REPORT TITLE

Comparative Evaluation of Absorbed Dose Estimates Derived From Passive Dosimetry Measurements With Those Derived From Biological Monitoring:

Validation of Exposure Monitoring Methodologies

REPORT DATE

December 8, 2006

SUBMITTED BY

Agricultural Handlers Exposure Task Force
c/o Dr. David R. Johnson
Johnson Management & Consulting, LLC
1720 Prospect Drive
Macon, MO 63552
TE (660) 395-9590

TABLE OF CONTENTS

I. INTRODUCTION 4

A. HISTORICAL PERSPECTIVE ON PASSIVE DOSIMETRY METHODS USED TO ESTIMATE FARM WORKER EXPOSURE AND RISK TO PESTICIDES 4
B. VALIDATION OF PASSIVE DOSIMETRY METHODS 5

II. BIOMONITORING AND PASSIVE DOSIMETRY VARIABLES 8

III. DERMAL ABSORPTION AND PHARMACOKINETICS: KEY EXPOSURE VARIABLES 10

IV. CLOTHING PENETRATION: ANOTHER KEY VARIABLE 11

V. BIOMONITORING AND PASSIVE DOSIMETRY STUDY SUMMARIES 12

A. PROPRIETARY DOCUMENTS ON CONCURRENT PASSIVE DOSIMETRY AND BIOMONITORING 12
Airblast Mixer/Loader (M/L), Applicator, and Cleanup Workers (Honeycutt and Day, 1994) 12
Open-Pour Aerial M/L (Knuteson et al., 1999) 13
Groundboom M/L, Applicator, Reentry Scout Exposure (Shurdut et al., 1993) 13
Open-Pour Groundboom Granular M/L/A (Murphy et al., 1998) 13
Citrus Pruners and Harvesters (Honeycutt and Day, 1993) 14
Hose-End Sprayers and Hudson Sprayer (Rosenheck, 2000) 14
Groundboom Applicators and Mixer/Loader/Applicators (Selman, 1996) 14
Groundboom Mixer-loader-applicators (Chester et al, 1989) 15
Backpack mixer-loader-applicators (Findlay, 1998) 15
B. DERMAL PASSIVE DOSIMETRY EXTRAPOLATION TO WHOLE BODY 16
C. PUBLISHED STUDIES INVOLVING PD AND BIOMONITORING MEASUREMENTS OF EXPOSURE 22
Open Pour Groundboom M/L/A (Grover et al., 1986) 22
Open Pour Groundboom MLA (Chester and Hart, 1986) 22
D. PUBLISHED POST-APPLICATION EXPOSURE MONITORING STUDIES CONDUCTED WITH CONCURRENT PD AND BIOMONITORING 25
Williams et al., 2003 25
Krieger et al., 2000 25
Williams et al., 2004 26
E. EXCLUSION OF PROPRIETARY AND PUBLISHED PD-BIOMONITORING STUDIES FROM QUANTITATIVE EVALUATION 28

VI. VALIDATION METHODS 32

A. STATISTICAL TREATMENT OF PD/BIOMONITORING DATA 32
B. VALIDATION OF THE DERMAL ABSORPTION FACTOR INFLUENCE 32
Association of PD/biomonitoring Ratio with Study Dermal Absorption Values 32
C. INSIGNIFICANCE OF THE DOSIMETRY "PASS THROUGH" COMPONENT OF EXPOSURE 36
D. CONSERVATIVE BIASES IN BOTH PASSIVE DOSIMETRY AND BIOMONITORING 37

VII. CONCLUSIONS 38

VIII. REFERENCES 39

LIST OF TABLES

Table 1: *In Vivo* Dermal Absorption of Selected Pesticides in Humans 11
Table 2 Proprietary Study Conditions and Passive Dosimetry Description..... 17
Table 3: Proprietary Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring..... 20
Table 4: Published Study Conditions and Passive Dosimetry Description 23
Table 5: Published Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring..... 24
Table 6: Post-Application Reentry Exposure Studies Using Jazzercise with Concurrent PD and biomonitoring 27
Table 7: Examples of Supporting Studies that Were Excluded for Various Reasons 30

LIST OF FIGURES

Figure 1: Association of PD/biomonitoring Ratio with Dermal Absorption 33
Figure 2: Plot of Passive Dosimetry on Biomonitoring for Individuals 34
Figure 3: Ratio of Absorbed Dose from Passive Dosimetry to Biomonitoring by Individual.... 35

I. INTRODUCTION

A. Historical Perspective on Passive Dosimetry Methods used to Estimate Farm Worker Exposure and Risk to Pesticides

Passive Dosimetry (PD) methods for measuring and estimating exposure to agricultural workers (i.e. persons handling agricultural chemicals and working in treated crops) have been in use since the 1950s and have evolved through refinement of the techniques (Batchelor and Walker, 1954; Durham and Wolfe, 1962; World Health Organization, 1982; Fenske, 1989). These methods have subsequently been applied to consumers in residential settings. Overall, a large number of studies was conducted in the 1950s through 1970s to characterize exposure. PD, as originally practiced, involved placement of gauze patches on the outside of work clothing in 1 to 6 body regions to characterize the areas of primary exposure. PD also included ambient air monitoring. Over time the method evolved to placement of patches on and under clothing to estimate the amount of pesticide reaching the skin. Thus, the number of locations was increased to 10 to represent all regions of the body (US EPA, 1986). In the 1980s the 'whole body' PD method was developed and became the standard method of measuring dermal exposure in agricultural workers exposed to pesticides (World Health Organization, 1982). As a result of considerable research and the long term acceptance of PD as a method for estimating agricultural worker exposure, these monitoring methods have been codified in international and national regulatory guidelines (OECD, 1997; US EPA, 1997).

Dermal PD methods are used in conjunction with inhalation dosimetry methods. These exposure or absorbed dose estimates can then be quantitatively compared to 'no effect' exposure levels for hazards identified in toxicology studies. This basic paradigm (hazard identification, dose-response-assessment, exposure assessment, and risk characterization) was summarized by the National Academy of Sciences and has become the standard for risk assessment for regulatory agencies (NAS, 1983; NAS, 2006).

As risk assessment methodology evolved, the concept of a tiered approach to the process applied to agricultural workers was developed (Carmichael, 1995; OECD, 1997). At its simplest, the tiered approach involves using default upper-bound assumptions and generic exposure data (e.g. from the Pesticide Handlers Exposure Database, PHED) for the first and most conservative Tier 1. If further refinement is necessary, Tier 2 utilizes more accurate data for dermal absorption and exposure mitigation factors, e.g. for the use of personal protective equipment, alongside the same generic exposure data. The most refined and therefore most accurate Tier 3 involves obtaining chemical-specific exposure data on the pesticide under consideration from either PD or biological monitoring (biomonitoring) field studies. The tiered approach has been used routinely since the 1990s in North America and elsewhere.

B. Validation of Passive Dosimetry Methods

Validation in the context of human exposure monitoring methods means that a method has been shown to accurately measure a delivered dose in humans. Validation of PD methods by isolating the various components or routes of exposure (e.g., hand wash alone) is very difficult. Such an approach has been successfully adapted to validate inhalation exposure monitoring for gases and vapors in humans (Nomiyama and Nomiyama, 1974). However, the respiratory system is reasonably localized, while the skin covers the entire body. Isolating and validating the recovery from hands or the face/neck, for instance, are much more challenging. Part of the challenge would be preventing contact of the treated hand or face/neck with any other surface for up to 8 hours to mimic a normal work day to allow for absorption loss but not redistribution to untreated surfaces. Further, in order to ensure the ability to monitor and quantitatively recover all of the applied test substance, the active ingredient would need to be radio-labeled.

Even with radiolabel, it may not be possible to account for bound skin residues that are not bio-available and might take several days to be removed through normal physiologic processes such as loss through sloughing dead skin cells (Thongsinthusak et al., 1999). In conducting human dermal absorption studies, this problem has been resolved by two methods. One is skin stripping (applying adhesive tape to an area and forcefully removing the tape up to 20 times). This method certainly wouldn't be favorably received by humans particularly on the face. The alternative method adapted from dermal absorption methodology is to administer the test compound intravenously and determine the fraction of labeled material excreted in urine. This is an indirect way of determining the relative fraction of dose on skin that would be excreted in urine (Feldmann and Maibach, 1974).

The most practical alternative to isolating parts of the epidermis for validating recovery methods is to utilize field exposure studies in which concurrent or consecutive measurements have been made with PD and biomonitoring in the same cohorts of workers. This method has the advantage of not using radio-labeled material, but rather whatever formulations are in common commercial use. Further, rather than intentionally applying a chemical to human subjects, the exposures described in the following sections have occurred during normal activities associated with pesticide use. In essence, the standard PD method for estimating dermal exposure is modified such that the dosimeters closely represent the normal work clothing and thereby permit the concurrent conduct of the biomonitoring phase. This ensures that a direct comparison can be made between the estimated exposure and the absorbed dose arising from this exposure. These variants of the PD-biomonitoring methods have been described previously by Chester (1993, 1995) and Honeycutt et al. (2000). In this current paper, the results of the two methods will be compared within each study as a means of validating all of the techniques typically used in a PD monitoring study. The approach also offers opportunities to examine the effect of dosimetry matrix pass-through, porosity or bypass, hand wash efficiency and other questions about the validity of the PD methods.

Biomonitoring, as a means of exposure measurement, is rarely required by government regulatory authorities. Historically, biomonitoring was developed in the fields of occupational medicine and industrial hygiene as an alternative to commonly used PD methods. It offers the best means of accurately assessing human exposure to specific chemicals because it determines actual, rather than potential, absorbed dose (Woollen, 1993). In the context of exposure to pesticides, Woollen defined biomonitoring as "Measurement of a pesticide or its metabolites in the body fluids of exposed persons, and conversion to an equivalent absorbed dose of the pesticide based on the knowledge of its human metabolism and pharmacokinetics". Biomonitoring is recognized as the "gold standard" (Sexton et al., 2004) against which other estimates of exposure can be compared; hence biomonitoring's value in this description of validating PD methods.

Biomonitoring has been used extensively in industrial settings as a measure of exposure and an adjunct with air sampling in hygiene monitoring and surveillance programs to prevent over-exposure and ensure compliance with limit values such as the 'Threshold Limit Values' (TLV) set by the American Conference of Governmental Industrial Hygienists (ACGIH). This organization also sets 'Biological Exposure Indices' based primarily on urinary biomarkers (http://www.acgih.org/Products/beiintro.htm). During the evolution of PD, biomonitoring was sometimes used as a "backup" or insurance method while conducting PD monitoring. In other instances biomonitoring was used as the primary means of measuring the absorbed dose by integrating all contributions from multi-route exposure, i.e., a means for method validation. If it did not produce a perceived or actual improvement in understanding measured exposure, governmental regulators would not request confirmatory biomonitoring studies as they have done, and industry would not perform them because of the great expense and additional time required to develop the supporting pharmacokinetic studies necessary to interpret a biomonitoring study.

An important issue in estimating human exposure is to demonstrate that the principal methodology used to generate the exposure data is valid. "Valid" in this context means that the exposure methodology is sound, defensible and capable of a sufficiently accurate estimate of true occupational or residential exposure for eventual use in human health risk assessment. This validation determines if the combined standardized PD methods in their entirety, when used collectively, give a reasonable estimate of the absorbed dose. In this context validation is not intended for each specific method in isolation, such as patches, whole body dosimeters, hand washes, face/neck wipes, etc., from the other methods used to determine the dermal and inhalation exposure. One means of validating PD is to compare the absorbed dose estimated by this exposure monitoring methodology with that estimated using biological monitoring.

There are several studies available (some published, and some proprietary) that have employed both these approaches. For the express purpose of validation of PD using biomonitoring, it would be ideal if concurrent measurement data could be compared. This is because the uncertainty associated with the assumption that the measured exposure is representative of that from which the biomonitoring absorbed dose is derived is minimized. For example, if PD and biomonitoring were to be measured consecutively in the same workers because of the use of fully interceptive whole body dosimetry, there would be some

degree of uncertainty as to whether the actual exposures of the workers were directly comparable on the two occasions when PD and biomonitoring were conducted. That is to say that more uncertainty exists because it cannot be excluded that the exposures differ for some reason, such as change in behavior, local conditions or variation in application equipment and associated variables such as amount of product used and application rate. If the exposures differ significantly, then the comparison of absorbed dose via the PD and biomonitoring routes is that much more uncertain, because of the potentially different starting points, i.e. dermal and inhalation exposure on the two occasions.

A frequently used approach, which has been adopted in the evaluation of most of the studies, is to simply calculate the estimated total absorbed dose by multiplying the PD dermal and inhalation exposure data by appropriate route-specific absorption factors and then summing the resulting dermal and inhalation doses to obtain a total absorbed dose estimate. This PD-based total absorbed dose estimate can then be compared to the estimate of total absorbed dose given by the biomonitoring data. This approach ignores any 'bypass' of the dermal PD method and assumes that all active ingredient is captured and retained by the dermal dosimeters, including the hand wash and face/neck wipe.

Studies involving concurrent measurement with PD and biomonitoring would most likely have employed partial dosimetry, i.e. clothing, to ensure that the biomonitoring is not compromised by use of unrepresentative clothing that workers would not ordinarily wear for the work activities under study. This variant of the whole body method is described in the OECD guidance document for the conduct of studies of occupational exposure to pesticides (OECD, 1997). Typically, outer dosimeters would consist of cotton or cotton/polyester long-sleeved shirt and trousers (normal work clothing) and inner dosimeters of T-shirt and briefs (normal underwear). Face wipes and hand washes would be used to estimate the dermal exposure of the face/neck area and hands, respectively. Inhalation exposure would be measured using a relevant personal air sampling technique in the breathing zone. Several studies of this type are available.

The validation process involves estimating the total absorbed dose arising from all routes of exposure. Using the PD approach, estimated actual dermal exposure (aggregation of estimated penetration of outer dosimeters to underlying skin, handwashes and face/neck wipes) is adjusted for an appropriate dermal absorption factor, preferably from a human study if available, to give the absorbed dose from the dermal route. The inhaled dose is estimated from the calculated airborne concentration and appropriate ventilation rate for the work activity. The total of the two dose routes gives the combined total absorbed dose estimated from the partial dosimetry which could be compared with the total absorbed dose determined though biomonitoring:

$$ADD = (ODE \times CPF \times DA) + (IDE \times DA) + (ADE \times DA) \quad \textbf{[1]}$$

$$AID = (IE \times IA) \quad \textbf{[2]}$$

$$TAD = (ADD + AID) \quad \textbf{[3]}$$

Where:
ADD is Absorbed Dermal Dose;
ODE is Outer Dermal Exposure (from outer dosimeter);
CPF is Clothing (or outer dosimeter) Penetration Factor*;
DA is Dermal Absorption factor;
IDE is Inner Dosimeter Exposure
ADE is Actual Dermal Exposure (from hand wash and face/neck wipe);
AID is the absorbed inhalation dose;
IE is Inhalation Exposure;
IA is Inhalation Absorption factor (default 100%);
TAD is Total Absorbed Dose.

* Derived from actual study data on penetration of outer dosimeter to inner dosimeter or based upon penetration data derived from other studies where outer and inner dosimeters have been measured for the same body area.

The purpose of this document is to summarize representative modern exposure monitoring studies for pesticide handlers and reentry exposure and to compare the estimates of dose given by PD and biomonitoring. This document summarizes some recent biomonitoring studies that have been conducted concurrently with PD or consecutively using the same subjects for both methods. The estimated absorbed doses using PD are then compared with those given by biomonitoring to determine if there is agreement and to test the hypothesis that PD does not underestimate the absorbed dose. Relevant statistical techniques are used to facilitate the comparisons.

II. BIOMONITORING AND PASSIVE DOSIMETRY VARIABLES

Pesticide biomonitoring studies typically involve collecting urine from individuals (Woollen, 1993). The urine is analyzed for a compound that is either the parent or a known human metabolite. The kinetics of excretion, preferably in humans, must be known. If this is impracticable, animal kinetics data may be considered; although the greater uncertainty associated with inter-species extrapolation must be recognized (OECD, 1997). Studies in closely related primate data may also carry least uncertainty in extrapolation. The essential information from the study is the fraction of administered dose excreted in the urine as metabolite(s) and/or parent compound. The basic method for calculating an absorbed dose from biomonitoring data is shown in equation [4].

$$AD\ (\mu g) = (\sum \mu g \text{ metabolite}) \times (\text{MW Parent} / \text{MW metabolite}) / \text{Fraction excreted} \quad \textbf{[4]}$$

Where, AD = Absorbed Dose and MW = molecular weight.

For PD, the absorbed dose is estimated as shown generically in equation [5].

$$AD = (\text{dermal exposure} \times \text{abs. fraction}) + (\text{inhalation exposure} \times \text{abs. fraction}) \quad \textbf{[5]}$$

Selection criteria for an ideal concurrent biomonitoring study for comparison with PD include the following:

a. Known human or closely related primate dermal absorption value (typically >1% of applied dose unless detection limits are very low), measured in the range of typical exposure;
b. Known human or closely related primate excretion pharmacokinetics and a metabolite standard;
c. Urinary excretion half-life less than 24 hours; (not essential but desirable to reduce the number of 24 hour urine collections);
d. Excretion levels greater than background for the first 24–48 hours;
e. Adequate number of individuals monitored;
f. Sequential 24-hour urinary collections;
g. The urinary metabolite must be a "major" metabolite (ideally ~30% or more of dose); metabolites representing smaller fractions of the parent molecule are acceptable if the fraction excreted is consistent, with minimal variation;
h. The urine metabolite should be unique to the active ingredient being monitored;
i. Knowledge of whether exposure was isolated (i.e., no prior exposure and no additional exposure during the collection interval) or "steady state";
j. No additional layer(s) of clothing that would not normally be worn under the prevailing conditions and would therefore be unrepresentative. The key difference between standalone PD studies and concurrent PD : biomonitoring studies is the modified inner dosimeter, usually consisting of a t-shirt/brief arrangement rather than a full inner dosimeter, e.g. 'long johns' that would interfere with the process of dermal contact and absorption. The important point is that all the dosimeter clothing should be completely representative of the normal clothing worn by the workers. An example would be use of normal outer clothing as dosimetry garments without any inner dosimeter.

Over time, a large number of concurrent or consecutive PD-biomonitoring studies have been conducted. Those that did not conform to the criteria outlined above were eliminated from quantitative comparison in the discussion that follows. For example, 34 studies were considered, but 14 studies were accepted for further quantitative comparison. While the selection criteria eliminated more studies than were accepted for quantitation, the concurrent or consecutive PD-biomonitoring studies summarized in this document represent a wide variety of common exposure scenarios. When the biomonitoring data from these studies are compared with the PD data for the same scenarios, conclusions may be drawn about the representativeness of the central tendency values from PD that have historically formed the basis for regulatory decision making.

For each study summarized, the data for dermal and respiratory exposure monitoring and total absorbed dosage as well as the absorbed dosage estimated from concurrent biomonitoring were recorded in spreadsheets for each subject. In this way statistical comparisons could be conducted on results from individuals and the central tendency in any given study.

III. DERMAL ABSORPTION AND PHARMACOKINETICS: KEY EXPOSURE VARIABLES

Dermal absorption is a key component of any risk assessment involving a pesticide when the magnitude and temporal profile of a systemically absorbed dose is of concern. With most pesticides, exposure occurs primarily via the dermal route with a minor inhalation component (Wolfe, 1976). An accurate measurement of dermal absorption is necessary to estimate dermal absorbed dosage from PD studies for comparison with data from biomonitoring studies. Variables that can affect absorption include exposure time, dose, site of application, formulation, and absorption time. The dermal absorption test species is also a crucial factor. Rat skin, in common with many animal species' skin, is not an ideal model for human dermal absorption. It has been shown to overestimate human dermal absorption by an average of approximately 5-fold (Ross *et al.*, 2001). For the purpose of comparing PD and biomonitoring absorbed doses in this analysis, there was a preference for using human dermal absorption data, if available. Table 1 shows the human *in vivo* dermal absorption of several pesticides for which there were concurrent or consecutive PD and biomonitoring data.

Because dermal absorption is so important for estimating the absorbed dermal dose from dermal PD data, it is worthwhile to discuss the uncertainties involved in measuring or estimating dermal absorption in humans. First, it is critical to recognize that all of the values listed in Table 1 were derived from human studies, so the uncertainty of animal surrogates is not a concern. Second, all of the *in vivo* human values were published in the peer-reviewed literature, which lends some credibility to the values reported. Third, when more than one level was tested in humans, the highest dermal absorption value (typically associated with the lowest application rate on human skin) was reported which was most similar to the dose density observed in the PD studies.

In most cases, human dermal absorption studies were conducted with male volunteers, and the vast majority of biomonitoring studies reported in this document were also conducted with male volunteers. Likewise, most human dermal absorption studies were conducted with a wash off of the applied dose after 8-10 hours, which is consistent with the upper bound of times individuals were exposed on the job during the biomonitoring studies and reducing (or conservatively overestimating) absorption due to differences in residence time of pesticide on the skin. Because the fraction of applied pesticide that is dermally absorbed is generally inversely related to application (dose) rate, it is important to test absorption at loading doses similar to those incurred by workers during pesticide use (Thongsinthusak et al., 1999).

Collection of urine must continue long enough to collect at least 3 urinary excretion half-lives (88%) to justify not correcting for incomplete excretion. For virtually every biomonitoring study discussed here, this guideline was followed. In some cases, the biomarker was excreted via other routes in addition to urine and some correction must be made for this differential e.g., Chlorpyrifos where only 70% is excreted in urine. Finally, the biomarker may represent only a fraction of the parent and some correction must be made for that factor. Listed in Table 1 in the right hand columns are the biomarker (metabolite) name, excretion half-life, and a combined factor that reflects both fraction excreted in urine and fraction of total dose

excreted as the biomarker. Data for three of the compounds in Table 1 regarding pharmacokinetics and metabolism were taken from summaries in the exposure monitoring studies, and these numbers were not verified from the original proprietary studies. In the narrative description of each study, there is an indication of duration of urine collection and any departure or other correction from these practices.

Table 1: *In Vivo* Dermal Absorption of Selected Pesticides in Humans

Pesticide	Human Absorption (%)	Dermal Absorption Assumed in Study (%)	Metabolite	Excretion Half-Life (hr)	Excretion Fraction (%)[m]
Atrazine	5.6[a]	5.6	chlorotriazines	12[i]	12
Chlorpyrifos	3.0[b]	1.0-9.6	TCP	27[i]	60-72
Cypermethrin (as surrogate for Cyfluthrin)	1.2[c]	1.2	4-FPBA	16[j]	100
Diazinon	3.6[d]	3.6	G 27550	~10	7.9
Diquat	0.3[e]	0.3	parent	4[k]	61
Fluazifop-butyl	8.0[f]	8.0	Fluazifop	9-37[i]	90
Paraquat	0.3[g]	0.3	parent	NA[l]	59
2,4-D	5.7[h]	5.7	parent	13	100

[a] Wester and Maibach 1993
[b] Nolan *et al.*, 1984; highest value measured
[c] Woollen et al., 1992
[d] Wester *et al.*, 1993b
[e] Feldman and Maibach, 1974
[f] Ramsey et al., 1992
[g] Wester et al., 1984
[h] Ross et al., 2005
[i] Following oral dosing
[j] Following dermal dosing
[k] Following intravenous dosing
[l] NA = Not Available
[m] Excretion fraction in urine at an interval of 3+ half-lives

IV. CLOTHING PENETRATION: ANOTHER KEY VARIABLE

As dose density to outer dosimeters increases, percent clothing penetration decreases resulting in an inverse relationship between challenge and penetration (Ross et al., 1997). This is consistent with the hypothesis that single-layer clothing percent penetration increases with decreasing outer dosimeter loading or challenge, i.e., a higher proportion of the outer dosimeter values appears on the corresponding inner dosimeters, as the outer values decrease. This is consistent with observations made in mammalian dermal absorption studies where the

fraction of applied dose penetrating the skin appears to increase at decreasing external dose. This phenomenon is associated with the use of the percent term; in pure quantitative terms, there tends to be more penetration with increasing external loading, although not in direct proportion. The same loading/absorption phenomenon applies to skin, so both dermal loading and dosimeter loading influence variability observed between individuals monitored.

Mean clothing penetration was calculated from 2129 paired inner and outer dosimeters and found to be 8 to 12 percent for whole body dosimeters (WBD) and patch dosimetry, respectively from the Pesticide Handlers Exposure Database (Ross et al., 2006a). Thongsinthusak et al., (1993) summarize results from a number of other exposure monitoring studies that support this observation. An average clothing penetration value of 10% was used in two exposure monitoring studies where clothing penetration could not be estimated from study data. This value was considered conservative, because in most studies whole body dosimetry or some variant was used, and in most cases there was substantial concentration on the outer dosimeter. Further supporting the conservatism of this default is the fact that the measured clothing penetration as recorded in Table 2 was consistently less than 10%.

V. BIOMONITORING AND PASSIVE DOSIMETRY STUDY SUMMARIES

Narrative summaries of study design are provided for those studies for which there were quantifiable PD and biomonitoring results for a majority of study participants. The preponderance of quantitative data was derived from 9 studies that are protected by data compensation requirements under FIFRA and are labeled "proprietary". Another group of 6 studies was published in the peer reviewed literature. Additional study details are provided in Tables 2 and 4.

A. Proprietary Documents on Concurrent Passive Dosimetry and Biomonitoring

<u>Airblast Mixer/Loader (M/L), Applicator, and Cleanup Workers (Honeycutt and Day, 1994)</u>
Fifteen applicators, 15 M/L, and 15 cleanup workers were monitored while handling Chlorpyrifos for airblast application on citrus in California. The M/L open-poured the Lorsban 4E from its container into a pail and/or directly into a nurse tank. Applicators drove open-cab tractors. Cleanup workers washed equipment post-use. Workers made applications from 0.4-9.8 hours per day (Table 2). All workers wore a minimum of an outer coverall over a short-sleeved shirt, long pants, underwear, socks, and boots. The underwear (T-shirt and briefs) were used as inner dosimeters, while coveralls were used as outer dosimeters. Additionally, workers wore helmets, a respirator, goggles, and chemical-resistant gloves. Inhalation exposure was monitored using a personal air pump with a flow rate of 1-2 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent. The workers were assumed to breathe at 1.5 m^3/hr. Face and neck exposure were estimated based on two 4"x4" patches placed on the helmet. Urine was collected from each worker one day prior to use and for four days after handling Chlorpyrifos. Urine was analyzed for 3,5,6-TCP. Replicates in each work category were examined for pre-study TCP levels greater than post-exposure TCP levels, and those replicates were excluded from further consideration.

Open-Pour Aerial M/L (Knuteson *et al.*, 1999)

Fifteen workers mixed and loaded Lorsban 4E for aerial application. The study was conducted in Texas and Arizona. Each worker opened, pierced the foil seal of, emptied, and rinsed 25–50 jugs containing 2.5 gallons each. After open-pouring the Lorsban 4E into the mix tank and adding water, each worker transferred the contents to planes via hose. Each worker mixed and loaded sufficient Chlorpyrifos to cover approximately 500 acres. Workers wore a coverall over underwear, goggles, a cap, a chemical-resistant apron, boots, and gloves. The underwear (T-shirt and briefs) were used as inner dosimeters, while coveralls were used as outer dosimeters. Inhalation exposure was monitored using a personal air pump with a flow rate of 1-2 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent, and workers were assumed to breathe at 1.5 m^3/hour. Urine was collected from each worker one day prior to use and for four days after handling Chlorpyrifos. Urine was analyzed for 3,5,6-TCP. The pre-exposure (background) TCP levels were subtracted from the daily post exposure analyses for TCP. Four of 15 replicates were not used in this study due to confounding caused by pre-exposure or post-exposure urinary metabolite concentrations.

Groundboom M/L, Applicator, Reentry Scout Exposure (Shurdut *et al.*, 1993)

Nine applicators were monitored during groundboom application of Chlorpyrifos to low crops using open-cab tractors in Michigan, Arizona and Florida. Each applicator handled 27–330 lb AI. Nine Mixer/Loaders used either Lorsban 50W or 4E. Ten scouts were monitored in Arizona and Florida 24 hours post-application. Mixer/Loaders and applicators wore coveralls over underwear, socks, baseball cap, goggles and chemical-resistant boots. Mixer/Loaders that handled Lorsban 50W also wore half-face respirators equipped with particulate filters and organic vapor cartridges. Scouts wore T-shirt and briefs, closed toe footwear, baseball cap, and coveralls with sleeves cut off above the elbows. Sweat bands served as forearm dosimeters. Concurrent PD consisted of underwear (T-shirt and briefs) used as inner dosimeters, while coveralls were used as outer dosimeters. Inhalation exposure was monitored using a personal air pump with a flow rate of 1-2 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent, and workers were assumed to breathe at 1.5 m^3/hr. Urine from applicators was taken one day before and for five days after application. Urine was analyzed for 3,5,6-TCP.

Open-Pour Groundboom Granular M/L/A (Murphy et al., 1998)

Sixteen mixer/loader/applicators were monitored while handling Chlorpyrifos for groundboom application during planting seed corn in Michigan and Kentucky. M/L open-poured the Lorsban 15G from its container into a hopper of a seed planter. Applicators drove open- and closed-cab tractors. Workers handled Chlorpyrifos for at least 3.1 hours per day (Table 3). All workers wore a minimum of an outer coverall over a short-sleeved shirt, long pants, underwear, socks, and boots. The underwear (T-shirt and briefs) were used as inner dosimeters, while coveralls were used as outer dosimeters. Additionally, they wore baseball caps. Inhalation exposure was monitored using a personal air pump at a flow rate of 1 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent, and workers were assumed to breathe at 1.5 m^3/hr. Urine was collected from each worker one day prior to use and for four days after handling Chlorpyrifos. Urine was analyzed for 3,5,6-TCP.

Citrus Pruners and Harvesters (Honeycutt and Day, 1993)

Fifteen reentry workers, 10 pruners, and 5 harvesters were monitored while reentering Chlorpyrifos-treated citrus following airblast application in California. Workers contacted treated foliage for at least 6.2 hours per day (Table 2). All workers wore a minimum of an outer coverall over underwear, socks, and tennis shoes. Additionally, the harvesters wore short-sleeved shirt, and long pants under the coveralls due to cold weather. The underwear (T-shirt and briefs) were used as inner dosimeters, while coveralls were used as outer dosimeters. Additionally, they wore baseball caps, forearm gauntlets of canvas and cotton or canvas gloves. Inhalation exposure was monitored using a personal air pump with a flow rate of 1 L/min through a cassette with a pre-filter followed by Chromosorb 102 sorbent, and workers were assumed to breathe at 1.5 m^3/hr. Urine was collected from each worker one day prior to use and for four days after handling Chlorpyrifos. Urine was analyzed for 3,5,6-TCP, and the higher value of either the kinetic or stoichiometric method was used to calculate exposure. Replicates in each work category were examined for pre-study TCP levels greater than post-exposure TCP levels, and those replicates were excluded from further consideration. Harvesters had no detectable residues on the inner dosimeter, so half the limit of detection was assumed for estimating dermal exposure.

Hose-End Sprayers and Hudson Sprayer (Rosenheck, 2000)

This PD-biomonitoring study involved the consecutive evaluation of PD and biomonitoring. Exposure was determined using the PD approach, followed by a biomonitoring phase in which the same individuals made further applications approximately 5 days later. Individuals within a handler scenario were monitoring first using cotton long johns worn under short sleeve shirt and short pants, and the same individuals within a use scenario were subsequently biomonitored. Three methods of application frequently used by homeowners were monitored:

- Hose-end sprayer with a ready-to-use (RTU) formulation; 11 handlers.
- Hose-end sprayer with an emulsifiable concentrate (EC) formulation; 12 handlers.
- Hudson pump-up type hand sprayer with wand; 10 handlers.

Each person using the hose-end sprayers applied 0.5 lb of active ingredient (AI) of Diazinon in a 946-mL container to approximately 5,000 square feet of turf. Hudson sprayer users mixed, loaded, and applied 0.021 lb AI of Diazinon EC to house perimeters, spot lawn treatments, ornamentals, and shrubs. All volunteers wore a T-shirt, shorts, socks, and shoes. All monitoring was conducted in North Carolina in 1999, and replicate duration was 18–122 minutes, depending on method of application. Urine was collected for one day before and four days after use; it was analyzed for G-27550, a Diazinon-specific metabolite.

Groundboom Applicators and Mixer/Loader/Applicators (Selman, 1996)

Groundboom applicators (n=7), mixer/loader/truck tenders (n=8), and mixer/loader/applicators (M/L/A, n=4) were biomonitored for urinary metabolites following use of Atrazine on corn in the Midwest. The workers in the study handled between 148 to 3450 lb Atrazine over a three day monitoring period during the early part of the pre-corn planting period during which the product is typically applied. The biomonitoring phase consisted of collection of urine samples on at least one day before being monitored and during each day of Atrazine use over the three days of monitoring. Replicate analyses of PD were conducted on the same workers on the first and second days, and the results averaged by

worker. The metabolite excretion data were adjusted for the fraction of dose excreted as chlorotriazines in humans to estimate the Atrazine absorbed dose. Workers wore long-sleeved shirts, long pants, and occasionally a sweatshirt in cold weather. The inner dosimeters consisted of 100% cotton T-shirts and 100% cotton briefs. Hand exposure was measured using a 0.01% Aerosol OT hand wash followed by a distilled water hand rinse. Head and neck exposure was estimated using two patches attached to a baseball cap. Inhalation exposure was measured using a filter and vapor collection tube attached to a personal air-sampling pump.

Groundboom Mixer-loader-applicators (Chester et al, 1989)

Fourteen vehicle groundboom mixer/loader/applicators were monitored concurrently with PD and biological monitoring during use of Fluazifop-P-butyl in the Netherlands. They handled, on average, 7.2 kg (3.8 to 14.6 kg) [15.8 lb (9.5 to 32 lb)] Fluazifop during a typical day's use of the product in field crops. They wore standardized dosimeters consisting of 100% cotton coveralls over cotton T-shirt. Soap and water handwashes were performed whenever the subjects wanted to wash their hands. There was additional wearing of sweatshirt (pullover) and pants by three subjects during colder weather. Inhalation exposure was not measured because this was assumed to be negligible for hydraulic groundboom application of an insignificantly volatile compound. Eight subjects complied with the label requirement for use of the chemical resistant gloves; none of the subjects elected to wear the label-required safety goggles, although one wore a faceshield. Twenty-four hour urine samples were collected from all subjects for a total of 11 days, including the day before the use of the product. Urine aliquots were analyzed for the metabolite Fl and creatinine as a check on the completeness of collection.

Backpack mixer-loader-applicators (Findlay, 1998)

Twenty mixer-loader-applicators were monitored concurrently with PD and biological monitoring during use of Diquat with hand-held backpack sprayers in banana plantations in Guatemala. The amounts of Diquat handled ranged from 0.29 to 0.38 kg (0.64 to 0.84 lb) during a typical day's use. Standardized dosimeters were used consisting of 100% cotton long-sleeved shirts and trousers. A soap and water handwash method was used to measure hand exposure whenever the subjects wanted to wash their hands so as not to interfere with biological monitoring phase. Inhalation exposure was measured using Institute of Occupational Medicine (IOM) inhalable fraction samplers attached to personal sampling pumps worn by the subjects. Protective gloves and faceshield were provided for use during mixing and loading the product in accordance with the product label recommendation, with which there was generally good compliance. Twenty-four hour urine samples were collected by each subject over a 7 day period, including the day before the day of use of the product. This period was based on the urinary elimination half-life determined in a human volunteer dosing study. Aliquots were analyzed for unchanged Diquat and creatinine as a check on completeness of urine collection.

Data from the biomonitoring studies summarized above are shown in Tables 2–3. It is important to note that the data from some of the biomonitoring studies (e.g., Knuteson, 1999; Honeycutt and Day, 1994; and Chester et al., 1989) contain results from individuals whose

work practices were apparently less careful than other individuals in these studies (or had verified accidents) resulting in much higher exposures on one or more body regions relative to other members of their cohort. Results from those individuals were included in the geometric mean values shown in Tables 2–3, even though they represent the upper extreme for those scenarios monitored. Additionally, there were studies in which individual handlers appeared to have no exposure (i.e., their post-handling excretion of the analyte was less than prior to exposure) such as Knuteson (1999) and Shurdut *et al.* (1993). These values were excluded as unrealistically low, and were probably due to work exposure shortly before the study. The concurrent PD from those individuals was also excluded, so that there was always the same number of PD and biomonitoring results in a given study. By retaining highly exposed individuals, it tested the limits of the comparison of PD to biomonitoring.

B. Dermal Passive Dosimetry Extrapolation to Whole Body

Two primary methods of dermal PD in conjunction with biomonitoring were utilized in the studies summarized in Tables 3, 5 and 6. All of the dermal exposure estimates in Tables 3 and 5 included hand wash and a face/neck wipe or head patch to estimate face/neck exposure. The most straight-forward sampling method to test exposure to the remaining body was where the same individual or group was tested consecutively. For example, Rosenheck (2000) used WBD under typical residential clothing (short-sleeve shirt and short pants) to measure exposure that would have occurred to bare lower legs and arms, and under a single layer of clothing to assess pesticide that penetrated or was not covered by typical residential clothing, and a few days later biomonitored the same individuals wearing only residential clothing without WBD. A variant of this method used co-located individuals wearing a single layer of WBD or a bathing suit to measure exposure to the same treated carpet, and both groups were biomonitored (Krieger et al., 2000). A completely different design used in several studies involved concurrent PD and biomonitoring in the same individuals all of whom wore normal work clothing over T-shirt or T-shirt and briefs (Chester et al. 1989; Honeycutt and Day, 1993, 1994; Murphy et al., 1998; Knuteson et al., 1999; Shurdut et al., 1993; and Selman, 1996). Scenario-specific clothing penetration was assessed by taking the ratio of residues measured on the T-shirt to residues on the work shirt minus lower arms. This clothing penetration factor was then applied to body areas covered by a single layer of clothing (e.g., lower arms or legs), and that dermal exposure was added to exposure measured on T-shirt and briefs, face and hand washes to obtain total dermal exposure. No attempt was made to account for clothing penetration (also known as pass through) in estimating dermal exposure from areas covered by a T-shirt and briefs dosimeter. However, clothing penetration was accounted for when only a single layer covered the skin.

Table 2 Proprietary Study Conditions and Passive Dosimetry Description

Study Reference[a]	Company Reference ID #	Scenario	Pesticide	Dosimeter Type: Outer (Inner)	Handwash solvent/ Volume (mL)	Number of Handwashes	Workday monitored (hr)	Inhalation monitoring method	Clothing Penetration (%)	PD Reference Page Numbers
Honeycutt, 1994	91-101HE	Liquid M/L[b], airblast	Chlorpyrifos	Coverall[c] + (TS[d] + brief), hat patch	0.008% DSS[e]→H_2O/ 250 each	2-3	7.6-9.8	Personal pump + sorbent (Chromosorb 102)	0.082	72-73, 299
Honeycutt, 1994	91-101HE	Applicator, Airblast	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% DSS→H_2O/ 250 each	2-3	5.9-9.6	Personal pump + sorbent (Chromosorb 102)	0.082	301
Honeycutt, 1994	91-101HE	Cleanup, Airblast	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% DSS→H_2O// 250 each	1-2	0.4-1.1	Personal pump + sorbent (Chromosorb 102)	0.082	303
Knuteson, 1994	HEA97038	Liquid M/L, aerial	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.004% Emcol[f]→H_2O/ 250 each	1	0.66-1.5	Personal pump + sorbent (Chromosorb 102)	6.2±10.5	16, 21, 33, 37, 38
Shurdut, 1993	HEH2.1-1-182	Liquid or WP[g] M/L	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% Emcol→H_2O/ 250 each	1	0.7-1.5	Personal pump + sorbent (Chromosorb 102)	7.0-8.9	22, 113-114
Shurdut, 1993	HEH2.1-1-182	Applicator, Ground-boom	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% Emcol→H_2O/ 250 each	??	3.8-5.3	Personal pump + sorbent (Chromosorb 102)	7.0-8.9	113

Table 2 (cont.): Proprietary Study Conditions and Passive Dosimetry Description

Study Reference[a]	Company Reference ID #	Scenario	Pesticide	Dosimeter Type: Outer (Inner)	Handwash solvent/ Volume (mL)	Number of Handwashes	Workday monitored (hr)	Inhalation monitoring method	Clothing Penetration (%)	PD Reference Page Numbers
Shurdut, 1993	HEH2.1-1-182	Scout, Low crops	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% Emcol→H_2O/ 250 each	??	3.9-4.1	Personal pump + sorbent (Chromosorb 102)	7.0-8.9	115
Murphy, 1998	HEH 311	Granular M/L/A[h]	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% DSS→H_2O/ 250 each	??	3.1-5.9	Personal pump + sorbent (Chromosorb 102)	3.5±1.9	11, 13-14, 24- 26,31
Honeycutt, 1993	91-102HE	Citrus pruner, harvester	Chlorpyrifos	Coverall + (TS + brief), hat patch	0.008% DSS→H_2O/ 250 each	2	6.2-7.6	Personal pump + sorbent (Chromosorb 102)	4.0, harvester 5.0, dry 12.3 damp pruners	40, 41, 62,63, 118-120,125, 128,130, 131, 265, 266
Rosenheck, 2000	1063-00	Hose end, RTU and hand pump	Diazinon	(Long johns), face/neck wipes	0.01% DSS/ 250 x 2	1	0.3-2.0	Personal pump + sorbent (XAD-2)	Not measured	9-15
Chester, 1989	TMF 3487	Tractor groundboom Field crops MLA Netherlands	Fluazifop	100% cotton coverall over cotton T-shirt, cotton-polyester socks	Proprietary 'Simple' soap/ 1L wash, 200mL aliquots taken	Variable (1-5), depending on when the workers wanted to wash their hands	3-8	Not monitored	5-12, 41	Chester et al (1989)

Table 2 (cont.): Proprietary Study Conditions and Passive Dosimetry Description

Study Reference[a]	Company Reference ID #	Scenario	Pesticide	Dosimeter Type: Outer (Inner)	Handwash solvent/ Volume (mL)	Number of Handwashes	Workday monitored (hr)	Inhalation monitoring method	Clothing Penetration (%)	PD Reference Page Numbers
Findlay, 1998	RR-97-004B	Backpack hydraulic nozzles Guatemala	Diquat	100% cotton long-sleeved shirt and long pants	Proprietary 'Simple' soap/ 1L wash	2, the first at break, the second at the end of work	Variable 4.6-5.4 h	Personal air sampling with IOM samplers	10-13	Findlay (1998)
Selman, 1996 (Amendment 1)	ABR-95133	Tractor-mounted application to corn, USA	Atrazine	cotton/ polyester sweatshirt (Cold weather) over cotton/ polyester long-sleeved shirt and cotton pants (100% cotton T-shirt and brief); head patches.	0.01% 'Aerosol OT[i] 200→200 distilled water 400 ml total volume.	2-3 samples/ subject	Variable, typical work days	Personal pump, cellulose ester filter and Chromosorb 102 sorbent	10%	Selman & Rosenheck (1996) Selman (1996) (Amendment 1)

[a] Reference citations use only the first author's last name to conserve space
[b] M/L = mixer/loader
[c] Workers wore short-sleeve shirt and long pants that were not analyzed for Chlorpyrifos under the coveralls and over the T-shirt and briefs
[d] TS = T-Shirt
[e] DSS = dioctyl sodium succinate (anionic surfactant)
[f] Emcol = Proprietary surfactant
[g] WP = wettable powder
[h] M/L/A = mixer/loader/applicator
[i] Aerosol OT = dioctyl sodium succinate

Table 3: Proprietary Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring

Study Reference	Scenario	Pesticide	Number[a] of Replicates	Dermal Dosage (µg/kg)[b]	Inhalation Dosage (µg/kg)[c]	Estimated Absorbed Dosage (µg/kg)[d]	Biomon. Dosage (µg/kg)[e]	Ratio[f] PD:BM	Reference Page Numbers[g]
Honeycutt, 1994	M/L	Chlorpyrifos	12/15	2.0	0.13	2.2	5.4	0.41	125, 287, 299, 318, 326
Honeycutt, 1994	Applicator	Chlorpyrifos	11/14	2.9	0.33	3.5	6.7	0.52	288, 301, 320, 327
Honeycutt, 1994	Cleanup	Chlorpyrifos	10/15	0.37	0.010	0.38	0.55	0.69	289, 303, 322, 328
Knuteson, 1994	M/L	Chlorpyrifos	11/15	0.34	0.23	0.68	0.71	1.0	70-72
Shurdut, 1993	M/L	Chlorpyrifos	9/9	3.9	0.34	4.9	7.5	0.65	117, 120, 122
Shurdut, 1993	Applicator	Chlorpyrifos	8/9	0.61	0.84	1.5	1.9	0.78	116, 119, 123
Shurdut, 1993	Scout	Chlorpyrifos	8/10	0.48	0.17	0.67	1.3	0.53	118, 121, 124
Murphy, 1998	M/L/A	Chlorpyrifos	12/16	0.027	0.10	0.14	0.30	0.47	45, 50, 51
Honeycutt, 1993	Citrus harvester	Chlorpyrifos	5/5	0.053	0.18	0.17	0.36	0.48	267, 286
Honeycutt, 1993	Citrus pruner, dry	Chlorpyrifos	5/5	0.29	0.50	0.79	6.3	0.13	268, 287
Honeycutt, 1993	Citrus pruner, wet	Chlorpyrifos	5/5	1.3	0.80	2.1	2.8	0.74	267, 286
Rosenheck, 2000	Hose end sprayer	Diazinon	12/12	1.0	0.070	1.2	1.0	1.2	46
Rosenheck, 2000	RTU hose end	Diazinon	11/11	0.32	0.26	0.63	0.84	0.76	47
Rosenheck, 2000	Hand pump	Diazinon	10/10	0.11	0.039	0.17	0.40	0.42	48

Table 3 (cont.): Proprietary Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring

Study Reference	Scenario	Pesticide	Number[a] of Replicates	Dermal Dosage (µg/kg)[b]	Inhalation Dosage (µg/kg)[c]	Estimated Absorbed Dosage (µg/kg)[d]	Biomon. Dosage (µg/kg)[e]	Ratio[f] PD:BM	Reference Page Numbers[g]
Chester, 1989	Groundboom MLA,	Fluazifop butyl	14/14	5.6	NA[h]	5.3	3.1	1.8	Tables 8, 9
Findlay, 1998	Backpack MLA	Diquat	20/20	204	0.070	0.65	0.08	8.6	19-22
Selman, 1996	groundboom ML	Atrazine	7/7	1.3	0.054	1.4	0.81	1.8	10-24 (Amendmt 1)
Selman, 1996	groundboom MLT	Atrazine	7/7	2.5	0.13	2.8	0.77	3.7	10-24 (Amendmt 1)
Selman, 1996	groundboom MLA	Atrazine	4/4	5.1	0.12	5.3	1.6	3.2	10-24 (Amendmt 1)
Selman, 1996[i]	groundboom ML	Atrazine	7/7	0.41	0.016	0.44	0.61	0.71	10-24 (Amendmt 1)
Selman, 1996[i]	groundboom MLT	Atrazine	7/7	1.3	0.070	1.5	0.56	2.7	10-24 (Amendmt 1)
Selman, 1996[i]	groundboom MLA	Atrazine	4/4	4.3	0.10	4.5	3.9	1.1	10-24 (Amendmt 1)

[a] Only replicates where post-application exposures were greater than pre-application based on biomonitoring were used. The first number indicates the number of replicates used, the second is the number of replicates actually monitored.
[b] Geometric mean absorbed dermal dosage derived by applying dermal absorption factor from Table 1.
[c] Geometric mean inhalation dosage based on respiratory protection (if used) and assuming 100% uptake and retention.
[d] Total of dermal + inhalation absorbed dose by replicate, then averaged as geometric mean.
[e] Excluding replicates where post-exposure excretion was less than pre-exposure or with aberrant excretion patterns.
[f] Ratio PD:biomonitoring = ratio of PD/biomonitoring dosage
[g] Key page numbers in the reviewed reference document supporting exposure methods or estimates.
[h] NA = not measured
[i] Data also quoted in terms of µg/lb a.i. because 2 or 3 days of product use were monitored, during which PD was used on 2 occasions and biomonitoring covered the 3 days continuously. Consequently it is considered feasible to express the data in this way because it is difficult to ascertain the daily absorbed dose of Atrazine from the composite biomonitoring data.

Although many of the proprietary studies of concurrent PD and biomonitoring were conducted according to GLP and are of more recent vintage, there is a wealth of information in the open literature on the subject. Following are some examples.

C. Published Studies Involving PD and Biomonitoring Measurements of Exposure

Open Pour Groundboom M/L/A (Grover et al., 1986)
Eight farmers in Saskatchewan applied 2,4-D while wearing two layers of cotton clothing. Patches were placed underneath the clothing to estimate dermal exposure to covered areas and an outer chest and back patch were used to estimate exposure to face and neck. Hands were washed once at the end of the day with a sodium bicarbonate solution. Total urine output was collected from each participant for 4-7 days post exposure. One of the 8 replicates was excluded (subject F) due to an unrealistically high (1.7 gram) dermal exposure that apparently was attributable to one of the outer dosimeters and had no corollary high biomonitoring output.

Open Pour Groundboom MLA (Chester and Hart, 1986)
Thirteen subjects were monitored consecutively using biological monitoring and then PD during mixing, loading and application of Fluazifop butyl with vehicle-mounted groundboom application equipment in Canada. Three other subjects were also monitored during mixing and loading only. Their data are not included in this assessment because PD was conducted only during the first, interim and final mixing/loading, and so the data are not directly comparable with the biologically monitored absorbed dose. The subjects each handled approximately 132 lb active ingredient during application to approximately 300 ac. The biological monitoring phase was conducted first, involving collection of 24-hour urine samples for 9 days, including the day before use of the product. Aliquots were analyzed for the major metabolite Fl. The absorbed doses of Fluazifop-butyl were estimated using the human pharmacokinetic data described previously. The potential and actual dermal exposures were measured using synthetic 'Tyvek' coveralls incorporating a hood, and gloves as dosimeters. Inhalation exposure was not measured because it was considered to be negligible for a compound of low volatility applied with hydraulic application equipment. The biological monitoring absorbed dose data for subject number 1 were excluded from the comparison because it was known that he had provided incomplete urine samples.

Table 4: Published Study Conditions and Passive Dosimetry Description

Study Reference[a]	Scenario	Pesticide	Dosimeter Type: Outer (Inner)	Handwash solvent/ Volume (mL)	Number of Handwashes	Workday monitored (hr)	Inhalation monitoring method	Clothing Penetration (%)	PD Reference Page Numbers
Grover, 1986	Open pour groundboom M/L/A[a]	2,4-D	(Patches)	0.9% $NaHCO_3$	1	1-14.5	none	NR[b]	75, 79, 81
Chester, 1986	Open pour groundboom M/L/A, M/L[c]	Fluazifop butyl	WBD coverall with hood, socks	Gloves	NA[d]	Variable but typical duration for region	none	NR[a]	142-148

[a] M/L/A = mixer/loader/applicator
[b] NR = No Record
[c] M/L = mixer/loader
[d] NA = Not applicable

Table 5: Published Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring

Study Reference	Scenario	Pesticide	Number[a] Replicates	Dermal Dosage (µg/kg)[b]	Inhalation Dosage (µg/kg)[c]	Estimated Absorbed Dosage (µg/kg)[d]	Biomon. Dosage (µg/kg)[e]	Ratio PD:BM[f]	Reference Page Numbers[g]
Grover, 1986	Open pour groundboom M/L/A	2,4-D	7/8	33.8	NA	33.8	14.3	2.4	79
Chester & Hart, 1986	Open pour groundboom M/L/A, ML	Fluazifop-butyl	10 M/L/A; 3 M/L[h]	7.9	NA	7.9	5.8	1.4	146

NA - Not included in data analysis because of units of expression – mg/kg ai that could not be converted to mg or µg
[a] Only replicates where post-application exposures were greater than pre-application based on biomonitoring were used. The first number indicates the number of replicates used, the second is the number of replicates actually monitored.
[b] Geometric mean absorbed dermal dosage derived by applying dermal absorption factor from Table 1.
[c] Geometric mean inhalation dosage based on respiratory protection (if used) and assuming 100% uptake and retention.
[d] Total of dermal + inhalation absorbed dose by replicate, then averaged as geometric mean.
[e] Excluding replicates where post-exposure excretion was less than pre-exposure or with aberrant excretion patterns.
[f] Ratio PD:biomonitoring = ratio of PD/biomonitoring dosage
[g] Journal page number where data is found
[h] Key page numbers in the reviewed reference document supporting exposure methods or estimates.

D. Published Post-Application Exposure Monitoring Studies Conducted with Concurrent PD and Biomonitoring

In addition to pesticide handler exposure monitoring studies, there are numerous published post-application exposure monitoring studies conducted with concurrent PD and biomonitoring. These studies started as early as 1954 with apple harvesters (Batchelor and Walker, 1954), but reliable studies where the whole body was adequately represented by the patch dosimetry configuration recommended by EPA's 1986 guidelines did not occur until the 1980s. Beginning in the 1990s several concurrent WBD and biological monitoring studies have also been conducted as summarized in Table 6.

Several studies have been conducted using structured activity (e.g., Jazzercise) in which volunteers participated in aerobic exercises on a treated surface for intervals of approximately 20 minutes (Ross et al., 1990). None of these studies have monitored individual inhalation exposure, and in the case of Chlorpyrifos, it has been demonstrated that inhalation exposure potential during the 20 minutes of surface contact is negligible [i.e., with maximum air concentrations of 14 $\mu g/m^3$ (Ross et al., 1992), the exposure from inhalation would constitute ~0.1 µg/kg assuming a breathing rate of 29 L/min and 100% uptake and retention]. In the studies summarized here, volunteers either wore dosimetry clothing and were concurrently biomonitored or individuals were monitored side by side (a cohort wearing dosimetry garments and another wearing minimal clothing). Following are short narrative descriptions of those studies accompanied by Table 6 that summarizes results from this genre of studies.

<u>Williams et al., 2003</u>
A commercial formulation of Cyfluthrin was broadcast applied using a calibrated wheeled system to the surface of nylon carpet and allowed to dry. Seven male volunteers wore a single cotton sock and cotton shorts and participated in a structured activity program (Jazzercise). Following exposure, the participants provided the sock and shorts for extraction and analysis. Only the socks were used for quantifying dermal dose. Whole body exposure was estimated using the value for sock divided by 0.12 which represents the fraction on a single sock from several WBD studies (Ross et al., 1990; Krieger et al., 2000; Selim and Krieger, 2006) divided by average participant body weight of 85 kg. They also collected their urine 12 hours pre-exposure and 72 hours post-exposure. Urine was analyzed for the biomarker, 4-fluoro-3-phenoxybenzoic acid.

<u>Krieger et al., 2000</u>
Total release foggers containing 1% Chlorpyrifos were applied to nylon carpet indoors. Two groups of volunteers (one group of 13 wearing cotton WBD and the other group of 21 wearing bathing suits) reentered the room following a two-hour drying interval. Each group exercised on the treated carpet using Jazzercise. The WBD were collected and analyzed for Chlorpyrifos. Both groups provided 24-hour pre-exposure and 72-hour post-exposure total urine collections. Urines were refrigerated during the 24-hour collection intervals and were analyzed for TCP. This study design allowed for testing penetration through WBD by clearly demonstrating an increase in excretion over pre-exposure. The ratio of biomonitored dose for individuals wearing WBD to those wearing minimal clothing gives a good indication of

penetration through a single layer of WBD (15 %) and is consistent with the value assumed for other studies not using both inner and outer dosimeters.

Williams et al., 2004

A mobile spray cart was used to uniformly apply 0.5% formulated Chlorpyrifos to new nylon carpets. While carpets dried, 21 volunteers wearing one cotton sock and cotton shorts were randomly assigned to two groups. One group was allowed to sit and rest while the other group performed aerobic Jazzercise in an untreated area to induce sweating. At this point, both groups performed a low impact Jazzercise routine on the treated carpet. Following the surface contact, each participant provided the socks and shorts for analysis of Chlorpyrifos. Only the socks were used for quantifying dermal dose. Whole body exposure was estimated using the value for sock divided by 0.12 which represents the fraction on sock from several WBD studies (Ross et al., 1990; Krieger et al., 2000; Selim and Krieger, 2006). Complete urine was collected 12 hours prior to exposure and through 5 days post-exposure and analyzed for TCP. Following a two-week hiatus, volunteers participated in a cross-over design in which the resting participants were those that had previously sweated and vice versa. Samples were collected as in the first part of the study.

Table 6: Post Application Reentry Exposure Studies Using Jazzercise with Concurrent PD and Biomonitoring

Study Reference	Pesticide	Number of Subjects[a]	Dose from dosimetry garment(s) (µg/kg)[b]	Estimated Absorbed Dose (µg/kg)[c]	Biomonitoring Absorbed Dose (µg/kg)	Ratio PD:BM
Williams, 2003	Cyfluthrin	7/7	42[c]	0.51	0.094	5.3
Krieger, 2000	Chlorpyrifos	11/13	110[e]	0.34[f]	0.80	0.43
Williams, 2004	Chlorpyrifos	41/41	69[d]	2.1	1.8	1.2

[a] Only replicates where post-application exposures were greater than pre-application based on biomonitoring were used. The first number indicates the number of replicates used, the second is the number of replicates actually monitored.
[b] The estimated absorbed dose from passive dosimetry was the value estimated for a whole body and divided by body weight.
[c] Value from previous column multiplied by dermal absorption fraction.
[d] Whole body exposure was estimated using the value for (sock ÷ 0.12, fraction on sock from Ross et al., 1990; Krieger et al., 2000; Selim and Krieger, 2006) divided by average participant body weight.
[e] Dosimetry garments included gloves, socks and long johns.
[f] Absorbed dose = WBD dose x 0.15 clothing penetration factor.

E. Exclusion of Proprietary and Published PD-Biomonitoring Studies from Quantitative Evaluation

Of studies reviewed, there were more in Table 7 and others mentioned below that were excluded from further quantitative analysis than in Tables 2, 4 and 5 combined. The basis for the exclusion criteria recommendation for studies with human/primate dermal absorption less than 1% was a practical recognition of the difficulty in establishing a validated LOQ that is sufficiently low to allow consistent detection (i.e., so that a majority of urine samples taken 1-2 days post exposure would have quantifiable levels). Several studies were examined that helped confirm this criterion. Some of those studies are listed in Table 7 because estimates of dosage from biomonitoring based on half the LOQ would substantially exceed the estimated PD dosage; therefore actual metabolite presence in urine was questionable. Examples include Chester et al., 1991; Findlay et al., 2000; Wojeck et al., 1983; Lavy et al., 1992; Krieger et al., 1996 and Cowell et al., 1991.

Some published studies on paraquat involving concurrent PD and biomonitoring were excluded primarily because the urinary concentrations of paraquat were less than the LOQ (e.g. Wojeck et al. 1983; Chester et al. 1993). The point of these observations is that the analytical sensitivity determines whether the absorbed dose estimated via PD is less than, greater than, or equivalent to the biomonitoring dose estimated by use of half the LOQ and urine volumes. Other studies e.g., Staiff et al., 1975 and Forbess et al., 1982 were not included in Table 7 because their urine LOQ was too high to measure the dose measured by passive dosimeters. In another example, the urinary LOQ was adequate, but failed to consistently measure exposure in the 2 of 11 workers that had detects (van Wendel de Joode et al., 1996).

Most of the studies listed in Table 7 were done with patch dosimetry. It has been hypothesized that patch dosimetry will tend to overestimate dermal exposure more than WBD (Ross et al., 2001) for a variety of reasons. However, to our knowledge, there has been no definitive two-cohort (side by side) or concurrent patch and WBD study conducted to test the hypothesis. Chester and Ward, (1983) conducted a study to examine the concordance of patch dosimetry and WBD done concurrently. Results of that study show that in 2 or 3 scenarios, the results are comparable, but in one, the patch dosimetry grossly underestimates results from WBD. Moreover, in general it has been shown that the patch dosimetry data from PHED tends to overestimate absorbed dose estimates obtained from biomonitoring using the same pesticide handling equipment and formulation type (Ross et al., 2006b). For this reason and others (some evident in Table 7) related to the age of the patch studies, these older studies may be useful to support an hypothesis or be used in the absence of more recent data, but should not be relied upon in preference to more recent, higher quality data. Further, as pointed out by Chester and Ward (1983) and Fenske (1990), dermal deposition over a body region represented by a patch is not uniform and patch placement to optimally capture exposure varies between work activities.

Other older studies similarly using patch dosimetry, hand washes and air monitoring have demonstrated that PD overestimates biomonitoring with pesticides having diverse physicochemical properties such as alachlor (Dubelman and Cowell, 1989), EPTC (Knaak et al., 1989), and malathion (Fenske, 1988). Despite exclusion from quantitative comparison of PD versus biomonitoring of a number of published and proprietary concurrent PD/biomonitoring studies shown in Table 7, for the most part these studies also support the hypothesis that PD does not underestimate biomonitoring. Among those excluded studies was a potentially relevant work by Fenske (1988) that involved concurrent PD with patches placed per Subdivision U on the outside of clothing and biomonitoring for M/L and applicators making airblast applications of malathion to citrus. Because individual data for each handler were not published it was not possible to analyze these data in the same manner as other studies discussed here. Further, because the dermal data were not normalized to body surface area represented by each patch and all locations were not included in the data calculations the data were incomplete. Despite these limitations, the author did find statistically significant correlations between patches and biomonitoring.

Table 7: Examples of Supporting Studies that Were Excluded for Various Reasons

Study	Scenario	Pesticide	Biomonitoring	Dermal Method	Inhalation Method	Reason for Exclusion
Cowell, 1987	Groundboom M/L/A	Alachlor	yes	Patches	None	No hand/inhalation monitoring, incomplete reporting (e.g., legs)
Cowell, 1991	Open pour, Hose reel MLA	Dithiopyr	yes	Patches, hand wash	Personal pump + sorbent (silica)	Extremely low primate dermal absorption rate that could not be verified from original data
Fenske, 1988	Airblast M/L, Appicator	Malathion	yes	Patches, Fluorescent	None	Incomplete reporting, no individual data
Bernard, 2001	Turf reentry	Chlorpyrifos	yes	WBD	None	Post exposure biomon was only slightly larger than pre
Krieger, 1996	Indoor reentry	Borax	yes	WBD	None	Post exposure biomon was not significantly larger than pre
Rotondaro, 1992a	Airblast or Groundboom Applicator	Vinclozolin	yes	T-shirt and briefs, forearm, face/neck wipe	Personal pump + fiber filters	No primate metabolism or dermal absorption
Rotondaro, 1992b	Aerial Applicator	Vinclozolin	yes	T-shirt and briefs, forearm, face/neck wipe	Personal pump + fiber filters	No primate metabolism or dermal absorption
Dubelman, 1989	Groundboom M/L, M/L/A	Alachlor	yes	Patches	None	No hand/inhalation monitoring, clothing penetration not calc'd
Lavy, 1980	Helicopter, backpack, mist blower	2,4,5-T	yes	Patches	Personal pump + sorbent	Some dermal samples lost, and no hand, lower arm, lower leg samples

Table 7 (cont.): Examples of Supporting Studies that Were Excluded for Various Reasons

Study	Scenario	Pesticide	Biomonitoring	Dermal Method	Inhalation Method	Reason for Exclusion
Wojeck, 1981	Airblast M/L and Applictr	Ethion	yes	Patches	Respirator pads	Fingers on cotton dosimeters not measured, no lower leg measure
Knaak, 1989	Groundboom M/L/A	EPTC	yes	Patches	Personal pump + sorbent	No primate metabolism or dermal absorption
Selim, 2006	Indoor reentry	Pyrethrin	yes	WBD	Area monitoring	Individual subject data not available
Chester, 1991	Groundboom MLA, ML	Tralkoxydim	yes	WBD	Not monitored	Exposed urine metabolite concentration ≤ LOQ
Findlay, 2000	Airblast MLA	Lambda Cyhalothrin	yes	WBD	Personal pump, IOM/ filter	Many urinary metabolites concentrations ≤ LOQ and variable
Chester, 1993	Backpack ML & A	Paraquat	yes	WBD	Not monitored	All urinary Paraquat concentrations < LOQ
Wojeck, 1983	Groundboom – low and high level A	Paraquat	yes	Patches, hand rinse or cotton gloves	Respirator and filter cartridge	Range and central tendency PD only, and not possible to calculate daily exposure; With exception of one sample, urinary concentrations <LOQ.
Lavy, 1992	Applicators, weeders and scouts	Glyphosate	yes	Patches, hand wash	Not monitored	All urine concentrations < LOQ
Van der Jagt, 2004	M/L/A hand pump spray	Chlorpyrifos	yes	WBD	Personal pump, IOM/ filter	Post exposure urine concentration < pre

VI. VALIDATION METHODS

The purpose of this section is to describe the possible ways in which validation of PD with biological monitoring may be accomplished. Occupational or residential exposure to pesticides during use and re-entry into treated areas for specific activities can be measured using PD and biological monitoring concurrently or consecutively in the same individuals and results compared.

A. Statistical Treatment of PD/biomonitoring Data

Typically, exposure monitoring results tend to be distributed log-normally (Kromhout and Vermeulen, 2001), so the best indication of the average population exposure from a particular study is the geometric mean. With the unique studies under examination in which passive dosimetry and biomonitoring have been conducted concurrently, the most appropriate comparison between methods for the same study may be the average exposure estimated using the geometric mean. In this particular case, the influence of any individual exposure (whether low or high with respect to the population mean) will have a direct corollary in the concurrent exposure measurement. Thus, if the measure of dermal exposure is high for a particular individual, one would expect if the passive dosimetry method reflects true exposure that the corresponding absorbed dose measurement for the biomonitoring component would also be high. The key test is whether passive dosimetry is representative of the absorbed dose determined through biomonitoring across a variety of exposure scenarios.

B. Validation of the Dermal Absorption Factor Influence

Association of PD/biomonitoring Ratio with Study Dermal Absorption Values

The results obtained from the 14 concurrent PD and biomonitoring studies were used to investigate the association between the PD/biomonitoring ratio and the dermal absorption factor used in each study (see Table 1). This was done using a type of linear regression of log PD/biomonitoring ratio on dermal absorption. That is:

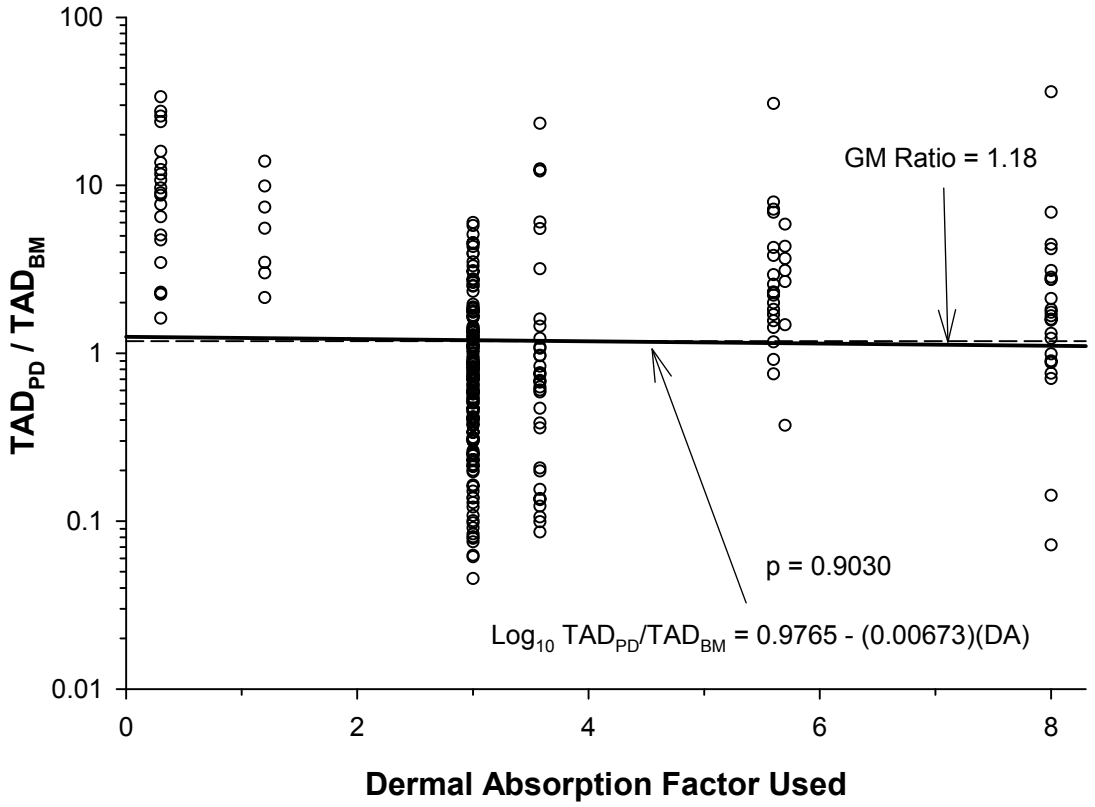
(1) $\text{Log } R_{ijk} = \alpha + \beta \times (DA_i) + A_i + B_{ij} + C_{ijk}$

Where R_{ijk} is the PD/biomonitoring ratio for individual k of scenario j in study i. DA_i is the dermal absorption factor used in study i. The intercept and slope of the regression line are just α and β, respectively. The extra terms A_i, B_{ij}, and C_{ijk}, are necessary to account for random study, scenario, and replicate effects, respectively. In simpler regression analyses these 3 random effects would just be lumped together into "residual error".

The results of this regression are summarized in Figure 1. There is no significant linear trend ($p=0.9030$) and the regression line is almost identical to the overall geometric mean of 1.18 (the dashed line in Figure 1). This result appears reasonable. Figure 2 shows the result of using the log of dermal absorption in the regression. In this case the regression line suggests a negative trend of log PD/biomonitoring with log DA. However, the slope is still not

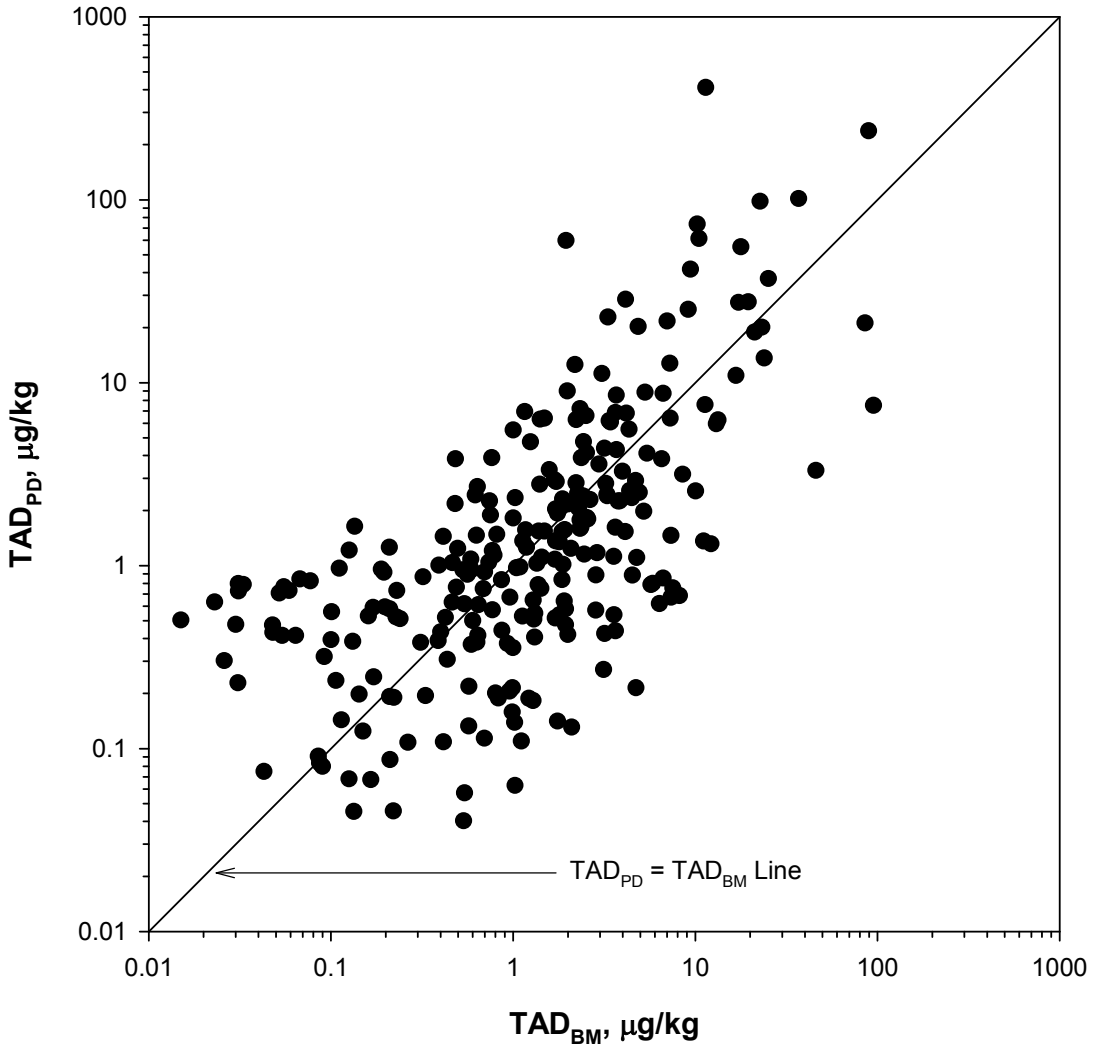
statistically significant from 0. The apparent trend is driven almost entirely by a single study using a dermal absorption factor of 0.3%. Consequently, there is no evidence in these data that the PD/biomonitoring ratio is associated with the dermal absorptions assumed in the particular studies.

Figure 1: Association of PD/biomonitoring Ratio with Dermal Absorption



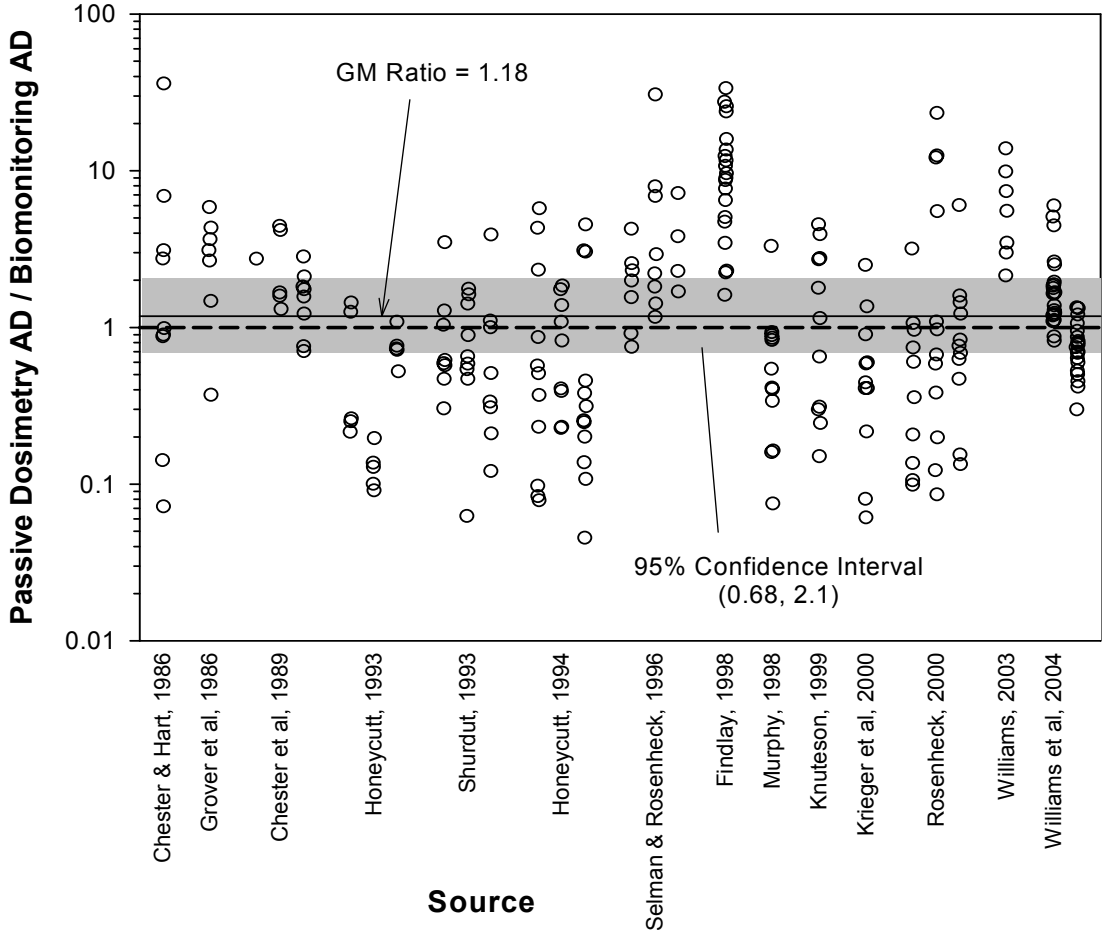
As shown in Figure 2, the two estimates of total absorbed dose are strongly correlated. The correlation between the logarithms of TAD_{PD} and $TAD_{biomonitoring}$ is 0.653 ($p<0.0001$). The Spearman (or rank) correlation between TAD_{PD} and $TAD_{biomonitoring}$ is 0.672 ($p<0.0001$).

Figure 2: Plot of Passive Dosimetry on Biomonitoring for Individuals



The following statistical analysis is a comparison of the ratios of the individual worker absorbed doses (PD)/(biomonitoring). A ratio of one indicates equivalence of the two methods. The following figure shows all the individual PD/biomonitoring ratios. These data are grouped by study and (when necessary) by scenario within study. The studies are arranged in chronological order of the reference. Shown in Figure 3 is a graphic presentation of results for each individual whose mean results are presented in Tables 3, 5 and 6.

Figure 3: Ratio of Absorbed Dose from Passive Dosimetry to Biomonitoring by Individual



The solid black line is the overall geometric mean ratio (1.18) and the shaded green area indicates the 95% confidence interval for the geometric mean (0.67, 2.1). Since this interval includes 1 (the dashed line), there is no evidence of any overall bias in the PD-derived absorbed dose compared with that derived from biomonitoring.

These results were obtained using a variance components analysis on the log of the individual PD/biomonitoring ratios. More specifically, the following model was fitted to the data:

$$\text{Log } R_{ijk} = \text{Log GM} + A_i + B_{ij} + C_{ijk}$$

Where R_{ijk} is the PD/biomonitoring ratio for individual k of scenario j in study i. The terms A_i, B_{ij}, and C_{ijk}, represent random sources of variation coming from studies, scenarios within studies, and individual replicates within scenarios, respectively. So, in words, the above model is simply:

Log PD/biomonitoring = Log GM + Study Effect + Scenario Effect + Individual Effect

In addition to the GM and confidence intervals given above, this analysis also indicated that much of the variation in individual PD/biomonitoring ratios (38%) comes from differences between studies. Variation between replicate individuals accounts for most of the remaining variation (56%). Only 6% of the variation in PD/biomonitoring ratios comes from differences between the scenarios within a study. These results are certainly reflected in the figure above.

The between-individual variation is probably reflecting the 'background' variation that would always be encountered regardless of any bias in PD absorbed dose estimates. It's a combination of individual differences and measurement variation in both PD and biomonitoring doses. The strong study-to-study differences, however, suggest that any given study could have strong biases in PD absorbed dose relative to the biomonitoring absorbed dose. However, such biases do not appear to favor either PD or BD overall. Such a pattern is commonly observed when there are study-specific imperfections in various 'adjustments' made (e.g. in this case to estimate absorbed dose). Study-specific biases in the analytical processing could also be a contributing factor. In any event, this study effect appears to operate the same on all individuals in a particular study, regardless of the scenario monitored.

C. Insignificance of the Dosimetry "Pass Through" Component of Exposure

Despite the outer and inner dosimetry, and occasionally use of impermeable gloves, there might be still measurable biomonitoring dose that exceeds the IE. If the biomonitoring actually measures an absorbed dose, then this biomonitoring dose must have been in part absorbed despite the presence of the partial dosimetry and so was not captured or intercepted by it. It could only have arisen through dermal or inhalation absorption, or incidental oral ingestion. Should part of the biomonitoring dose be factored back into the PD exposure estimate to give a more precise value for the express purpose of comparing the estimates of absorbed dose given by the two methods? The OECD guidance document states that estimates of actual dermal exposure in the variant of the whole body method should include the dose estimated to have been absorbed dermally (OECD, 1997). The decision depends upon the work activity and whether the dermal route is significant or perhaps the predominant route of exposure and absorption, e.g. for vehicle groundboom hydraulic downward application. The <u>concurrently</u> measured dermal biomonitoring dose could have arisen through:

- penetration via the outer dosimeter to underlying skin not covered by an inner dosimeter, e.g. lower legs or forearms;
- penetration via the outer dosimeter though a T-shirt to underlying skin, e.g. torso;
- absorption via the hands in between serial hand washes, or from residual material on the hands not removed by the hand wash;
- absorption via the face/neck area similar to the hand wash issue above.

At least some of the uncertainty of "dosimeter pass-through" was eliminated in the older PD studies where foil-backed patches were used, because with this configuration, the full amount of both outer and inner dose was fully intercepted.

The biomonitoring dose resulting from hand, face/neck or body parts covered by dosimeter clothing: $\text{biomonitoring}_{TAD}$ – AID (AID derived from IE measurement), could be added to the measured dosimetry clothing dermal exposure value. The distribution of dermal exposure indicated by the dermal PD might provide insight into the relative contributions of the different body sites to total actual dermal exposure.

Inclusion of the biomonitoring dose fraction attributable to absorption from skin areas covered by outer dosimeters in the estimate of total dermal exposure may be necessary because the porosity of the dosimetry clothing is frequently greater than the dermal absorption of the active ingredient, thereby leaving residual active ingredient on the skin surface beneath the outer dosimeter. This dermal exposure is the partial source of the biomonitoring dermally absorbed dose and is not captured or intercepted by the partial clothing PD.

If the hand wash data indicate that hands are a significant contributor to dermal exposure and thus absorption, inclusion of the biomonitoring dose fraction attributable to absorption from the hands in the estimate of total dermal exposure is also necessary. The key difference between the body areas washed and those covered by dosimeter clothing is that the hand and face are typically directly exposed.

An estimate of dosimetry garment pass through can be derived as follows:

$$\text{Pass Through} = (\text{Biomonitoring} - \text{AID}) - (\text{ODE} \times \text{CPF} + \text{IDE}) \times \text{DA} \quad \textbf{[6]}$$

Given the relative uncertainties all possible means of validation of PD with biomonitoring were investigated using the data available, in the ways described above. However, regarding the dosimetry pass through issue, it is clear from examining Figure 2 or 3 that about half of the data points lay below the line, suggesting that there may be a component of pass through. On the other hand, half lay above the line which would give negative numbers for pass through. Further complicating this approach is that for some data, the inhalation component alone exceeds the biomonitoring dose. Overall, these data suggest that dosimetry pass through is not a significant issue. Two concurrent PD: biomonitoring studies conducted with only a single outer dosimetry layer allow one to calculate the "pass through" that occurs through whole body dosimetry garments and it falls in the range of 8-15% (Krieger et al., 2000; Findlay, 1998), which is basically the same range measured for clothing penetration in many other PD studies (Ross et al., 2006c).

D. Conservative Biases in Both Passive Dosimetry and Biomonitoring

Contributing to conservatism (tendency to overestimate exposure) in the PD studies was the practice of taking the simple ratio of inner to outer dosimeters as an estimate of clothing penetration (e.g., Shurdut, 1993 and a majority of the other studies where it was utilized) rather than the more rigorous (and correct) method of dividing the inner dosimeter residue by the outer plus inner residues. The net difference between these two methods is typically less than 10%.

It is noteworthy that inhalation dosimetry as frequently interpreted by regulators tends to be upper bound. Several studies reviewed here used the old default value of 29 L/min respiration rate. In some cases the inhalation exposure exceeded the exposure estimated from biomonitoring, even when results were adjusted for physiologically compatible respiration rates.

Another point worth mentioning is that the dermal absorption factor usually applied to mixer-loader-applicator exposure data is that defined for the dilute spray material, i.e. the higher percent value derived from a relevant dermal absorption study. This is done in the interests of conservatism and also because it is not possible to distinguish the relative contributions from exposure to the concentrated formulated product and the diluted product.

A conservative bias not often considered is that many workers wear underwear. By adding another layer of clothing (which is not included in the estimates of protection when estimating exposure from PD), the true dermal dose is reduced by up to 10-fold to the body regions covered by underwear that represents approximately half the total body surface area.

Biomonitoring for some pesticides is conservative, because the workers (especially reentry, but also M/L and applicators or reentering consumers) can contact the prehydrolyzed pesticide. A pertinent example is Chlorpyrifos and hydrolysis to TCP. The TCP can probably be absorbed through the skin equal to or greater than the parent Chlorpyrifos based on structural similarity to triclopyr (Carmichael, 1989; Barr and Angerer, 2006). In some studies (e.g., Krieger et al., 2000) the background was not subtracted from daily collection of urine, also making those results conservative.

Biomonitoring data have been used historically as validation of PD. However, biomonitoring extrapolated to dermal dose may tend to overestimate handler dermal exposure for two reasons (Duggan *et al.*, 2003):

1. The biomonitored moiety typically represents a hydrolysis product of the parent chlorpyrifos can have greater environmental persistence, allowing more contact by humans.
2. Biomonitoring integrates all routes of exposure including dietary, non-dietary ingestion, incidental contact, inhalation, and dermal. The non dietary ingestion during and after PD monitoring and incidental contact with contaminated machinery following PD monitoring both contribute unknown but potentially significant biomonitored exposure.

VII. CONCLUSIONS

Use of PD in the 1950s through 1970s was instrumental in producing a dramatic reduction in acute pesticide illness in both handlers and reentry workers (Maddy et al., 1990) based on rudimentary knowledge of routes of exposure and particular regions of the body that tended to be the most highly exposed (e.g., hands). Beginning in the 1980s, the quantitative risk assessment paradigm adopted by regulators required not just preventing acute illness, but also proving quantitatively that exposures would not approach the toxicological no-effect level.

This change in the risk paradigm required a change in the way PD measurements were made to reflect the refinements in dose estimates that were required.

Because it is difficult to isolate and validate particular dermal dosimetry methods, the best validation is a comparison of the sum of PD methods against the biomonitored dose. The data examined (both proprietary and public) demonstrates an excellent correlation between PD and biomonitoring. Passive dosimetry as a measure of dosage appears to be consistent with biomonitoring with no bias, i.e., there is no tendency to over or under estimate exposure.

In this report, 14 concurrent or consecutive PD-biomonitoring studies were quantitatively evaluated and 18 different methods of application or reentry scenarios for 8 different active ingredients for which measured human kinetics and dermal absorption data existed. This evaluation demonstrated that the total absorbed dose (or daily dosage) estimated using PD for important handler and reentry scenarios is generally similar to the measurements for those same scenarios made using human urinary biomonitoring methods. Further, this is strongly supported by statistical analysis of individual worker PD: biomonitoring ratio and variance within and between studies. The PD techniques currently employed yield a reproducible, standard methodology that accurately and reliably quantifies exposure and does not underestimate daily absorbed dose. Based on these observations, PD has been successfully validated by biomonitoring.

VIII. REFERENCES

Barr, D.B. and Angerer, J. (2006). Potential uses of biomonitoring data: a case study using the organophosphorus pesticides Chlorpyrifos and malathion. Environ Health Perspect. [minimonograph].

Batchelor, G.S. and Walker, K.C. (1954). Health hazards involved in the use of parathion in fruit orchards of North Central Washington. *Am. Med. Assoc. Arch. Indust. Hygiene* 10: 522-529.

Bernard, C.E., Nuygen, H., Truong, D., and Krieger, R.I. (2001). Environmental residues and biomonitoring estimates of human insecticide exposure from treated residential turf. Arch Environ Contam Toxicol. 41: 237-40.

Brouwer, D.H., Hoogendoorn, L., Bos, P.M.J., Boogaard, P.J., and van Hemmen, J.J. (1998). Proposal for the assessment of quantitative dermal exposure limits in occupational environments: part 2. Feasibility study of application in an exposure scenario for MDA by different dermal exposure sampling methods.

Carmichael, N.G., Nolan, R.J., Perkins, J.M., Davies, R., and Warrington, S.J. (1989). Oral and dermal pharmacokinetics of triclopyr in human volunteers. Hum Toxicol. 8: 431-437.

Carmichael, N.G. (1995). Pesticide exposure: Overview of the tiered approach, in: Proceedings of the Workshop on Methods of Pesticide Exposure Assessment, October 5-8, 1993, Ottawa, Canada.

Chester, G. and. Ward R.J (1983). An accurate method for measuring potential dermal exposure to pesticides. (Abstract) Human Toxicol. 2 (3), 555-556.

Chester, G. and Hart, T.B. (1986). Biological monitoring of a herbicide applied through backpack and vehicle sprayers. Toxicology Letters, 33, 137-149.

Chester, G., Dick, J.P., Loftus, N.J. and Woollen, B.H. (1989). Fluazifop: dermal exposure of and absorption by workers using tractor sprayers in the Netherlands. ICI Agrochemicals Report No TMF 3487.

Chester, G., Dick, J.P., Earl, M., Marsh, J.R. and Woollen, B.H. (1991). Tralkoxydim: exposure of and absorption by workers using 'Achieve' DF. ICI Agrochemicals No TMF 3587.

Chester, G. (1993). Evaluation of agricultural worker exposure to, and absorption of, pesticides. Ann. Occup. Hyg. 37: 509-523.

Chester, G., Gurunathan, G., Jones, N. and Woollen, B.H. (1993). Occupational exposure of Sri Lankan tea plantation workers to Paraquat. Bull. World Health Organization 71: 625-632.

Chester G. (1995). Revised Guidance Document for the conduct of field studies of exposure to pesticides in use. In: Methods of Pesticide Exposure Assessment. Edited by P.B. Curry et al. Plenum Press, New York.

Cowell, J.E., Danhaus, R.G, Kunstman, J.L., Hackett, A.G., Oppenhuizen, M.E. and Steinmetz, J.R. (1987). Operator exposure from closed system loading and application of alachlor herbicide. Arch. Environ. Contam. and Toxicol. 16, 327-332.

Cowell, J.E., Lottman, C.M., and Manning, M.J. (1991). Assessment of lawn care worker exposure to DTP. Arch. Environ. Contam. Toxicol. 21: 195-201.

Davis, J.E., Stevens, E.R., and Staiff, D.C. (1983). Potential Exposure of Apple Thinners the Azinphosmethyl and Comparison to Two Methods for Assessment of Hand Exposure. Bull Environ Contam Toxicol 31:631-638.

Driver, J.H., Whitmyre, G.K., Konz, J.J., Roy, T.A., Yang, J.J., and Krueger, A.J. (1989). Dermal exposure assessment for toxicants in soil: soil adherence to skin and dermal bioavailability. In: Total Exposure Assessment Methodology: A New Horizon. Proceedings of the EPA & A&WMA Specialty Conference. Las Vegas, NV. pp 597-618.

Dubelman, S., and Cowell, J.E. (1989). Biological monitoring technology for measurement of applicator exposure In: Wang RGM, Franklin, CA Honeycutt, RC and Reinert, JC (eds). Biological monitoring technology for pesticide exposure. ACS Symposium Series No. 382. 240-250.

Duggan, A., Charnley, G., Chen, W., Chukwudebe, A., Hawk, R., Ross, J., Krieger, R.I., and Yarborough, C. (2003). Di-alkyl phosphate biomonitoring data: Assessing cumulative exposure to organophosphate pesticides. Reg. Pharmacol. Toxicol. 37: 382-395.

Durham, W.F. and Wolfe, H.T. (1962). Measurement of the exposure of workers to pesticides. Bull. WHO 26: 75-91.

Feldmann, R.J., and Maibach, H.I. (1974). Percutaneous penetration of some pesticides and herbicides in man. Toxicol. Appl. Pharmacol. 28: 126-32.

Fenske, R.A. (1988). Correlation of fluorescent tracer measurements of dermal exposure and urinary metabolite excretion during occupational exposure to malathion. Am Ind. Hyg. Assoc. J. 49: 438-444.

Fenske, R., Birnbaum, S., Methner, M., and Soto, R. (1989). Methods for assessing fieldworker hand exposure to pesticides during peach harvesting. Bull Environ Contam Toxicol 43:805-813.

Fenske, R.A. (1989). Validation of environmental monitoring by biological monitoring, Fluroescent tracer technique and patch technique. In: Biological monitoring for pesticide exposure, Measurement, estimation and risk reduction. R.G.M. Wang, C.A. Franklin, R.C. Honeycutt, and J.C. Reinert, eds. ACS Symposium Series 382. pp 70-84.

Fenske, R.A., (1990). Nonuniform dermal deposition patterns during occupational exposure to pesticides. Arch. Environ. Contam. Toxicol. 19: 332-337.

Fenske, R.A., and Day, E.W., Jr. (2005). Assessment of exposure for pesticide handlers in agricultural, residential and institutional environments. In: Occupationa and Residential Exposure Assessment for Pesticides. C.A. Franklin and J.P. Worgan, eds. John Wiley and Sons, Ltd.

Fenske, R.A. (1989). Validation of Dermal Exposure Monitoring by Biological Monitoring: The Fluorescent Tracer Technique and the Patch Technique. In Chemical Basis for Biological Monitoring: ACS Symposium Series, edited by R. Wang, C, Franklin and R. Honeycutt. Washington, D.C.: American Chemical Society.

Findlay, M.L. (1998). Diquat: worker exposure during mixing, loading and application of Reglone® with knapsack sprayers. Zeneca Ag Products Report No. RR97-004B.

Findlay, M.L., and Wiseman, J.M., (2000). Lambda-cyhalothrin: Worker exposure during mixing, loading and application of a 50 g/kg wettable granule formulation to orchards with tractor-mounted air-assisted sprayers. Zeneca Agrochemicals Report No. WER 005. (9th October 2000).

Fisher, J.W., D. Mahle, and R. Abbas. (1998). A human physiologically based pharmacokinetic model for trichloroethylene and its metabolites, trichloroacetic acid and free trichloroethanol. Toxicol. Appl. Pharmacol. 152: 339-59.

Forbess, R.C., Morris, J.R., Lavy, T.L., Talbert, R.E. and Flynn, R.R. (1982). Exposure measurements of applicators who mix and spray Paraquat in grape vineyards. HortScience 17(6): 955-956,.

Geer, L.A., Cardello, N., Dellarco, M.J., Leighton, T.J., Zendzian, R.P., Roberts, J.D., and Buckley, T.J. (2004). Comparative analysis of passive dosimetry and biomonitoring for assessing Chlorpyrifos exposure in pesticide workers. Ann Occup Hyg. 48: 683-95.

Griffin, P., Mason, H., Heywood, K., and Cocker, J. (1999). Oral and dermal absorption of chlorpyrifos: a human volunteer study. Occup Environ Med. 56: 10-3.

Grover, R., Franklin, C.A., Muir, N.I., Cessna, A.J. and Riedel, D. (1986). Dermal Exposure and Urinary Metabolite Excretion in Farmers Repeatedly Exposed to 2,4-D Amine. Toxicol. Letters. 33:73-83.

Heinrich-Ramm, R., Jakubowski, M. Heinzow, B., Molin Chistensen, J., Olsen, B. E. and Hertel, O.. (2000). Biological monitoring for exposure to volatile organic compounds (VOCs). Pure Appl. Chem. 72: 385-436.

Honeycutt, R.C. and Day, E.W. (1993). Worker re-entry exposure to Chlorpyrifos in citrus treated with 'Chlorpyrifos formulation 4E' insecticide. DowElanco Study ID 91-102HE.

Honeycutt, R.C., and Day, E.W. (1994). Evaluation of the potential exposure of workers to Chlorpyrifos during mixing and loading, spray application and clean-up procedures during the treatment of citrus groves with Chlorpyrifos formulation 4E insecticide. DowElanco Study ID 91-101HE.

Honeycutt, R.C. (2000). Use of simultaneous biological monitoring and dermal dosimetry techniques to detemine the exposure of chlorpyrifos to applicators and reentry workers. In: Worker Exposure to Agrochemicals-Methods for Monitoring and Assessment. Edited by R.C. Honeycutt and E. Day. Published by Lewis.

Jakubowski, M. and Trzcinka-Ochocka, M. (2005). Biological monitoring of exposure: trends and key developments. J. Occup. Health 47: 22-48.

Knaak, J.B., Al-Bayati, M.A., Raabe, O.G., Wiedmann, J.L., Pensyl, J.W., Ross, J.H., Leber, A.P., Jones, P. (1989). Mixer-Loader-Applicator Exposures and Percutaneous Absorption Studies Involving EPTC Herbicide: Safety Related to Exposure. *In: Biological Monitoring for Pesticide Exposure*. American Chemical Society Symposium Series 382 (Washington, D.C.).

Knuteson, J.A., Barnekow, D.E., Cook, W.L., and Meitl, T.J. (1999). Evaluation of potential exposure to workers mixing and loading Chlorpyrifos formulation 4E insecticide products for aerial application. Dow AgroSciences, LLC, Indianapolis, IN. Study ID#HEA97038.

Krieger, R.I. (1995). Pesticide exposure assessement. Toxicol. Lett. 82: 65-72.

Krieger, R. I., Dinoff, T. M. and Peterson, J. (1996). Human Disodium Octaborate Tetrahydrate (DOT) Exposure Following Carpet Flea Treatment Not Associated with Significant Dermal Absorption. J. Exposure Analysis & Environ. Epidemiol. 6: 279-288.

Krieger, R.I., Dinoff, T.M., Fell, L., Osimitz, T.G., Ross, J.H., and Thongsinthusak, T. (1998). Biomonitoring and Whole Body Cotton Dosimetry to Estimate the Potential Human Dermal Exposure to Semivolatile Chemicals Used Indoors. J. Expos. Anal. Environ. Epidemiol., 10: 50-57.

Krieger, R.I., and Dinoff, T.M. (2000). Captan fungicide exposures of strawberry harvesters using THPI as a urinary biomarker. Arch Environ Contam Toxicol. 38: 398-403.

Krieger, R., Dinoff, T., Williams, R., Zhang, X., Ross, J., Aston, L., and Myers, G. (2003). Preformed biomarkers in produce inflate human organophosphate exposure assessments. Environ. Health Persp. 111: A688-689.

Kromhout, H. and Vermeulen, R. (2001). Temporal, personal and spatial variability in dermal exposure. *Ann Occup. Hyg.* 45: 257-273.

Lavy, T.L., J.S. Shepard and J.D. Mattice. (1980). Exposure Measurements of Applicators Spraying (2,4,5-Trichlorophenoxy) acetic Acid in the Forest. J. Agric. Food Chem. 28:626- 630.

Lavy, T., Cowell, J.E., Steinmetz, J.R., and Massey, J.H. (1992). Conifer Seedling Nursery Worker Exposure to Glyphosate. Arch. Environ. Contam. Toxicol. 22, 6-13.

Maddy, K.T., Edmiston, S., and Richmond, D. (1990). Illness, injuries, and deaths from pesticide exposures in California 1949-1988. Rev Environ Contam Toxicol. 114: 57-123.

Mage, D.T. Dermal absorption of chlorpyrifos. (2006). Ann Occup Hyg. 50: 638-9; author reply 639-40.

Marsh, J.R., Woollen, B.H. and Wilks, M.F. (1994). The metabolism and pharmacokinetics of lambda-cyhalothrin in man. Zeneca CTL Report No. CTL/P/4208.

Meuling, W.J., Ravensberg, L.C., Roza, L., and van Hemmen J.J. (2005). Dermal absorption of chlorpyrifos in human volunteers. Int Arch Occup Environ Health. 78: 44-50.

Morgan, S. (1997). The Biological Exposure Indices: A Key Component in Protecting Workers from Toxic Chemicals. Environ Health Perspect, Volume 105, Number S1, February 1997, 14 pages.

Murphy P.G., Beard, K.K., Marino, T.A., Myers.C.R., Ormand, J.R., and Timchalk, C. (1998). Evaluation of Chlorpyrifos exposures to workers during loading and application of 'Chlorpyrifos formulation 15G Granular Insecticide' during corn planting. Dow Chemical Company Report HEH 311.

National Research Council. National Academy of Sciences. (1983). Risk assessment in the federal government: managing the process. National Academy Press. WashingtonDC. 1-191.

NAS (National Research Council). (1991). Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities. Committee on Advances in Assessing Human Exposure to Airborne Pollutants, Board on Environmental Studies and Toxicology, Commission on Geosciences, Environment, and Resources. National Research Council. The National Academy Press, Washington, D.C.

NAS (National Research Council). (2006). Human Biomonitoring for Environmental Chemicals. Committee on Human Biomonitoring for Environmental Toxicants, Board on Environmental Studies and Toxicology, Division of Earth and Life Sciences, National Research Council. The National Academy Press, Washington, D.C.

Nolan, R.J., Rick, D.L., Freshour, N.L., and Saunders, J.H. (1984). Chlorpyrifos: Pharmacokinetics in human volunteers following single oral and dermal doses. Toxicol. Appl. Pharmacol. 73: 8-15.

Nomiyama, K., and Nomiyama, H. (1974). Respiratory retention, uptake, and excretion of organic solvents in man. *Int. Arch. Arbeitsmed* 32: 75-83.

OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application. (1997). OECD Environmental Health and Safety Publications. Series on Testing and Assessment No. 9. OECD/GD(97)148.

Osterloh, J.D., Wang, R., Schneider, F., and Maddy, K. (1989). Biological monitoring of dichloropropene: air concentrations, urinary metabolite, and renal enzyme excretion. Arch Environ Health. 44: 207-13. AND Arch Environ Health. (1990) 45: 250-5.

Ramsey, J.D., Woollen, B.H., Auton, T.R., Batten, P.L., and Leeser, J.E. (1992). Pharmacokinetics of Fluazifop-butyl in human volunteers. II: Dermal dosing. Hum Exp Toxicol. 11: 247-54.

Reinert, J. C., Nielsen, A. P., Lunchick, C., Hernandez, O. and Mazzetta, D. M. (1986). The United States Environmental Protection Agency's guidelines for applicator exposure monitoring. Toxicol. Lett. 33: 183-191.

Rosenheck, L.A. (2000). Evaluation of Diazinon exposure monitoring data and risk assessment for homeowners mixing, loading and applying the liquid formulation of Diazinon to residential outdoor sites. Novartis Study Number 1063-00.

Ross, J.H., Thongsinthusak, T., Fong, H.R., Margetich, S., and Krieger, R.I. (1990). Measuring Potential Dermal Transfer of Surface Pesticide Residue Generated from Indoor Fogger Use: An Interim Report. *Chemosphere* 20:349-360.

Ross, J.H., Fong, H.R., Thongsinthusak, T., Margetich, S., and Krieger, R.I. (1991). Measuring Potential Dermal Transfer of Surface Pesticide Residue Generated from Indoor Fogger Use: Using the CDFA Roller Method, Interim Report II. *Chemosphere* 22:975-984.

Ross, J.H., Powell, S., Thongsinthusak, T., Haskell, D., Dow, M.I., Worgan, J., (1997). Harmonization of issues involving pesticide exposure assessment in North America. HS-1763, California Department of Pesticide Regulation, Sacramento, CA, USA.

Ross J.H., Dong, M.H., and Krieger, R.I. (2000). Conservatism in Pesticide Exposure Assessment. Reg. Toxicol. Pharmacol. 31: 53-58.

Ross, J.H., Driver, J.H., Cochran, R.C., Thongsinthusak, T. and Krieger, R.I. (2001). Could Pesticide Toxicology Studies Be More Relevant to Occupational Risk Assessment? Ann. Occup. Hygiene 45 (Suppl 1): 5-17.

Ross, J.H., Driver, J.H., Harris, S.A., and Maibach, H.I. (2005). Dermal Absorption of 2,4-D: A Review of Species Differences. Reg. Toxicol. Pharmacol. 41: 82-91.

J. Ross, Driver, J., Mihlan, G., Lunchick, C., and Landenberger, B. (2006a). Derivation of single-layer clothing penetration factors from the pesticide handlers exposure database. Draft report.

Ross, J.H., and Driver, J.H. (2006b). Evaluation of exposure values from PHED compared with those derived from biological monitoring. Draft Report.

Ross, J.H., J.H. Driver, C. Lunchick, C. Wible, and F. Selman (2006c). Pesticide Exposure Monitoring Databases in Applied Risk Analysis. Rev Environ. Contam. Toxicol. 186: 107-132.

Rotondaro, A. and Schuster, L. (1992a). Worker mixer/loader, applicator exposure to Ronilan® DF. Pan-Ag Study Number AE-91-504/BASF Study No 91164.

Rotondaro, A. and M^c^Kane, E. (1992b). Worker mixer, loader, applicator exposure to Ronilan® WP. Pan-Ag Study Nos. EF-90-02 and AL-106.

Selim, S. and Krieger, R.I. (2006). Indoor human pyrethrins exposure: Contact absorption, metabolism, and urine biomonitoring. In: Assessing Exposures and Reducing Risks to People from the use of Pesticides. R. Krieger, J. Seiber and N. Ragsdale, eds. ACS Series Publication 951, Oxford University Press, in press.

Selman, F. (1996). Evaluation of the potential exposure of workers to Atrazine during commercial mixing, loading and spray application to corn. Ciba Geigy Corporation Report No ABR-95133.

Sexton, K., Needham, L.L., and Pirkle, J.L. (2004). Human biomonitoring of environmental chemicals. Am. Scientist 92: 38-45.

Shurdut, B.A., Murphy, P.G., Nolan, R.J., and McNett, D.A. (1993). Chlorpyrifos formulation 4E and 50W insecticides: Assessment of the Chlorpyrifos exposures to applicators, mixer/loaders, and reentry personnel during and following application to low crops. DowElanco DERBI No 6568.

Smith, C., Welsh, A., Saiz, S., Haskell, D., Dong, M., Begum, S., and Carr, J. (1991). Comparison of three methods used to monitor hand exposure to pesticides in grape vineyard workers. HS-1630, Sacramento, CA. Cal/EPA Department of Pesticide Regulation, Worker Health and Safety.

Staiff, D.C., Comer, S.W., Armstrong, J.F. and Wolfe, H.R. (1975). Exposure to the herbicide, Paraquat. Bull. Environ. Contam. &Toxicol. 14, 334-340.

Thongsinthusak, T., Ross, J. H., and Meinders, D. (1993). Guidance for the preparation of human pesticide exposure assessment documents (HS-1612), California Department of Pesticide Regulation, Sacramento, CA, USA.

Thongsinthusak, T., Ross, J.H., Saiz, S., and Krieger, R. (1999). Estimation of Dermal Absorption Using the Exponential Saturation Model. Reg. Toxicol. Pharmacol. 29: 37-43.

USEPA (1992). Dermal Exposure Assessment: Principles and Applications," January 1992 Interim Report, EPA/600/8-91/011B (Exposure Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, EPA; http://www.epa.gov/ncea/pdfs/derexp.pdf.

USEPA (U.S. Environmental Protection Agency). 2006 (online). OPPTS Harmonized Test Guidelines: 875.2500 Inhalation Exposure. http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/875_Occupational_and_Residential_Exposure_Test_Guidelines/index.html.

USEPA (1986). Pesticide Assessment Guidelines, Subdivision U, Applicator Exposure Monitoring, U. S. EPA, Washington, D.C.

USEPA (1997). Series 875-Occupational and Residential Exposure Test Guidelines, Group B: Post Application Exposure Monitoring Test Guidelines. U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances. Washington, DC.

Vaccaro, J.R. (1993). Risks Associated with Exposure To Chlorpyrifos and Chlorpyrifos Formulation Components. *In*: Pesticides in urban environments: Fate and significance: Racke, K.D. and A. R. Leslie (Eds.). ACS Symposium Series, 522. American Chemical Society, Washington, D.C. pp. 297-306.

Vaccaro, J.R., Nolan, R.J., Murphy, P.G., and Berbrich, D.B. (1996). The Use of Unique Study Design to Estimate Exposure of Adults and Children to Surface and Airborne Chemicals. American Society for Testing and Materials, West Conshohocken, PA, Std. Tech. Publ. 1287, pp.166-183.

Van der Jagt, K., Tielemans, E., Links, I., Brouwer, D. and van Hemmen, J. (2004). Effectiveness of Personal Protective Equipment: Relevance of Dermal and Inhalation Exposure to Chlorpyrifos Among Pest Control Operators J. Occup. Environ. Hygiene, 1: 355-362.

Van Hemmen, J.J. (1992). Estimating Worker Exposure for Pesticide Registration. Rev. Environ. Contam. Toxicol. 128: 43-54.

Van Wendel de Joode, B.N., De Graaf, I.A.M., Wesseling, C. and Kromhout, H. (1996). Paraquat exposure of knapsack spray operators on banana plantations in Costa Rica. Int. J. Occup. Environ. Health. 2: 294-304.

Wester, R.C., Maibach, H.I., Bucks, D.A.W and Aufrere, M.M. (1984). In Vivo Percutaneous Absorption of Paraquat from Hand, Leg and Forearm of Humans. J. Toxicol. Environ. Health, 14: 759-769.

Wester, R.C., and Maibach, H.I. (1993). Animal models for percutaneous absorption. In *Health Risk Assessment: Dermal and Inhalation Exposure and Absorption of Toxicants* (R.G.M. Wang, J.B. Knaak, and H.I. Maibach, Eds.), pp. 89-103. CRC Press, Boca Raton, FL, USA.

Wester, R.C., Sedik, L., Melendres, J., Logan, F., Maibach, H.I, and Russel, I. (1993). Percutaneous absorption of Diazinon in humans. Food Chem.Toxicol. 31: 569-572.

Williams, R.L., Bernard, C.E., and Krieger, R.I. (2003). Human exposure to indoor residential Cyfluthrin residues during a structured activity program. J Expo Anal Environ Epidemiol. 13: 112-9.

Williams, R.L., Aston, L.S., and Krieger, R.I. (2004). Perspiration increased human pesticide absorption following surface contact during an indoor scripted activity program. J Expo Anal Environ Epidemiol. 14:129-36.

Wojeck, G.A., H.N. Nigg, H.J. Stamper and D.E. Bradway (1981). Worker Exposure to Ethion in Florida Citrus. Arch. Environ. Contam. Toxicol. 10: 725-735.

Wojeck, G.A., Price, J.F., Nigg, H.N. and Stamper, J.H. (1983). Worker exposure to Paraquat and Diquat. Arch. Environ. Contam. Toxicol. 12: 65-70,.

Wolfe, H.R. (1976). Field exposure to airborne pesticides. In *Air Pollution from Pesticides and Agricultural Processes* (R. E. Lee, Ed.), pp. 137-161. CRC Press, Boca Raton, FL.

Woollen, B., Marsh, J., Lairdm W., and Lesser, J. (1992). The metabolism of Cyp in man: differences in urinary metabolite profiles following oral and dermal administration. Xenobiotica 22: 983–991.

Woollen, B. (1993). Biological Monitoring for Pesticide Absorption. Ann. Occup. Hyg. 37: 525-540.

World Health Organization (1982). Field surveys of exposure to pesticides. Standard Protocol. VBC/82.1.