

**Series on Testing and Assessment
No. 9**

**Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During
Agricultural Application**

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris

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OECD Environmental Health and Safety Publications

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of Occupational Exposure to Pesticides
During Agricultural Application**

Environment Directorate

Organisation for Economic Co-operation and Development

Paris 1997

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**OECD Environment Directorate,
Environmental Health and Safety Division**

**2 rue André-Pascal
75775 Paris Cedex 16
France**

Fax: (33-1) 45 24 16 75

E-mail: ehscont@oecd.org

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This publication was produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC).

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, FAO, WHO, UNIDO and the OECD (the Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. UNITAR joined the IOMC in 1997 to become the seventh Participating Organization. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

FOREWORD

This Guidance Document presents an internationally harmonized approach to the conduct of studies of occupational exposure to pesticides during agricultural application.

Work on the development of harmonized guidance for the assessment of occupational exposure to agricultural pesticides began with the international workshop on Risk Assessment for Worker Exposure to Agricultural Pesticides held in the Hague, the Netherlands, in May 1992. One of the documents discussed at this workshop was a draft guidance document on evaluation of worker exposure to agricultural pesticides prepared by Dr Graham Chester of Zeneca Agrochemicals, UK. Dr Chester's document was revised in light of the workshop discussions and published as part of the workshop proceedings in the *Annals of Occupational Hygiene*.¹

The guidance document agreed at the workshop in the Hague was subsequently discussed at the Workshop on Methods of Pesticide Exposure Assessment held in Ottawa, Canada, in October 1993. This Workshop was a joint effort of Health Canada and the North Atlantic Treaty Organisation (NATO), and was officially supported by the US Environmental Protection Agency (EPA) and the OECD.

After intensive discussion at the Ottawa workshop, the guidance document was revised by a Revision Committee, then reviewed by a Peer Review Committee. Both committees (see Annex IV) were established at the workshop, and their composition was agreed by the workshop participants. The peer-reviewed document was submitted by Canada to the OECD in March 1995 with the request that it be developed and published as an OECD Guidance Document. To this end, the document received from Canada was circulated to OECD Member countries for comment. The document was revised in light of comments received and again circulated to countries with the request that it be derestricted. This document is published on the responsibility of the Secretary-General of the OECD.

¹ G. Chester, Evaluation of agricultural worker exposure to, and absorption of, pesticides. *Ann. Occup. Hyg.* 37, No. 5, 509-523, 1993.

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Introduction

The evaluation of worker exposure to pesticides is an integral part of risk assessment, both for product safety and regulatory assessment purposes and for post-registration surveillance of pesticides in use. The purpose of this document is to review and compare the available methods for measuring pesticide exposure and to provide guidance on the design of studies for the determination of exposure to, and absorption of, pesticides by workers involved in their use.

The focus of this document is on mixer/loader/applicator exposure during agricultural uses of pesticides. Some of the information may also apply to the assessment of post-application exposure or to the assessment of exposure arising from non-agricultural pesticide uses. The document is not intended to cover biological effect monitoring, which may be used as an adjunct to exposure or absorbed dose measurement. Non-occupational exposure to pesticides and the exposure of pesticide manufacturing and formulation workers are also beyond the scope of this document and will not be addressed.

Annexes provide details on methods for the evaluation of exposure and absorbed dose and on quality control and quality assurance. *It is emphasised that the Annexes provide guidance only and are not intended to be used as study protocols.* A glossary of important terms is also appended.

Rationale for guidance on the conduct of worker exposure studies

The essential components of a quantitative risk assessment for workers involved in pesticide use are a detailed evaluation of the toxicity of the pesticide, an estimate or measurement of the exposure and/or amount of pesticide absorbed by the workers as a consequence of its use, and the likelihood of the expression of any toxicological effect in the workers. Although the evaluation of the toxicity of new pesticides is conducted according to internationally accepted guidelines using harmonized methods and protocols, no such internationally accepted guidelines exist for measuring exposure (although there are different nationally agreed approaches). This guidance document therefore proposes harmonized methods and approaches for the quantitative evaluation of exposure.

Guidelines and standard protocols for the measurement of exposure have been published previously; notable examples are the World Health Organization (WHO) standard protocol (WHO, 1982) and the US Environmental Protection Agency (EPA) guidelines on applicator/operator exposure (US EPA, 1987). Since their publication, there has been a marked shift in emphasis in regulatory risk assessment in several countries to take account of the extent of occupational exposure and, in particular, the absorbed dose of the compound in question. This shift has led to the development of more sophisticated approaches and methods, notably the increasing use of biological monitoring to measure the extent of absorption of pesticides. The increased use of biological monitoring has developed from the traditional use of biological effect monitoring to assess health effects or modification of normal biochemical indices in workers. There is therefore a need to draw together and review the available methods and present a standardised approach.

The tier approach

A tier approach to risk assessment for pesticides has been discussed by experts at international workshops in The Netherlands and Canada (Henderson et al., 1993; Carmichael, 1995). Emphasis is placed on maximum flexibility to enable the investigator to choose the most appropriate means of estimating or measuring the exposure to, or absorbed dose of, a pesticide. A detailed discussion of the tiered approach is outside the scope of this document, but the approach is summarised schematically in **Figure 1**.

The first tier generally involves comparing generic exposure data from published databases with no-observed-effect levels from toxicology studies relevant to the use pattern under consideration to see whether the predicted exposure leads to an acceptable margin of safety. Several databases have been developed, such as the North American Pesticide Handlers Exposure Database (PHED, 1992), the UK Predictive Operator Exposure Model (Martin, 1990), the German model (Lundehn et al., 1992) and the Dutch model (van Hemmen, 1992). In the European Union, a database and model that will take European agriculture into consideration are under development (Watts and Chen, 1995). In a Tier 1 assessment, the source and type of data used should be clearly identified and the database or model used must be validated and applied correctly.

The second tier involves using dermal absorption data (if available) to refine the estimate of absorbed dose from the dermal exposure route. Exposure mitigation measures (e.g. protective clothing, respirators) can also be taken into account.

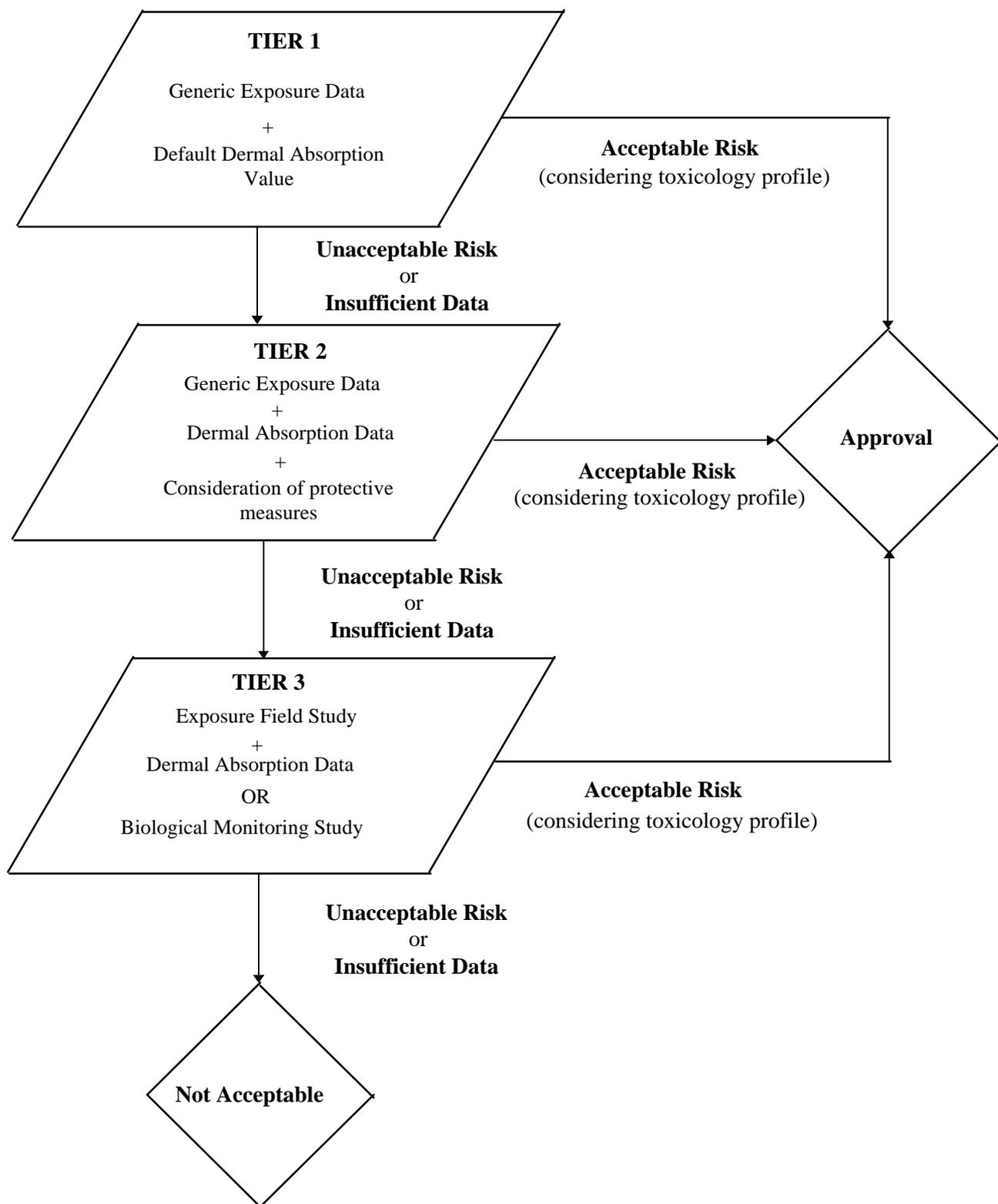
In the third tier a field study should be considered for use patterns for which no acceptable generic exposure data are available, or when margins of safety are inadequate based on generic exposure and dermal absorption data, if it is judged that generating additional exposure data alone will improve the quality of the risk assessment. It may be better to consider a biological monitoring approach, as absorbed dose data, interpreted with the aid of pharmacokinetics data, are likely to be more accurate than the estimate of absorption given by exposure data and correction for dermal absorption. If the risk assessment still indicates excessive exposure, further risk mitigation factors may be considered to reduce the absorbed dose to an acceptable level.

Review and comparison of methodology

Previous reviews

Early extensive reviews of methodology were published by Durham and Wolfe (1962), Wolfe (1976) and Davis (1980). These reviews, particularly the methodology of Durham and Wolfe (1962), formed the basis of the WHO standard protocol for the measurement of exposure (WHO, 1975, 1982). The first WHO protocol (1975) was aimed primarily at the measurement of exposure to, and absorption of, organophosphorus insecticides and included the Durham and Wolfe (1962) patch methodology to estimate dermal exposure. The revised WHO protocol (1982) was designed to assess all classes of pesticides and included an alternative method for the measurement of dermal exposure (the whole body clothing method) as well as an overview of biological monitoring as a means of measuring absorption arising from all routes of exposure. This revised protocol formed the basis of the US National Agricultural Chemicals Association (NACA) guidelines for mixer-loader-applicator exposure studies (Mull and McCarthy, 1986), although the NACA guidelines placed primary emphasis on the use of the Durham and Wolfe (1962) patch methodology, with scant reference to the more recently developed whole body method that had figured prominently in the revised WHO protocol.

Figure 1 Tier approach to risk assessment



In 1985, NACA also published guidelines for the conduct of field biological monitoring studies as a means of measuring the absorption of pesticides (NACA, 1985). Both the EPA (US EPA, 1987) and NACA guidelines contained detailed and useful reviews of the advantages and limitations of the various approaches to the measurement of exposure to, and absorption of, pesticides. More recently, the International Group of National Associations of Manufacturers of Agrochemical Products (GIFAP) published a position paper on broad aspects of monitoring studies in the assessment of worker exposure to pesticides (GIFAP, 1990). These guidelines were intended to inform the non-specialist of the various approaches to exposure/absorption evaluation and their significance. They were not intended to give detailed descriptions of the various monitoring methods or to recommend a specific approach.

Curry and Iyengar (1992) reviewed and compared the currently available guidelines (published and unpublished) for the evaluation of exposure of individuals using pesticides or exposed to pesticide residues in indoor and outdoor environments. Harmonized exposure and biological monitoring guidelines (and the tier approach to evaluation) were proposed in a workshop involving international experts held in the Netherlands (Chester, 1993; Henderson et al., 1993). The Worker Health and Safety Branch of the California Environmental Protection Agency published a guidance document on the preparation of pesticide exposure assessment documents (Thongsinthusak et al., 1993). The document gives information on default values for an exposure assessment, such as body surface areas, body weights, ventilation rates and clothing protection factors, and describes facets of the risk assessment process in California in detail.

Fenske (1993) evaluated the relevance of current dermal exposure sampling methods within the context of a dermal exposure assessment strategy for hazardous chemical substances in general.

Methods for measuring dermal exposure (see Annex I for details)

Patch method

In the patch method, the potential contamination of the workers' skin and clothing is measured using a variable number of absorbent cloth or paper patches attached to defined areas of the body, inside and outside clothing. The patches are the so-called dosimeters in passive dosimetry and act as a collection medium for the pesticide. After a defined or measured period of exposure, the patches are removed and analysed for pesticide content. In many published studies, the number of patches used per worker represented about 8 per cent of the total body area of approximately 2 m². The quantity of a pesticide on a patch of known area is related to the area of limb or other body part using standard body part surface areas (US EPA, 1987; see also Table A-1 in Annex I), assuming that the pesticide has been uniformly deposited over the body part. This assumption is perhaps the principal disadvantage of the patch method, as the extrapolation of the value given by the limit of quantification (LOQ) to the total body part may give a substantial under- or overestimate of exposure. This disadvantage can be addressed in part by increasing the number of patches located on body parts predicted to receive significant exposure. Individual body part exposure values are then added to give a total potential dermal exposure, expressed in mg/h, mg/d or mg/kg product handled or applied.

In the WHO protocol, fewer patches are recommended (representing only 3 per cent, instead of 8 per cent, of the body area), as only the pesticide contacting the normally unclothed area of skin is used to calculate actual exposure. In temperate climates, however, about 10 per cent of the total body area is normally unprotected during use of pesticides and other agricultural activities. Furthermore, normal work clothing, such as cotton trousers or shirts, is absorbent and may retain and allow penetration of a proportion of the pesticide. Therefore, it is necessary to estimate exposure to the covered areas of the body as well as exposure to the unclothed areas.

The amount of pesticide penetration through clothing is often measured using patches attached beneath the clothing. Without such inside patches, an estimate of penetration of normal clothing is usually proposed. However, penetration of clothing by pesticides may be influenced by such factors as the type of formulation (liquid or solid), the amount or volume of deposition on the clothing, the dampness of the clothing, the location of deposition (e.g. seams) and the type of fabric. Further uncertainties are introduced by the method of sampling.

The patch method may give significant under- or overestimates of exposure, depending on whether the patches have captured the non-uniform, random deposition of concentrate splashes or spray droplets. This limitation applies equally to crop re-entry procedures, such as harvesting, where contact with the crop is not a uniform process. One solution to the problem of non-uniform exposure is an increase in sample size. The development of the Pesticide Handlers Exposure Database (PHED, 1992) is an attempt to give more accurate estimates of exposures to different body regions. Despite its readily apparent limitations, the patch method can serve as a cost-effective method for evaluating pesticide exposure, particularly in comparative studies.

Whole body method

One means of overcoming the inherent problems of the patch method is the use of lightweight coveralls or similar types of clothing as dosimeters in the whole body method (WHO, 1982; Abbott et al., 1987). Exposure of the head is assessed by incorporating a hood into the coverall or using a separate cotton hat. Any protective clothing and equipment recommended for the product under study are worn over the sampling clothing, thus enabling an evaluation of their protection. Cotton undergarments (long pants and long-sleeved T-shirts) may also be worn as dosimeters beneath the coveralls to estimate dermal exposure of the covered part of the body. Use of the whole body method overcomes the problem posed by the assumption of uniformity of deposition in the patch method, as it is not necessary to extrapolate from small target areas to larger body regions. Most of the pesticide is likely to be captured if woven protective materials are used as the sampling medium. For these reasons, the whole body method is believed to give a more accurate estimate of potential dermal exposure, although this has not yet been verified.

A variant of the whole body method is the normal clothing approach. This approach involves the use of clothing and underwear that represents what the workers would normally wear, as outer and inner dermal dosimeters (Chester et al., 1990). Any protective clothing and equipment recommended for the product under study are worn over the sampling clothing. Exposure of the skin beneath the clothing can be estimated by taking account of the ratio of outer to inner clothing penetration or transfer of the pesticide, assuming that the permeation and transfer properties of the outer and inner clothing are the same. For analytical considerations, it may be necessary to use non-coloured, white materials such as cotton or cotton/polyester mixtures. As in the standard whole body method, the clothing is sectioned into individual body parts and analysed separately to determine the regional distribution of total potential and actual dermal exposure. It is important to have a good appreciation of the range of normal work clothing worn by the worker population under study. The selection of sampling clothing should err on the cautious side by utilising the minimum clothing that might be worn under the prevailing conditions. This method is particularly relevant for countries where the typical work clothing consists of a T-shirt, long-sleeved shirt, socks and long trousers and/or coveralls.

An advantage of the normal clothing variant of the whole body method is that it can be used to estimate dermal exposure concurrently with the use of biological monitoring to measure absorbed dose. Whereas the patch and standard whole body methods place sampling media between the pesticide and the clothing or skin (thus acting as a barrier and interfering with the process of skin contamination and percutaneous absorption), this method mimics the capture, retention and penetration properties of normal work clothing as closely as possible.

It should be noted that little attempt has been made to validate methods for the monitoring of dermal exposure (e.g. using biological monitoring to compare the derivations of absorbed dose). Until the methods are validated, they should all be regarded as providing only an indicative measure of dermal exposure. The challenge is to find a sampling medium that mimics skin in its pesticide capture and retention characteristics and thus can predict actual exposure. Given that biological monitoring for determination of absorbed dose does not lend itself to all pesticides, there remains a strong need to develop and refine exposure methods.

Use of fluorescent tracers and visible dyes to quantify exposure by analysis or video imaging²

Dermal exposure can be quantified by measuring the deposition of tracer chemicals, such as fluorescent materials or visible dyes, on the clothing and/or skin. The tracer can be extracted from passive dosimeters and analysed in the same way as the pesticide. By adjusting for concentration differences, an estimate of exposure to the pesticide can be obtained.

The fluorescent tracer/video imaging method (Fenske et al., 1986a,b; Fenske, 1990) involves the incorporation of a fluorescent tracer in a pesticide formulation and subsequent visual and quantitative analysis using a video imaging method. This method reveals non-uniform patterns of exposure that escape detection by the patch method. An important advantage of this method is that the skin serves as a collection medium, rather than dosimeter patches or clothing. The main limitations of this method are the assumptions that the relative transfer of the tracer and the pesticide in the field and their permeation of the clothing are equivalent. However, these assumptions are analogous to those involving generic exposure data: that is, the exposure to a pesticide measured under a given set of conditions is assumed to represent that associated with a second pesticide under the same conditions. Possible differences in the relative transfer of the tracer and the pesticide can be assessed by conducting ancillary studies. The method may be useful for the training of operators by demonstrating the extent of their contamination, thus allowing them to modify their working practices to reduce exposure. A second-generation imaging system with improved exposure quantification is now available (Fenske et al., 1990).

If an investigator chooses to use a tracer compound or visible dye, he/she should validate its performance and suitability as a surrogate for the intended measurement before the field study. Apart from the usual criteria of quality control (QC) acceptability that are applicable to all pesticides, the surrogate compound should not significantly alter the physical properties of the formulation or spray mixture. The key question regarding the utility of a tracer or dye is whether it impacts, is retained by or penetrates clothing alongside the pesticide of interest. Clearly, it can be used only in ambient exposure monitoring and not in biological monitoring (although it can be used with concurrent biological monitoring of a pesticide). Tracers may be particularly useful as substitutes in exposure studies for pesticides that are unstable during the sampling and analytical phases.

The main advantages and limitations of the above methods for estimating dermal exposure (other than hand exposure) are summarised in **Table 1**.

² This method is not discussed further in Annex I.

Table 1 Main advantages and limitations of the methods for estimating dermal exposure of the body

Dermal exposure method	Main advantages	Main limitations	Use with concurrent biological monitoring
Patch	Ease of analysis	Assumes uniform deposition	Yes
Whole body	No body region size or surface area correction necessary Less time-consuming in the field	Analysis may be more cumbersome May be uncomfortable for operator	No
Variant of whole body (normal clothing)	Collects most pesticide not reaching skin No extrapolation required for body surface area Less time-consuming in the field	Analysis may be more cumbersome	Yes
Dyes/video imaging	Visual and quantitative analysis (conventionally or video imaging) Measures exposure directly from skin (video imaging) Useful for training operators	Assumes equivalent clothing permeation by dye and pesticide	Yes

Hand exposure

Monitoring of hand exposure may be the most important measurement in a dermal exposure study. The contribution of the hands to total exposure has been well documented by many investigators, using a variety of methods (US EPA, 1987). The methods include the use of lightweight absorbent gloves or sections cut from gloves, swabbing or rinsing the hands in various solvents (US EPA, 1987), and using the normal process of washing the hands with soap and water to provide an estimate of exposure during concurrent biological monitoring (Chester et al., 1990). All these approaches have their advantages and limitations, and it is not possible to evaluate the accuracy of any procedure. The best that can be achieved for a hand wash or hand rinse method is a laboratory validation of the efficiency of recovery of material from the hands of human volunteers. This has been investigated recently by Fenske and Lu (1994) for the insecticide chlorpyrifos using a solvent hand rinse method. Their findings suggest that exposure to pesticides that are well absorbed by, or adsorbed to, the skin may not be estimated accurately by a hand rinse method. Where countries have ethical or practical guidelines on the use of human volunteers, they should be considered.

The US EPA (1987) stated that the use of gloves as a monitoring method may result in a significant overestimation of total dermal exposure, owing to their capacity to retain more of the pesticide than would be retained by the skin. Gloves also contain foreign materials which, unless pre-extracted, may be co-extracted with the pesticide. This may be a problem at low levels of contamination, although the levels of glove contamination due to dirt and grease are a greater problem in this respect. The hands also tend to incur significant levels of pesticide contamination, and low-level interference may not be as significant a problem as inferred by the US EPA (1987).

Washing the hands with a solvent is considered by some to disrupt skin barrier function and enhance percutaneous absorption of the pesticide. The US EPA (1987) claimed that there is little actual evidence for this, and recommended washing using the bag rinse method developed by Durham and Wolfe (1962). The EPA appears to prefer the bag rinse method over washing of the hands in a bowl because the bag rinse method is a standardised procedure, and because the data generated by it are consistent with those in the existing database.

In conclusion, it is not possible to recommend one method for estimating hand exposure over another insofar as accuracy of measurement is concerned.

Where exposure measurements and biological monitoring are to be conducted concurrently, a hand-washing procedure involving soap and water is proposed for use whenever the workers would normally wash their hands and where it is feasible to do so. The rationale for this proposal is that when absorption is assessed, there should be no interference with the normal process of dermal contamination and percutaneous absorption. Therefore, the use of absorbent gloves or a solvent washing or rinsing method is inappropriate, as the gloves would retain pesticide otherwise available for absorption and the solvents could potentially disrupt the barrier function of the skin. By performing a hand wash with ordinary soap and water whenever the worker chooses to wash his/her hands, this normal process of contamination and absorption is not unduly influenced, and the investigator is simply collecting what would be disposed of under normal circumstances. This method may provide an estimate of hand exposure, particularly if the worker chooses to wash at frequent intervals, such as after mixing or at meal breaks. The efficiency of the washing procedure for removal of the pesticide can be gauged by laboratory validation studies using the chosen soap and the normal process of hand washing. The major disadvantage is the loss of standardisation between workers owing to the variable number of hand washes. Variation could also arise from the type of soap used, water hardness, etc. An important analytical consideration is the laboratory validation of the extraction efficiency of the chosen soap and water prior to the field study. It is recommended that the soap be standardised for all workers in the study to ensure consistency of extraction efficiency. Any protective gloves worn, together with any protective glove washings, may also be taken for analysis to determine the potential exposure of the hands.

The main advantages and limitations of the methods for estimating the dermal exposure of the hands are summarised in **Table 2**.

Methods for measuring inhalation exposure (see Annex I for details)

One of the earliest but most complete reviews of the methodology for field monitoring of airborne pesticides was by Lewis (1976). Van Dyk and Visweswariah (1975) had previously reviewed the media available for collection of pesticides, but with particular emphasis on static environmental sampling. A personal air sampling method is the method of choice for the determination of airborne concentrations of pesticides in the breathing zones of workers. Several methods are available, ranging from the use of gauze pads in respirators, pioneered by Durham and Wolfe (1962), to the use of solid adsorbents and filter cassettes attached to battery-powered personal sampling pumps. A personal sampling method, involving sampling devices mounted in the breathing

zone and sampling pumps, is preferred. Use of the personal air sampler permits any label-recommended use of respirators or dust masks, but it does not measure inhalation exposure of workers wearing respiratory protection.

The choice of sampling medium is dictated by the nature of the pesticide, in that a suitable filter cassette or sampling head should be used for spray particulates and a solid adsorbent material for volatile compounds. Examples of suitable adsorbent materials for some volatile compounds are activated charcoal, Tenax and XAD-2 resins mounted in stainless steel or glass tubes. The choice of material should be determined by analytical retention (trapping efficiency) and extractability studies before monitoring. The inspirable fraction (all material capable of being drawn into the nose and mouth), which is the most relevant fraction to measure (Vincent and Mark, 1987). Part of this fraction will reach the alveoli and part will be retained in the upper airway or ingested.

It may be necessary to sample concurrently for particulates and vapour, in which case the filter sampling head is mounted in front of the vapour trap in a sampling train. This train allows retention on the resin of any vapour stripped off the filter. The material on the filter can be analysed and an estimate can be made of the pesticide content of the particulate sample. Where use of such a sampling train is indicated, laboratory validation of the sampling efficiency, particularly of the adsorbent resin, is necessary owing to the possibility that material may be stripped from the resin by the relatively high flow rate (typically 1-4 L/min).

Table 2 Main advantages and limitations for estimating the dermal exposure of the hands

Hand exposure method	Main advantages	Main limitations	Use with concurrent biological monitoring
Absorbent gloves	Ease of use	Possible overestimation of exposure	No
Solvent/swab rinse wash	Standardised method enabling comparison with most previous data	May disrupt barrier function of skin Laboratory validation requires human volunteers Possible underestimation of exposure	No
Hand wash (soap and water)	Does not interfere with process of skin contamination and absorption	Possible lack of standardisation among workers Laboratory validation requires human volunteers Possible underestimation of exposure	Yes

The measurement of the inspirable fraction and the use of adsorbent resins for the vapour component are recommended as the method of choice for estimating exposure by inhalation. The advantages and limitations of this method are summarised in **Table 3**.

Table 3 Main advantages and limitations of the method for estimating inhalation exposure

Inhalation exposure method	Main advantage	Main limitation	Use with concurrent biological monitoring
Personal air sampler (inspirable/vapour)	Measures potential inhalation and subsequent oral ingestion	The need to estimate ventilation rate	Yes

Methods for measuring the absorbed dose (biological monitoring) (see Annex I for details)

Biological monitoring is a method of evaluating the absorption of chemicals by measuring the chemical or its metabolites in body fluids, usually urine, blood or exhaled breath. Biological effect monitoring (use of biomarkers) has been used in the chemical industry for many years to assess health effects or modification of normal biochemical indices in workers as a consequence of exposure. In the context of pesticides, it has been used most frequently for assessing exposure to organophosphorus compounds by measuring blood cholinesterase activity (see, for example, Peoples and Knaak, 1982).

Analysis of body fluids and excreta, most commonly blood and urine, for the parent compound or its metabolites can provide both a qualitative and a quantitative measurement of absorbed dose for those pesticides considered suitable candidates for biological monitoring. This measurement of absorbed dose is perceived as the principal advantage of biological monitoring over ambient exposure monitoring, as it evaluates actual, rather than potential, absorption. It integrates absorption from all possible routes of exposure: dermal, inhalation, and primary and secondary oral ingestion. However, differentiating the contributions to the absorbed dose from different aspects of the work can be done only with a specifically tailored study design. For details and wider-ranging discussions of biological monitoring, the reader is referred to Van Heemstra-Lequin and Van Sittert (1986), Wang et al. (1989) and Henderson et al. (1993).

In order to obtain quantitative data on the amount of pesticide absorbed by workers, it is necessary to understand the metabolism and pharmacokinetics of the compound in humans. This requirement has been dealt with in detail by Woollen (1993). Field biological monitoring studies that have utilised or described human metabolism and pharmacokinetics data, either to interpret the absorbed dose or used as an adjunct, include those on the herbicides fluazifop-butyl (Chester and Hart, 1986) and 2,4-D amine (Grover et al., 1986; Ritter and Franklin, 1989). Data from such human volunteer dosing studies enable a correct field sampling strategy and define the body matrix of choice. Urine is the ideal sampling matrix, as its collection is non-invasive and the collection of 24-hour voids is often practicable. It is advisable to inform the participant of the importance of total urine collection and to check the completeness of 24-hour urine collections by measuring the concentration of creatinine and expressing excretion as g/d. Substantially incomplete collections are readily apparent; they can either be excluded or an allowance made for them – for example, by using a correction factor based upon the average daily urine volume for the individual concerned (Woollen, 1993). Other

parameters, such as specific gravity and osmolarity, may also be useful in this respect (Alessio et al., 1985). The utility of creatinine as a tool for checking compliance and in correcting urinary concentrations of excreted substances has been reviewed by Boeniger et al. (1993). It may also be necessary to use correction factors when 24-hour urine collection is not practicable and alternate sampling regimes are used. Whenever human volunteers are used in a study, all relevant ethical and practical guidelines should be considered.

The need for an understanding of the metabolism and pharmacokinetics in humans is perceived by some as a major disadvantage of biological monitoring (NACA, 1985). However, this potential disadvantage must be weighed against the more accurate assessment of absorbed dose provided by a properly designed, interpretable biological monitoring study. Such a study may also provide a better understanding of the relevance of the toxicity data to the risk assessment for occupational exposure.

Some pesticides are unstable, or highly volatile, and therefore are not good candidates for ambient exposure monitoring despite efforts to accurately assess in-field, storage and transit losses. Biological monitoring should be considered for such pesticides and may, in fact, be the only means of obtaining adequate quantitative data from which the absorbed dose can be derived.

If, based on technical or ethical considerations, a human volunteer study is regarded as impracticable, animal metabolism and pharmacokinetics data may be considered. It must be recognised that extrapolating between species carries with it a degree of uncertainty. Clear examples that demonstrate the pitfalls of adopting this approach are described in detail by Woollen (1993). Apart from inter-species differences in metabolism, there is the possibility of dose-dependent differences, pointing to the need for metabolism studies in animals and human volunteers at doses similar to the anticipated workplace exposures. In the absence of human metabolism and pharmacokinetics data, the principal advantage of biological monitoring – i.e. to provide an accurate assessment of the absorbed dose – is reduced.

Certain pesticides may not lend themselves to a biological monitoring strategy – for example, if they are extensively metabolised to a large number of minor metabolites. A minor metabolite may not provide an adequate basis for an accurate assessment of the absorbed dose of the parent compound, particularly if the proportion of the parent compound excreted as the metabolite is subject to inter-individual variability. However, depending on the nature of the risk assessment, such metabolites can provide some useful information as a biological indicator in the absence of more abundant biological monitoring markers. Another example is a substance that is retained in the skin. There may be no measurable residues in urine at any time of the assessment.

Quality assurance/quality control data (see Annex II for details)

Quality assurance/quality control (QA/QC) data on the validity of the analytical methods and on the stability of the pesticide and its metabolites under field, storage and transit conditions are an essential requirement for field studies of occupational exposure.

The process of method development involves the application of chemical principles and laboratory methods to the reliable analysis of a compound in a specific matrix. It is necessary to demonstrate that reproducible results can be obtained when measuring analytes at the desired level of sensitivity, and for all sampling matrices prior to the initiation of field studies.

The process of method validation involves designing and performing experiments to establish the expected accuracy, precision and specificity of a procedure for specific concentration

ranges of each analyte of interest in a specific matrix. It includes the determination of a method limit of quantitation (LOQ), and the analysis of a range of recovery samples, and may include an evaluation of the stability of the analytes in or on the matrices under storage conditions. The necessary LOQ will depend on the toxicological end point of interest. At a minimum, the LOQ should be sufficient to assess exposures at the no-observed-effect level divided by an appropriate safety factor. Validation studies should ideally be completed prior to the initiation of a field study.

Laboratory recovery data are generated to determine the efficiency with which the analyte can be recovered from fortified sampling matrices. These data are usually obtained during the method development and method validation processes. Laboratory recoveries reflect losses that may occur during laboratory operations, such as extraction, clean-up and analytical measurement, as well as contamination. It is advisable to include at least one procedural laboratory recovery in each sample analytical run to account for day-to-day variation in the efficiency of the method. Laboratory recoveries are an essential requirement for each study and should cover the range of concentrations anticipated in the field samples.

A storage stability study may also be required, and can precede or be conducted concurrently with a field study. Its purpose is to determine the stability of the analytes in or on sampling matrices under the same storage conditions that will be used to store field samples. If at all possible, it is recommended that a storage stability study be conducted prior to the initiation of the field study to determine the maximum duration of storage time that is feasible.

Evaluation of field recovery is essential to enable correction of the test sample data for losses that occur during all phases of sample collection and analysis. Specifically, field recovery samples account for the losses that occur during sample collection, sample handling and storage in the field, transportation from the field to the laboratory, storage in the laboratory, sample extraction and analysis. In addition to field recovery samples, travel recovery samples prepared in the field and shipped and stored with the experimental samples can provide a basis for estimating the losses that occur during sample shipment and storage, as opposed to those that occur during sample collection.

General features of field study strategy and design

The primary aim of a field exposure and/or biological monitoring study is to generate data for use in a risk assessment. This process must also involve characterisation of the population at risk and the distribution of exposures within this population (National Academy of Sciences, 1983). The sampling strategy and study design should therefore take account of the need to characterise the central tendency and variability of the exposures incurred by these individuals. There may be extensive prior knowledge of worker populations, working conditions and practices. For products and use patterns for which this is not the case, a useful means of acquiring such information is to conduct a survey of the working conditions and practices. This helps to identify those worker subgroups and procedures with significant exposure potential. Moreover, it will help determine those sites that should be included in the field study. This information will help in the development of an optimum field study protocol with the best possible study design. This design inevitably must take into account the practical and financial limitations inherent in human studies under difficult conditions in the field.

Exposure/biological monitoring field studies can be separated into two types: pre- and re-registration studies, and post-registration surveillance studies. Studies of the first type would be conducted in full compliance with the requirements of the anticipated or existing product label – in particular, use of recommended application rates, protective clothing and equipment, and procedures for dealing with product spillage. Therefore, the study design would automatically have some influence on the amount and variability of exposures. Studies of the second type would be done

essentially in the interests of good product stewardship and surveillance. Concerns may arise, for example, over some new toxicological findings with a pesticide or because of reported adverse effects on the health of workers, or there may be a need to study the extent of compliance with product label precautions and recommendations. Therefore, the study design would incorporate the need to evaluate exposure under well documented *actual* conditions of use and would be free of the constraints imposed on pre- or re-registration studies.

Before starting a field study, investigators should consider whether ambient exposure and biological monitoring need to be conducted concurrently. Both may be justified, to provide data for inclusion in generic databases, to examine the relationship between exposure, and absorption and to provide a second measurement should one fail. One useful feature of the tier approach (Henderson et al., 1993) is that insight into the likely routes of exposure may be gained from the generic exposure databases, thus enabling a decision on the routes on which to concentrate in the field study. For example, it is well established that mixing, loading, and high-volume application of non-volatile pesticides (saturation vapour pressure $<10^{-2}$ Pa; Lundehn et al., 1992), other than wettable powder and dusty granular formulations, do not usually generate significant amounts of inspirable particulates.

Other factors that may influence the sampling strategy include possible concern over specific work activities during pesticide use. Passive dosimetry may be more useful than other strategies, in that it enables separate measurements of the respective contributions of these activities to the total exposure. However, if ambient exposure and biological monitoring are conducted concurrently, then these contributions may be assessed simultaneously. Identifying the differences in the magnitude of exposure attributable to these activities permits the use of different regulatory options for mitigating exposure – for example, the recommended use of additional protective equipment during procedures with greater potential for exposure.

The choice of sampling methods for studies in hot and humid climates should be made with due regard to the possible discomfort and encumbrance imposed by passive dosimeters. The use of biological monitoring in these circumstances is advantageous and should be considered, provided that the requisite criteria for a scientifically valid study can be met.

If adequate exposure data are available on the pesticide and use pattern in question, biological monitoring may be conducted on the subjects wearing their normal work clothing and any additional protective clothing and equipment required by the label. This approach has the advantage of removing all doubt about possible interference of the exposure sampling dosimeters with the process of skin contamination and absorption.

As stated previously, the emphasis in this document is on maximum flexibility. This applies not only to the different approaches to exposure assessment, but also to the specific methodology used to determine the exposure or absorbed dose. For example, the investigator may believe that use of the dermal patch method will provide adequate data for his/her purpose. It is essential that a scientifically sound protocol is followed, and it is recommended that the approval of the regulatory authority is sought.

An important consideration is the number of measurements of exposure and/or absorbed dose needed in the field study. As a general guide, a minimum of ten subjects is required. The choice of the number of subjects should be based on a consideration of the likely end use of the data, the nature of any identified toxicological end point, the required level of statistical confidence, and the overall manageability of the field study. Where feasible, subjects should be randomly selected from the relevant worker population. It is recommended that a sufficient number of measurements be made in different locations to cover the range of use procedures, conditions and application equipment for which evaluation of exposure and/or absorbed dose is required. These comments also apply to crop

re-entry procedures; in harvesting, for example, variation in work procedures may be substantial, even within the same crop.

The inherent variability in exposure under field conditions is best addressed by increasing the number of subjects, rather than repeated monitoring of the same individuals, as variability between workers is generally greater than that encountered when monitoring the same worker. This is discussed in more detail by Fenske and Teschke (1995). Equally, consideration should be given to including as many sites as is feasible rather than repeating measurements on subjects using the same equipment under the same conditions. This applies particularly where location is believed to have a significant impact on the variability of the exposure measurements. Certain types of pesticide application procedures, such as those involving aerial application, render management of the study difficult. In such cases, repeated monitoring of the same individuals is an option, although the limitations of such a choice should be recognised. Should biological monitoring be necessary, a further limitation is introduced, in that inter-individual variation in metabolism of the pesticide would be less well evaluated. The duration of the study would be prolonged owing to the possible need to collect urine samples over several days for each individual. As a result, repeat monitoring could not commence until urine collection was complete. These difficulties should be considered if using biological monitoring in such circumstances.

Ideally, the duration of a single measurement of exposure or absorbed dose should be representative of the typical working day, so that there is a greater chance that all the work activities that might result in exposure, such as equipment repair and clean-up, are assessed. This criterion applies particularly to studies involving biological monitoring; unlike ambient exposure data, absorbed dose data may not lend themselves to extrapolation on the basis of time or amount of active ingredient used. In studies involving passive dosimetry and a volatile or unstable pesticide, a shorter monitoring period should be considered, based on a consideration of the physico-chemical properties of the compound. The choice of monitoring duration should take account of the possibility of dosimeter saturation. Ideally, a single set of dosimeters should be used per worker; however, a change of dosimeters during the work day may be necessary if different tasks are to be monitored separately.

The choice of use pattern (including application equipment) should be based on consideration of such factors as whether it is the predominant one for the product or a minor one for which no generic data are available. In pre-registration studies, the product should be used in the study at a representative recommended rate of application and on the likely maximum area of crop treatable in a working day under local conditions. It should also be applied in accordance with all the label recommendations for use. These principles also apply to studies involving crop re-entry and for which exposure should be determined after the shortest permissible re-entry period (if known). In post-registration surveillance studies, these criteria should not be enforced; this ensures maximum representation of actual use conditions and exposure variability.

Where the product label recommends the use of protective clothing and/or equipment, these should be provided to the subjects in pre-registration studies by the supervisory team to ensure standardisation. It is recognised that the use of new clothing will not measure any exposure due to clothing contamination from previous applications. However, such standardisation will aid the scientific interpretation of the data, as possible variation in standards of protection by different types of protective equipment will have been removed. It will also ensure that the exposure and risk assessment for the product are evaluated in accordance with the label recommendations for its regulatory use. Efforts should be made to ensure that the recommended protective clothing and equipment are practical and realistic to use under local conditions. In post-registration surveillance studies, use of protective clothing and equipment should not be mandatory, although ethical or legal viewpoints on product label recommendations in this respect should be considered.

Test subjects

The test subjects in a field study should be normal workers rather than inexperienced volunteers. If this is not possible, the use of non-professional personnel may have to be considered provided they are given the requisite training in the handling and use of the pesticide and equipment. The limitations of this choice in terms of reducing representativity should be recognised. Males or females may be considered for inclusion in ambient exposure studies. However, in those studies involving biological monitoring, it is preferable that both sexes be included, particularly if it is likely that the product will be used by both sexes, owing to possible sex differences in metabolism and pharmacokinetics.

The informed consent of all subjects should be obtained by providing them with the requisite information on the pesticide in an easily understood form. A consent form should be signed by each subject. Test subjects should not be chosen on the basis of either known careful use of pesticides or good personal hygiene and working practices; they should be representative of the working population under study. Furthermore, they should be told to use the pesticide and carry out work activities according to their normal practice. The subjects should consider themselves to be in normal good health. Consideration should be given to the toxicity of the pesticide and the need for the screening of subjects for any pre-existing conditions that may be affected by use of the pesticide under study. It is useful to give a simple questionnaire to the subjects before a field study to gather information on their experience in the use of pesticides and application equipment, their use of protective equipment, and their general health status. It should be made clear to all potential participants that they are free to withdraw from the monitoring study at any time. Consideration should be given to providing the subjects with their individual results.

Management of the study

The field study must be managed and supervised by people trained and experienced in the conduct of exposure studies. Emphasis should be placed upon training and competence of the supervisory team in the field sampling and observational procedures.

Good Laboratory (Field) Practice

The field study should be conducted in accordance with the principles of Good Laboratory Practice (GLP) as applied to field studies and recommended, for example, by the Organisation for Economic Co-operation and Development (OECD, 1992) and others.

Annex I

Passive dosimetry and biological monitoring methods for assessment of exposure and absorbed dose

Dermal exposure

Patch method

Patch description

The patch dosimeter acts as a barrier to entrap pesticide that would impact on the clothing or, if the patch is located beneath the clothing, would otherwise reach the skin. Therefore, the composition of the patch and its location on each body region should be considered based on the type of pesticide formulation handled, the application equipment used, and the crop.

It is recommended that the collection area of each patch be approximately 10 cm × 10 cm (100 cm²) in size. Patches smaller than 50 cm² are generally inadequate.

For liquid pesticide formulations, patches should be made of an appropriate absorbent material such as surgical gauze, paper-making pulp (alpha-cellulose), clothing material, blotter paper, or preparative chromatography paper. The patch material should be absorbent enough to retain all liquid residues anticipated to be in contact during an actual field study, as if it were the clothing or the skin, depending on the location of the patches. Multilayer patches can be constructed by stapling together several patches of the same material.

For dry pesticide formulations, patches should be porous enough to collect dusts or dried residues. Surgical gauze is currently the most appropriate collection medium for dry formulations.

The collection medium should be backed by an appropriate impermeable material to prevent the contamination of the patches by residues on the skin or clothing and to prevent seepage through the pad onto the clothing underneath. Suggested backing materials include aluminium foil, polyethylene and glassine paper.

The exposed surface area of the patch should be standardised by placing the patch in a holder envelope with an open window of a standardised area or by trimming the patch to a standard size (i.e. 10 cm × 10 cm) after removing it from the subject.

Location of patches

Inner and outer patches should be attached at the locations listed in **Table A-1**. These patch placement locations are consistent with the EPA Sub-division U Guidelines for Applicator Exposure Monitoring (US EPA, 1987). Patch location may vary on a case-by-case basis, however, and additional patches should be placed in areas where, for given conditions, significant exposure is expected. For example, if a worker must carry bags of formulated product, patches may be required on the chest/abdomen area.

**Table A-1 Surface areas for regions of adult body (80th percentile male)
and locations of dermal exposure dosimeters¹**

Region of body	Surface area (cm ²)	Location of dosimeters
Head and face (Face)	1300 (650)	Head (front of cap, hood)
Back of neck	110	Back (outside dosimeter)
Front of neck (includes V of chest)	150	Chest (outside dosimeter)
Back	3550	Back (inside dosimeter)
Chest/stomach	3550	Chest (inside dosimeter)
Upper arms	2910	Each upper arm
Forearms	1210	Each forearm
Upper legs	3820	Each thigh
Lower legs	2380	Each lower leg (shin)
Feet	1310	Each foot or sock
Hands	820	Absorbent glove or hand wash method used ²

Note: *Surface areas include both arms, both legs, both hands.*

¹ One patch on head, back, chest, each forearm, each upper arm, each thigh and each lower leg.

² No surface area calculation is required when either the absorbent glove or the hand wash method is used.

Source: Adapted by US EPA (1987) from Berkow (1931) and US EPA (1985).

A head patch may be used to estimate deposition on the head. The patch may be affixed to the worker's headwear or directly to the head if headwear is not worn.

Attachment of patches

The patches should be securely attached to the skin using suitable material such as surgical tape or sweatbands and/or to the clothing and headwear using safety pins, staples and tape. If attachment to the skin is a concern because of, for example, the contact sensitisation potential of the tape, consideration should be given to attaching patches to the underside of clothing (inner surface). During attachment, suitable handling methods should be employed to avoid contamination of the patches.

Outside patches should be attached to the outer layer of clothing. Inside patches should not be occluded by the outer patches. They should be placed under the normally worn clothing. They should be attached to the skin or underclothing, but not to the clothing used for the attachment of the outer patches.

Every effort should be made to assess areas likely to receive maximum penetration (e.g. seams, openings, etc.) when positioning patches on the specified body areas.

Patch removal

Patches should be replaced immediately if they become saturated or torn; this entails continual observation and frequent examination of the condition of the patches.

If a lengthy time period occurs between monitoring exposures (e.g. morning and evening applications), dosimeters should be replaced between exposures.

Patches should be removed using a suitable method that minimises the potential for contamination. The patches should be trimmed (if necessary) to a standard size.

Standard whole body dosimeter method

Dosimeter description

The whole body dosimeter acts as a barrier to entrap pesticide that would otherwise contact the clothing or, in the case of an inner dosimeter, would penetrate through the clothing to the skin. The dosimeter should cover the body, including the arms and legs to the wrists and ankles, and should fit well enough to avoid interference with hand washing or other activities. It should be constructed of suitable absorbent materials, such as cotton or cotton/polyester undergarments, socks, trousers, long-sleeved shirts and coveralls. Garments made of non-absorbent materials may be unsuitable for certain types of formulation. The whole body dosimeter method may not be suitable for granular or wettable powder pesticide formulations, unless the materials are representative of normal clothing in terms of impaction, penetration and retention properties. The materials mentioned above meet this criterion.

The inner whole body dosimeter, which is meant to mimic the skin, should be worn under appropriate layers of clothing. Normal work clothes and other protective equipment should be worn over the dosimeter. This is analogous to the inner patches from the patch method.

Outer deposition may also be measured to permit comparison of inside and outside contamination and to allow an evaluation of penetration through clothing and protective equipment. The outer dosimeter must not constitute an additional clothing layer over that normally worn.

Exposure to the head, neck and face should be determined by measuring deposition on a cotton hat or cap, on a hood as part of the whole body dosimeter, or on a head patch as for the patch method. Exposure to the face and neck could also be determined through the use of wipe samples.

Exposure to the feet should be estimated from deposition on socks, which are part of the outer deposition dosimeters.

Donning and wearing of the whole body dosimeters

Unused sampling garments, treated in the same manner as in the method validation work (e.g. pre-extracted and laundered), should be issued to the test subjects immediately before the start of the monitoring period. The clothing should be donned in an area free from contamination with the test material or other chemical contaminants and worn throughout the monitoring period, usually the working day or the duration of some specified work activity.

Removal of dosimeter

The dosimeter should be removed and replaced immediately should saturation occur or be anticipated during the work day; this requires continual observation and frequent examination of the condition of the garments. After exposure, the whole body dosimeter should be removed, turned inside out to minimise loss of test material, and sectioned for storage, extraction and analysis, using suitable standardised methods that will not result in contamination. If the test material is a granular or powdered product, turning the dosimeter inside out may result in loss through handling; the decision to do this should therefore be considered carefully. This activity should take place in an area free from contamination with the test material and other chemicals. To help minimise cross-contamination, individual garment samples should be handled sequentially in order of increasing contamination potential. The following outer dosimeter sections are recommended:

- Forearms – elbow to wrist
- Upper arms – elbow to shoulder
- Lower legs – knee to ankle
- Upper legs – knee to groin
- Chest/torso
- Back/torso

These sections can be varied according to the typical clothing worn by the workers and the body parts of interest in terms of distribution of exposure. Inner dosimeters may be analysed whole (or in larger sections) to help minimise the potential inaccuracy of summing individual residue values based on half of the limit of detection for samples where nothing was detected.

Depending on the number of applications or the work task of interest, the number of samples may be reduced by combining both upper limbs, both lower limbs and the chest/torso and back/torso. However, keeping data separate may be useful in assessing anomalous values. It is important to remember that the trouser tops (sectioned at upper thigh groin level) represent the lower part of the torso and therefore should be included with the upper garment.

Variant of whole body dosimeter method for use with concurrent biological monitoring

This variant of the whole body method involves the utilisation of clothing as dosimeters to represent as closely as possible the normal work clothing of the worker population under study. Such clothing would include both the outer clothing (e.g. shirt and pants) and inner clothing (e.g. T-shirt and briefs). The method has particular merit in studies involving concurrent biological monitoring of the absorbed dose. Use of representative clothing ensures that there is no undue interference with the process of clothing penetration, dermal contamination, and percutaneous absorption. The method and procedures used for sectioning and processing samples are essentially the same as those described for the standard whole body method. The key differences are in the calculations to estimate the dermal exposure.

Hand exposure

Hand rinse method

The selected solvent (previously evaluated for analytical suitability and human safety) should be placed in a polyethylene bag that is capable of withstanding vigorous shaking. The amount of solvent should be adequate to sample the entire hand. (The pesticide should be assessed for analytical compatibility with polyethylene before the field study.) A possible variation is to use a larger bag and wash both hands at the same time.

The bag should be held tightly at the wrist(s) of the subject and the hand(s) shaken vigorously approximately 50 times. Each hand should be rinsed a second time with fresh solvent and a new bag. Each bag and its solvent should then be placed in an individual appropriate container (e.g. mason jar or stainless steel container).

The hands of the worker should first be rinsed with the selected solvent prior to the field study, to remove any background contaminants.

During the course of the exposure study, hand rinses should be done each time the worker would normally wash his/her hands, as well as at the end of the day. Even if gloves are recommended on the product label, the worker should rinse his/her hands to establish whether any contamination occurred beneath the gloves.

If gloves are worn during the exposure study for a new product and it is not known whether gloves will be required on the label, both protective glove rinses and hand rinses should be done. Rinses of the outside of the protective gloves should be done in the same manner as hand rinses, or full analysis of the protective gloves should be done in order to estimate potential hand exposure for workers not wearing gloves.

Any significant deviations from the standardised method described above should be adequately validated.

Hand wash with soap and water

The hand wash method is recommended when exposure measurements and biological monitoring are to be conducted concurrently.

The subject should be asked to wash his/her hands as normal in a known volume of water (typically 750 mL), using a standardised soap, in a clean plastic or stainless steel washing bowl.

The hands should then be rinsed with a known volume of water (typically 250 mL). This is best achieved with assistance from a study investigator.

The soap and the procedure should have been validated in the laboratory for appropriate analytical recovery/extractability criteria.

The bowl may be reused for subsequent hand washes for the same subject, but not for other subjects.

Duplicate 200- or 250-mL aliquots of the pooled 1-L wash and rinse solutions should be taken and placed in suitable containers (e.g. glass or polyethylene) prior to frozen or cold storage. The containers should have been validated analytically in the laboratory for compatibility with the test material and the soap and water matrix.

The hand wash should be done whenever the worker normally washes his/her hands (e.g. before breaks and at the end of the working day). This ensures that there is no undue interference with the process of dermal hand contamination and percutaneous absorption.

Absorbent glove method

Lightweight absorbent gloves made of materials such as cotton should be selected for the study. To remove any substances that might interfere with pesticide residue analysis, gloves should be pre-tested and pre-extracted, if necessary, with the selected sample extraction solvent and allowed

to dry before use. The practice of monitoring hand exposure by cutting sections from the palm or back of the absorbent gloves is not recommended, as hand exposure is often significant and the error in extrapolating from a smaller area to the whole hand may be large.

The hands of the worker should be washed thoroughly with soap and water or rinsed with a suitable solvent (e.g. distilled water, ethanol) to remove any interfering substances before he/she puts on the absorbent gloves.

If protective gloves are worn, the absorbent gloves should be worn beneath them.

If the absorbent gloves appear close to, or are anticipated to reach, saturation, they should be collected for analysis and a new pair of gloves used for the remainder of the day.

Absorbent gloves should be peeled off and replaced at times when the worker normally washes his/her hands and at the end of the work day and placed in an appropriate container (e.g. glass bottle, plastic bag).

Backup hand rinses, as described above under Hand rinse method, may be required when hands are normally washed and at the end of the work day to sample pesticide residues that may have penetrated through the glove dosimeters, if the level of hand contamination or degree of saturation is suspected to be high.

It should be recognised that it is difficult to interpret the data from several sets of saturated absorbent gloves, as they have more absorption and retention capacity than the skin of the hands.

Storage of samples

All exposure samples should be stored temporarily in cool boxes containing dry ice or ice packs as necessary. (N.B. Dry ice can crack glass or plastic when in direct contact.) They should be transferred to a deep-freeze as soon as possible. The times of sample collection and deposition in the deep-freeze should be recorded (as should all other essential sampling and storage information) and included in the Study File.

Data reporting and calculations

All data (uncorrected and corrected, where necessary for field recovery) should be reported in tables.

For each replicate, data should be presented in appropriate metric units such as mg or μg of active ingredient per patch or per body region (whole body dosimeter). Data for both inside and outside dosimeters should be reported.

In general, for values below the limit of detection of the analytical technique, one-half the limit of detection should be reported and used in the calculations.

Outside patch or uncovered whole body dosimeter data should be used for all uncovered body regions, whereas inside patch or whole body dosimeter data should be used for the body regions covered by normal work clothing and protective equipment.

Calculations – patch method

The µg/patch or mg/patch value should be divided by the exposed patch surface area (cm²) to give the patch value in µg/cm² or mg/cm².

The µg/cm² or mg/cm² value should be multiplied by the corresponding regional body areas (Table A-1) to arrive at µg/body region or mg/body region.

Total potential dermal exposure should be calculated by summing the data based on the outer patches. Estimated actual exposure should be calculated by summing the data from inner and outer patches as appropriate to the clothing scenario.

Calculations – whole body methods

Total potential dermal exposure should be calculated by summing the data for the individual outer and inner dosimeters.

For the Standard Whole Body Method, estimated actual exposure should be calculated by summing the data from the inner dosimeter, on the basis that it represents the skin. Where two layers of clothing are used as outer and inner dosimeters, the residues on the outer and inner dosimeters can be used to estimate penetration through a single layer of clothing. The Penetration Factor (PF) is calculated as follows:

$$\text{Penetration Factor (PF)} = \frac{\text{residue on inner dosimeter}}{\text{residues on outer} + \text{inner dosimeters}} \times 100$$

PFs for individual body parts can be used separately if the variance is large. Alternatively, a mean PF can be calculated from all the individual body parts per subject, or even groups of subjects, if the variance is small.

For the variant of the whole body method (normal clothing method), the penetration factor can be used to calculate how much residue will penetrate the normal work clothing and reach the skin.

In studies involving concurrent biological monitoring, estimates of actual dermal exposure should include the dose estimated to have been absorbed percutaneously. In studies of use patterns where the dermal route of exposure is known to predominate, it can be assumed that all of the absorbed dose is derived from percutaneous absorption. The matter is more complicated for use patterns where the inhalation and/or oral routes are significant or if the pesticide is volatile. If inhalation exposure is measured, the percutaneously absorbed fraction can often be estimated by subtracting the inhaled dose from the total absorbed dose (presuming the absence of oral intake).

Inhalation exposure

Personal air sampling method

An appropriate type of monitor must be selected and validated before use. It may be advisable to use a two-stage sampler if both vapours and aerosols are expected to be present. This should be determined during the sample medium selection process prior to the study, taking account of the physico-chemical properties of the pesticide. The vapour sampling medium would be located behind the aerosol sampling medium to collect any vapour stripped off the particulate during the

sampling period. Retention/breakthrough efficiency studies are required to validate samples prior to field trials. These studies should be performed under conditions similar to those anticipated in the field.

The pump should be calibrated with the sampling device and collection medium in-line before and after each sampling period, and the flow rates should be reported for each replicate. Selection of a flow rate should reflect expected study conditions, considering such things as the length of the sampling replicate, concentration of pesticide in the air, and retention of analyte. Variation in the pump flow rate greater than 5 per cent of the initial flow should be considered when interpreting sampling results.

The pump may be attached to the worker's belt. The sampling tube should be clipped on the lapel in the breathing zone of the worker. The placement of the tubing should not restrict the normal activities of the worker. The location of the sampling tube – i.e. left or right lapel – should be noted. It is advisable to standardise the location of the sampling tube or adjust its location according to whether the worker is left- or right-handed. The sampling tube should be pointed downward to simulate the anatomy of the nose and to prevent the collection of large droplets that would not normally be inhaled by the worker.

Unless potential for exposure continues during break and lunch periods, the sampling pump should be shut off during these times to provide a realistic measure of airborne concentrations of pesticide during the work periods.

The collection medium should be removed from the sampling tube at the end of the work day using suitable standardised methods that will not result in contamination.

Storage of samples

On completion of sampling, filter cassettes and tubes should be stored temporarily in a cool box containing dry ice or ice packs as necessary. The samples should be transferred to the deep-freeze as soon as possible after collection. In conditions where such storage is extremely difficult, a preliminary storage study at ambient temperatures could help determine appropriate storage requirements.

Inhalation exposure samples should be stored in cool boxes and freezer compartments separate from those used for dermal exposure, hand wash, and urine samples.

Data reporting and calculations

All data should be reported in tables.

If necessary, data should be corrected for field recovery (see section on 'Total exposure and absorbed dose calculations and interpretation' below).

For each replicate, data on the amount of pesticide found on the sampling medium should be presented in appropriate metric units, such as mg or µg per sampling tube or respirator.

Values below the limit of detection of the analytical technique should be reported as non-detectable, and one-half the limit of detection should be used in subsequent calculations.

Unless absorption information is available, 100 per cent absorption is assumed for inhalation estimates.

The mean pump flow rate and exposure time for each replicate should be reported.

The airborne concentration (mg/m^3) should be calculated from:

$$\text{Concentration (mg / m}^3\text{)} = \frac{\text{Amount found (mg)}}{\text{Flow rate (L / min)} \times \text{Sampling time (min)}} \times 1000\text{L / m}^3$$

The amount inhaled per replicate can be estimated by multiplying the airborne concentration by the appropriate ventilation rate for the work task. This can be obtained by reference to, for example, US EPA's Exposure Factors Handbook (US EPA, 1989). The selected ventilation rate should be adequately documented by the investigator.

Biological monitoring

Urine sampling

Urine sampling is the preferred method for biological monitoring in the field because it is non-invasive and because urine is relatively easy to collect.

Test subjects should be asked to ensure that they have no exposure to the test pesticide or structurally related product for an appropriate period of time before participating in the monitoring study. The appropriate period of time would be that required to ensure complete urinary clearance of the compound or any metabolites, based on pharmacokinetic data. Ideally, subjects should handle no other pesticide during this period to circumvent the possibility of interference in the analyses of residues of the test material and/or its metabolites. It is recognised that this may not always be possible without undue interference with the working practices of the subjects; this, in turn, may affect their willingness to participate in the study.

Ideally, complete 24-hour urine collections should be obtained from subjects starting on the day before their use of the product, on the day(s) of use and for an appropriate period of time after use, depending upon the excretion kinetics of the compound. It may be useful to obtain a 24-hour sample in advance of the study to allow for corrective instruction if necessary. Urine samples should be collected in new, unused collection bottles. The material used in the construction of the collection bottles (e.g. polyethylene) should have been previously checked for analytical compatibility with the analytes of interest.

The 24-hour collection should start with the first void after commencing work activities on the day of use of the pesticide and finish with the first void the following morning. This cycle should be repeated for subsequent days' collections, with the first sample of the morning voided into the container issued the previous day. Each 24-hour interval should start at the time noted for the void at the start of the trial and the last sample should be given at the same time each day. Each 24-hour interval should start at the time noted for the void at the start of the trial, and the last sample should be given at the same time each day. It is advisable to ensure that subjects understand that they must keep their containers available at all times throughout the day and collect all of their urine. Subjects should be told to exercise care in giving samples to avoid contamination of the urine with material present on their hands.

The total volume of each 24-hour sample should be measured, and two (e.g. 50 mL) aliquots should be taken and stored. One set of samples should be shipped to the laboratory for analysis, while

the other set remains in local deep-frozen storage as a reserve. All necessary precautions should be taken during sample collection and subsampling to avoid contamination of samples.

Specific issues that may arise and require consideration are (Woollen, 1993):

1. Volatility – If the pesticide or its metabolites are volatile, it may be necessary to take measures to minimise losses in the head space in urine collection vessels.
2. Light sensitivity – If the pesticide or its metabolites are degraded by light, it may be necessary to use amber bottles.
3. Adsorption – Polypropylene or polyethylene collection and storage vessels and caps are normally preferred, but glass bottles can be used if the pesticide or its metabolites bind or adsorb to polypropylene or polyethylene in the presence of urine. Polytetrafluoroethylene (PTFE) (or other inert) materials may be used for caps.
4. Temperature – The 24-hour stability of the compound and its metabolites at temperatures likely to be encountered in the field study must be known. If necessary, samples should be refrigerated or cooled with ice packs.
5. Preservatives – Preservatives such as sodium azide are sometimes added to urine. Usually, samples can be frozen without preservatives.

Blood sampling

Blood monitoring to measure absorbed dose in workers occupationally exposed to pesticides has rarely been used because of the invasive nature of the collection method and the difficulty in obtaining a good correlation between blood concentrations and absorbed dose. The measurement of acetylcholinesterase (AChE) or pseudocholinesterase depression in plasma and red blood cells provides a semi-quantitative measure of exposure to organophosphorus and carbamate pesticides. The usefulness of the measurement in quantitative risk assessment is limited unless a good correlation between level of AChE depression and systemic dose is demonstrated.

Where investigators believe that blood monitoring is warranted, the following specific blood collection and storage issues would need to be considered (Woollen, 1993):

1. Volatility – Special procedures may be needed if the pesticide or its metabolites are volatile. A possible option is collection of blood in heparinized blood glass syringes, which can be sealed and centrifuged. Plasma could then be transferred to a vial for analysis using procedures that minimise losses into head space.
2. Anticoagulants – Possible interactions between the analytes and different anticoagulants should be considered. Lithium heparin is suitable for many applications.
3. Adsorption – Adsorption of analytes to blood syringes or collection tubes should be investigated.
4. Centrifugation – A suitable centrifuge must be available at the site of the field study if plasma is required.
5. Infections – Different containment requirements apply to handling blood samples from groups considered to be low, medium or high risk in relation to hepatitis B or HIV. If possible, potential donors should be screened for either or both of these infections before

starting the study and excluded if positive. Ideally, all samples should be handled in accordance with the procedures recommended for medium- or high-risk blood samples according to local guidelines (e.g. ACDP, 1990). Particular attention should be given to packaging samples securely during transit; on receipt, samples should be opened in an appropriate containment facility.

Data reporting and calculations

All data should be reported in tables. For each subject, the following data are required:

- body weight in kg;
- urine volume in mL and collection times;
- urine volume in mL/24 h;
- creatinine values in g/24 h.

A typical calculation of estimated absorption of a pesticide is as follows:

$$\text{estimated absorbed dose (mg)} = A \text{ (mg)} \times \frac{M1}{M2} \times \frac{100}{R}$$

where:

- A = total amount of metabolite in all urine samples collected;
- M1 = molecular weight of pesticide;
- M2 = molecular weight of metabolite;
- R = average percent recovery of the administered dose excreted as metabolite in urine in human volunteer study.

A further correction would be needed if the compound or metabolite measured degraded in stored urine or if urine collection was incomplete (i.e. to correct for compound and/or metabolites not yet excreted).

Shipment of samples

Following completion of the field phase of the study, all samples should be shipped (if necessary, in a deep-frozen or cold condition) to the laboratory for analysis. Because the samples must remain deep-frozen or cold, it is essential that proper, documented procedures be put into place to minimise the possibility of the samples thawing out or being lost in transit. The method and route of transit must therefore be known and arranged before shipment takes place. Appropriate chain of custody documentation should be used to satisfy GLP needs in these respects.

Total exposure and absorbed dose calculations and interpretation

When the results have been compiled and tabulated, total potential and/or actual exposure should be calculated for each replicate. Field recovery results less than 95 per cent should be used to correct the ambient exposure monitoring results. Recovery results greater than 95-100 per cent should be noted but not used to correct the data.

Passive dosimetry

For calculating total dermal exposure, all values for dermal deposition for each body region (including hands) should be summed for each replicate. The inhalation value should be treated separately. The sum is normalised by dividing by kg active ingredient (ai) handled. Each subject's exposure is expressed in terms of the appropriate standardised body weight (e.g. 70 kg).

Depending on the use conditions, exposure values may be normalised for other parameters such as hectares (ha) treated, amount of produce treated (e.g. seed or wood), or time (h or min). This normalisation is done to account for differences in work practices between individuals, and for the variation in individual work practices during a full work day. It also standardises all measured exposures to a common parameter, so that results can be compared between individuals.

The mean, range, standard deviation and coefficient of variation interval are calculated from the normalised results. Geometric mean, range and standard deviation may be calculated if the data are shown to be log-normally distributed. Other measures of central tendency may also be examined at the discretion of the investigator.

Biological monitoring

Normalisation of biological monitoring of absorbed dose data in terms of the parameters mentioned above under Passive Dosimetry might not be as appropriate as for ambient exposure data. This is because the assumption of direct proportionality between percutaneous, oral and inhalation absorptions and the standard parameters mentioned above may not be tenable. However, with this limitation in mind the investigator may wish to examine the relationships between absorbed dose and these parameters.

Each subject's absorbed dose should be expressed in terms of body weight using his/her own measured value.

The arithmetic mean, range, standard deviation, and coefficient of variation are calculated from the results. Geometric mean, range and standard deviation may be calculated if the results are shown to be log-normally distributed. Other measures of central tendency may also be examined at the discretion of the investigator.

Study records

Standard forms may be used to document all parts of the field study, to cover the following aspects:

1. personal details of subjects, including relevant agricultural experience;
2. observations of work practice;
3. trial location details, including site/field history and maps;
4. details of number, size and design of formulation packs;
5. details of application equipment, including calibration;
6. calibration of air sampling pumps;
7. spray tank sampling;
8. records of urine volumes and dates of collection and sub-sampling;
9. study data form, including loading, weather and sampling information;
10. field fortification of dermal and inhalation exposure sampling matrices;
11. field fortification of urine;
12. deep-freeze sample deposition;

13. chain of custody and other shipping information;
14. incidents;
15. study team personnel.

All the above documentation should be included in the Study File. Following completion of the field study, all study records should be indexed and, after preparation of the final report, transferred to a GLP (Good Laboratory Practice) Archive and stored for an indefinite period.

Reporting requirements

The following information is required:

1. test material, purity, stability, product specification of formulation, batch numbers, nominal and actual concentrations;
2. description of study design;
3. exact locations of study sites, including site maps;
4. description of mixing, loading and application equipment, clean-up procedures, application rate(s), crop areas treated/harvested, number and length of tasks for each worker;
5. description of work procedures of workers, to include any use of protective clothing and equipment;
6. detailed description of all sampling methods used, e.g. dermal, inhalation, biological monitoring, environmental conditions, field recovery evaluation;
7. conditions of sample storage and shipment;
8. description of analytical methodology, extraction, detection, validation;
9. calculations and extrapolation factors;
10. results of analysis, to include uncorrected and corrected residues, laboratory and field recoveries, extrapolated exposure and absorbed dose values, environmental conditions;
11. tabulation of: all relevant analytical data; extrapolation results, e.g. dermal, inhalation, exposure, absorbed dose (from biological monitoring); environmental conditions;
12. photographic record;
13. discussion and interpretation of results;
14. conclusions;
15. location of raw data;
16. references.

Annex II

Quality assurance/quality control

Quality assurance/quality control data are required to support field studies of occupational exposure. These data fall into three areas:

1) Pre-field laboratory considerations covers those experiments associated with developing an analytical method for the analyte(s) of interest and validating its expected accuracy, precision and specificity in a specific sample matrix. This area includes determining the laboratory recovery efficiency, limit of detection and quantification and the working concentration range of the method. Recommended additional experiments include those determining the stability of the samples under the expected conditions of storage, as well as the recovery from fortified samples exposed under simulated field conditions.

2) Field study considerations covers the major aspects of proper sample collection and validation. Sample collection needs include, but are not limited to, calibrating sampling equipment and ensuring that samples are properly handled and stored. Sample validation experiments include the preparation and collection of field recovery samples.

3) Post-field analytical considerations covers the need for regular laboratory instrument maintenance and calibration programmes, the use of standard calibration curves to correct for day-to-day instrument variability, and the preparation and analysis of concurrent laboratory recovery samples to verify that the losses during extraction, clean-up, analysis, etc. are within acceptable limits as defined by the pre-field method validation work.

Pre-field laboratory considerations

Analytical methods and sample collection procedures should be developed and validated before the field monitoring portion of a study is undertaken. Many aspects of the overall study design, such as the nature of the active ingredient and the end use product in question, the proposed sampling method(s) and duration, the anticipated time and conditions of sample storage, etc., can influence the method development and validation process. In addition, the relevant toxicological end points (e.g. acute and chronic) for the compound in question should be considered during the method development and validation phase of the study so that acceptable margins of safety can be demonstrated in the event that exposure samples yield values below the limit of detection or of quantification (LOD/LOQ).

Analytical method validation

Analytical method validation establishes the performance of a particular method (e.g. the expected accuracy, precision, and specificity of a procedure for specific concentration ranges) within an analytical environment (e.g. within the laboratory that will perform the analysis of field samples). Method validation includes the analysis of a range of recovery samples for each matrix fortified with the neat analyte. Performance criteria should include a demonstration of the capability to attain reproducible results when measuring analytes at the desired level of sensitivity for all substrates *prior* to the initiation of field studies.

The analytical method validation should include the following:

1. establishment of the method's working concentration range to cover expected values from the field studies;
2. determination of detector response over a reasonable standard concentration range;
3. determination of the accuracy and precision of the method within the analytical environment through an experiment which should usually include the analysis of at least seven replicates of each fortification level indicated below for each matrix:
 - the method limit of quantitation (LOQ),
 - an intermediate concentration level (e.g. 10X LOQ),
 - the maximum concentration of the validation range (e.g. 100 - 1000X LOQ), and
 - blank or control matrix.

An accuracy value between 70-120 per cent (average recovery) and a precision value less than or equal to 20 per cent (coefficient of variation) generally demonstrate the analytical laboratory's capability to perform accurate and precise analysis.

The necessary LOQ will depend on the toxicological end point of interest. At a very minimum, the LOQ should be sufficient to assess exposures at the no-observed-effect level (NOEL) divided by an appropriate safety factor. It is desirable and recommended that the LOQ be sufficient to quantify exposures well below the NOEL divided by an appropriate safety factor.

Post-method development validation studies

Storage stability

The purpose of a storage stability study is to determine the stability of analyte(s) in or on appropriate sample matrices under similar storage conditions that will be used to store field samples. Conducting a storage stability study prior to study initiation may eliminate the need for generating storage recovery data during the field study. If problems are encountered, the sampling procedures or materials can be changed and the study repeated for the type of sample affected.

A storage stability study should usually include the following parameters:

- preparation and analysis of at least three blanks, three low-level fortifications (2-10X the LOQ), and three high level fortifications in the expected range of field samples for each storage interval, including the longest interval planned for storage of field samples. The number of concentration levels should be adjusted according to the reproducibility of the method and the stability of the test material; and
- storage of samples under the same conditions of storage as planned for the field samples (e.g. sample matrices or extracts, ambient temperature and/or frozen).

A storage stability study, done before or in conjunction with the field study, is optional if the field recovery samples are stored and analysed with the actual field samples.

Pre-trial field recovery

A pre-trial field recovery study is recommended in some cases. It may allow for a reduced field recovery programme during the exposure study. The purpose of a pre-trial field recovery study is to estimate the potential loss of analyte from sample collection devices when subjected to environmental conditions (e.g. temperature, light, relative humidity, wind) and sample durations representative of those anticipated during collection of the actual field exposure samples. This study may be done under actual or simulated field conditions. Laboratory incubators can be used to simulate anticipated field temperature and humidity conditions. If environmental conditions are anticipated to change during the actual field study, then a worst-case scenario (i.e. most chances for volatilisation/degradation) should be used.

Sample collection devices

During pre-field study design, investigators should give consideration to selecting the most appropriate sample collection devices and methodologies available for monitoring the pesticides and use scenarios in question. The following should be considered:

- dermal dosimeters and other sample collection devices should be durable enough to survive the physical stress and duration of the overall monitoring procedure, including sample collection, transportation and analysis. In addition, reasonable judgement should be used in the selection of sample collection devices to ensure that their absorptive capacity is not exceeded (i.e. become saturated) during the sample collection process.
- sampling media should be selected that do not contain substances that might interfere with analysis. Pre-extraction may be required to remove co-extractants and contaminating substances.

Field considerations

Field recovery samples are collected, handled, transported and stored in conjunction with the experimental samples and account for losses that occur during all phases of sample collection, sample handling and storage in the field, transportation from the field to the laboratory and storage in the laboratory. Additionally, field recovery samples that are analysed concurrently with the experimental samples account for residue losses that occur during sample extraction and analysis. Travel recovery samples can also be prepared in the field and shipped and stored with the experimental samples. The results of the travel recovery samples provide a basis for estimating the losses that occur during sample shipment and storage, as opposed to those which occur during sample collection. The inclusion of travel recovery samples is recommended, but not essential.

Field recovery during exposure study

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, wind) and duration as field exposure samples.

Ideally, a separate set of field recovery samples should be collected at each site on each day of monitoring for each relevant matrix. However, it may be acceptable to collect a single set of field recovery samples for all replicates monitored on the same day at different sites provided that ambient conditions are similar. It may also be acceptable to collect a single set of field recovery samples for all replicates monitored at a given site over the course of a few days if the environmental conditions are similar each day. This approach is recommended for compounds that are *very stable only*, and in

locations where the climate does not change appreciably from one day to the next during monitoring. The investigator who chooses this approach to generate field recovery data should demonstrate the stability of the compound (see “Storage stability” under “Post-method development validation studies” above), as well as the day-to-day consistency of the climate at the study site(s).

A complete set of field recoveries should consist of three or more each of blank control samples, low level fortifications, and high level fortifications. More than three samples may be warranted for compounds known to be unstable in the field or having little history of field evaluation. The low and high level fortifications should be in the range of the anticipated level of the chemical on the substrate. If the highest expected level is more than 100X the lowest spiking level, it is recommended that a mid-level of fortification be included.

It is advisable to generate sufficient field recovery samples to be analysed at the same time as the actual field samples, to serve as concurrent laboratory recovery samples. At a minimum, a complete set of field recoveries, preferably fortified with the formulated product, would consist of the following, when applicable:

1. Air sampling matrices. The analyte should be added to the collection matrices in the field at the time of the study. After fortification and evaporation of the delivery solvent, the fortified matrices should be exposed to ambient conditions and attached to air pumps. The pumps should be operated in clean air at a flow rate, and for the length of time, equivalent to the field samples.
2. Patches. The number of field recovery patches is irrespective of whether the worker wears one patch or 22 patches. However, if some of the patches are covered by clothing (inside patches versus outside patches), a separate set of fortified patches may be prepared and covered by clothing during the exposure period at the control site.
3. Whole Body Dosimeters (WBDs). Pieces of test garments should be used for fortification as field recovery samples and controls. Investigators should use discretion when preparing samples. For example, investigators could split a garment designated for QC purposes into samples that are reflective of the field samples (e.g. arms or legs) or into smaller fabric swatches (e.g. 100 cm²) and fortify the individual samples.

However, several issues exist which should be considered:

- Fortification levels must reflect the relative size of the QC fabric swatch samples compared to a typical field sample (i.e. the fortification level should be similar to the anticipated field sample levels on a per area basis, as analytical background may be important in the data interpretation);
- The total solvent extraction volume should be proportional to the surface area for both the field exposure samples and the field recovery samples (e.g. if a solvent volume of 1000 mL is used to extract a 2000 cm² section of a field exposure sample, then a solvent volume of 50 mL should be used to extract a 100 cm² field recovery swatch).
- QC sample swatches should be prepared in the same manner (e.g. pre-extraction) as the monitors used to collect the actual field samples.
- The quantitation limit for each particular matrix must be considered when specifying fortification levels (e.g. the determination of low fortification levels when prorating based on the surface area of the sample). The use of the fabric swatches will conserve considerable storage space and solvent usage. The similarity of recoveries should be

established during method development and validation. If it is established that the fortification of fabric swatches yields results similar to whole sections of the WBD, it is acceptable to use swatches for field recovery samples.

4. Exposed dosimeters, such as gloves, should be fortified at both the low and high levels. Covered items, such as briefs, may only need to be fortified at the low level, covered, and exposed to the elements at the control site.
5. Hand rinses. It is not appropriate to expose hand rinse samples to the environment during the field phase of a study, as they are collected, processed and stored immediately without significant exposure to the elements. However, all samples should be handled using the same procedures as the actual field samples. For example, fortified hand rinse solutions should be set out for as long as it takes to conduct a hand wash prior to storage or packing for shipment.
6. Urine/blood. If urine or blood is collected for biological monitoring, it is recommended that at least three samples of control (non-participant or pre-participation) urine or blood be fortified at each of two levels of the analyte (parent or metabolite(s), whichever is appropriate) for each experimental site. These fortifications may be made just prior to going to the field, carried into the field, exposed in a manner similar to participants' urine or blood, and stored and shipped with experimental samples. If stability of the analyte(s) has been established prior to study initiation, investigators may choose to reduce or eliminate this component from the study design as it is a burdensome task.

Travel recovery

Travel recovery samples refers to data from experiments conducted to determine the stability of the analyte on each sampling matrix during shipment and possibly storage. Travel recovery samples are optional and are left up to the discretion of the investigator. These recovery samples are prepared concurrently with the field portion of the study. They are then shipped and stored with the appropriate experimental samples. The travel recovery samples are different than field recovery samples, in that they are not exposed to the environmental conditions during the sample collection period. Thus, the results of the travel recovery samples reflect losses which may occur during shipment and storage only as opposed to those which occur during sample collection, shipment and storage. It is suggested that one set of travel recovery samples be prepared for each experimental site to aid in the interpretation of losses that may occur in field recovery samples. If field recovery samples indicate no significant losses, the travel recovery samples do not need to be analysed.

Fortification of sampling matrices

If the pesticide is to be applied as a spray, the fortification of exposure sampling devices should be made with the formulated pesticide product diluted in the spray matrix (usually water). For products applied as a solid (granules, pellets), or for formulations in which it is difficult to get a uniform suspension, and for air sampling media, it is recommended that a solution of the analyte, usually in an organic solvent, be used. Such a solution is also recommended for fortifying hand rinse solutions and for fortifying urine samples (analyte or metabolite).

Spray tank sample analysis

During the study, an appropriate number of tank mix samples should be taken and analysed to verify the application rate, and the amount of active ingredient loaded and applied per tank. As tank mixes are not always homogenous, it is important to ensure that samples are representative.

Quality control and sample generation

Any sample collection equipment used in a study by an investigator should be validated and/or calibrated. Examples include: personal sampling pumps should be calibrated using a device which is traceable to a primary standard (e.g. bubble meter, or magnahelic or Buck type calibrator); thermometers used in any study must be traceable to a National Institute of Science and Technology (NIST) primary standard; and weights used to calibrate analytical balances should be traceable to NIST primary standards (e.g. class P or better).

Post-field analytical considerations

The basis for any modern analytical method is the instrumentation. Instrumental methods that are both sensitive and stable should be developed. Peaks of interest should readily be separated from contaminant peaks by intervals (e.g. time, wavelength, etc.) that are large enough to allow for accurate resolution and quantification of the peaks of interest. The lowest level analytical (i.e. calibration) standard should produce a signal that is at least three times greater in magnitude than the signal to noise ratio. In other words, the instrumental signal to noise ratio must be ≥ 3 for the lowest standard.

Instrument performance

Instrument performance should be monitored regularly to ensure the reliability of the measurements. Techniques that can be used to establish instrument performance include, but are not limited to: 1) internal standards, 2) daily comparison of peak areas of analytical standards, and 3) calculation of a correlation coefficient for a particular standard curve. Investigators should establish their own guidelines for determining whether an instrument is functioning properly, as this determination is dependent upon the analytical method, instrument operating parameters, and background levels observed/anticipated in the samples.

Determining the proper instrument operational quality control procedures is difficult. Investigators should develop operational standards that are pertinent to the pesticide(s) being studied (e.g. detector response patterns affect calibration techniques). Investigators should also develop criteria for scrutinising daily method performance data. It is recognised that recovery results are proportional to the extraction and instrumental methods, as well as the physical/chemical characteristics of the pesticide(s) being studied. Therefore, studies for which the recovery results are marginal should be considered on a case-by-case basis. Investigators should be careful to provide justifications as to why their analytical methods and results appear to be marginal.

Calibration techniques

As described above, results can be calculated in a variety of ways. Interpretation of basic results, however, demands generating a standard (i.e. calibration) curve to which responses from sample extracts can be compared. If calculations are to be done manually, for example, a linear regression analysis can be performed. Investigators should describe all techniques used to calibrate instruments and calculate residue levels. Data integration systems, besides enabling investigators to manipulate/interpret data in a variety of ways (i.e. various peak integration techniques), also typically generate calibration curves as well as calculating and summarising results. Several options for generating calibration curves are usually available in each system (e.g. linear regression for all points, point to point calibration, average values based on multiple analysis, etc.). Investigators should be careful to consider the response patterns of a particular instrumental system (i.e. linear, exponential, threshold, etc.) prior to selecting a means to generate the calibration curve.

Concurrent laboratory recovery

Concurrent laboratory recovery data are data analysed in the analytical laboratory at the same time as the field samples to determine the recovery efficiency of the analyte from substrates and the day-to-day variation in the method sensitivity. Laboratory recoveries, typically fortified with analytical standards, reflect losses which occur during laboratory operations (extraction, clean-up, analytical measurement, etc.). They do not account for losses which occur during sample collection, shipping or storage. It is recommended that a minimum of 10 per cent of the field samples be represented by a laboratory recovery sample for each analytical batch/run, and they should cover the range of concentrations anticipated in field samples.

Concurrent laboratory recovery samples can be either field recovery samples analysed concurrently with the actual field samples or laboratory samples generated (i.e. fortified) in the laboratory. It is recommended that the field recovery samples be used as concurrent laboratory samples. When used in this manner, the field recovery samples could be used to correct the field samples for losses in both the field and laboratory. However, if the investigator is not confident of the fate of the compound in the field and during storage, recovery samples generated in the laboratory should be used to identify where the losses may have occurred (i.e. field or analytical method).

Annex III

Glossary of terms

active ingredient:	That ingredient of a pesticide to which the pest control effects of the pesticide are primarily attributed.
actual dermal exposure:	The amount of pesticide coming into contact with bare (uncovered) skin and the fraction transferring through protective and work clothing or via seams to the underlying skin, and which is therefore available for percutaneous absorption.
ambient monitoring:	A method of measuring the amount of a substance that is available for uptake: composed of environmental monitoring and personal monitoring.
analyte:	Chemical moiety (pesticide or metabolite) that is the subject of chemical analysis.
biological monitoring:	<p>A method of assessing the absorption of chemicals by measuring the parent compound or its metabolites in body fluids, usually blood, urine or exhaled breath.</p> <p>Woollen (1993) refined this term in the context of pesticides and assessment of absorbed dose for risk assessment: 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.</p>
breakthrough:	The passage of a chemical through a sampling medium (e.g. air sampling tube) or penetration of a chemical through protective clothing or devices (e.g. gloves, respirator).
breathing zone:	The area around the nose and mouth from which air is inhaled.
bystander:	A person potentially exposed to pesticides but not necessarily engaged in the application procedure.
closed system:	A system of mixing and/or loading and transfer in which the chemical is isolated from the ambient environment at all points from the original container to the spray tank.
cycle:	A recurring sequence composed of one mixing, one loading and one application event.
dermal absorption:	Movement of a pesticide into and through the skin; includes that taken up into the systemic circulation and that retained in the skin compartment.

dislodgeable residue:	Residue of an applied pesticide that may be removed from a treated or untreated surface by solvent rinse.
dose:	The amount of a pesticide systemically available.
drift:	The movement of pesticide by wind or air currents to non-target areas.
environmental monitoring:	A method of measuring the amount of a pesticide present in an environmental medium.
exposure:	A condition of oral, dermal, respiratory or ocular contact between a person and a pesticide.
extrapolation:	Quantitative estimate of values outside the range of measured values.
field blank:	A sampling device subjected to the same conditions as the field samples but not exposed to the product under study.
field recovery:	The recovery of analyte from sample collection devices fortified and subjected to the same environmental conditions, exposure times, handling, shipping, storage and laboratory operations as field exposure samples.
flagger:	A person engaged in marking the border between treated and untreated areas during pesticide application.
formulation:	A mixture of an active ingredient with diluents, carriers and other materials to form the packaged product.
inspirable fraction:	That fraction of airborne particulate capable of entering the respiratory tract via the nose and the mouth, so providing a source of absorption into the body, either from direct inhalation or from subsequent oral ingestion.
label:	Any legend, word, mark, symbol or design applied or attached to, included in, belonging to or accompanying any control product.
laboratory recovery:	The recovery of the analyte from sample collection devices fortified in the laboratory; refers to laboratory operations only and does not refer to losses due to storage conditions or environmental factors.
limit of detection:	The level at which a pesticide can be detected but not quantified for a given analytical procedure.
limit of quantification:	The smallest amount of the pesticide that can be quantified by the analytical method.
normalisation:	A standardised expression of exposure as a function of another variable (e.g. $\mu\text{g}/\text{amount active ingredient handled}$, $\mu\text{g}/\text{time}$, $\mu\text{g}/\text{area treated}$).
passive dosimetry:	A method of measuring the amount of pesticide coming into contact with an individual.

personal monitoring:	(see passive dosimetry)
pesticide:	Any substance or mixture of substances intended for preventing or controlling any unwanted species of plants and animals; also includes any substances or mixture of substances intended for use as a plant growth regulator, defoliant or desiccant.
pharmacokinetics:	The study of the absorption, distribution, metabolism and excretion of a substance in any living system.
potential dermal exposure:	The total amount of pesticide coming into contact with the protective clothing, work clothing and exposed skin.
re-entry period:	A period of time that elapses before an individual re-enters a treated area, or the period of time that defines when individuals may re-enter a treated area.
replicate:	A measurement of exposure to a worker during one typical work day, which includes all job functions related to pesticide use.
site:	A location at which one or more replicates are monitored.
storage stability:	The recovery of analyte from sample collection devices fortified and subjected to the same handling, shipping, storage and laboratory operations as field exposure samples.
surrogate data:	Exposure data collected for one pesticide that are used to estimate exposure to a similar pesticide.
ventilation rate:	Breathing rate used for calculating inhalation exposure.

Annex IV

Revision Committee/Peer Review Committee

Revision Committee

Graham Chester	-	Zeneca Agrochemicals, United Kingdom
John Worgan	-	Health Canada, Canada
Patricia Curry	-	Health Canada, Canada
Mary Mitchell	-	Health Canada, Canada

Peer Review Committee

Neil Carmichael	-	Rhone Poulenc Agro Chimie, France
Monty Eberhart	-	Miles Inc., USA
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Curt Lunchick	-	Jelinek, Swartz and Connolly, USA
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Marco Maroni	-	International Centre for Pesticide Safety, Italy
Alan Nielsen	-	US Environmental Protection Agency, USA
John Ross	-	California Environmental Protection Agency, USA
Joop van Hemmen	-	TNO Nutrition and Food Research, The Netherlands

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