposure assessments (e.g. residential exposure in agricultural areas, direct exposure to drift, and exposures from the use of pesticides in schools, daycare centers and other public places).
5. Agreement on the role of toxicology triggers, if any, in the tiered approach to occupational and residential exposure and risk assessment.
6. Generation of biocide applicator data. These include, in order of priority, high-pressure spray, low-pressure spray, painting (roller/brush), wipe/mop, place solids, aerosol spray, painting (airless), pour solid, pour liquid and pump liquid.
7. Characterization of secondary exposure scenarios relevant to wood preservative use, and corresponding data requirements to conduct exposure assessments.
8. Strategy for assessing potential exposure to biocides contained in consumer articles (e.g. textiles and cutting boards).

METHODOLOGICAL GUIDANCE

9. Methodological guidance for conduct of exposure studies to measure post-application exposure in non-agricultural settings, including residential.
10. Methodological guidance for deriving transfer metrics for post-application exposure scenarios in agricultural settings when the treated surface of interest is not foliage, e.g. soil.
11. Methodological guidance for conduct of exposure studies to measure other exposure scenarios (e.g. residential exposure in agricultural areas, direct exposure to drift, and exposures from the use of pesticides in schools, daycare centers and other public places).
12. Validation of *in vitro* dermal absorption methodology.
13. Development of guidance on the interpretation of residues remaining on the washed skin in *in vivo* dermal absorption studies.
14. Agreement regarding acceptability, from an ethical perspective, of dermal absorption studies conducted with human volunteers.

DEVELOPMENT AND UTILITY OF DATABASES

15. Upgrade the PHED database or develop a new database to reflect a broader range of mixer, loader and applicator functions and advances in agricultural application technology.
16. Investigate feasibility of combined existing mixer/loader/applicator databases (e.g. EUROPOEM and PHED).

MODELING INITIATIVES

17. Development of harmonized guidance regarding model validation criteria, good modeling practices and criteria for model-based assessments.

DATA ANALYSIS

18. Where defensible, harmonization of exposure factors, including physiological, pesticide usage and lifestyle factors.
19. Guidance for selecting an appropriate mathematical approach for a given exposure scenario (deterministic versus probabilistic) and guidance regarding conduct of acceptable probabilistic assessments.
20. Harmonized guidance for specific data analysis issues (i.e. corrections for incomplete field recovery, interpretation of residues present below the limit of detection, guidance for interpretation of outliers and atypical observations).
21. Harmonized guidance for appropriate expressions of exposure (daily, time-weighted average or amortized expressions of exposure).

METRIC SELECTION

22. Guidance on central tendency selection, and on appropriate metrics to use for risk assessments addressing significant acute toxicity endpoints.
23. Guidance on appropriate expressions of dose (daily, time-weighted average or amortized).

RESEARCH NEEDS

24. Development of a harmonized research strategy designed to inform occupational and residential exposure and risk assessments for pesticides.

EXPOSURE MITIGATION

25. Uniform defaults regarding protection provided by personal protective apparel (clothing and gloves), equipment (respirators) and engineering controls.

RISK ASSESSMENT

26. Common expression of risk (i.e. AOELs versus MOEs).
27. Guidance on appropriateness of route-specific risk assessment approaches.
28. Consistent approaches to application of uncertainty and safety factors.
29. Co-ordinated method development for aggregate and cumulative risk assessment.

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Glossary

Note: The source of many of the terms presented here was the *Glossary of Exposure Assessment – Related Terms: A Compilation*, prepared by the Exposure Terminology Sub-Committee of the International Programme for Chemical Safety (IPCS) (of the World Health Organization (WHO)) Exposure Assessment Planning Workgroup, November 1, 2001.

Absorbed dose In exposure assessment, the amount of a substance that penetrates an exposed organism's absorption barriers (e.g. skin, lung tissue and gastrointestinal tract) through physical or biological processes. This term is synonymous with internal dose (USEPA, 1997b).

Absorption barrier Any of the exchange barriers of the body that allow differential diffusion of various substances across a boundary. Examples of absorption barriers are the skin, lung tissue and gastrointestinal tract wall (USEPA, 1992a,b).

Absorption fraction The relative amount of a substance on the skin that penetrates through the epidermis into the body; reported as the unitless fraction of the applied dose or as the percentage absorbed (USEPA, 1992b).

Absorption percentage (percentage absorbed) The relative amount of a substance that penetrates through a barrier into the body, reported as a unitless fraction (USEPA, 1997c).

Acceptable Daily Intake (ADI) The ADI of a chemical is the estimate of the amount of a substance in food and/or drinking water, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk to the consumer on the basis of all of the known facts at the time of the evaluation. It is usually expressed in mg of the chemical per kg of body weight (FAO/WHO, 1997).

Acceptable Operator Exposure Level (AOEL) The acceptable operator exposure level is the maximum amount of active substance to which the operator may be exposed without any adverse health effects. The AOEL is expressed in mg of the chemical per kg of body weight of the operator. The AOEL is based on the highest level at which no adverse effect is observed in tests in the most sensitive relevant animal species or, if appropriate data are available, in humans. Appropriate safety factors (SFs) are also taken into consideration, i.e. NOAEL/SF = AOEL (UKPSD, 2003).

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Active ingredient (a.i.) The chemical component of a pesticide formulation or end-use product that is intended to act as a pest deterrent; also known as the biologically active chemical agent in a pesticide product (USEPA, 1997c).

Administered dose *see* Dose.

Adverse effect An adverse effect is one that causes functional impairment or pathological lesion affecting the performance of the organism or reducing its ability to respond to additional challenge. Adverse effects are those which have an adverse health consequence as opposed to those which are normal physiological responses (Sielken, Ch. 8).

Aggregate dose The dose resulting from the aggregate exposure (Sielken, Ch. 8).

Aggregate exposure (single pesticide) The combined exposure of a target to a single pesticide via all relevant pathways and sources (Norman, Ch. 10).

Aggregate exposure (multiple pesticides) The sum of exposures to pesticide chemical residues with a common mechanism of toxicity from multiple sources and multiple routes of exposure (Food Quality Protection Act, 1996) (USEPA, 1997a).

Aggregate exposure assessment A process for developing an estimate of the extent of exposure of a defined population to a given chemical by all relevant routes and from all relevant sources (ILSI, 1998).

Aggregate risk The likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance (USEPA, 2001).

Ambient measurement A measurement (usually of the concentration of a chemical or pollutant) taken in an ambient medium, normally with the intent of relating the measured value to the exposure of an organism that contacts that medium (USEPA, 1992a).

Ambient monitoring A method of measuring the amount of a substance that is available for uptake – composed of both environmental monitoring and personal monitoring (OECD, 1997).

Application of a pesticide The treatment (spraying, etc.) of a field, lawn or house, either by hand or by using equipment. Application does not include the preparation (e.g. mixing or loading) of the pesticide (Sielken, Ch. 8).

Applied dose The amount of a substance in contact with the primary absorption boundaries of an organism (e.g. skin, lung or gastrointestinal tract) and available for absorption (USEPA, 1992b).

Average (absorbed) daily dose (ADD) Calculated dose rate averaged over a pathway-specific period of exposure expressed as a daily dose on a per-unit-body-weight basis. The ADD is used for exposure to chemicals with non-carcinogenic and non-chronic effects. This parameter is usually expressed in terms of mg/kg/d or other mass/mass/time units (USEPA, 1997c; IRIS, 1999).

Benchmark dose (BMD) One of a number of possible specified dose values which is used as a reference point. For example, a No Observed Adverse Effect Level (NOAEL) and an effective dose (e.g. ED_{10}) are both benchmark doses (Sielken, Ch. 8).

Biological marker (biomarker) Indicators of changes or events in human biological systems. Biological markers of exposure refer to cellular, biochemical or molecular measures that are obtained from biological media such as human tissues, cells or fluids and are indicative of exposure to environmental contaminants (NRC, 1991).

Biological monitoring (biomonitoring) Measurement of a pesticide or its metabolites in the body fluids of exposed persons and conversion to an equivalent absorbed dose of the pesticide based on a knowledge of its human metabolism and pharmacokinetics (OECD, 1997).

Biologically effective dose The amount of a deposited or absorbed chemical that reaches the cells or target site where an adverse effect occurs, or where that chemical interacts with a membrane surface (USEPA, 1992a, 1997b; REAP, 1995).

Bound An upper or lower limit on the value of an unknown quantity. For example, an upper bound on risk is not equal to the true risk but attempts to be sufficiently large so that it is unlikely that the true risk is greater than the upper bound. A point estimate of risk (as opposed to a bound on risk) attempts to be equal to the true risk (Sielken, Ch. 8).

Bounding estimate An estimate of exposure, dose or risk that is higher than that incurred by the person in the population with the highest exposure, dose or risk. Bounding estimates are useful in developing statements that exposures, doses or risks are 'not greater than' the estimated value. (USEPA, 1992a, 1997b; REAP, 1995).

Breathing zone A zone of air in the vicinity of an organism from which respired air is drawn. Personal monitors are often used to measure pollutants in the breathing zone (USEPA, 1992a).

Case-control study The observational epidemiological study of persons with the disease (or another outcome variable) of interest and a suitable control (comparison or reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the *Risk Factor* are compared between cases and controls (Heederik and Teschke, Ch. 7).

Closed cab A vehicle used for pesticide application that is at least partially sealed from (closed to) the outside environment, such as an air-conditioned tractor (Sielken, Ch. 8).

Closed system Mixing the active pesticide ingredient or its formulation with other substances such as water in a closed container as opposed to an open environment and/or loading the pesticide (mixture) into application equipment in a closed environment (such as pumping the pesticide from one closed container to another) (Sielken, Ch. 8).

Commercial or commercial operator A person who handles pesticides for multiple clients, as opposed to a farmer who handles pesticides in conjunction with his own crop production (Sielken, Ch. 8).

Conservative Used in risk assessment to describe a policy or choice attempting to be 'health-protective', i.e. selected to be reasonably certain that exposure or risk is not underestimated and to err on the side of overestimating the exposure or risk (Sielken, Ch. 8).

Contact (applied) dose *see* Dose.

Continuous random variable A random variable that can take on any value in an interval, e.g. durations, weights and concentrations are all continuous random variables (Sielken, Ch. 8).

Cross-sectional study Examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in defined populations at one particular time. The relationship between a variable and disease can be evaluated in terms of the prevalence of disease in different populations, or of the variable in terms of presence or absence of the variables in the diseased and non-diseased populations (Last, 2001).

Cumulative Assessment Group (CAG) A subset of chemicals selected from a common mechanism group for inclusion in a refined quantitative estimate of risk. The chemicals in the CAG, as well as their pathways/routes and pesticide uses, are judged to have a hazard and exposure potential that could result in the expression of a cumulative risk. Thus, negligible contributors are not included in quantifying the risk (USEPA, 2002).

Cumulative distribution function (cdf) For a random variable (X), this is a function (F) such that for any value t, $F(t)$ is the probability that X is less than or equal to t. For example, if the random variable X is the margin of exposure, then the cumulative distribution function evaluated at 100, i.e. $F(100)$, is the probability that the margin of exposure is less than or equal to 100, while $F(1000)$ is the probability that the margin of exposure is less than or equal to 1000 (Sielken, Ch. 8).

Cumulative exposure The combined exposure of a target to two or more pesticides (with a common mechanism of action) via all relevant pathways and sources (Norman, Ch. 10).

Cumulative risk The risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity (USEPA, 2002).

Cumulative risk assessment An analysis, characterization and possible quantification of the combined risks to humans or the environment from multiple agents or stressors (USEPA, 2003).

Cutaneous Of, relating to, or affecting the skin (USEPA, 1992b).

Default value In the absence of specific data to use in a risk assessment, a default value may be used that is of sufficient magnitude to provide reasonable certainty that exposure or risk is not underestimated and that errs on the side of overestimating the exposure or risk (Sielken, Ch. 8).

Delivered dose The amount of a chemical available for interaction by any particular organ or cell (USEPA, 1992a, 1998).

Dermal absorption (dermal penetration) Movement of a pesticide into and through the skin; includes that taken up into the systemic circulation and that retained in the skin compartment (OECD, 1997).

Dermal exposure The quantifiable measure of the amount of residue deposited on skin, normally expressed as a density, or mass per unit time, deposited on a defined skin surface area (e.g. mg/h hand exposure); equivalent to potential dose for the dermal route (USEPA, 1998).

Dermally absorbed dose The amount of the applied material (the dose) which becomes absorbed into the body (USEPA, 1992b).

Deterministic (point estimates) model A mathematical model in which the parameters and variables are not subject to random fluctuations, so that the system is at any time entirely defined by the initial conditions chosen – contrast with a stochastic model (Swinton, 1999).

Direct exposure Exposure to a subject who comes into contact with an agent via the medium in which it was initially released to the environment. Examples include exposures mediated by cosmetics, other consumer products, some food and beverage additives, medical devices, 'over-the-counter' drugs and single-medium environmental exposures (REAP, 1995).

Direct method Measures a pesticide residue in environmental media or on the skin surface before it has entered the body in order to estimate the potential dose. Examples of direct methods are those that determine residues in air, water, on surfaces and in food (Lewis, Ch. 3).

Discrete random variable A random variable that can take on only a countable number of different values, e.g., the number of children in a household is a discrete random variable (Sielken, Ch. 8).

Dislodgeable (transferable) residue That part of the residue of a chemical deposited on a solid surface which may be transferred by direct contact to human skin or clothing (ASTM International, 2003). It is generally estimated by means of mechanical devices, although bare-skinned or clothed human subjects are sometimes used (Lewis, Ch. 3). Note – some authors specify dislodgeable residues as those derived from the shaking methodology (using crop foliage) and transferable residues as those derived from wipe methodology (usually from turf).

Distribution The set of all possible values for a random variable and the relative likelihood of each of the possible values (e.g. the distribution of dose in a population is the set of all doses in the population and the relative likelihood or frequency of each dose) (Sielken, Ch. 8).

Distributional technique An analytical method incorporating uncertainty and/or variability into a distribution of values. Distributional techniques are probabilistic techniques and include Monte Carlo simulation (Sielken, Ch. 8).

Dose The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism.

(1) The **potential dose** is the amount of chemical that could be inhaled without wearing a respirator, or which could be deposited on the skin without wearing clothing. Potential dose is typically expressed as mass per unit body weight per unit time (e.g. mg/kg/d) (USEPA, 1998).
(2) The **applied (contact) dose** is the amount of a substance presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism) (USEPA, 1992a, 1997c).
(3) The **absorbed dose** is the amount crossing a specific absorption barrier (e.g. the exchange boundaries of skin, lung and digestive tract) through uptake processes (USEPA, 1992a, 1997c).

(4) The **internal dose** is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries (USEPA, 1992a, 1997c).
(5) The amount of the chemical available for interaction by any particular organ or cell is termed the **delivered dose** for that organ or cell (USEPA, 1992a, 1997c).
(6) The **biologically effective (target) dose** is that portion of the delivered dose that reaches the site(s) of toxic action (Driver *et al*., Ch. 4).

Dose additivity It is assumed that each chemical behaves as a concentration or dilution of every other chemical in the Cumulative Assessment Group (or chemical mixture). The response of the combination is the response expected from the equivalent dose of an index chemical. The equivalent dose is the sum of the component doses, scaled by each chemical's toxic potency relative to the index chemical (USEPA, 2002).

Dose–response The relationship between the dose of a pollutant and the response (or effect) it produces on a biological system (CARB, 2000).

Dosimeter Instrument to measure dose; many so-called dosimeters actually measure exposure rather than dose (USEPA, 1992a,b).

Effective dose (ED) The dose corresponding to a specified increase in the probability of a specified adverse health effect, e.g. the ED_{10} is the dose corresponding to an increase of 0.10 in the probability of a specified adverse health effect above the background probability at zero dose (Sielken, Ch. 8).

Epidemiology The study of the distribution and determination of health-related states or events in specified populations and the application of this study to control of the health problems. Distribution refers to analysis by time, place and classes of persons affected (Last, 2001).

Exposure Contact of an organism with a chemical or physical agent, quantified as the amount of chemical available at the exchange boundaries of the organism and available for absorption. Usually calculated as the mean exposure, and some measure of maximum exposure (AIHA, 2000, attributed to USEPA, 1989).

Exposure assessment The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration and route of exposure (USEPA, 1992a,b, 1997c; REAP, 1995; AIHA, 2000).

Exposure duration Length of time over which contact with the contaminant lasts, or the total time an individual is exposed to the chemical being evaluated (USEPA, 1997c).

Exposure factors The inputs used to translate unit exposure values (μg/kg a.i. handled) to estimates of an individual's daily exposure (μg/kg b.wt./d), which can then be compared to no effect levels in mammalian toxicology studies or acceptable operator exposure levels (AOELs). Exposure factors can be categorized as (i) physiological (inhalation rates, body weights and lifespan), (ii) pesticide usage (duration of activity, acreage treated per day, etc.) and (iii) lifestyle (activity patterns and co-occurrence information) (Norman, Ch. 10).

Exposure frequency The number of times an exposure occurs in a given period; exposure may be continuous, discontinuous but regular (e.g. once daily) or intermittent (e.g. less than daily, with no standard quantitative definition) (REAP, 1995).

Exposure level The amount (concentration) of a chemical at the absorptive surfaces of an organism (USEPA, 1997b; USDOE, 2000).

Exposure medium (media) Any one of the basic categories of material surrounding or contacting an organism (e.g. outdoor air, indoor air, water, soil or sediments) through which chemicals or pollutants can move and reach the organism (USEPA, 1992b).

Exposure pathway The physical course a chemical or pollutant takes from the source to the organism exposed (USEPA, 1992a,b, 1997b,c; REAP, 1995; AIHA, 2000). Some examples of exposure pathways are drinking water ingestion, dietary consumption, pesticide handling, contact with an exposure media, or an activity that brings an individual into contact with an exposure media (Sielken, Ch. 8).

Exposure route The avenue by which a chemical comes into contact with an organism, e.g. inhalation, ingestion, dermal contact, injection, etc. (USEPA, 1997b).

Exposure scenario A set of facts, assumptions and inferences about how exposure takes place that aids the exposure assessor in evaluating, estimating or quantifying exposures (USEPA, 1992a,b, 1997c; REAP, 1995).

Field recovery Data generated to determine the loss of analyte from sample-collection devices fortified in the field, when subjected to the same environmental conditions (e.g. temperature, light, relative humidity, wind, etc.) and duration as field-exposure samples (OECD, 1997; Norman, Ch. 10).

Formulation The form in which the pesticide is delivered to the user. Some different types of formulations are flowable formulations (FFs), emulsifiable concentrates (ECs) or water-dispersible granules (WDGs) (Sielken, Ch. 8).

Fugacity The tendency for a substance to move from one environmental compartment to another (Mackay, 2001). The fugacity model is formulated by using the concept of fugacity and can be used in chemical processing calculations (Matoba and van Veen, Ch. 6).

Geometric mean The nth root of the product of n values (USEPA, 1992a,b, 1997c). Thus, the geometric mean of the scores 1, 2, 3 and 10 is the 4th root of $1 \times 2 \times 3 \times 10$, i.e. the 4th root of 60 ($= 2.78$). The formula can be written as follows: geometric mean $= (\Pi X)^{1/n}$, where ΠX represents taking the product of all of the values of X (Hyperstat Online).

Health-relevant exposure In epidemiology studies, it is considered that not all exposures lead to, or are associated with, a certain health risk. Depending on the disease of interest, only specific time-periods of exposure (windows of exposure) are considered relevant (Heederik and Teschke, Ch. 7).

High-end exposure (dose) estimate A plausible estimate of individual exposure or dose for those persons at the upper end of an exposure or dose distribution, conceptually above the 90th percentile, but not higher than the individual in the population who has the highest exposure or dose (USEPA, 1992a; REAP, 1995).

Histogram Graphical display in which the range of possible values is subdivided into intervals and either the frequency, percentage or proportion of values in each interval is indicated by the height of the bar drawn above that interval (Sielken, Ch. 8).

Indirect method Estimates the minimum absorbed dose by measuring residues in excreta, body fluids or tissues after exposure has occurred. Indirect methods may involve determination of the levels of specific pesticides, their metabolites or biological indicators ('biomarkers'), such as protein- or DNA-adducts, in blood, urine, feces, sputum, sebum, cerumen or adipose tissue (Lewis, Ch. 3).

Inhaled dose The amount of an inhaled substance that is available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism (USEPA, 1997c).

Intake The process by which a substance crosses the outer boundary of an organism without passing an absorption barrier, e.g. through ingestion or inhalation (*see also* (potential) dose) (USEPA, 1992a,b, 1997c).

Intake rate Rate of inhalation, ingestion and dermal contact depending on the route of exposure. For ingestion, the intake rate is simply the amount of food containing the contaminant of interest that an individual ingests during some specific time-period (units of mass/time). For inhalation, the intake rate is the rate at which contaminated air is inhaled. Factors that affect dermal exposure are the amount of material that comes into contact with the skin, and the rate at which the contaminant is absorbed (USEPA, 1997c).

Internal dose The amount of a substance penetrating across the absorption barriers (the exchange boundaries) of an organism, via either physical or biological processes. This term is synonymous with absorbed dose (USEPA, 1992a,b, 1997c; REAP, 1995).

Lifetime average daily dose (LADD) Dose that is averaged over an individual's lifetime, taking into account the frequency, duration and intensity of exposure events. LADDs are usually expressed in units of mg/kg/d (USEPA, 1998).

Lifetime exposure Total amount of exposure to a substance that a human would receive in a lifetime (usually assumed to be 70 years) (USEPA, 1997b; USDOE, 2000).

Limit of detection (LOD) The lowest concentration of a substance that can be reliably measured (CARB, 2000).

Limit of quantification (LOQ) The lowest pesticide residue that can be accurately quantified in a reproducible fashion (USEPA, 1998).

Linear dose–response relationship The probability that a specified response changes as a linear function of the dose (e.g. probability increasing in direct proportion to the increase in dose) (Sielken, Ch. 8).

Lowest Observed Adverse Effect Level (LOAEL) The lowest dose of a substance that has been observed to produce either a statistically or biologically significant increase in the frequency or severity of an adverse effect when compared to the frequency or severity at zero dose (Sielken, Ch. 8).

Margin of Exposure (MOE) Represents the ratio of a No Observed Adverse Effect Level (NOAEL) to an estimated dose/exposure level (USEPA, 1998).

Maximum likelihood estimation Criterion under which the best estimate is the one which maximizes the likelihood of the observed event. Maximum likelihood estimation is the classical statistical criterion for estimating unknown parameter values from observed data (Sielken, Ch. 8).

Mean transfer efficiency The ratio of the transfer rate to the pesticide deposition rate (Lewis, Ch. 3).

Median The middle value in a population distribution, above and below which lie an equal number of individual values; midpoint (CARB, 2000).

Model A mathematical function with parameters that can be adjusted so that the function closely describes a set of empirical data. A mechanistic model usually reflects observed or hypothesized biological or physical mechanisms, and has model parameters with 'real-world' interpretation. In contrast, statistical or empirical models selected for particular numerical properties are fitted to data; model

parameters may or may not have 'real-world' interpretation. When data quality is otherwise equivalent, extrapolation from mechanistic models (e.g. biologically based dose–response models) often carries higher confidence than extrapolation using empirical models (e.g. a logistic model) (IRIS, 1999).

Modeling Use of mathematical equations to simulate and predict real events and processes (REAP, 1995).

Monte Carlo simulation (Monte Carlo technique) A repeated random sampling from the distribution of values for each of the parameters in a generic (exposure or dose) equation to derive an estimate of the distribution of (exposures or doses in) the population (USEPA, 1992a,b, 1997c; IRIS, 1999; AIHA, 2000).

Multimedia exposure Exposure to a toxic substance from multiple pathways such as air, water, soil, food and breast milk (CARB, 2000).

Nonlinear dose–response relationship Any dose–response relationship that is not linear. For example, a dose–response relationship in which the probability of a specified response changes either faster (supralinear) or slower (sublinear) than linear as the dose increases (i.e. probability either not increasing, or not decreasing at all, or changing slower or faster than in direct proportion to the increase in dose) (Sielken, Ch. 8).

No Observed Adverse Effect Level (NOAEL) The highest dose of a substance at which there are neither statistically nor biologically significant increases in the frequency or severity of adverse effects between the exposed population and the unexposed population (Sielken, Ch. 8).

Open pour Mixing the active pesticide ingredient with other substances such as water in an open environment (such as mixing in an open container), as opposed to a closed environment and/or loading the pesticide (or mixture containing the pesticide) into application equipment in an open environment (such as pouring the pesticide into an unsealed opening) (Sielken, Ch. 8).

Passive dosimetry A method of measuring the amount of pesticide coming into contact with an individual (OECD, 1997).

Percentile The smallest value such that the random variable is less than or equal to that value at least the specified percentage of the time. If a random sample contains five distinct values, then the 20th sample percentile is the smallest sample value (Sielken, Ch. 8).

Percutaneous absorption The process by which pesticides pass through the skin barrier and enter systemic circulation; normally expressed as flux (mass per unit skin surface area per unit time), but may also be expressed as a percentage (fraction of amount deposited on skin (exposure) reaching systemic circulation times 100) per unit time (USEPA, 1998).

Personal exposure monitor A device worn on or near the contact boundary that measures concentration (Zartarian *et al*., 1997).

Personal measurement A measurement collected from an individual's immediate environment using either active or passive devices to collect the samples (USEPA, 1992b).

Pesticide usage factors Those factors needed to characterize the amount of pesticide an individual is potentially exposed to each day, as well as the duration, frequency and interval of potential exposures. For example, for mixer/loader applicators, this would include hectares typically treated per day, typical application rates, types of equipment used, and whether application is conducted by the farmer or a custom applicator (Norman, Ch. 10).

Physiological factors Those factors that are key to deriving expressions of exposure, such as standard reference values for body weights, body surface areas, life expectancy, working lifetime and inhalation rates (Norman, Ch. 10).

Population The set of all individuals being characterized. The exposure may vary among the individuals in the population, and some people may not be exposed at all. A population may be composed of multiple subpopulations (e.g. the USA population can be partitioned/subdivided into 50 state subpopulations) (Sielken, Ch. 8).

Potential dose *see* Dose.

Prevalence The number of events, e.g. instances of a given disease or other condition, in a given population at a designated time; sometimes used to mean prevalence rate-existing disease cases, and is not the same as disease incidence (Last, 2001).

Primary exposure (biocides) That occurring to the person when using the preservative, and other persons involved in the mixing and loading, application or post-application phases, such as equipment maintenance and handling of freshly treated wood (OECD, 2000).

Probabilistic analysis Calculations and expression of health risks using multiple-risk descriptors to provide the likelihood of various risk levels. Probabilistic risk results approximate a full range of possible outcomes and the likelihood of each, which is often presented as a frequency distribution graph, thus allowing uncertainty or variability to be expressed quantitatively (USEPA, 1999).

Probabilistic uncertainty analysis A technique that assigns a probability density function to each input parameter, and then randomly selects values from each of the distributions and inserts them into the exposure equation. Repeated calculations produce a distribution of predicted values reflecting the combined

impact of variability in each input to the calculation. The Monte Carlo approach is a common type of probabilistic uncertainty analysis (USEPA, 1997c; USDOE, 2000).

Probability The chance that a particular event will occur given the population of all possible events (*see* definition for **Risk**) (USDOE, 2000).

Probability density function (pdf) Indicates the relative likelihood of the different possible values of a random variable. For a discrete random variable, say X, the pdf is a function, say f, such that for any value x, $f(x)$ is the probability that $X = x$. For example, if X is the number of pesticide applications in a year, then $f(2)$ is the probability density function at 2 and equals the probability that there are two pesticide applications in a year. For a continuous random variable, say Y, the pdf is a function, say g, such that for any value y, $g(y)$ is the relative likelihood that $Y = y$, $0 \leq g(y)$, and the integral of g over the range of y from minus infinity to plus infinity equals 1. For example, if Y is body weight, then $g(70)$ is the probability density function for a body weight of 70 and the relative likelihood that the body weight is 70. Furthermore, if $g(70)/g(60) = 2$, then the body weight is twice as likely to be 70 as it is to be 60 (Sielken, Ch. 8).

Prospective cohort study A study in which subsets of a defined population who are, have been, or in the future, may be exposed and unexposed individuals are selected and followed concurrently over time to determine whether or not they develop the disease(s) of interest and with what frequency (Heederik and Teschke, Ch. 7).

Protective clothing Clothing provided to personnel to minimize the potential for skin, personal and company-issued clothing contamination. Also referred to as 'anticontamination clothing', 'anti-Cs' and 'PCs' (USDOE, 1998).

Random sample A sample selected from a statistical population such that each individual has an equal probability of being selected (USEPA, 1992a, 1997c).

Random variable A quantity that takes on numerical values depending upon an experimental outcome. For example, the unknown number of liters of drinking water consumed in a day is a random variable, and the observed value of the random variable might be 1.4. Each number in the range of possible values for a random variable does not have to be equally likely; different values may have different probabilities. (Sielken, Ch. 8).

Range The difference between the largest and smallest values in a measurement data set (USEPA, 1992a, 1997c; REAP, 1995).

Reasonable maximum exposure (RME) Used in conservative exposure assessment calculations – based not on a 'worst-case' scenario, but on 90 % and 95 % upper confidence limits on input parameters (AIHA, 2000).

Reasonable 'worst-case' A semiquantitative term referring to the lower portion of the high end of the exposure, dose or risk distribution. The reasonable 'worst-case' has historically been loosely defined, synonymously with maximum exposure or 'worst-case', and assessors are cautioned to look for contextual definitions when encountering this term in the literature. As a semiquantitative term, it is sometimes useful to refer to individual exposures, doses or risks that, while in the high end of the distribution, are not in the extreme tail. For consistency, it should refer to a range that can conceptually be described as being above the 90th percentile in the distribution, but below about the 98th percentile (compare maximum exposure range, 'worst-case') (USEPA, 1992a).

Re-entry dose level (RDL) Dose level at which re-entry into an area previously treated with a chemical can occur with negligible deleterious effects caused by exposure to the chemical because the biological mode of action threshold for that chemical has not been met (mg/kg/d) (USEPA, 1998).

Reference dose (RfD) An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (USEPA, 2003).

Relative likelihood Indicates the chance that a value or an event will occur. If the random variable is a discrete random variable, then the relative likelihood of a value is the probability that the random variable equals that value. If the random variable is a continuous random variable, then the relative likelihood at a value is the same as the probability density function at that value (Sielken, Ch. 8).

Replicate The OECD guidance document defines a replicate as a measurement of exposure to a worker during one typical workday, which includes all job functions related to pesticide use (OECD, 1997).

Restricted entry intervals (re-entry intervals) The time after application of a pesticide during which workers are not allowed to enter the treated area (Whitmyre *et al*., Ch. 2).

Risk The likelihood that an individual will develop a specified adverse health effect. Risk can be characterized in quantitative terms, such as the probability of the adverse health effect or the margin of exposure which is the ratio of the dose with a specified probability of the adverse health effect and an individual's dose from exposure (Sielken, Ch. 8).

Risk assessment Frequently described as involving four components, i.e. hazard identification, exposure assessment, dose–response assessment and risk characterization. Risk assessment may be an input to risk management (Sielken, Ch. 8).

Risk characterization The quantitative or qualitative description of risk. For example, a quantitative risk characterization could be either a point estimate of risk (a single value for the risk, as opposed to a range of values), an upper bound on risk (which implies a range of values for the risk) or a distribution of risk (which implies a range of values for the risk and the relative likelihood of each value in that range) (Sielken, Ch. 8).

Scenario evaluation An approach to quantifying exposure by measurement or estimation of both the amount of a substance contacted, and the frequency/duration of contact, and subsequently linking these together to estimate exposure or dose (USEPA, 1992a,b; REAP, 1995).

Secondary exposure (biocides) Post-application exposure via the environment, namely bystanders and consumers, including children, who may be inadvertently exposed to wood preservatives by inhalation, dermal contact or by ingestion, and have little or no control over this exposure (OECD, 2000).

Sink term In residential models, this term removes pesticide from the residential environments (e.g. degradation of the pesticide, diffusion into room materials etc.) (Matoba and van Veen, Ch. 6).

Source term In residential models, this term add pesticide to the residential environment (e.g. evaporation of the pesticide from a surface) (Matoba and van Veen, Ch. 6).

Stakeholder An interested or affected party in an ongoing or contemplated project (usually involving a group or team planning the project, analyzing one or more problems, and making decisions for possible actions on the basis of the interpretation of that analysis) (USEPA, 2003).

Stochastic model A mathematical model which takes into consideration the presence of some randomness in one or more of its parameters or variables. The predictions of the model therefore do not give a single point-estimate but a probability distribution of possible estimates (contrast with deterministic) (Swinton, 1999).

Stressor Any physical, chemical or biological entity that can induce an adverse response. A stressor may also be the lack of an essential entity, such as a habitat (USEPA, 2003).

Sublinear dose–response relationship A dose–response relationship in which the probability of a specified adverse health effect is either not increasing at all or increasing slower than linearly (i.e. slower than in direct proportion to the increase in dose) (Sielken, Ch. 8).

Subpopulation A subset or subgroup within a larger population (e.g. population can be partitioned into male and female subpopulations, and these can be further subdivided into five subpopulations – infants, children 1 to 6 years old, children 7 to 12 years old, teenagers 13 to 17 years old, and adults) (Sielken, Ch. 8).

Surrogate data Substitute data or measurements on one substance (or population) used to estimate analogous or corresponding values for another substance (or population) (PMRA, 2003).

Total human exposure Accounts for all exposures a person has to a specific contaminant, regardless of environmental medium or route of entry (inhalation, ingestion and dermal absorption). Sometimes, total exposure is used incorrectly to refer to exposure to all pollutants in an environment. Total exposure to more than one pollutant should be stated explicitly as such (NRC, 1991).

Transfer coefficient Residue transfer rate to humans during the completion of specific activities (e.g. cm^2/h), calculated using concurrently collected environmental residue data (USEPA, 1998).

Transferable residue *see* Dislodgeable (transferable) residue.

Uncertainty Represents a lack of knowledge about factors affecting exposure or risk and can lead to inaccurate or biased estimates of exposure. The types of uncertainty include scenario uncertainty, parameter uncertainty and model uncertainty (USEPA, 1997c).

Uncertainty factor (UF) (*sometimes also called* ***safety factor*** or ***modifying factor***) One of several, generally 10-fold factors, used in operationally deriving the reference dose (RfD) from experimental data. UFs are intended to account for (1) the variation in sensitivity among members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of 'less-than-lifetime' exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data (USEPA, 1995, 1997b; USDOE, 2000).

Upper bound An plausible upper limit to the true value of a quantity. This is usually not a true statistical confidence limit (IRIS, 1999).

Uptake The process by which a substance crosses an absorption barrier and is absorbed into the body (USEPA, 1992a,b, 1997c).

Variability Arises from true heterogeneity across people, places or time, and can affect the precision of exposure estimates and the degree to which they can be generalized. The types of variability include spatial variability, temporal variability and inter-individual variability (USEPA, 1997c).

'Worst-case' A semiquantitative term referring to the maximum possible exposure, dose or risk that can conceivably occur, whether or not this exposure, dose or risk actually occurs, or is observed in a specific population. Historically, this term has been loosely defined in an ad hoc way in the literature, and so assessors are cautioned to look for contextual definitions when encountering this term. It *should* refer to a hypothetical situation in which everything that can plausibly happen to maximize exposure, dose or risk does, in fact, happen. This 'worst-case' may occur (or even be observed) in a given population, but since it is usually a very unlikely set of circumstances, in most cases, a 'worst-case' estimate will be somewhat higher than that which occurs in a specific population. As in other fields, the 'worst-case' scenario is a useful device when low-probability events may result in a 'catastrophe' that must be avoided even at great cost, but in most health risk assessments, a 'worst-case' scenario is essentially a type of bounding estimate (USEPA, 1992a; REAP, 1995).

'Worst-case' scenario A method of conducting an exposure assessment in which the most conservative value of each input parameter is selected (AIHA, 2000).

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Index

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