United States
Environmental Protection
Agency

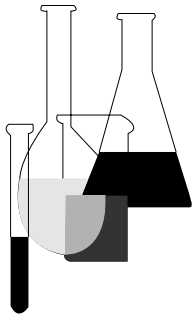
Prevention, Pesticides
and Toxic Substances
(7101)

EPA 712–C–96–261
February 1996

EPA

Occupational and Residential Exposure Test Guidelines

OPPTS 875.1000 Background for Application Exposure Monitoring Test Guidelines



INTRODUCTION

This guideline is one of a series of test guidelines that have been developed by the Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency for use in the testing of pesticides and toxic substances, and the development of test data that must be submitted to the Agency for review under Federal regulations.

The Office of Prevention, Pesticides and Toxic Substances (OPPTS) has developed this guideline through a process of harmonization that blended the testing guidance and requirements that existed in the Office of Pollution Prevention and Toxics (OPPT) and appeared in Title 40, Chapter I, Subchapter R of the Code of Federal Regulations (CFR), the Office of Pesticide Programs (OPP) which appeared in publications of the National Technical Information Service (NTIS) and the guidelines published by the Organization for Economic Cooperation and Development (OECD).

The purpose of harmonizing these guidelines into a single set of OPPTS guidelines is to minimize variations among the testing procedures that must be performed to meet the data requirements of the U. S. Environmental Protection Agency under the Toxic Substances Control Act (15 U.S.C. 2601) and the Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C. 136, *et seq.*).

Final Guideline Release: This guideline is available from the U.S. Government Printing Office, Washington, DC 20402 on *The Federal Bulletin Board*. By modem dial 202–512–1387, telnet and ftp: fedbbs.access.gpo.gov (IP 162.140.64.19), internet: http://fedbbs.access.gpo.gov, or call 202–512–0132 for disks or paper copies. This guideline is also available electronically in ASCII and PDF (portable document format) from the EPA Public Access Gopher (gopher.epa.gov) under the heading ‘‘Environmental Test Methods and Guidelines.’’

OPPTS 875.1000 Background for application exposure monitoring test guidelines.

(a) **Scope**—(1) **Applicability.** This guideline is intended to meet testing requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136, *et seq.*).

(2) **Background.** The source material used in developing this harmonized OPPTS test guideline is OPP guideline 230.

(b) **FIFRA and applicator exposure—a regulatory overview.** The increasing concern over pesticides in the environment during the 1960's caused a shift in the thrust of pesticide regulation from one of efficacy (protection of pesticide users from fraudulent product claims) to one of protection of the environment and public health. The legislative basis for the regulation of pesticides is the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). This Act was amended significantly in 1972 with the creation of a criterion set forth to prevent ''unreasonable adverse effects on the environment.'' This is defined as ''any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide.'' Amendments to FIFRA in 1975, 1978, 1988, and 1980 have not altered this basic risk criterion for regulatory decision making.

(1) Scientists in the Occupational and Resident Exposure Branch (OREB) of the Health Effects Division (HED) of OPP have the responsibility for estimating actual worker exposure. Agricultural scientists in OPP's Benefits and Economic Analysis Division (BEAD) supply pertinent use information along with estimates of the frequency and duration of each application activity for which an exposure assessment is prepared. The estimated exposure for the required time interval (daily or annually depending on whether the assessment is for an acute or chronic toxicological concern) is given to HED's Toxicology Branch (TB), where it is considered along with the results of the biological effects studies to produce a quantitative risk assessment. The risk assessment is considered in the risk/benefit analysis required for regulatory decisions under FIFRA.

(2) To implement the 1972 amendments to FIFRA, the Agency developed the Rebuttable Presumption Against Registration (RPAR) process and published the criteria which trigger the detailed determination of unreasonable adverse effects associated with a given pesticide use under paragraph (h)(22) of this guideline. At the onset of the RPAR process it was apparent that the risks to individuals who apply pesticides are distinct from those to the general population, and must be considered under the broad umbrella of the unreasonable adverse effects criterion under paragraphs (h)(23), (h)(24), (h)(25), and (h)(26) of this guideline.

(3) It became apparent during the early RPARs that few data were available for estimating the occupational exposure of pesticide applicators

and mixer/loaders. The components of a quantitative risk assessment are hazard assessment, usually a study of the toxicological response of laboratory animals to a chemical, and exposure. Occupational exposure could not generally be estimated with any certainty. A committee of the National Research Council (NRC), commissioned with the task of analyzing the effectiveness of the RPAR process, noted under paragraph (h)(66) of this guideline:

> In estimating exposure, as in other phases of its work, OPP is constantly hampered by lack of adequate data, and is forced to resort to indirect and inaccurate methods in its effort to make plausible estimates.

(4) A 1978 amendment to FIFRA emphasized the importance of accurately evaluating exposure in OPP's regulatory decisions. Section 3(c)(8) was added to FIFRA and states (in part):

> Notwithstanding any other provision of this Act, the Administrator may not initiate a public interim administrative review process to develop a risk-benefit evaluation of the ingredients of a pesticide or any of its uses prior to initiating a formal action to cancel, suspend, or deny registration of such a pesticide, required under this Act, unless such interim administrative process is based on a validated test or other significant evidence raising prudent concerns of unreasonable adverse risk to man or the environment.

(5) While ''exposure'' does not appear in this section of FIFRA, this is clearly what Congress intended with the phrase ''prudent concerns of unreasonable adverse risk.'' The House-Senate Conference Report discussing this section of the 1978 amendments under paragraph (h)(9) of this guideline states:

> Human exposure to pesticides through any medium or pathway is a central issue in evaluating the unreasonable adverse effects of pesticide products. Where this issue can be resolved without an RPAR being initiated, it shall be.

(6) In discussing the amendments, Rep. Foley stated under paragraph (h)(10) of this guideline:

> To avoid the time consuming RPAR process, the Administrator is directed to establish suitable scientific protocols for development of human exposure data . . . and then to evaluate and weigh such data prior to initiating an RPAR process.

(7) The RPAR triggers promulgated in 1975 were based solely on toxicological hazards and did not take exposure into account. These triggers have now been replaced by new criteria initiating the assessment of unreasonable adverse effects which do consider the likely level of exposure. The RPAR process is now called the ''Special Review'' process under paragraph (h)(30) of this guideline.

(8) A consequence of the 1978 amendments to FIFRA is that applicator risk assessments, traditionally done only for registered pesticides under

RPAR review, must now be undertaken for pesticides undergoing registration or reregistration (Registration Standard) review as well as Special Review, when a potential toxicological concern has been identified.

(9) While the unreasonable adverse effects criterion of FIFRA does not make a distinction between indoor and outdoor uses of pesticides, historically most regulatory attention has been focused on the outdoor uses of pesticides under paragraph (h)(75) of this guideline. The review of many of the older, persistent pesticides used on food crops has been very resource-intensive and has lessened the Agency's ability to address concurrently the indoor uses. With the recent increased concern for human health and the indoor environment under paragraph (h)(84) of this guideline, activity in the areas of monitoring and evaluating the indoor uses of pesticide chemicals has increased.

(10) Consequently, these guidelines will cover exposure monitoring studies for both outdoor and indoor sites. For many indoor uses, the individual who applies the pesticide also works or resides in the building. As stated in the previous section, indoor exposure to pesticides is not currently addressed in other subdivisions of these guidelines. Accordingly, both application and ambient exposure will be addressed for indoor uses.

(11) Individuals who have contact with pesticides in the course of their work activities will be exposed to these chemicals through different routes and to a different extent than the general population. The purpose of OPPTS guidelines 875.1100 through 875.1700 is to aid pesticide registrants and others in designing and carrying out field studies which measure, using personal monitoring techniques, potential dermal and respiratory exposure to pesticides when used according to widespread and commonly recognized practice. These guidelines address direct exposure encountered during any pesticide application operation and related occupational activities including weighing and mixing the concentrated chemical, loading the material into the application equipment, etc. These guidelines also include indoor testing procedures to measure postapplication exposure to persons as a result of indoor use of pesticides.

(c) **Monitoring exposure using passive dosimetry and biological monitoring**—(1) **Definitions.** (i) *Passive dosimetry* estimates the amount of a chemical impinging on the surface of the skin or the amount of the chemical available for inhalation through the use of appropriate trapping devices.

(ii) *Biological monitoring* estimates internal dose from either a measurement of body burden in selected tissues or fluids or from the amount of pesticide or its metabolites eliminated from the body.

(2) **Theoretical and practical advantages and disadvantages of both approaches—**(i) **Passive dosimetry.** Traditionally, applicator exposure monitoring studies carried out for the Agency have employed passive

dosimetry techniques. Because of this history of use, experimental design and execution of exposure studies by passive dosimetry are routine for many investigators.

(A) The major advantages of direct entrapment procedures are the ability to differentiate exposure received during discrete work activities within a work day and in differentiating the relative contributions of the dermal and respiratory exposure routes for each separate work activityunder paragraph (h)(20) of this guideline. These advantages are extremely important for evaluating exposure reduction safety practices such as personal protective equipment for the various work activities associated with pesticide application. For example, if a substantial fraction of total exposure for a work day occurs to the hands, forearms, and face during the short period of time a worker pours a concentrated pesticide formulation into a mix tank, risk may be mitigated significantly by requiring chemical resistant gloves, a face shield, and/or a closed mixing system for this short duration/high exposure period. Since passive dosimetry measures only the amount of chemical potentially available for absorption, independent estimates of dermal and lung absorption are required to estimate dosage for hazard assessment purposes. These absorption estimates are generally difficult to derive and interpret using data available from either in vivo or in vitro penetration studies. In addition, when using passive dosimetry, assumptions concerning the value of the clothing worn on the interception of pesticide residues must also be made.

(B) A potential source of error in the use of patches for sample collection is the extrapolation from the residues on the relatively small surface area of the trapping devices to entire body surface areas. Also, when using the patch technique, crucial areas of exposure may be missed depending on the location of the trapping devices under paragraph (h)(34) of this guideline. A unique advantage of passive dosimetry is the ability to create large generic data bases from studies carried out with different pesticides. The use of the generic approach is discussed in detail in paragraph (f) of this guideline. Another advantage in using passive dosimetry is that the study participants are typically under the supervision of the investigator during the entire period when exposure data are being collected. A more detailed description of the methods used in passive dosimetry is contained in paragraph (e) of this guideline.

(ii) **Biological monitoring.** (A) The distinct theoretical advantage of the biological monitoring approach is that, under proper conditions, actual dose may be estimated from the results of the monitoring study. Biological monitoring implies that a biological measurement is intrinsic to the experimental design of an exposure assessment study. The use of the information derived from biological monitoring studies varies, from the early detection of a health effect to establishing a correlation between concentration of a chemical in fluids to absorbed dose.

(B) An example of the application of biological monitoring to the detection of a health effect is the analysis of cholinesterase levels in blood as an indicator or worker exposure to organophosphate pesticides under paragraph (h)(69) of this guideline. In this approach, medical surveillance of workers allows the expedient implementation of preventive measures, as dictated by blood cholinesterase inhibition levels under paragraphs (h)(46) and (h)(74) of this guideline. A quantification of exposure from cholinesterase inhibition is not a goal in this situation. Attempts to correlate levels of cholinesterase inhibition with concentrations of parent pesticides or their metabolites in either blood or urine have not been successful (under paragraphs (h)(5), (h)(19), and (h)(77) of this guideline). A major contributor to this failure is the wide variability of cholinesterase levels among individuals (see paragraph (h)(72) of this guideline. In its current practice, this type of medical surveillance is carried out by estimating a baseline, preexposure level for each worker and an arbitrary inhibition level is set at which the worker is removed from further exposure.

(C) Correlations between levels of exposure and concentrations of metabolites in blood have been documented for some industrial chemicals. The parameter monitored in this case is the formation of covalent adducts between the chemical, or a metabolite, and hemoglobin. (See paragraphs (h)(87) and (h)(70) of this guideline.) Examples reported in the literature where this technique has been applied include ethylene oxide under paragraph (h)(6) of this guideline, chloroform under paragraph (h)(70) of this guideline, and aniline under paragraph (h)(67) of this guideline. The route of exposure in these cases was predominantly inhalation.

(D) The basis for this approach is the ability of the chemical to alkylate hemoglobin. The reaction may take place directly as with ethylene oxide or may require metabolic activation to a reactive species as reported for chloroform and aniline. The selection of hemoglobin as an internal dosimeter is based on several features:

(*1*) Hemoglobin contains nucleophilic groups, histidine and cysteine, thus maximizing trapping efficiency.

(*2*) Hemoglobin is readily available in large amounts.

(*3*) The life span of hemoglobin, and its adducts, is about 18 weeks in humans, providing a stable marker for monitoring work environments which could be particularly useful for situations involving low-level chronic exposure.

(E) The reaction rate constants for the alkylation reaction of electrophiles with hemoglobin can be determined in vitro and may be used in conjunction with the adduct concentration to estimate the in vivo dose. At this time, this type of analysis has been fully documented in humans only in the case of exposure to ethylene oxide. For a group of workers handling ethylene oxide sterilizers, a correlation was established between

external exposure dose and the amount of covalent adduct formed per gram of hemoglobinunder paragraph (h)(6) of this guideline.

(F) A different approach, which does not require the intermediacy of reactive species, involves the measurement of concentrations or parent chemical(s) and/or corresponding metabolites in urine under paragraph (h)(1) and (2) of this guideline. Empirical correlations have been developed for some industrial chemicals which allow estimation of the exposure based on the rate of urinary excretion of selected markers. Through the application of biological monitoring to industrial settings, it has become possible to identify workers at high risk and proceed to modify the operations or conditions leading to an undesirable high exposure.

(G) For pesticides, urinary metabolites have been used to detect exposure during field operations: Swan, under paragraph (h)(86) of this guideline measured paraquat in the urine of applicators; Gollop and Glass, under paragraph (h)(41) of this guideline, and Wagner and Weswig, under paragraph (h)(89) of this guideline, measured arsenic in timber applicators; Lieben et al., under paragraph (h)(57) of this guideline, and Durham and Wolfe, under paragraph (h)(20) of this guideline, measured *p*-nitrophenol in urine after parathion exposure. A chlorobenzilate metabolite was detected in citrus workers (Levy et al., under paragraph (h)(55) of this guideline); phenoxy acid herbicide metabolites in farmers, (Kolmodin-Hedman et al., under paragraph (h)(49) of this guideline); and organophosphate metabolites in the urine of people exposed to mosquito treatments (Kutz and Strassman, under paragraph (h)(50) of this guideline). Davies et al., under paragraph (h)(12) of this guideline, used urine metabolites of organophosphates and carbamates to confirm poisoning cases. These studies documented exposure, but no quantification of exposure was typically made from urinary metabolites alone.

(H) Because applicators are often exposed to the same pesticide numerous times over a growing season, proper interpretation of urine data is difficult unless the pesticide is excreted fairly rapidly or multiple dosing and overlapping excretion patterns are well understood. Some experiments have contributed to understanding these problems and illustrate typical differences in the rate of absorption and excretion of various pesticides. Drevenkar et al., under paragraph (h)(18) of this guideline, studied the excretion of phosalone metabolites in one volunteer. Excretion reached a peak in 4–5 h, and was not complete in 24 h. Funckes et al., under paragraph (h)(39) of this guideline, exposed the hand and forearm of human volunteers to 2 percent parathion dust. During the exposure the volunteers breathed pure air and placed their forearm and hand into a plastic bag which contained the parathion. The exposure took place for 2 h and at various temperatures. There was increased excretion of *p*-nitrophenol with increasing temperature. More importantly, *p*-nitrophenol could be detected in the urine 40 h later.

(I) In another human experiment, Kolmodin-Hedman et al., under paragraph (h)(48) of this guideline, applied methylchlorophenoxyacetic acid (MCPA) to the thigh. MCPA appeared in the urine for 5 days with a maximum concentration in about 48 h. When administered orally, MCPA peaked in urine in 1 h and about 40 percent of the dose was excreted in 24 h.

(J) Seven different organophosphates were fed to rats at two doses for 3 days. The rats were removed from exposure after the 3rd day, and urine was collected for the next 10 days (Bradway et al., under paragraph (h)(5) of this guideline). The percent of the total dose excreted in urine over 10 days averaged (high and low doses): Dimethoate 15 percent; dichlorvos 10 percent; ronnel 11 percent; dichlofenthion 57 percent; carbophenothion 67 percent; parathion 41 percent; and leptophos 52 percent. Very little of this excretion occurred beyond the 3rd day after exposure.

(K) In another experiment, rats were dosed dermally and intramuscularly with azinphosmethyl (Franklin et al., under paragraph (h)(36) of this guideline). About 78 percent of the dermal dose had been excreted in urine in 24 h. For the intramuscular dose the rate of excretion peaked in 8–16 h, continued at about the same rate for 16 h and declined to a steady level in 48 h. There was a linear relationship between dose and urinary excretions.

(L) While biological monitoring theoretically offers a distinct advantage, there are inherent difficulties in study design, execution, and data interpretation. Prior to establishing specific testing procedures, the experimenter must have a broad knowledge of the chemical being tested. The pharmacokinetics of the chemical of interest must be known and fully understood so that the appropriate tissue, fluid, or excretion pathway, as well as the appropriate time periods for monitoring, can be chosen with regard to this information. Because this level of detailed information is currently unavailable for many pesticides, extrapolations back to the actual dose are difficult.

(M) When measuring exposure via a human substrate one must consider the different ways through which a substance may be eliminated (sweat, urine, saliva, etc.) or that it may be stored in adipose and other tissues. Because the measurements relevant to the estimation of workers' exposure to pesticides must be carried out under field conditions, the Agency believes that urine analysis is a realistic and practical approach to implement biological monitoring. This emphasis on a particular method is based on a consideration of the type of information desired and what is feasible to obtain under field conditions. It should be understood, however, that this observation is not intended to exclude other methods which are demonstrably effective.

(N) Biological monitoring clearly lacks the definition of source of exposure provided by the passive dosimetry method. The results of an appropriate biological monitoring study provide an integrated exposure picture. Biological monitoring should be considered a chemical-specific approach. The potential for extrapolating results of an exposure study to other pesticides appears limited by probable differences in absorption, metabolism and excretion profiles. Thus the opportunity for developing generic data bases, such as those from passive dosimetry studies, does not appear promising. This difficulty, however, may be overcome by the application of structure activity principles which would allow the grouping of pesticides according to chemical descriptors, thus providing a reasonable foundation for a useful, predictive data base.

(O) A potential difficulty that may be encountered when using a biological method is obtaining strict cooperation and adherence to protocols from study participants when collecting samples (urine, saliva, etc.). Monetary incentives are sometimes needed to increase cooperation. This may be true particularly when monitoring requires invasive collection techniques such as blood sampling. Invasive techniques could also raise legal and medial questions associated with the field collection of human tissues and fluids.

(P) A plan for intensive study oversight is necessary to ensure participant compliance in collection, storage and handling of urine samples including before, during, and after exposure to pesticides. It is not always practical, however, since investigators are usually on site during the work activities only, while exposure data are collected beyond the supervised period.

(Q) When a registrant believes that the problems associated with biological monitoring as described in this section can be overcome for a particular pesticide and chooses to monitor worker exposure using biological monitoring, the Agency will carefully evaluate the results and, if judged valid, use the results in the risk assessment process. In these circumstances, the theoretical advantage of biological monitoring discussed earlier in this section would naturally dictate the use of such data. Prior to initiating a biological monitoring study, however, the registrant must receive Agency approval of the study protocol.

(R) An examination of the limitations of the trapping devices presently used in passive dosimetry has suggested exposure scenarios where it could be necessary to utilize biological monitoring to estimate exposure. Examples of specific situations not amenable to current passive dosimetry methodologies include measuring exposure to pesticides in swimming pools, in dishwashing detergents, or measuring dermal exposure to volatile organic chemicals. The perceived advantages and disadvantages of passive dosimetry and biological monitoring are summarized in the following Table 1. The observations listed in Table 1. may be considered as initial

guidance in determining the feasibility of conducting an exposure study by either method.

Table 1.—The Perceived Advantages and Disadvantages of Estimating Occupational Exposure with Passive Dosimetry and Biological Monitoring

Advantages	Disadvantages
Passive Dosimetry	
Routes and areas of exposure clearly defined[1]	Dermal and respiratory absorption must be estimated[1]
Routine experimental design and execution	Extrapolation from patch to body surface area must be made
Participant under supervision of investigator	Not all exposure scenarios are amenable
Generic data bases may be created	
Biological Monitoring	
Actual dose may be measured[1]	Pharmacokinetics must be known[1]
Unnecessary to adjust for value of garment/protective clothing	Routes of exposure cannot be distinguished
	Difficult to ensure participant cooperation
	Potential problems when using invasive techniques required for specimen collection

[1] These factors considered most important.

(3) **Problems with the simultaneous use of passive dosimetry and biological monitoring.** (i) The simultaneous application of passive dosimetry and biological monitoring has been explored by several groups. Attempts have been made to establish a correlation of exposure measurements by both methods. Passive dosimetry has been combined with urinary metabolite determinations to compare worker exposure as a function of application method under paragraph (h)(93) and (h)(7) of this guideline; formulating plant worker exposure under paragraph (h)(8) of this guideline; and homeowner exposure under paragraph (h)(85) of this guideline. Numerous other studies have similarly attempted to correlate exposure estimates obtained by the use of patches with urine levels of pesticide and/or its metabolites under paragraphs (h)(52), (h)(53), (h)(35), (h)(37), (h)(91), (h)(92), and (h)(93) of this guideline. In most of these studies, no clear cut correlation was found between exposure estimated by both methods.

(ii) A publication under paragraph (h)(37) of this guideline reported a good correlation between urinary metabolites and amount of active ingredient (azinphosmethyl) sprayed. More relevant to the subject, a comparison was also made between dermal exposure estimates derived from urinary metabolites and patches for the same studies. Both methods gave comparable estimates at one application rate, but biological monitoring proved more responsive to variations in the application rate. For two application rates differing by a factor of 2.5, passive dosimetry estimated essentially identical dermal exposure while biological monitoring estimates reflected the difference in application rates. It should be noted, however, that the results reported in the Franklin study were obtained by the concurrent ap-

plication of passive dosimetry and biological monitoring methods on the same individuals. Unfortunately, the results as obtained did not allow a conclusive assessment of potential interferences arising from the simultaneous use of both monitoring approaches. This concern is discussed in more detail in paragraph (c)(3)(iii) of this guideline.

(iii) A careful analysis of the information available on the simultaneous use of passive dosimetry and biological monitoring suggests that if a registrant chooses the latter for exposure measurements, no direct dermal exposure methods should be used concurrently on the same individuals. This becomes necessary because the trapping devices used in passive dosimetry for estimating dermal exposure, by definition, intercept chemical residues. This prevents potential absorption, introducing an unnecessary and potentially confounding variable into the study. Until proper experimentation clarifies this situation, the Agency discourages the concurrent use of passive dosimetry and biological monitoring on the same individual in exposure studies.

(iv) It may be possible to design a study that would allow correlation between passive dosimetry and biological monitoring methods. An example might be to alternate the two monitoring methods, using the same group of individuals and allowing enough time in between so as to minimize possible interference. The Agency strongly encourages research in the area of comparing exposure estimated by passive dosimetry and biological monitoring.

(v) Specific criteria which must be met before proceeding with an exposure study are described in OPPTS 875.1100 through 875.1400 for passive dosimetry and in OPPTS 875.1500 for biological monitoring.

(d) **New approaches to field studies using passive dosimetry—**(1) **Method development.** Improving test methodology for measuring exposure, as in all areas of scientific research, is an ongoing process. However, little progress has been made in developing new methodology post Durham and Wolfe. The Agency strongly encourages new method development and stresses that the methodologies detailed herein are subject to change. Research in developing innovative and more efficient ways of measuring dermal and inhalation exposure would be of obvious benefit to those estimating the level of risk to persons handling pesticides.

(2) **Examples of recent developments.** (i) Several alternative methods have recently been developed and used in the field. The World Health Organization, under paragraph (h)(94) of this guideline, proposed the use of entire portions of garments, rather than patches, to test dermal exposure. This approach has distinct advantages and disadvantages.

(A) One advantage of collecting residues using clothing that covers an entire part of the body is that it provides a more thorough representation of the areas being measured, thus eliminating the uncertainty associated

with extrapolation from pads. Unfortunately, it is very difficult to change clothing or underclothing after each exposure period under conditions usually encountered in the field. Also, it is nearly impossible to remove these garments without contaminating them with residues from other areas of the body, especially those on the workers' hands and hair. When using entire items of clothing, adequate preextraction of interfering additives requires large volumes of solvent, extensive extraction equipment, and lengthy extraction periods. These problems also arise when extracting the items of clothing from the field in the laboratory. Experimentation may lead to the discovery of methods that could make exposure monitoring less troublesome and more accurate. An example is the measurement of exposure to fumigants. Popendorf et al., under paragraph (h)(73) of this guideline, used charcoal impregnated cloth (hand dosimeters) to measure hand exposure to 1,3-dichloropropene. The treated cloth measures dermal exposure to ambient air levels as well as direct contact. The hand dosimeter introduces an alternative method of measuring hand exposure that may lessen the burden of a troublesome task.

(B) Fluorescent tracers may be useful in quantifying exposure beneath clothed areas. Franklin et al., under paragraph (h)(35) of this guideline, added a fluorescent whitening agent (FWA) to azinphosmethyl in the spray mixture. After removing the exposed pads and clothing, each applicator was examined with ultraviolet light. Unclothed areas such as the face and neck were not monitored with pads, but the tracer revealed that these were significant areas of exposure. The tracer was also found beneath the protective and ordinary clothing, confirming the qualitative penetration of dye, and supporting the concept that there may have been penetration of azinphosmethyl as well.

(C) A similar experiment was conducted by Fenske et al., under paragraphs (h)(32) and (h)(33) of this guideline. The tracer, 4-methyl-7-diethylaminocoumarin, was added at the rate of 300 g to each 5 lb bag of diazinon 50 percent wettable powder. The tracer concentration on the exposure pads and on the subjects was evaluated through a scanning television apparatus. There was a discrepancy in the amount of tracer actually found on the face and the amount that had been estimated. The pad technique estimated much more exposure to the head than the tracer indicated.

(ii) New approaches for measuring applicator exposure will be accepted if they can be shown to be comparable or superior to the methods described in these guidelines. Registrants are encouraged to explore and discuss new approaches and techniques with the Agency before submitting protocols for approval.

(e) **Measuring applicator exposure**—(1) **A historical perspective.**Shortly after the first acutely toxic synthetic insecticide, parathion, became widely used in agriculture, a number of worker poisonings resulted. It became evident that quantification of occupational exposure to pesticides

would be a vital link to evaluating worker safety. In order to minimize occupational exposure to pesticides, it was necessary to determine the routes and amounts of exposure that workers received while engaged in various activities.

(i) The first pesticide exposure study was reported by Griffiths et al. under paragraph (h)(42) of this guideline. They determined the amounts of parathion trapped on respirator filter discs to compare the exposure received during applications to citrus, by either hand spray guns or airblast sprayers. Batchelor and Walker, under paragraph (h)(3) of this guideline, expanded exposure monitoring by including pads attached to workers' clothing to estimate potential dermal exposure. This allowed the determination of both the total potential for exposure associated with various tasks and the relative contribution by the dermal and respiratory routes. Durham and Wolfe, under paragraph (h)(20) of this guideline, reviewed all methodology that had been used to monitor pesticide exposure and provided some experimental validation for the best of that methodology. Subsequent to these pioneering studies, a number of investigators have utilized minor modifications of the original monitoring technique. However, little significant improvement in the accuracy of exposure assessment has been provided by these modifications.

(ii) With the advent of the rebuttable presumption against registration (RPAR) process by the EPA, the ultimate use of exposure monitoring data was drastically changed. It could no longer be used simply as a basis for the recommendation of the safest application procedures or as a guide for dealing with acutely toxic hazards. Now, quantitative assessments of risk for specific deleterious effects are required. These effects may be the result of a subtle physiological event resulting from chronic exposure. Therefore, the exposure workers will receive during use of pesticides must be estimated as reliably as possible. The purpose of these guidelines is to suggest the best methods currently available for this estimation.

(iii) Most of the methods recommended in these guidelines have been extensively reviewed under paragraphs (h)(14), (h)(20), and (h)(96) of this guideline. This guideline borrows heavily from those reviews, with the intent of providing the users of these guidelines with a single source of historical information and justification for the selected methods. Some of the more recently developed methods currently in use may prove superior to those detailed in these guidelines. The methods discussed here have been shown to be satisfactory in field use and were used to collect the majority of exposure data available at this time. Other methodologies demonstrated to be effective will of course be accepted by the Agency.

(iv) The following abbreviated review of exposure monitoring by passive dosimetry is divided into dermal and respiratory exposure, with major emphasis on the former. Dermal monitoring is subdivided into exposure for all areas of the body with a separate section for hand exposure. Also

included under dermal monitoring are the body surface area values and a discussion of exposure due to the penetration of clothing by pesticides.

(v) A very important consideration that must be kept in mind when selecting methods for exposure monitoring is that the monitoring method should not subject the participants to any more exposure than is absolutely necessary. For instance, if the pesticide label specifies that respirators that have been approved by the National Institute for Occupational Safety and Health (NIOSH) must be worn during application, no method may require a participant to wear a respirator that would provide less protection. Every monitoring method must be chosen to ensure that human safety will not be compromised.

(2) **Dermal exposure monitoring**—(i) **Monitoring of exposure to all areas of the body except the hands.** (A) The amount of pesticide potentially available for absorption through the skin of a worker can be estimated by trapping the material before it contacts the skin, or by removing material that has contacted the skin before it has been absorbed. This is done using various types of pads or articles of clothing to trap impinging residues, or by removing residues from the skin by swabbing or rinsing with an appropriate solvent.

(B) A major portion of currently available data concerning dermal exposure to pesticides was collected using α-cellulose and multilayered gauze pads described by Durham and Wolfe under paragraph (h)(20) of this guideline. However, other investigators have employed cellulose filter paper discs (Batchelor and Walker, under paragraph (h)(3) of this guideline); combined filter paper and surgical gauze pads (Lavy et al., under paragraph (h)(51) of this guideline); entire items of clothing (Miller et al., under paragraph (h)(65) of this guideline); patches cut from various types of fabric and backed with surgical gauze to collect residues that penetrate the fabric (Knaak et al., under paragraph (h)(47) of this guideline); skin swabbing (Durham and Wolfe, under paragraph (h)(20) of this guideline); and pads impregnated with lanolin to simulate the slightly greasy surface of the skin (Fletcher et al., under paragraph (h)(34) of this guideline).

(C) If pads are used to entrap residues that would have impinged on the skin, the material used for construction of the pads must be absorbent enough to retain all the liquid that contacts them, or if used for collecting dusts or dried residues, must be porous enough to collect these materials. The pads must be strong enough to hold up under the abuse they will receive in the field. They must not contain additives such as sizing that will interfere with the chemical analysis of extracted residues. Additives can usually be removed by preextraction of the pads. However, some interfering compounds cannot be adequately removed to allow analysis of low levels of residue. Cellulose filter paper pads are usually unsatisfactory

because they are quickly saturated with spray and do not have the necessary mechanical strength.

(D) Pads constructed from several layers of filter paper covered with multiple layers of surgical gauze may eventually prove to be a superior monitoring device. The filter paper readily absorbs liquids while the gauze collects impinging dry residues and provides extra mechanical strength. Unfortunately, use of this type of pad under actual field conditions has been rather limited. Therefore, data regarding the trapping efficiency of these pads is also limited.

(E) Another problem encountered when using external pads to monitor dermal exposure is the need to estimate how much of the material collected on the pads would have eventually penetrated clothing. Monitoring dermal exposure with pads constructed from squares of fabric backed by an absorbent pad can provide the investigator with a rough estimate of how much residue would have penetrated through the clothing to the skin of the worker. However, there are also problems associated with this type of pad. Pretreatment of the fabric, special finishes, and the type of fabric used can influence the collection, retention and penetration of residues. Also, use of this type of pad only provides simulation of the penetration of residues through freshly laundered clothing during the first exposure period of the day. These problems will be discussed in greater detail in paragraph (2)(iv)(C), concerning exposure due to residues that penetrate clothing.

(F) Some dermal exposure monitoring techniques have proved to be less than advantageous. Fletcher et al., under paragraph (h)(34) of this guideline, found that analytical difficulties encountered when using their lanolin impregnated pads made the use of this type of monitoring device impracticable. Skin swabbing is a laborious way to monitor dermal exposure. Durham and Wolfe, under paragraph (h)(20) of this guideline, found that it took 25 strokes with each of four ethanol soaked swabs to remove an average of 91 percent of the total amount of parathion that was deposited on the hands.

(G) Taking into account the advantages and disadvantages of the various monitoring devices listed above, the simple o-cellulose and multilayered gauze pad methods are recommended for monitoring dermal exposure to pesticides. Durham and Wolfe, under paragraph (h)(20) of this guideline, first described the construction and use of these monitoring devices. Davis, under paragraph (h)(14) of this guideline, repeated much of this work and included information on validation of methodology and problems encountered during field monitoring. Durham and Wolfe, under paragraph (h)(20) of this guideline, also reported on the testing of these monitoring devices. They demonstrated the effectiveness of α-cellulose pads in reflecting the amount of pesticide deposited on spraymens' forearms. This was accomplished by comparing the residues found on pads

to those found on adjacent areas of skin swabbed with ethanol. Unfortunately, they did not carry out a similar study to determine how well multilayered gauze pads reflect the ability of skin to entrap dry residues. However, they did test the ability of these pads to retain dusty residues. When dust was applied to the surface of these pads, and the pads were inverted and shaken mechanically, approximately 90 percent of the applied dust was retained. Both of these types of pads are easy to construct and use. High quality materials are available for their construction, and if such materials are used, preextraction is usually not necessary. Extraction of residues from both these types of pads is relatively easy to perform and extraction efficiencies are usually very high.

(H) The practicality of α-cellulose and multilayered gauze pads has been demonstrated by their usefulness in collecting field data for over 25 years. Most applicator dermal exposure data were collected using these dosimeters. It is imperative that applicator exposure data collected in the future be at least comparable to the existing data base. If dermal exposure data are to be collected using any other methodology, an appropriate demonstration of the comparability or superiority of that method should be included in the study protocol when it is submitted for review.

(ii) **Monitoring hand exposure.** Any brief review of the literature concerning dermal exposure of pesticide applicators will demonstrate the important contribution of hand exposure. To illustrate this, references on hand exposure to workers during various spray operations are shown in the following Table 2.

Table 2.—Contribution of Hand Exposure to Total Potential Dermal Exposure for Pesticide Applicators

Activity	Hand exposure as percent of total dermal exposure	Reference (under paragraph (h) of this guideline)
Drivers of tractors equipped with canopies during air-blast spraying of citrus	41	(93)
Bulk spray suppliers for above application	52	(93)
Drivers of ordinary tractors during boom spraying of tomatoes	25	(94)
Applicators using hand guns to spray aquatic weeds from airboats	47	(94)
Drivers for airboats for above application	89	(94)
Aerial applicators	55	(63)
Flaggers for above application	39	(63)
Applicators spraying lawns, trees, and gardens with power sprayers	37	(55)
Applicators spraying lawns with hose-end sprayers	98	(17)

(A) The exposure of workers' hands to pesticides has been monitored with lightweight absorbent gloves or sections cut from the back and palm of such gloves (under paragraphs (h)(16) and (h)(91) of this guideline)

or by swabbing or rinsing the hands with various solvents in several different ways (under paragraphs (h)(20), (h)(90), and (h)(61) of this guideline). All of these methods except those that employ absorbent gloves will not remove residues that are absorbed into the skin during the exposure period. However, the use of absorbent gloves may overestimate hand exposure. Even smooth surfaced nylon gloves may retain several times more residue than would have adhered to flesh (under paragraph (h)(16) of this guideline). Since hand exposure is often such a large component of total exposure, the use of gloves may result in a significant overestimation of total dermal exposure.

(B) Gloves also contain foreign materials such as sizing which may be difficult to remove by preextraction and which may interfere with chemical analysis of low levels of residue. Swabbing the hands with solvent is not satisfactory because of difficulties in adequately removing residues from between the fingers and around the fingernails. Durham and Wolfe, under paragraph (h)(20) of this guideline, found that they could recover approximately twice as much residue from workers' hands by using a bag rinse method rather than swabbing. Washing the hands in a stream of solvent or in a basin containing solvent is probably as effective and faster than shaking the hands in plastic bags containing solvent, but is not as standardized or as convenient as the bag rinse.

(C) A problem with any washing procedure is finding a solvent that will provide adequate removal of residues without causing injury to the skin or increased absorption of a pesticide. For many years, hundreds of contaminated workers' hands have been rinsed with 95 percent ethanol, water, or water containing detergent, without evidence of skin injury or increased absorption of pesticides. However, there have been several instances of problems with degradation of residues or interference with analyses due to the solvent used.

(D) Most existing hand exposure data were collected using some type of rinsing procedure and it is imperative that any such data collected in the future be comparable to the existing data base. Therefore, it is recommended that exposure of the hands be assessed by washing and the most convenient washing procedure for use in the field is the bag rinse method developed by Durham and Wolfe under paragraph (h)(20) of this guideline. Lightweight monitoring gloves have also been routinely used and this technique is also acceptable to the Agency. If a registrant elects to employ some other procedure, it will be necessary to obtain prior Agency approval for the data to be acceptable.

(iii) **Additional considerations**—(A) **Use of dermal pads.** After an investigator has determined which monitoring devices and processes are suitable for the exposure situation being studied, there are still several questions that must be answered before monitoring can begin. These are: how many dermal pads are required to assess each exposure and where

should these pads be located on the workers; how many replicate exposures are necessary and what constitutes a replicate; what monitoring is necessary when the workers are required to wear protective garments; and how long is an acceptable exposure period? Enough data must be gathered so that the exposure estimates resulting from the study will reflect the range and magnitude of exposure that a typical user of the pesticide will receive. When all the resources necessary for planning, implementing, and completing an exposure study are addressed, extra replicates or extra pad locations should be considered to ensure valid conclusions.

(B) **Number and location of dermal pads.** (*1*) Most investigators have essentially adopted the number and location of dermal pads used by Durham and Wolfe (see paragraph (h)(20) of this guideline). They recommended that each worker be monitored with a set of 10 pads. The Agency requires the use of at least 10 pads attached at the following locations:

(*i*) In front of the legs just below the knees.

(*ii*) In front of the thighs.

(*iii*) In back of the forearms.

(*iv*) On top of the shoulders.

(*v*) In back of the neck at the edge of the collar.

(*vi*) On the upper chest near the jugular notch.

Moving these pads to locations other than those specified must be approved by the Agency. However, the investigator is free to include any additional pads he feels necessary for a better estimation of exposure, e.g. head patches. The relationship of these pads to various areas of the body will be discussed in a following section.

(*2*) Assuming that the workers' shirts and trousers will be constructed of different materials and that one will want to estimate how much residue will penetrate the clothing, extra pads could be attached under the appropriate clothing. These pads should be placed adjacent to but not covered by one of the outer pads. The locations chosen for these extra pads should be in areas of the body that are expected to receive the highest exposure. Pesticide penetration of clothing will also be discussed in a later section.

(*3*) If it is suspected that an exposure situation will result in extraordinary exposure to an area of the body that is not well represented by the normal pad locations, pads should be moved or extra pads added to assess such exposure. For example, if a mixer often carries large bags of a dry formulation, the investigator would need to move the forearm pads to the inside of the arms and add an extra pad on the stomach to

determine exposure that occurred in these areas due to contact with the outside of bags.

(*4*) To reduce laboratory work, pads from opposite sides of the body can be combined prior to extraction. However, the back and chest pads cannot be combined, as separate residue values are needed from these pads for calculations. Also, pads from opposite sides of the body should not be combined if one of these pads is to be used in conjunction with an adjacent pad under the clothing to assess penetration.

(*5*) It is advised that supervisors instruct workers participating in the study to avoid touching the exposure pads. Some investigators have found it useful to employ photographic records to assist in the documentation of pad placement.

(C) **Monitoring when workers are required to wear protective garments.** If the pesticide being studied is, or will be, registered for use only when wearing protective garments, dermal monitoring is slightly different. In addition to the standard external patches, the Agency may require that investigators monitor workers with extra pads under the protective garments to assess penetration. These pads should be located in regions that are expected to receive maximum exposure such as beneath garment seams. Since the maximum exposure or area of penetration cannot always be accurately anticipated, additional pads should be placed under unseamed areas of protective garments in all the same locations as specified for dermal exposure monitoring of workers not wearing protective clothing. Pads under protective garments should be near, but not covered by any pads on the outside of the clothing. Even if the label specifies that protective gloves must be worn, hand exposure under the gloves must be assessed. Maddy et al., under paragraph (h)(62) of this guideline, as well as other investigators, have clearly demonstrated that workers, even when wearing rubber gloves, can receive significant hand exposure.

(D) **Acceptable exposure periods.** (*1*) It is difficult to specify in advance the optimal exposure period to monitor. This will depend on the nature of the material being applied and the activity being studied. The ideal period is long enough to collect sufficient residue for analysis but not so long that there is significant loss of residue through evaporation, absorption, or chemical conversion.

(*2*) Serat et al., under paragraph (h)(78) of this guideline, found significant losses of both parathion and dicofol after fortified fabric patches were exposed to ambient conditions for 4 to 6 h. Their tests included cotton gauze but not α-cellulose pads. However, Durham and Wolfe, under paragraph (h)(20) of this guideline, detected no loss of either parathion or DDT from α-cellulose pads compared to worker's fore-arms, unless the loss occurred at the same rate from both surfaces. They did not specify the exposure period, but usually monitored workers for 30 min to 2 h.

(*3*) It is also convenient to change monitoring media and perform hand rinses at some natural break in the workers' schedule. The items shown in the following Table 3. will provide some idea of exposure periods that have proven useful for monitoring various activities.

Table 3.—Exposure Periods from Selected Pesticide Exposure Monitoring Studies

Activity	Exposure Period	Reference (under paragraph (h) of this guideline)
Ground-sprayer application	30 to 120 min	(62)
Mixing/loading for above application	10 to 30 min	
Pilots for aerial application	1 to 10 h	(69)
Mixing/loading for above application	1 to 10 h	
Flagging for above application	1 to 7 hrs.	
Application to crawl spaces or around slab foundations for termite control.	1.5 to 2 h	(61)
Tractor drawn low-pressure boom sprayers	2 h	(14)
Backpack type hand sprayers	3 to 4 h	(14)
Application to lawns and shrubs with compressed air or hose-end sprayers.	15 to 30 min	(17)
Air blast application to orchards	20 min to 2 h	(96)

(iv) **Dermal exposure calculations.** After the amount of residue on a unit area of exposure pad during a unit time of exposure has been determined, several assumptions are used to estimate the worker's potential dermal exposure. It is necessary to extrapolate the amount of pesticide found on each unit area of pad to the amount that would have impinged on the total body region represented by the pad. This assumes that certain pads represent certain regions of the body and that the surface areas of these regions are known. An assumption would also be made as to how much of the residue found on a pad would have penetrated the worker's clothing.

(A) **Assumptions concerning the surface area of regions of the body and pad locations that represent these regions.** (*1*) Most of the literature describing pesticide exposure monitoring (refer to paragraphs (h)(14), (h)(20), and (h)(96) of this guideline) has recommended the use of surface areas based on the method of Berkow (under paragraph (h)(4) of this guideline). Popendorf and Leffingwell (under paragraph (h)(72) of this guideline) examined the surface area values that several investigators proposed for various regions of the human body. They concluded that extrapolating exposure from the pad to the body region using Berkow's method is inappropriate because Berkow specifically adjusted body region surface areas for their relative importance to burn victims. Popendorf and Leffingwell (under paragraph (h)(72) of this guideline) developed regional surface areas based on anatomic modeling of the 50th percentile man.

(*2*) The Exposure Assessment Group/Office of Health and Environmental Assessment (OHEA) (under paragraph (h)(31) of this guideline) investigated previous research on the surface area of body regions. Based on this review, the model

$SAP = a_0 W^{a1} H^{a2}$

where

SAP is body part surface area in meters squared,

W is body weight in kilograms,

H is height in centimeters,

a_0, a_1, and a_2 are constants for each body region.

was developed and compared to data collected from the Second National Health and Nutrition Examination Study (NHANES II). The coefficient of determination for adult males was greater than 0.7 for all body regions with the exception of the head, upper arms, hands and feet. Foot exposure is rarely measured, and hand exposure is measured directly using hand rinses or cotton gloves.

(*3*) The following Table 4. shows the surface area estimates presented by Berkow and those derived from the OHEA report. A comparison of the two sets of estimates shows close agreement for the trunk area, forearms, and lower legs. The OHEA estimates for upper arm and thigh surface areas are substantially greater than the Berkow estimates.

Table 4.—Surface Areas for Regions of the Adult Male Body

Region of the Body	Surface Area of Region (Berkow)	Surface Area of Region (OHEA)[1]
	(cm^2)	(cm^2)
Head	–	1,300
Face	650	–
Trunk[2]	–	7,390
Back of Neck	110	–
Front of Neck	150	–
Chest/Stomach	3,550	–
Back	3,550	–
Upper Arms	1,320	2910
Forearms	1,210	1,310
Hands	820	990
Thighs	2,250	3,820
Lower Legs	2,380	2,560
Feet	–	1,310

[1] for 50th percentile man (NHANES II, under paragraph (h)(31) of this guideline).
[2] Includes the neck.

(*4*) The Agency recommends that the surface areas presented in the following Table 5. be used in calculating exposure to body regions. For consistency with past practices and in recognition that the Berkow and OHEA estimates closely agree, the Berkow estimates have been retained with the exception of the upper arms and thighs. The OHEA estimates for the thighs and upper arms have replaced the Berkow estimates.

Table 5.—Surface Areas for Regions of the Adult Body and Locations of Dermal Exposure Pads that Represent These Regions

Region of the Body	Surface Area of Region (cm^2)	Location of Pads Representing Region
Head	1,300[1]	Shoulder, Back, Chest[2]
Face	650	Chest
Back of Neck	110	Back
Front of Neck[3]	150	Chest
Chest/Stomach	3,550	Chest
Back	3,550	Back
Upper Arm	2,910	Shoulder and Forearm/ Upper Arm
Forearm	1,210	Forearm
Hand	820	
Thigh	3,820	Thigh
Lower Leg	2,380	Shin
Feet	1,310	

[1] Surface area for the head includes the 650 cm^2 face surface area.
[2] Exposure to the head may be estimated by using the mean of the shoulder, back and chest patches, or by using a head patch.
[3] Includes ''V'' of the chest.

(*5*) Davis, under paragraph (h)(14) of this guideline, suggested that certain exposure pads be used to represent various regions of the body. However, his representation of vertical facial areas by horizontal shoulder pads may well lead to the overestimation of facial exposure. Therefore, it is recommended that future exposure studies employ the pad locations shown in Table 5. for extrapolation from residues found on dermal pads to exposure estimates for adjacent regions of the body.

(B) **Penetration of residues through clothing.** (*1*)The problem of accounting for protection from exposure by a worker's clothing is not easily dealt with because of the scarcity of appropriate data. Assumptions ranging from complete protection of covered areas (under paragraph (h)(20) of this guideline) to complete lack of protection (under paragraph (h)(93) of this guideline) have been used to circumvent this problem. Maddy et al., under paragraph (h)(62) of this guideline, monitored a total of 102 individual exposure situations of mixers, loaders, flaggers, and applicators. They found that an average of approximately 23 percent of total dermal exposure was due to residue that penetrated 7–oz, 65 percent Dacron polyester, 35 percent cotton twill coveralls. Gold et al., under paragraph (h)(40) of this guideline studied the exposure of 38 urban applicators and found that the mean penetration of carbaryl through clothing was only 6.1 percent. Their data appeared to indicate that penetration was not greatly affected by formulation (2.4 percent to 11 percent penetrated), crop (2.3 percent to 11 percent penetrated), or type of application equipment used (4.7 percent to 16 percent penetrated). The same group of investigators (Leavitt et al., under paragraph (h)(54) of this guideline) also studied the penetration of carbaryl to the skin of five professional applicators wearing jumpsuits of unspecified material with open collars and short sleeves. The workers used power sprayers to treat trees and their exposure resulted from

mixing, applying and equipment cleaning. An average of 5 percent of the material that contacted their clothing penetrated to the skin. Although the mean values of total pesticide contacting the different regions being monitored ranged from 0.84 to 13 μg/cm²/h, the average amounts that penetrated ranged from 3.4 to 6.9 percent. Spear et al., under paragraph (h)(82) of this guideline, and Popendorf et al., under paragraph (h)(71) of this guideline, reported that up to approximately 50 percent of pesticide residues impinging on the clothing of fruit harvesters would have penetrated to the skin. Freed et al., under paragraph (h)(38) of this guideline found that up to approximately 50 percent of the active ingredient from simulated sprays penetrated a 65 percent polyester, 35 percent cotton fabric, but that 100 percent cotton fabric was much more resistant to penetration.

(*2*) Because existing data indicate such extreme variability in permeation and/or penetration of clothing (including protective) by pesticides, study investigators should consider laboratory testing procedures to supplement field studies in some cases. The Agency believes that laboratory testing of a variety of protective clothing materials would provide additional valuable data, since it is unrealistic to assume that all users of a particular pesticide product would wear exactly the same type of protective clothing. Registrants are encouraged to discuss study design involving protective clothing or equipment performance with Agency personnel before submitting protocols for approval.

(3) **Respiratory exposure monitoring**—(i) **Exposure to applicators.** (A) When equipment used for monitoring respiratory exposure during the application of pesticide sprays has been properly designed, it is found that respiratory exposure is usually a very small component of total exposure. This is demonstrated by the first five exposures shown in the following Table 6. Assuming that 100 percent of the material that is potentially available for respiratory exposure is absorbed, a situation is rarely found where the respired dose would be a significant portion of the total dose received during normal spray operations. However, as illustrated by the last two lines of the following Table 6., there are situations when respiratory exposure can be significant. These situations usually involve the application of dusts, aerosols, and fumigants or the application of sprays in enclosed spaces. Also, as the dermal penetration of the pesticide decreases, the relative importance of the inhalation route becomes greater.

Table 6.—Contribution of Respiratory Exposure to Total Potential Exposure for Pesticide Applicators

Activity	Physical Form of Pesticide Used	Respiratory Exposure as percent of Total Exposure	Reference (under paragraph (h) of this guideline)
Drivers of tractors equipped with canopies during air-blast spraying of citrus.	Spray	0.029	(93)
Bulk spray suppliers for above application	Unspecified	0.004	(93)
Drivers of ordinary tractors during boom spraying of tomatoes.	Spray	0.04	(94)
Applicators using hand guns to spray aquatic weeds from airboat.	Spray	none detectable	(94)
Drivers of airboats for above application	Spray	none detectable	(94)
Applicators using aerosol generator for mosquito control.	Aerosol	9.1	(11)
Applicators using hand knapsack mister for spraying tomatoes.	Mist	3.1	(81)

(B) In view of the preceding, registrants may not be required to monitor for respiratory exposure unless the Agency has reason to believe that such exposure would be significant. However, respiratory exposure monitoring will be required if the material in question has been demonstrated to cause an adverse biological effect that is associated with or accentuated by respiratory exposure; if the formulation or application method is expected to result in significant respiratory exposure; or if the formulation or application method has an unknown potential for respiratory exposure.

(iii) **Choice of method.** No single methodology can be specified as best for respiratory exposure monitoring in all cases. The method of choice will depend on the chemical and physical nature of the material being studied and may also depend on the activity being monitored. An extremely wide variety of methods are available. Investigators concerned with such monitoring are referred to the following extensive reviews. The methodology used for personal air monitoring was reviewed by Linch, under paragraph (h)(59) of this guideline. However, he did not emphasize sampling media that are most useful for the collection of pesticides. On the other hand, Van Dyk and Visweswariah, under paragraph (h)(88) of this guideline, reviewed the various media available for collection of pesticides but with major emphasis on high volume sampling. One of the latest and most complete reviews of all methodology used for field monitoring of airborne pesticides was by Lewis, under paragraph (h)(56) of this guideline. Other sources of information that will be of help in planning and implementing studies of respiratory exposure to pesticides are the protocol under paragraph (h)(57) of this guideline and articles under paragraph (h)(14) and (20) of this guideline.

(iv) **Personal monitoring of respiratory exposure.** (A) These guidelines require that potential exposure by the inhalation route be estimated

using personal monitors. Several techniques are available to the investigator. These range from simple gauze pads used in place of dust filters in modified respirators to rather exotic solid sorbents used with battery-powered personal air samplers. The various media and pumping systems that may be applicable have been reviewed under paragraphs (h)(56) and (h)(59) of this guideline.

(B) The gauze pad procedure (under paragraph (h)(20) of this guideline) is convenient because it is simple to construct the necessary pads and to modify the respirators, and exposed pads can usually be extracted in the same manner as exposed dermal pads. Also, the test subject produces the air flow for trapping so that breathing rate and total volume inhaled do not have to be estimated separately. However, the investigator must ensure that the respirator pads are an efficient trap for the material under study, that the respirator is well fitted to the test subject's face, and that the subject does not remove the mask during the exposure period. Construction of respirator pads, details of respirator modification, and a description of field operations used with this procedure appear in paragraph (i)(3) and (4) of this guideline.

(C) In the past, the second most commonly employed procedure for assessing respiratory exposure to pesticides under field conditions utilized ethylene glycol as a sampling medium. The use of this material in midget impingers presents some problems for personal monitoring since the liquid is easily spilled as a worker goes about his duties and the liquid may also be drawn into the pump mechanism. These problems may be alleviated by using the ''spill-proof'' microimpingers described by Linch, under paragraph (h)(59) of this guideline. Even with spills eliminated, this procedure, as with all procedures employing a mechanical pump, requires an estimation of a worker's ventilation rate. This varies with the amount of exertion employed. Another problem that may be encountered with this system is loss of residue. Some materials are not trapped by ethylene glycol or are rapidly lost from solution during prolonged sampling. Other materials are degraded in ethylene glycol, probably by hydrolysis since the ethylene glycol also traps considerable moisture from the air.

(D) The use of solid sorbents for personal monitoring of pesticide exposure is gaining in popularity and this technology is developing rapidly. The major disadvantage of using sorbents, in addition to the need to estimate the worker's ventilation rates, is the restriction of airflow by finely divided particles. Another drawback is degradation or chemical conversion of some pesticides bound to active sorbents. A description of the use of personal monitoring pumps and samplers appears under paragraph (i)(2) and (4) of this guideline.

(v) **High volume air sampling.** In atypical cases where levels of toxicants in the air are too low to be sampled by personal monitors or where suitable monitoring media are not available, investigators may have to re-

sort to the use of high volume samplers. The use of such samplers has been described in a number of publications (under paragraphs (h)(56), (h)(57), and (h)(88) of this guideline). These are not generally recommended for monitoring occupational exposure in the field unless absolutely necessary. For this reason they will not be discussed further in these guidelines.

(4) **Dermal and respiratory exposure monitoring at indoor sites.** (i) In general, monitoring of exposure during application of pesticides at indoor sites involves the same considerations as monitoring during outdoor applications. Even though some of the types of sprayers used for indoor applications may produce aerosols with a greater potential for respiratory exposure than is generally found for outdoor applications, monitoring methods that are satisfactory for outdoor applications should also be satisfactory for indoor sites.

(ii) It has been estimated (under paragraph (h)(27) of this guideline) that pesticides are used in more than 80 percent of U.S. households. This fact and several others lead to the special concern one must have for the exposure of individuals occupying dwellings that have been treated with pesticides. Indoor residues can persist for significantly greater periods of time compared to similarly applied outdoor residues (see paragraph (h)(13) of this guideline). This increased indoor persistence may be due to an environment that protects residues from sunlight and moisture, provides for different degradation pathways, and inhibits their dissipation by limiting ventilation of vapors. Since modern construction methods have produced dwellings that are energy efficient and greatly restrict air exchange, they may exacerbate problems with indoor air pollution (see paragraph (h)(84) of this guideline).

(iii) It is recommended that the dermal and respiratory exposure of applicators be monitored using the same methodology that is recommended for outdoor applications. However, since more respiratory exposure to aerosols and vapors is expected, the investigator should ensure that the trapping medium used to assess this exposure is particularly efficient in trapping these forms.

(iv) For postapplication respiratory exposure monitoring, a battery operated pump fitted with a trapping medium that is an efficient trap for vapors may also be used. However, the sampler need not be worn by a test subject, but only placed at breathing level in the room. Since concentrations of pesticide vapors may be low after application, the investigator may have to sample for extended periods to collect enough material for analysis.

(v) Although one can determine the postapplication levels of residues on surfaces by swabbing or by the analysis of material on collection surfaces such as mylar squares that are left in a room for various periods

of time after application, the Agency does not feel that any satisfactory system has yet been devised and sufficiently tested to ensure that it will reliably allow one to relate such residues to the potential for dermal exposure. Therefore, surface residue monitoring is not required. Postapplication monitoring for estimation of potential dermal exposure will be required, using the same technique as for monitoring dermal exposure to applicators, only on a case by case basis and will depend on the type of pesticide product and its use.

(vi) Since the potential for postapplication respiratory exposure will be dependent on the nature of the pesticide product used, the sampling schedule for postapplication respiratory exposure monitoring will have to be determined in consultation with Agency scientists. This sampling schedule will be created such that the pattern of decline of potential respiratory exposure as a function of time can be defined.

(f) **The use of surrogate data and the development of generic predictive correlations.** (1) Many difficulties and variables associated with carrying out exposure monitoring studies in the field during actual application have been discussed previously in this document. Many of the variables, such as climatic conditions and the degree of care exercised by individuals, are not under the control of the scientist supervising the study. These uncontrolled variables usually result in a wide variation in experimental results. The amount of resources required to do field studies for every controllable variable (such as crop, application method, or pesticide) would be very high. For these reasons, and for the scientific reasons discussed below, the Agency policy (under paragraphs (h)(28) and (h)(76) of this guideline) is to use ‘‘surrogate’’ data to estimate applicator exposure when appropriate.

(2) ‘‘Surrogate’’ or ‘‘generic’’ exposure data are defined herein as exposure monitoring data collected for other pesticide chemicals applied using comparable methods and under similar conditions as for the pesticide under assessment. The mechanics of the use of surrogate data have been discussed in detail in public forums and in the published scientific literature in recent years (under paragraphs (h)(43), (h)(45), (h)(76), and (h)(79) of this guideline. The assumption in the use of surrogate data is that in many application scenarios, the physical parameters of application, not the chemical properties of the pesticide, are most important in determining the level of exposure. Note that when using a passive dosimetry monitoring method, what is measured is the amount of chemical impinging on the skin surface, or available for inhalation, not the actual dose received. Factors such as dermal penetration are, of course, expected to be highly chemical-dependent. A review of all available information on pesticide exposure during application activities, as discussed earlier, supports the use of surrogate data for applicator exposure assessments.

(3) There is general agreement that the principal application parameter that determines the level of exposure is the method of application. One application technique for which there is a great deal of exposure monitoring data is ground application to orchards using high pressure or airblast equipment. The Agency has evaluated these exposure data to attempt to derive statistically valid and useful predictive correlations. A significant correlation was found between application rate and dermal exposure. A Spearman Rank Correlation Analysis (under paragraph (h)(81) of this guideline), a test to determine if an increase in exposure is associated with an increase in application rate, indicated a statistically significant correlation. A less significant correlation was found for another application parameter, tank concentration.

(4) All of the studies included in the airblast data base are from published or publicly available sources. The results of studies carried out by registrants according to these guidelines, like any other data generated in support of a registration application or continued registration, may be considered proprietary, or involve data compensation matters. A proposal has been put forward, however, to accommodate the routine use of registrant-generated exposure data on a generic basis so that the overall data base for estimating applicator exposure would be significantly expanded (under paragraph (h)(43) of this guideline). The National Agricultural Chemicals Association, Health Canada, and the Agency actively pursued this proposal.

(5) In June 1992, the Office of Pesticide Programs announced the availability of the Pesticide Handler Exposure Database (PHED) to registrants and the public. The development of this generic data base is a procedure which the Agency will continue to pursue. The Agency believes that it is more reliable to estimate exposure based on an extensive, scientifically sound and appropriate data base rather than from the results of an individual study with a limited number of replicates, even if that single study is judged valid by the Agency. As the Agency receives additional valid exposure data from any source, the data will be added to the existing data base, thus expanding that data base and improving its reliability for estimating exposure for other pesticides. For more information on PHED, contact the Occupational and Residential Exposure Branch at the Environmental Protection Agency, Office of Pestiide Programs, Health Effects Division (7509C), 401 M St., SW., Washington, DC 20460.

(g) **General information and exposure methodology common to occupational and residential test guidelines; applicator exposure monitoring, OPPTS Series 875, Group A.** (1) The studies carried out according to these guidelines will be acceptable to the EPA, but investigators may find additional helpful information under paragraphs (h)(14), (h)(20), and (h)(96) of this guideline. The article by Davis (paragraph (h)(14) of this guideline) should be particularly helpful because it was written as a

primer for those who have never conducted an exposure study. It contains may practical tips about field operations.

(2) It cannot be overemphasized that investigations carried out according to these guidelines must be properly designed to provide for maximum protection of the study subject's health. Studies conducted to obtain human exposure data must not violate section 12(a)(2)(P) of FIFRA. Informed consent should be obtained in writing from all subjects who will be exposed as a result of these studies, and proposed protocols may need to be approved by the appropriate human studies committee for the State in which the exposure will occur. Also, guidelines for the Protection of Human Subjects of the Department of Health and Human Services should be considered of the design of such studies (HHS 1981).

(3) Proper administration is vital for successful exposure monitoring studies, as well as to ensure the safety of the workers being studied. It is most important that field studies have professional supervision by persons who are knowledgeable and experienced in exposure assessment. Inexperienced investigators are strongly urged to arrange to accompany an experienced investigator during an entire exposure study before attempting a study on their own.

(4) All conditions specified on the label for legal application of registered pesticides must be observed. Existing or proposed labels with inappropriate information concerning protective clothing will be addressed on a case-by-case basis as protocols are submitted. Chemical resistant gloves, NIOSH-approved respirators, or any other protective gear that is required, must not be removed during the exposure monitoring period. Any protective clothing and equipment required for the workers must not be altered in any manner that would result in decreased protection.

(5) Studies must be designed so that an exposure is measured separately for each activity associated with an application even when, in actual practice, an individual is involved in more than one activity. For example, separate estimates shall be made for the exposure received during mixing/ loading the pesticide and while driving the tractor that pulls the ground boom sprayer. Any differences in the magnitude of exposure for these two activities may be addressed by different regulatory options. The Agency recognizes, however, that for certain atypical application scenarios, it would be impractical to measure exposure for each work activity, and monitoring of combined activities will be allowed on a case-by-case basis.

(6) Tests must be carried out at label application rates using the actual formulation and packaging that will be commercially available. The EPA may require the estimation of exposure to active ingredients, inerts or contaminants, any other chemicals present in the formulation, any degradation or transformation products, or any combination thereof. Also, all data must

be collected and documented in accordance with applicable sections of Good Laboratory Practice Standards at 40 CFR 160.

(7) Investigators must exercise care to ensure that all operations contributing to the exposure under investigation are carried out in a manner that is consistent with typical use. Outside applications must be performed under weather condition (e.g. wind speeds) that are consistent with label restrictions or that are generally recognized as acceptable for spraying. Registrants must submit proposed exposure study protocols to the EPA for review and receive Agency approval prior to initiating the study.

(8) The type and completeness of exposure data required by the EPA will depend on the toxicity of the chemicals involved, the proposed uses for the formulation, the proposed methods of application, and the availability of data from studies using similar formulations and application methods. Complete studies will not be required for every product being registered, and the need for new data is expected to decrease as the exposure data base increases. Exposure data may be required for any method of application proposed by the registrant.

(9) It is impossible to specify a particular duration of exposure that would give satisfactory results for a given operation. The exposure period must be long enough to collect measurable residues, if exposure is occurring, but short enough to avoid excessive losses due to volatilization or decomposition (refer to Table 3. under paragraph of (e)(2)(iii)(D)(*3*) of this guideline for examples of exposure periods that have proved useful for monitoring various activities).

(10) The Agency requires that each exposure situation be evaluated using at least 15 replicates. Each replicate is a measure of the exposure to one worker for one exposure period. To obtain a single ‘‘typical’’ exposure for the situation being studied, individual values must be obtained under as many different conditions that are expected to affect exposure significantly as is possible. Three variables that are expected to have the significant effect on exposure are differences in application equipment, wind conditions during outdoor application, and, most importantly, different work practices and attitudes toward safety of the study subjects. Therefore, to obtain a reasonable cross-section of the variation of individual exposure values, the Agency requires that 15 replicates by obtained from a minimum of 5 replicates from each of a minimum of three application sites. It is strongly recommended that the replicates be obtained using as many different workers as possible. Fewer replicates will be acceptable under special circumstances. For example, when applying an experimental pesticide by air where the availability of subjects is limited, a minimum of nine replicates obtained from three replicates each at a minimum of three sites will sufficient.

(11) Many of the supplies and equipment described in these guidelines will be followed by a trade name and/or suggested source. This is meant as a guide to assist locating supplies, constructing dosimeters, or to describe methods that have been effective in the past. Any mention of trade names or commercial products does not constitute endorsement by the Agency, and does not imply that only those items or methodologies are acceptable. Investigators are encouraged to develop new methods for measuring exposure that may prove more effective than those described.

(h) **References.** The following references should be consulted for additional background material on this test guideline.

(1) Aitio, A. et al., (eds.). Biological monitoring and surveillance of workers exposed to chemicals. Hemisphere Publishing Corporation, New York (1984).

(2) Baselt, R.C., Biological monitoring methods for industrial chemicals. Biomedica Publications, Davis, CA (1980).

(3) Batchelor, G.S. and K.C. Walker, Health hazards involved in the use of parathion in fruit orchards of North central Washington. *A.M.A. Archives of Industrial Hygiene* 10:522–529 (1954).

(4) Berkow, S.G., Value of surface area proportions in the prognosis of cutaneous burns and scalds. *American Journal of Surgery* 11:315–317 (1931).

(5) Bradway, D.E. et al., Comparison of cholinesterase activity, residue levels, and urinary metabolite excretion of rats exposed to organophosphorus pesticides. *Journal of Agricultural and Food Chemistry* 25:1353–1358 (1977).

(6) Calleman, C.J. et al., Monitoring and risk assessment by means of alkyl groups in hemoglobin in persons occupationally exposed to ethylene oxide. *Journal of Environmental Pathology and Toxicology* 2:427–442 (1978).

(7) Carman, G.E. et al., Pesticide applicator exposure to insecticides during treatment of citrus trees with oscillating boom and airblast units. *Archives of Environmental Contamination and Toxicology* 11:651–659 (1982).

(8) Comer, S.W. et al., Exposure of workers to carbaryl. *Bulletin of Environmental Contamination Toxicology* 13:385–391 (1975).

(9) Conference Report. Federal Pesticide Act of 1978. Committee on Agriculture, Nutrition, and Forestry. United States Senate. January, 1979. p. 21.

(10) Congressional Record. Report on S. 1678 Federal Pesticide Act of September 19, 1978. H10119

(11) Culver, D. et al., Studies of human exposure during aerosol application of malathion and chlorthion. *A.M.A. Archives of Industrial Health* 13:37–50 (1956).

(12) Davies, J.E. et al., Developments in toxicology and environmental science. Pesticide monitoring studies. The epidemiologic and toxicologic potential of urinary metabolites. Pp. 369–380 in Toxicology and Occupational Medicine. W.B. Deichman, ed. NY (1979).

(13) Davis, J.E. et al., Persistence of methyl and ethyl parathion following spillage on concrete surfaces. *Bulletin of Environmental Contamination and Toxicology* 18:18–25 (1977).

(14) Davis, J.E., Minimizing occupational exposure to pesticides: personnel monitoring. *Residue Reviews* 75:33–50 (1980).

(15) Davis, J.E. et al., Potential exposure of apple thinners to phosalone. *Bulletin of Environmental Contamination Toxicology* 29:592–598 (1982).

(16) Davis, J.E. et al., Potential exposure of apple thinners to azinphosmethyl and comparison of two methods for assessment of hand exposure. *Bulletin of Environmental Contamination Toxicology* 31:631–638 (1983).

(17) Davis. J.E. et al., Potential exposure to diazinon during yard applications. *Environmental Monitoring Assessment* 3:23–28 (1983).

(18) Drevenkar, V. et al., The rate of urinary excretion of phosalone residues in occupationally exposed persons. *Science of the Total Environment* 13:235–243 (1979).

(19) Drevenkar, V. et al., Occupational exposure control by simultaneous determination of *N*-methylcarbamates and organophosphorus pesticide residues in human urine. *International Journal of Environmental Analalytical Chemistry* 14:215–230 (1983).

(20) Durham, W.F. and H.R. Wolfe, Measurement of the exposure of workers to pesticides. *Bulletin of the World Health Organization* 26:75–91 (1962).

(21) Durham, W.F., Introduction. Pp. xiii-xiv in Dermal Exposure Related to Pesticide Use. R.C. Honeycutt, G. Zweig, and N.N. Ragsdale, eds. ACS Symposium Series 273 (1985).

(22) EPA. Part 162—Regulations for the Enforcement of FIFRA, Subpart A—Registration, Reregistration and Classification Procedures. *Federal Register* 40:28268 (1975).

(23) EPA. Chlorobenzilate Position Document 2/3. July 11, 1978, pp. 28–35 (1978).

(24) EPA. Amitraz Position Document 2/3, January 16, 1979. pp. 27–29 (1979).

(25) EPA. Pronomide Position Document 2/3. January 15, 1979. pp. 13–21 (1979).

(26) EPA. Dimethoate Position Document 2/3. November 19, pp. 53–81 (1979).

(27) EPA. National household pesticide usage study, 1976– 1977. Report EPA/549/9–80–002 (1980).

(28) EPA. *Federal Register* 45:42858 (1980).

(29) EPA. Requirements for Data Submission. *Federal Register* 49:37956 (1984).

(30) EPA. 40 CFR Parts 154, 162 and 17— Special Reviews of Pesticides; Criteria and Procedures; Final Rule. *Federal Register* 50:49003 (1985).

(31) EPA. Development of statistical distributions or ranges of standard factors used in exposure assessments. EPA/600/8–85/010 , (1985).

(32) Fenske, R.A. A fluorescent tracer technique for assessing dermal exposure to pesticides. Northern California Occupational Health Center Report No. NCOHC 84–B–1, Berkeley, CA 270 pp. (1984).

(33) Fenske, R.A. et al., Evaluation of fluorescent tracer methodology for dermal exposure assessment. American Chemical Society Symposium Series 273, pp. 377–394 (1985).

(34) Fletcher, T.E. et al., Exposure of spray-men to dieldrin in residual spraying. *Bulletin of the World Health Organization* 20:15–25 (1959).

(35) Franklin, C.A. et al., Correlation of urinary pesticide metabolite excretion with estimated dermal contact in the course of occupational exposure to guthion. *Journal of Toxicology and Environmental Health* 7:715–731 (1981).

(36) Franklin, C.A. et al., Correlation of urinary dialkyl phosphate metabolite levels with dermal exposure to azinphos-methyl. Pp. 221–226 in Human Welfare and the Environment. J. Miyamoto, ed. IUPAC Pesticide Chemistry, Pergamon, NY (1983).

(37) Franklin, C.A. et al., The use of biological monitoring in the estimation of exposure during the application of pesticides. Presented at

the seventh Workshop ‘‘Biological Monitoring of Workers Manufacturing, Formulating and Applying Pesticides.’’ Szeged, Hungary, April, (1986).

(38) Freed, V.H. et al., Minimizing occupational exposure to pesticides: repellency and penetrability of treated textiles to pesticide sprays. *Residue Reviews* 75:159–167 (1980).

(39) Funckes, A.J. et al., Urinary excretion of paranitrophenol by volunteers following dermal exposure to parathion at different ambient temperatures. *Journal of Agricultural and Food Chemistry* 11:455–456 (1963).

(40) Gold, R.E. et al., Exposure of urban applicators to carbaryl. *Archives of Environmental Contamination Toxicology* 11(1):63–67 (1982).

(41) Gollop, B.R. and W.I. Glass, Urinary arsenic levels in lumber treatment operators. *New Zealand Medical Journal* 89:10–11 (1979).

(42) Griffiths, J.T. et al., Parathion hazards encountered spraying citrus in Florida. *Journal of Economic Entomology* 44:160–163 (1951).

(43) Hackathorn, D.R. and D.C. Eberhart, Data base proposal for use in predicting mixer-loader/applicator exposure. American Chemical Society Symposium Series 273, pp. 341–355 (1985).

(44) Health and Human Services. 45 CFR Part 46—Protection of Human Subjects. *Federal Register* 46:8386 (1981).

(45) Honeycutt, R.C., The usefulness of farm worker exposure estimates based on generic data. American Chemical Society Symposium Series 273, pp. 369–375 (1985).

(46) Kay, K. et al., Parathion exposure and cholinesterase response of Quebec apple growers. *Industrial Hygiene and Occupational Medicine* 6:252–262 (1952).

(47) Knaak, J.B. et al., Worker Reentry study involving phosalone application to citrus groves. *Toxicology and Applied Pharmacology* 46:363–374 (1978).

(48) Kolmodin-Hedman B. et al., Studies on phenoxy acid herbicides. I. Field Study on occupational exposure to phenoxy acid herbicides (MCPA, dichloroprop, mecoprop, and 2,4–D) in agriculture. *Archives of Toxicology* 54:257–265 (1983).

(49) Kolmodin-Hedman, B. et al., Studies on phenoxy acid herbicides. II. Oral and dermal uptake and elimination in urine of MCPA in humans. *Archives of Toxicology* 54:267–273 (1983).

(50) Kutz, F.W. and S.C. Strassman, Human urinary metabolites of organophosphate insecticides following mosquito adulticiding. *Mosquito News* 37:211–218 (1977).

(51) Lavy, T.L. et al., Field worker exposure and helicopter spray pattern of 2,4,5-T. *Bulletin of Environmental Contamamination and Toxicology* 24:90–96 (1980).

(52) Lavy, T.L. et al., Exposure measurements of applicators spraying (2,4,5-Trichlorophenoxy) acetic acid in the forest. *Journal of Agricultural and Food Chemistry* 28:626–630 (1980).

(53) Lavy, T.L. et al., (2,4-Dichlorophenoxy) acetic acid exposure received by aerial application crews during forest spray operations. *Journal of Agricultural and Food Chemistry* 30:375–381 (1982).

(54) Leavitt, J.R.C. et al., Exposure of professional pesticide applicators to carbaryl. *Archives of Environmental Contamination Toxicology* 11:57–62 (1982).

(55) Levy, K.A. et al., Chlorobenzilate residues in citrus worker urine. *Bulletin of Environmental Contamination Toxicology* 27:235–238 (1981).

(56) Lewis, R.G., Sampling and analysis of airborne pesticides. Pp. 51–94 in Air Pollution from Pesticides and Agricultural Processes. R.E. Lee, Jr., ed. CRC Press, Cleveland, OH (1976).

(57) Lewis, R.G. et al., Protocol for Assessment of Human Exposure to Airborne Pesticides. Health Effects Research Laboratory, Office of Research and Development, US EPA. NTIS EPA–600/2–80–180, 46 pp. (1980).

(58) Lieben, J.R. et al., Urinary excretion of paranitrophenol following exposure to parathion. *Industrial Hygiene and Occupational Medicine* 7:93–98 (1953).

(59) Linch, A.L., Evaluation of Ambient Air Quality by Personnel Monitoring. CRC Press, Cleveland, OH (1974).

(60) Maddy, K.T. et al., A study in southern California in July 1979 of the potential dermal and inhalation exposure of applicators and other persons who might later enter or occupy areas treated with chlordane used against subterranean termites under houses. Worker Health and Safety Unit Report HS–683, California Department of Food and Agriculture, Sacramento, CA. 13pp. (1979).

(61) Maddy, K.T. et al., A study of dermal and inhalation exposure of mixer/ loaders and applicators to nitrofen in Monterey and Santa Barbara counties of California. Worker Health and Safety Unit Report HS–745, California Department of Food and Agriculture, Sacramento, CA. 35pp. (1980).

(62) Maddy, K.T. et al., Dermal exposure monitoring of mixers, loaders, and applicators of pesticides in California. Worker Health and Safety

Unit Report HS–1069, California Department of Food and Agriculture, Sacramento, CA. 7pp. (1983).

(63) May, L.L., Dynamic Risk/Benefit Analysis in Pesticide Regulation: The Case of Toxaphene. Master's Thesis in Economics. University of California, Riverside, CA (1984).

(64) Melcher, R.G. et al., Collection of chlorpyrifos and other pesticides in air on chemically bonded sorbents. *Analytical Chemistry* 50:251–255 (1978).

(65) Miller, C.S. et al., Exposure of pesticide applicators to arsenic acid. *Archives of Environmental Contamination Toxicology* 9:281–288(1980).

(66) National Research Council. Regulation Pesticides. A report prepared by the Committee on Prototype Explicit Analyses Pesticides. National Research Council, National Academy of Sciences. p. 73 (1980).

(67) Neumann, H., Analysis of hemoglobin as a dose monitor for alkylating and arylating agents. *Archives of Toxicology* 56:1–6 (1984).

(68) Peoples, S.A. et al., Monitoring of potential exposure of mixer/loaders, pilots, and flaggers during application of tributyl phosphorothioate (DEF) and tributyl phosphorotrithioite (Folex) to cotton fields in the San Joaquin Valley of California in (1979). Worker Health and Safety Unit Report HS–676, California Department of Food and Agriculture, Sacramento, CA. 22pp. (1979).

(69) Peoples, S.A. and J.B. Knaak, Monitoring pesticide blood cholinesterase and analyzing blood and urine for pesticides and their metabolites. In Pesticide Residue and Exposure, J.R. Plimmer, Ed., ACS Symposium Series, No. 182, American Chemical Society, Washington, DC, pp. 41–57 (1982).

(70) Pereira, M.A. and L.W. Chang, Hemoglobin binding as a dose monitor for chemical carcinogens. In Bradway Report 13, Indicators of Genotoxic Exposure, B.A. Bridges, B.E. Butterworth, and I.B. Weinstein, Eds., Cold Spring Harbor Laboratory, pp. 177–187 (1982).

(71) Popendorf, W.J. et al., Harvester exposure to Zolone (phosalone) residues in peach orchards. *Journal of Occupational Medicine* 21:189–194 (1979).

(72) Popendorf, W.J. and J.T. Leffingwell, Regulating organophosphate pesticide residues for farmworker protection. *Residue Reviews* 82:125–201 (1982).

(73) Popendorf, W.J. et al., Nematocide Exposure Assessment Field Studies 1981–(1982). Pesticide Hazard Assessment Project (PHAP), University of California and University of Iowa. Final Report (1983).

(74) Quinby, G.F. et al., Public health hazards involved in the use of organic phosphorous insecticides in cotton culture in the delta area of Mississippi. *Journal of Economic Entomology* 51:831–838 (1958).

(75) Reinert, J.C., Pesticides in the indoor environment. Indoor air: recent advances in the health sciences and technology. *Swedish Council for Building Research* 1:233–238 (1984).

(76) Reinert, J.C. and D.J. Severn, Dermal exposure to pesticides: EPA's viewpoint. American Chemical Society Symposium Series 273, pp. 357–368 (1985).

(77) Roan, C.C. et al., Blood cholinesterases, serum parathion concentrations and urine *p*-nitrophenol concentrations in exposed individuals. *Bulletin of Environmental Contamination Toxicology* 4:362–369 (1969).

(78) Serat, W.F. et al., Loss of pesticides from patches used in the field as pesticide collectors. *Archives of Environmental Contamination and Toxicology* 11:227–234 (1982).

(79) Severn, D.J., Exposure assessment for agricultural chemicals. Pp. 235–242 in Genetic Toxicology, an Agricultural Perspective. R.A. Fleck and A. Hollander, eds., Plenum, NY (1982).

(80) Simpson, G.R. and A. Beck, Exposure to parathion. *Archives of Environmental Health* 11:784–786 (1965).

(81) Snedecor, G.W. and W.G. Cochran, Nonparametric methods: Rank correlation. Pp. 192–193 in Statistical Methods. Iowa State University Press, IA (1980).

(82) Spear, R.C. et al., Fieldworkers' response to weathered residues of parathion. *Journal of Occupational Medicine 19:406–410 (1977).*

(83) Spector, W.S., Handbook of Biological Data. W.B. Saunders Co., Philadelphia, PA (1956).

(84) Spengler, J.D. and K. Sexton, Indoor air pollution: a public health perspective. *Science* 221(4605):9–17 (1983).

(85) Staiff, D.C. et al., Exposure to the herbicide, paraquat. *Bulletin of Environmental Contamination Toxicology* 14:334–340 (1975).

(86) Swan, A.A.B., Exposure of spray operators to paraquat. *British Journal of Industrial Medicine* 26:322–329 (1969).

(87) Tannenbaum, S.R. and P.L. Skipper, Biological aspects to the evaluation of risk: dosimetry of carcinogens in man. *Fundamentals of Applied Toxicology* 4:S367–S373 (1984).

(88) Van Dyk, L.P. and K. Visweswariah, Pesticides in air: sampling methods. *Residue Reviews* 55:91–134 (1975).

(89) Wagner, S.L. and P. Weswig, Arsenic in blood and urine of forest workers. *Archives of Environmental Health* 28:77–79 (1974).

(90) Ware, G.W. et al., Establishment of reentry intervals for oganophosphate-treated cotton fields based on human data II. Azodrin, Ethyl and Methyl Parathion. *Archives of Environmental Contamination Toxicology* 2:117–129 (1974).

(91) Wojeck, G.A. et al., Worker exposure to ethion in Florida citrus. *Archives of Environmental Contamination Toxicology* 10:725–735 (1981).

(92) Wojeck, G.A. et al., Worker exposure to arsenic in Florida grapefruit spray operations. *Archives of Environmental Contamination Toxicology* 11:661–667 (1982).

(93) Wojeck, G.A. et al., Worker exposure to paraquat and diquat. *Archives of Environmental Contamination Toxicology* 12:65–70 (1983).

(94) World Health Organization, Field surveys to pesticides: technical monograph No. 7. Geneva, Switzerland. 5pp. (1982).

(95) Wolfe, H.R. et al., Exposure of spraymen to pesticides. *Archives of Environmental Health* 25:29–31 (1972).

(96) Wolfe, H.R., Field exposure to airborne pesticides. Pg. 137–161 in Air Pollution from Pesticides and Agricultural Processes. R.E. Lee, Jr., ed. CRC Press, Cleveland, OH (1976).