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Reassessment of Worker Exposure Rates
FINAL REPORT

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AEL	adverse-effect level
a.e.	acid equivalent
a.i.	active ingredient
ALS	acetolactate synthase
APHIS	Animal and Plant Health Inspection Service
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
calc	calculated value
CBI	confidential business information
ChE	cholinesterase
CI	confidence interval
cm	centimeter
CNS	central nervous system
DAA	days after application
DAT	days after treatment
DER	data evaluation record
d.f.	degrees of freedom
EC_x	concentration causing X% inhibition of a process
EC_{25}	concentration causing 25% inhibition of a process
EC_{50}	concentration causing 50% inhibition of a process
EHE	2-ethylhexyl ester
EFED	Environmental Fate and Effects Division (U.S. EPA/OPP)
ExToxNet	Extension Toxicology Network
F	female
FH	Forest Health
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
g	gram
GLP	Good Laboratory Practices
ha	hectare
HED	Health Effects Division (U.S. EPA/OPP)
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IRED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
k_a	absorption coefficient
k_e	elimination coefficient
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
$K_{o/w}$	octanol-water partition coefficient
K_p	skin permeability coefficient
L	liter
lb	pound
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LOC	level of concern
m	meter
M	male

mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mL	milliliter
mM	millimole
mPa	millipascal, (0.001 Pa)
MOS	margin of safety
M/L/A	mixer/loader/applicator
MRID	Master Record Identification Number
MSDS	material safety data sheet
MSMA	monosodium methanearsonate
MW	molecular weight
NAWQA	USGS National Water Quality Assessment
NCI	National Cancer Institute
NCOD	National Drinking Water Contaminant Occurrence Database
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NOS	not otherwise specified
NRC	National Research Council
NTP	National Toxicology Program
OM	organic matter
OPP	Office of Pesticide Programs
OPPTS	Office of Pesticide Planning and Toxic Substances
OSHA	Occupational Safety and Health Administration
Pa	Pascal
PBPK	physiologically-based kinetic
PPE	personal protective equipment
ppm	parts per million
RBC	red blood cells
RED	re-registration eligibility decision
RfD	reference dose
SERA	Syracuse Environmental Research Associates
TEP	typical end-use product
T.G.I.A.	Technical grade active ingredient
TIPA	Triisopropanolamine
TRED	Tolerance Reassessment Eligibility Decision
T1	workers using normal work practices the Lavy et al. (1987) study
T2	workers using special precautions to reduce exposure in the Lavy et al. (1987) study.
UF	uncertainty factor
U.S.	United States
USDA	U.S. Department of Agriculture
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey
WHO	World Health Organization

To convert ...	Into ...	Multiply by ...
acres	hectares (ha)	0.4047
acres	square meters (m^2)	4,047
atmospheres	millimeters of mercury	760
centigrade	Fahrenheit	1.8℃+32
centimeters	inches	0.3937
cubic meters (m^3)	liters (L)	1,000
Fahrenheit	centigrade	0.556℉-17.8
feet per second (ft/sec)	miles/hour (mi/hr)	0.6818
gallons (gal)	liters (L)	3.785
gallons per acre (gal/acre)	liters per hectare (L/ha)	9.34
grams (g)	ounces, (oz)	0.03527
grams (g)	pounds, (oz)	0.002205
hectares (ha)	acres	2.471
inches (in)	centimeters (cm)	2.540
kilograms (kg)	ounces, (oz)	35.274
kilograms (kg)	pounds, (lb)	2.2046
kilograms per hectare (hg/ha)	pounds per acre (lb/acre)	0.892
kilometers (km)	miles (mi)	0.6214
liters (L)	cubic centimeters (cm^3)	1,000
liters (L)	gallons (gal)	0.2642
liters (L)	ounces, fluid (oz)	33.814
miles (mi)	kilometers (km)	1.609
miles per hour (mi/hr)	cm/sec	44.70
milligrams (mg)	ounces (oz)	0.000035
meters (m)	feet	3.281
ounces (oz)	grams (g)	28.3495
ounces per acre (oz/acre)	grams per hectare (g/ha)	70.1
ounces per acre (oz/acre)	kilograms per hectare (kg/ha)	0.0701
ounces fluid	cubic centimeters (cm^3)	29.5735
pounds (lb)	grams (g)	453.6
pounds (lb)	kilograms (kg)	0.4536
pounds per acre (lb/acre)	kilograms per hectare (kg/ha)	1.121
pounds per acre (lb/acre)	mg/square meter (mg/m^2)	112.1
pounds per acre (lb/acre)	µg/square centimeter ($\mu g/cm^2$)	11.21
pounds per gallon (lb/gal)	grams per liter (g/L)	119.8
square centimeters (cm^2)	square inches (in^2)	0.155
square centimeters (cm^2)	square meters (m^2)	0.0001
square meters (m^2)	square centimeters (cm^2)	10,000
yards	meters	0.9144

Note: All references to pounds and ounces refer to avoirdupois weights unless otherwise specified.

CONVERSION OF SCIENTIFIC NOTATION

Scientific Notation	Decimal Equivalent	Verbal Expression
$1 \cdot 10^{-10}$	0.0000000001	One in ten billion
$1 \cdot 10^{-9}$	0.000000001	One in one billion
$1 \cdot 10^{-8}$	0.00000001	One in one hundred million
$1 \cdot 10^{-7}$	0.0000001	One in ten million
$1 \cdot 10^{-6}$	0.000001	One in one million
$1 \cdot 10^{-5}$	0.00001	One in one hundred thousand
$1 \cdot 10^{-4}$	0.0001	One in ten thousand
$1 \cdot 10^{-3}$	0.001	One in one thousand
$1 \cdot 10^{-2}$	0.01	One in one hundred
$1 \cdot 10^{-1}$	0.1	One in ten
$1 \cdot 10^{0}$	1	One
$1 \cdot 10^{1}$	10	Ten
$1 \cdot 10^{2}$	100	One hundred
$1 \cdot 10^{3}$	1,000	One thousand
$1 \cdot 10^{4}$	10,000	Ten thousand
$1 \cdot 10^{5}$	100,000	One hundred thousand
$1 \cdot 10^{6}$	1,000,000	One million
$1 \cdot 10^{7}$	10,000,000	Ten million
$1 \cdot 10^{8}$	100,000,000	One hundred million
$1 \cdot 10^{9}$	1,000,000,000	One billion
$1 \cdot 10^{10}$	10,000,000,000	Ten billion

EXECUTIVE SUMMARY

The current report is an update to methods that have been used in Forest Service risk assessments to estimate pesticide exposures to workers involved in pesticide applications (SERA 1998). These methods are based on studies in which exposures are estimated from measures of absorbed doses in workers involved in pesticide applications – i.e., absorption-based methods. The U.S. EPA's Office of Pesticide Programs typically bases estimates of worker exposure on studies involving the deposition of pesticides on workers – i.e., deposition-based methods. While the current report is focused on absorption-based methods, this is not to imply that absorption-based methods are necessarily or uniformly better than deposition-based methods. Studies appropriate for deriving absorption-based worker exposure rates are more limited than studies which may be used to derive deposition-based rates. In practice, Forest Service risk assessments may use either absorption-based methods, deposition-based methods, or a combination of the two methods. The current analysis, however, is focused on absorption-based methods.

In the current analysis, worker exposure rates are derived in units of mg/kg bw per lb a.i. handled – i.e., milligram of pesticide absorbed per kilogram of body weight for each pound of active ingredient (a.i.) handled by a worker. In estimating exposure for a specific application, the worker exposure rate is multiplied by the amount of pesticide handled by the worker, and the dose to the worker is expressed in units of mg/kg bw.

Variability among individuals is a striking characteristic of studies on worker exposure. In order to reflect this variability as fully as possible, estimates of worker exposure rates are given as mean values with both confidence and prediction intervals. Confidence intervals reflect the range over which the true mean for a group of workers is likely to occur. Prediction intervals reflect the range over which individual measurements (i.e., exposures to individual workers) are likely to occur. As a convention, both confidence and prediction intervals are expressed at the 95% level. While the EXCEL workbook which accompanies this report includes analyses of untransformed and log-transformed rates, all worker exposure rates derived in this report are based on log-normal distributions. This approach is taken based on both the fit of the data to the log-normal distribution as well as considerations of the multiplicative processes which underlie worker exposure rates and lead to the assumption of a log-normal distribution for worker exposure rates.

Table E-1: Recommended Worker Exposure Rates

Application Method	Reference Chemical [Dermal k_a]	Worker Exposure Rate (mg/kg bw per lb) [Confidence Intervals] (Prediction Intervals)	Adjust for Dermal Absorption
Directed Ground			
Backpack Directed Foliar and Greenhouse Applications	Glyphosate [0.00041 $hour^{-1}$]	0.0003 [0.0002-0.0005] (0.00006-0.002)	Yes
	2,4-D [0.00066 $hour^{-1}$]	0.005 [0.003-0.008] (0.001-0.02)	Yes
	Triclopyr BEE [0.0031 $hour^{-1}$]	0.01 [0.008-0.01] (0.002-0.06)	Yes
Hack-and-squirt	2,4-D [0.00066 $hour^{-1}$]	0.004 [0.001-0.01] (0.00003-0.5)	Yes
Basal Bark	Triclopyr BEE [0.0031 $hour^{-1}$]	0.001 [0.0006-0.003] (0.0001-0.02)	Yes
Ground Broadcast			
Broadcast foliar	2,4-D [0.00066 $hour^{-1}$]	0.0001 [0.00004-0.0002] ($2x10^{-6}$-0.005)	Optional
Aerial			
All aerial broadcast	2,4-D [0.00066 $hour^{-1}$]	0.00002 [0.000006-0.00007] ($5x10^{-7}$-0.0008)	Optional
Aquatic			
Aquatic broadcast	2,4-D [0.00066 $hour^{-1}$]	0.0009 [0.0004-0.002] (0.0002-0.005)	Optional

Worker exposure rates are derived for different groups of application methods as summarized in Table E-1 of this executive summary. Note that this table is a simplification of Table 14 in the main body of this document. For directed ground applications, separate exposure rates can be developed for backpack directed foliar, hack-and-squirt, and basal bark applications. For ground broadcast, aerial, and aquatic applications, the available data support only single generic worker exposure rates for each application method. The worker exposure rates for backpack directed foliar applications may be applied to greenhouse applications based on the limited data on greenhouse applications (Section 3.2.3.4.2).

There is a reasonably compelling and statistically significant correlation of worker exposure rates with dermal absorption rates based on studies involving directed foliar applications of glyphosate, 2,4-D, and triclopyr BEE – i.e., the butoxyethyl ester of triclopyr. Consequently, the following equation is recommended for estimating a worker exposure rate for the pesticide of concern ($ExpRt_P$) based on the worker exposure rate for a reference chemical ($ExpRt_{Ref}$), the first-order dermal absorption rate coefficient for the pesticide of concern (ka_P), and the first-order dermal absorption rate coefficient for the reference pesticide (ka_{Ref}):

$$ExpRt_P = \frac{ka_P}{ka_{\mathrm{Ref}}} \times ExpRt_{\mathrm{Ref}}$$

The above equation is given in the main body of this document as Equation 22 and is discussed further in Section 4.1.6. In plain language, the above equation simply states that the worker exposure rate is directly proportional to the dermal absorption rate. As summarized in Table E-1, three reference pesticides are given in the current analysis – i.e., glyphosate, 2,4-D, and triclopyr BEE. The preferred approach to selecting a reference chemical is to minimize extrapolation. Nonetheless, other factors such as chemical structure, chemical properties, and mode of action could be considered. Thus, the rationale for selecting a reference chemical is left as a matter of judgment that must be articulated in any application of the above equation. Worker exposure studies on other pesticides suitable for the development of worker exposure rates will become available over time. In such cases, it may be appropriate and preferable to use worker exposure rates for pesticides other than those included in the current analysis.

For ground broadcast, aerial, and aquatic applications, the available information is insufficient to directly support the application of the above equation. Intuitively, however, the assertion that worker exposure rates should be related to dermal absorption rates seems reasonable. In the absence of additional information, however, the adjustment of worker exposure rates based on dermal absorption rates is considered optional and is left as a matter of judgment that should be articulated on a case-by-case basis.

1. INTRODUCTION

1.1. Background

The potential exposure of pesticide applicators is a major focus in Forest Service risk assessments (SERA 2011a, 2014). The concern for applicator exposure is motivated by obvious ethical considerations as well as the understanding that pesticide applicators are likely to be the individuals who are most exposed to the pesticide during the application process.

Two general types of methods are most often used in applicator exposure modeling: deposition-based methods and absorption-based methods. The U.S. EPA/OPP most often uses a deposition-based approach (e.g., PHED Task Force 1995). Forest Service risk assessments typically use an absorption-based approach based on biomonitoring studies. An overview of the two approaches is given in Table1.

In the absorption-based methods, the amount of chemical absorbed is estimated from the amount of chemical handled and estimated absorbed dose rates—e.g., mg/kg bw/day per lb pesticide handled. In deposition-based methods, the amount of chemical absorbed is based on estimates of the amount of chemical deposited on skin surface as well as estimates of the dermal absorption rate and inhalation rate per unit of chemical handled.

Forest Service risk assessments typically use the absorption-based models, rather than deposition-based models, because of two common observations from field studies. First, as discussed in the review by van Hemmen (1992), most studies that attempt to differentiate occupational exposure by route of exposure indicate that dermal exposure is much greater than inhalation exposure for pesticide workers. Second, most studies of pesticide exposure that monitor both dermal deposition and chemical absorption or some other method of biomonitoring note a poor correlation between the two values (e.g., Cowell et al. 1991; Franklin et al. 1981; Lavy et al. 1982; Spencer et al. 2000; Zhang et al. 2011). For example, in the recent study by Zhang et al. (2011) on applications of 2,4-D and triclopyr, deposition based methods overestimated exposures to 2,4-D by factors of 2-3 but underestimated exposures to triclopyr by factors of 3-4.

In USDA Forest Service exposure assessments for workers, the primary goal is to estimate absorbed dose so that the absorbed dose estimate can be compared with available information on the dose-response relationships for the chemical of concern. Thus, if dermal deposition does not correlate well with absorbed dose and if the inhalation route is not a substantial factor in worker exposure, the absorption-based approach may have some advantages when compared to the deposition-based approach. The worker exposure rates currently used in Forest Service risk assessments are summarized in Table 2.

While the Forest Service prefers absorption-based methods for estimating worker exposures, Forest Service risk assessments will sometimes use deposition-based methods developed by the U.S. EPA either for comparison or because deposition-based methods support a much larger number of application methods and application variables than the absorption-based methods summarized in Table 2. Deposition-based methods typically use the Pesticide Handlers Exposure Database (PHED Task 1995). U.S. EPA/OPP summarizes surrogate exposures from

PHED for 37 types of exposures, involving mixer-loaders, flaggers, and applicators, for several different types of formulations (e.g., liquid, granular, and wettable powders) applied with ground or aerial equipment (Keigwin 1998). Using the estimates of deposited dose and concentration of the pesticide in air, the absorbed dose for workers can be calculated if estimates are available on absorption rates for inhalation and dermal exposure. The rates from Keigwin (1998) were updated recently by U.S. EPA/OPP (2012). Table 3 provides an overview of the standard exposure rates, adopted from Keigwin (1998) with selected updates from U.S. EPA/OPP (2012).

Another benefit of the PHED method is that the U.S. EPA is routinely able to present different exposure scenarios for workers using different levels of personal protective equipment (PPE) based on studies in PHED. In EPA risk assessments such as those used to support the reregistration of a pesticide, the risks associated with different levels of PPE may be used to set regulatory requirements for the use of PPE during pesticide applications. Forest Service risk assessments consider PPE only when it is required by EPA, which is most often the case with some insecticides. When PPE is considered in Forest Service risk assessments, estimates of the effectiveness of PPE are based on chemical-specific studies, if available. Otherwise, estimates of the effectiveness of PPE are taken from EPA assessments of the specific chemical or are developed from the PHED database.

While the U.S. EPA/OPP generally uses deposition-based methods for worker exposures, the Agency will sometimes prefer biomonitoring data, as indicated in the following quotation for the Reregistration Eligibility Decision for alachlor.

> *Generally, biomonitoring data are preferable to passive-dosimetry data. The use of a dermal absorption factor is not necessary for biomonitoring data. Biomonitoring data can give a more accurate estimate of absorbed dose.*
>
> U.S. EPA/OPP 1998b, p. 65

As should be evident by the above discussion, the current report is focused on exposure methods based on biomonitoring data but this is not to imply that exposure assessments based on biomonitoring are necessarily or uniformly preferable to deposition-based methods for worker exposures. The utility of considering both methods in worker exposure assessments is discussed further in Section 4.3.1.

Regardless of whether a deposition-based or absorption-based model is used to estimate worker exposure, the general algorithms for estimating doses for workers (*D*, in units of mg/kg bw/day) are similar and are calculated as the product of the exposure rate (*ExpRate* in units of mg/kg bw per lb handled) and the amount of the pesticide that is handled by the worker (*Amnt* in units of lb handled/day):

$$D = Amnt \times ExpRate \qquad \text{(Eq. 1)}$$

Typically, the amount of pesticide handled is calculated as the product of the application rate (*ApRt* in lbs/acre) and the number of acres treated per day:

$$Amnt = ApRt_{lbs/acre} \times Acres/day \quad \text{(Eq. 2)}$$

While this basic algorithm is used in Forest Service and EPA risk assessments, the number of acres treated per day for a particular application method differs among Forest Service and EPA risk assessments. The estimated number of acres treated per day is generally based on Forest Service Environmental Impact Statements (e.g., USDA/FS 1989a,b,c), as summarized in Table 2. The corresponding values used in EPA risk assessments vary according to the risk assessment, reflecting information from registrants as well as judgments made by the EPA concerning the maximum application rate. The EPA's Science Advisory Council for Exposure Policy (Sandvig 2001) proposed standard values for daily acres treated in agriculture, and these guidelines are cited in some EPA risk assessments. In some cases in which standard Forest Service values are not applicable, the number of acres treated per day may be taken from Sandvig (2001) or EPA occupational exposure assessments.

1.2. Motivation for Reassessment

During the 1980s and for most of the 1990s, worker exposure assessments in Forest Service risk assessments estimated worker exposure rates based on well-documented worker exposure rates for 2,4-D, adjusting the exposure rate for the chemical under review by its estimated dermal absorption rate relative to the dermal absorption rate for 2,4-D (e.g., USDA/FS 1989a,b,c). Using this approach, the worker exposure rate (in mg/kg bw/day per lb handled) for a pesticide other than 2,4-D ($ExpRt_P$) is estimated from the first-order dermal absorption rate constant (in units of reciprocal time) for the pesticide (ka_P), the corresponding rate for 2,4-D ($ka_{2,4\text{-}D}$), and the occupational exposure rate for 2,4-D ($ExpRt_{2,4\text{-}D}$) using the following algorithm:

$$ExpRt_P = \frac{ka_P}{ka_{2,4-D}} \times ExpRt_{2,4-D} \quad \text{(Eq. 3)}$$

This approach was initially adopted in Forest Service risk assessments prepared by SERA.

The units for worker exposure rates are given in this analysis as mg/kg bw per lb applied or handled. In most Forest Service risk assessments, care is taken to express the rates as either a.i. (active ingredient) or a.e. (acid equivalent). Nevertheless, the value of the exposure rate is constant regardless of whether or not a.i. or a.e. is used so long as both the mg absorbed and pounds handled are expressed in the same manner—i.e., both are expressed as a.i. or both are expressed as a.e. In the current analysis, the worker rate is simply expressed as mg/kg bw/day per lb handled without the a.i. or a.e. specification.

By rearrangement of Equation 3, it is evident that that the explicit assumption is that the relative worker exposure rate is equal to the relative dermal absorption rate:

$$\frac{ExpRt_P}{ExpRt_{2,4-D}} = \frac{ka_P}{ka_{2,4-D}} \quad \text{(Eq. 4)}$$

where the left-hand side of Equation 4 is the relative worker exposure rate (in this case relative to 2,4-D) and the right-hand side of Equation 4 is the relative dermal absorption rate. The current analysis is concerned primarily with absolute worker exposure rates (e.g., the left-hand side of Equation 3) in units of mg/kg bw per lb applied. Relative exposure rates and relative absorption rates, however, are discussed and addressed specifically in Section 4.1.

For some studies involving applications of mixtures (e.g., Libich et al. 1984), absolute worker exposure rates in units of mg/kg bw per lb handled cannot be calculated because the amount of the pesticides handled cannot be estimated. If the amount of the pesticides excreted ($Excr_x$) and the relative amount (RA_x) of each pesticide in the mixture is known, then the relative exposure rate (Exp_R) can be calculated as:

$$Exp_R = \frac{Excr_1 \div RA_1}{Excr_2 \div RA_2} \quad \text{(Eq. 5)}$$

Examples of applications in Equation 5 are discussed further in Section 4.1.

In the application of Equation 3, examples were encountered in which the use of dermal absorption rates to estimate worker exposure rates appeared to be incorrect – i.e., there did not appear to be a correlation between dermal absorption rates and occupational exposure rates. In response to this observation, the Forest Service requested a reevaluation of the algorithm (Equation 3).

SERA (1998) reviews worker exposure studies that could be used to relate absorbed dose to the amount of chemical handled per day. As illustrated in Figure 1 and summarized in Table 4, the review indicated that there was no empirical support for a dermal absorption rate correction. As discussed in SERA (1998), two factors may be involved in this unexpected lack of association:

- algorithms for estimating dermal absorption rates have large margins of error and

- actual levels of worker exposure are likely to be far more dependent on individual work practices or other factors such as terrain or field conditions than on differences in dermal absorption rates among workers.

In the absence of data to suggest an alternative approach, Forest Service risk assessments conducted since 1998 make no corrections for differences in dermal absorption rate coefficients or other indices of dermal absorption (SERA 2011a).

Concerns with the current approach to worker exposure assessment, however, were raised in a Forest Service risk assessment on triclopyr (SERA 2011c). The concern was based on an analysis of three studies not included in the SERA (1998) report: Middendorf (1992b), Spencer et al. (2000), and Zhang et al. (2011). The study by Middendorf (1992b) was inadvertently overlooked in the SERA (1998) report; the other two studies were published after the report. As discussed in Section 3, all three of these studies involved backpack directed foliar applications of triclopyr BEE which led to higher worker exposure rates than those currently used in Forest Service risk assessments for backpack applications (Table 2). Another study not reviewed in the SERA (1998) report is the backpack study with glyphosate by Middendorf (1993). This unpublished study was encountered in the process of conducting a recent Forest Service risk assessment on glyphosate (SERA 2010a). As discussed further in Section 3, Middendorf (1993) indicates worker exposure rates that are much lower than those developed in the SERA (1998) analysis. Because glyphosate is poorly absorbed relative to many other herbicides, including triclopyr, the Middendorf (1993) study suggests that the association of worker exposure rates with dermal absorption rates required reexamination.

Given the above concerns, the Forest Service determined that a reassessment of worker exposure rates was necessary, and the current report constitutes the expanded analysis and reevaluation. The primary questions addressed in the current report are:

1. Do the current worker exposure rates used in Forest Service risk assessments (Table 2) need to be revised based on studies identified since the 1998 report?

2. Does the consideration of the additional worker studies continue to support the assumption that corrections for dermal absorption rates are unnecessary?

2. MATERIALS AND METHODS

2.1. Literature Search, Screening, and Classification

All literature covered in the SERA (1998) report was re-reviewed. In addition, literature searches were conducted in TOXNET (http://toxnet.nlm.nih.gov/) covering the period from 1997 to 2012. Because the type of worker exposure literature required for the current effort (discussed below) is very difficult to identify, the search terms were extremely broad—e.g., pesticides AND workers. This approach to the literature search in TOXNET yielded a total of 1545 citations. Most of these citations involve epidemiology studies, case reports, and analytical methods. These studies are not relevant to the current effort and are not discussed further.

Supplemental searches on the Internet for gray literature were also conducted using Google and Google Scholar. In addition, all Forest Service risk assessments conducted since 1998 were reviewed to ensure that all new worker exposure studies discussed in these risk assessments are considered in the current analysis.

The approach to screening focused on four levels of relevance:

- **Primary Studies**: Studies that appear to contain information on both the amount of pesticide handled as well as an estimated amount of pesticide absorbed for individual workers. As discussed in SERA (1998) and in Section 3 of the current report, the variability in estimated exposure rates among individual workers involved in a given application is extremely broad. Consequently, studies that provide the basis for estimating exposure rates for individual workers are the most relevant.
- **Secondary Studies**: Studies that contain information on both the amount of pesticide handled as well as an estimated amount of pesticide absorbed for groups of workers but not individual workers.
- **Tertiary Studies**: Studies that cannot be used to derive absolute exposure rates for workers but are useful for deriving relative exposure rates for different subgroups of workers—e.g. mixer-loaders versus applicators versus bystanders. As discussed in Section 1, the current methods used in Forest Service risk assessments provide exposure rates only for applicators involved in three types of applications. Tertiary studies may be useful in expanding the number of worker exposure rates that can be derived.
- **Other Studies**: These studies cannot be used to derive absolute or relative worker exposure rates but may provide other types of useful information—e.g., the effectiveness of PPE.

Based on the above criteria, a total of 174 papers were obtained and are included in the bibliography (Section 5). These studies are also summarized in Appendix 1. This appendix lists the study citation, a brief description of the topic addressed in the publication, and notes on the study.

Following the initial screening of studies, a subgroup of studies that appeared to be potentially useful for deriving or otherwise assessing worker exposure rates was screened in greater detail and this subgroup of studies is summarized in Appendix 2: *Summary of Studies Assessed for Worker Exposure Rates*. Appendix 2 provides information on the following topics: application method, worker groups examined, pesticides applied, location of study, terrain or field conditions, vegetative cover or crops, protective clothing used, application rates, kinetic considerations, description of biomonitoring, other monitoring (e.g., passive deposition, air levels), and other notes. The subgroup of studies on which worker exposure rates were derived is given in Section 3 of this report.

The criterion used for the final selection of studies is relatively simple and follows from the basic definition of worker exposure rates—i.e., mg absorbed dose/kg bw/day per lb pesticide handled.

1. The study must provide reasonably reliable estimates of absorbed dose in either individual workers or groups of workers.

2. The study must provide a reasonable estimate of the amount of pesticide handled per day which corresponds to the estimates of absorbed dose.

These criteria were relaxed only for worker exposure studies involving mixtures of pesticides. Studies reporting reliable estimates of worker exposure to each component in the mixture can be used to derive relative worker exposure rates in the absence of information on the amount handled. In practice, Libich et al. (1984) is the only study quantitatively considered in this report in which only relative rather than absolute worker exposure rates are estimated. This study is discussed in Section 3.2.3.

The analyses presented in this report involve many data sets, some of which are analyzed in several different ways, depending on the nature of the data. These analyses as well as the specific data used in the analyses are given in Attachment 1, an EXCEL workbook. Most of the worksheets in Attachment 1 give the mean as well as the 95% confidence intervals and 95% prediction intervals for the group based on both untransformed data and log transformed data. Other worksheets give custom analyses of data sets as detailed further in Section 3. Attachment 1 is intended to isolate and explicitly document the calculations discussed in the body of this report. For the most part, the data and analyses given in Attachment 1 are discussed but not reproduced in the main body of this report. Worksheets covering a single data set are named according to the study from which the data are taken. If only a single data set from a study is considered—e.g., Chester et al. (1987) and Cowell et al. (1981)—the worksheet is given the name of the study. If more than one data set is analyzed, the worksheet is named based on the study citation followed by a dash (-) and an integer—e.g., **`Lavy et al. 1982-1`** through **`Lavy et al. 1982-9`**. In order to more clearly distinguish a reference to a study from a reference to a worksheet, all worksheet names are given in **`Bold Courier font`**.

The third worksheet in Attachment 1 (named **`TOC`**) is the table of contents. The table of contents consists of columns specifying the worksheet number, the name of the worksheets, the study covered by the worksheet, and a brief summary of the analysis done in the worksheet. Attachment 1 contains macros and, if macros are enabled, double clicking on the row with the worksheet name will activate the worksheet. Otherwise, macros do not need to be enabled to use this workbook. Given the naming conventions used for the worksheets, using this macro facility will substantially facilitate navigation of the workbook. Thus, macros should be enabled when using Attachment 1.

2.2. First-Order Dermal Absorption Rate Coefficients

First-order rate processes are used in pharmacology as well as many other branches of science to describe a process that operates on a constant proportion of a chemical or other matter per unit time. First-order dermal absorption is a model in which a chemical on the skin is absorbed at a constant proportion of amount of chemical on the skin surface per unit of time (e.g., Goldstein et al. 1974).

Since the 1998 analysis (SERA 1998), Forest Service risk assessments were conducted or updated for several pesticides relevant to the current analysis—i.e., 2,4-D (SERA 2006a), malathion (SERA 2008a), glyphosate (SERA 2010a), triclopyr (SERA 2011c), and picloram (SERA 2011d). In many instances, these updates resulted in modifications to dermal absorption rate coefficients from those used in the 1998 analysis. These differences are discussed, as necessary, in the text of this report. Information on pesticides for which no Forest Service risk assessments are available is taken from U.S. EPA/OPP Reregistration Eligibility Decisions (REDs). In the absence of experimental data on dermal absorption, first-order dermal absorption rate coefficients were estimated using the quantitative structure-activity (QSAR) algorithm described in SERA (2014):

$$\log_{10} k_a = -1.49 + 0.233 \log_{10} K_{ow} - 0.00566\,MW \qquad \text{(Eq. 6)}$$

EPI Suite (2011), an estimation program developed by the U.S. EPA, was used as a supplemental source for molecular weights and K_{ow} values.

2.3. Statistical Analyses

Confidence intervals and prediction intervals for means are calculated following standard methods (e.g., Ramirez 2009). Specifically, the confidence intervals are calculated as:

$$\overline{\mathrm{X}} \pm t_{1-\frac{\alpha}{2},\, n-1}\; s\sqrt{\frac{1}{n}} \qquad \text{(Eq. 7)}$$

and the prediction intervals are calculated as

$$\overline{\mathrm{X}} \pm t_{1-\frac{\alpha}{2},\, n-1}\; s\sqrt{1+\frac{1}{n}} \qquad \text{(Eq. 8)}$$

where ***t*** is the value from the Student's *t*-distribution, ***n*** is the sample size, and ***s*** is the sample standard deviation. The sample standard deviation (***s***) is calculated as:

$$s = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \overline{y})^2}{d.f.}} \qquad \text{(Eq. 9)}$$

where $\overline{y}$ is the sample mean and y_i is the value of the ith element in the sample and ***d.f.*** (degrees of freedom) is ***n-1*** (e.g., Samuels and Witmer 2003).

Standard linear regression is conducted in EXCEL and used to explore the relationship of dermal absorption rates to occupational exposure rates (Section 4.1). EXCEL does not provide confidence or prediction intervals on the regression analyses. For the regression analyses, confidence intervals and prediction intervals are calculated following standard methods (e.g., Mendenhall 1975). Specifically, the confidence intervals are calculated as:

$$\hat{y} \pm t_{1-\frac{\alpha}{2},\, n-2}\; s\sqrt{\frac{1}{n} + \frac{(x_p - \bar{x})^2}{SS_x}} \qquad \text{(Eq. 10)}$$

and the prediction intervals are calculated as

$$\hat{y} \pm t_{1-\frac{\alpha}{2},\, n-2}\; s\sqrt{1 + \frac{1}{n} + \frac{(x_p - \bar{x})^2}{SS_x}} \qquad \text{(Eq. 11)}$$

where $\boldsymbol{x_p}$ is the value of the dependent variable, $\bar{x}$ is the average value of the dependent variable in the data set, and SS_x is equivalent to $\sum_{i=1}^{n}(x_i - \bar{x})^2$). The standard deviation, s, is calculated as,

$$s = \sqrt{\frac{SSE}{d.f.}} = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y})^2}{d.f.}} \qquad \text{(Eq. 12)}$$

where the degrees of freedom (*d.f.*) is n-2, if both the slope and intercept are estimated in the linear regression, or n-1, if only the slope is estimated and the intercept is constrained to zero.

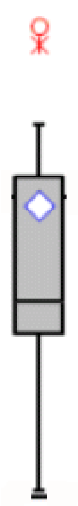
As indicated in Equations 7 and 8, prediction intervals are wider than confidence intervals, and this difference reflects the differences between what the two intervals are intended to encompass. A confidence interval indicates the region in which the true mean of the population lies. In other words, repeated and essentially replicate experiments will yield mean values that fall within a confidence interval. A prediction interval, on the other hand, indicates the region in which a future observation is likely to lie. For example, a prediction interval based on 10 observations indicates the region in which an 11^{th} observation is likely to lie (Ramirez 2009).

Prediction intervals are commonly used in sampling analyses of monitoring data (e.g., Eldridge 2011; U.S. EPA/ORCR 2009; U.S. EPA/ORD 1999). The rationale for using prediction intervals in the analysis of worker exposure rates is that concern for atypically high rates of exposure in an individual is appropriate for any assessment involving human health. While uncertainties in the estimate of mean exposures are appropriately handled by the confidence interval, uncertainties in estimates of individual observations are considered more fully using the prediction interval. Thus, while the previous assessment of worker exposure rates (SERA 1998) considered only confidence intervals, the current analysis considers both confidence intervals and prediction intervals.

Another difference between the previous and current analysis involves missing values. In the previous analysis, missing values were addressed using trimmed means (e.g., Gilbert 1987). For example, if a study on 20 workers found no detectable exposures in three workers, the three workers with the highest exposures were censored from the analysis. In the current analysis, missing values are handled by replacing the missing values with one-half of the lowest value from the sample under consideration. This approach is only modestly more conservative (albeit statistically biased) than the approach taken in 1998. In practice, the use of one-half of the lowest value rather than the trimmed mean does not have a substantial impact on the worker exposure rates derived in this report. Differences between the use of one-half of the lowest value rather than the trimmed mean are discussed as appropriate for the data sets with non-detects.

Data distributions are assessed using the Kolmogorov–Smirnov test in Statgraphics Plus (Manugistics 1997). Notably, the Kolmogorov–Smirnov test indicates an increasingly better fit to a distribution as the *p*-value increases. For example, a *p*-value of 0.05 or less would generally be viewed as indicating a significant lack of fit; whereas, *p*-values greater than 0.05 would generally be viewed as suggesting that the data fit the tested distribution. Very high *p*-values (e.g., 0.5 or more) indicate a very good fit to the distribution.

As in the previous analysis (SERA 1998) as well as the current analysis, the recommended exposure rates are based on a logarithmic transformation of worker exposure rates. As detailed further in Section 3.2.1 (Expression of Exposure Rates), the logarithmic transformation is based on the assessment that the worker exposure rates have a log-normal distribution as well as the well-documented association of the log-normal distribution with multiplicative models (e.g., Barnett et al. 2008; Limpert 2001; Mitzenmacher 2004; Ott 1995, p. 251ff). As detailed in Section 4, the equations used to estimate worker exposures are multiplicative models. More initiatively, the use of untransformed worker exposure rates (i.e., fit to a standard normal distribution) often leads to confidence or prediction intervals with lower bounds below zero – e.g., Worksheets **Chester et al. 1987**, **Cowell et al. 1991**, and **Dubelman and Cowell 1989-1** in Attachment 1. Negative worker exposure rates are, of course, not sensible.



Statistical outliers are defined as values that fall outside the lower or upper quartile ± 1.5 times the interquartile range (e.g., Samuels and Witmer 2003, pp. 35-36). Far outliers are defined as values that fall outside the lower or upper quartile ± 3 times the interquartile range (Statistical Graphics 1991). The use of outliers in the analyses is discussed in Section 3.2.4.

Box-and-Whisker plots are used to illustrate some data sets—e.g., directed applications in Figure 5. As illustrated in the embedded and unnumbered figure to the left, the large diamond in the box-and-whisker plots designates the arithmetic mean. The shaded box defines the first and third quartiles—i.e., regions encompassing 25% to 75% of the observations. The line running through the shaded box is the median. Points indicated by x marks denote statistical outliers—i.e., points greater than 1.5 times the inner quartile range (the distance between the first and third quartile) from the third quartile. The circles represent far outliers—i.e., points greater than 3 times the inner quartile range from the third quartile. The capped lines extending from the shaded box represent the range of values, excluding statistical outliers.

As a convention, values from the statistical analyses discussed in this report are given to three significant places. Use of this convention is not intended to imply that all of the data sets support significance to three digits. As with the SERA (1998) analysis, recommended worker exposure rates are rounded to one significant digit (Section 4.2).

3. RESULTS

3.1. Overview of Studies and Pesticides

3.1.1. Worker Exposure Studies

The studies used quantitatively in the current analysis are summarized in Table 5. Of the 174 studies identified in the literature search (Appendix 1) and the 38 studies selected for detailed review (Appendix 2), only 20 studies were selected. With the exception of the Libich et al. (1984) study, the selected studies meet the two criteria discussed in Section 2.1—i.e., both exposure rates and amounts handled can be estimated. Libich et al. (1984) does not meet these criteria. Nonetheless, as discussed further in Section 3.2, the study involves applications of mixtures of 2,4-D and picloram to rights-of-way and provides adequate information on total urinary excretion of both 2,4-D and picloram. Consequently, Libich et al. (1984) can be used to estimate relative exposure rates (Equation 5) for these two herbicides.

Five studies have become available since the 1998 analysis (Cessna and Grover 2002; Cruz Márquez et al. 2001; Lunchick et al. 2005; Spencer et al. 2000; Zhang et al. 2011). In addition, the literature search identified three additional studies published prior to 1998 that were not included in the 1998 analysis (Dubelman and Cowell 1989; Grover et al. 1986; Middendorf 1992b). One study on aquatic applications (Nigg and Stamper 1983a) is included in Table 5. Aquatic applications are not considered in the SERA (1998) analysis; however, they are addressed in several more recent Forest Service risk assessments (e.g., SERA 2006a, 2008b,c; 2010a; 2011c).

While some studies on pesticide workers involved large numbers of female workers (e.g., Lavy 1990a), few female subjects are included in the studies from which exposure rates based on biomonitoring can be derived (Table 5). As indicated in Table 5, most of the available studies in which gender is specified involve male workers. Although several of the studies do not state whether the workers are male or female, it is quite likely that most, if not all, of the workers are male. Only three studies identify the presence of female subjects—i.e., Middendorf (1992a, 1993) and Nash et al. (1982). In each of these studies, only one female is included in each of the groups of workers. Thus, observations on the female workers are literally *anecdotal* in the statistical sense of the term, a single observation. Middendorf (1992a, 1993) does identify the sex of the workers in reporting individual data, and these data are considered in the discussion of variability in worker exposure rates (Section 3.2.4). Nash et al. (1982) indicates that two female workers are included in two groups of workers, one female per group, but does not provide individual data on the male or female workers.

Table 6 lists the pesticides covered in the 20 studies from Table 5. A total of 17 forms (i.e., acids and/or esters) of 12 pesticides are included. Four of these pesticides, including 2,4-D, dichlorprop, picloram, and triclopyr, are weak acid herbicides. The list also includes glyphosate, another herbicide that is particularly interesting because it is a zwitterion, a molecule with regions that has both positive and negative charges. The remaining pesticides include neutral herbicides (alachlor, bromoxynil, dithiopyr) and insecticides (azinphos-methyl, cypermethrin, ethoprop, malathion).

3.1.2. Dermal Absorption Rates

As discussed in Section 1.2, one of the primary goal of the current analysis is to evaluate the relationship between worker exposure rates (mg/kg bw/day per lb handled) and first-order dermal absorption rate coefficients (in units of reciprocal time). Consequently, the quality of the dermal absorption data on the pesticides covered in the current analysis is critical.

The available information on the first-order dermal absorption rate coefficients, in units of hour^{-1}, is given in Table 7. This table includes the estimated first-order dermal absorption rate coefficients with 95% confidence intervals using Equation 6, the structure-activity algorithm commonly used in Forest Service risk assessments (SERA 2011a, 2014).

Table 7 also summarizes the available measured first-order dermal absorption rates. As indicated in this table, rate coefficients in humans are available on six of the pesticides—i.e., 2,4-D acid (Feldmann and Maibach 1974), azinphos-methyl (Feldmann and Maibach 1974), cypermethrin (Woolen et al. 1992), malathion (Feldmann and Maibach 1974), picloram (Nolan et al. 1984), and triclopyr BEE (Carmichael et al. 1989). With the exception of cypermethrin, each of these estimates is discussed in some detail in recent Forest Service risk assessments (SERA 2006a, 2010a, 2011a,b).

Rate coefficients from studies in monkeys are available on alachlor (U.S. EPA/OPP 1998b) and glyphosate (Wester et al. 1991). The data on glyphosate are discussed in the Forest Service risk assessment on this herbicide (SERA 2010a). The first-order dermal absorption rate coefficient for alachlor is taken from a registrant-submitted study summarized in the U.S. EPA/OPP (1998b) Reregistration Eligibility Decision (RED) in which the EPA gives an absorption factor of 24% for a 12-hour exposure period in rhesus monkeys. Under the assumption of first-order absorption, the absorption rate coefficient (k_a) is estimated as:

$$k_a = -\frac{Ln(1-P)}{t} \qquad \text{(Eq. 13)}$$

where P is the proportion absorbed and t is the duration of exposure. Thus, the first-order dermal absorption rate coefficient for alachlor is estimated as 0.0229 hour^{-1} [ln(1-0.24) ÷ 12 hours].

A similar method is used to estimate the first-order dermal absorption rate coefficient for cypermethrin in humans from the study by Woolen et al. (1992). This paper reports an average absorption of 1.2% over an 8 hour exposure period. Thus, the first-order dermal absorption rate coefficient from this study is estimated as 0.015 hour^{-1} [ln(1-0.012) ÷ 8 hours].

Rate coefficients from studies in rats are available on azinphos-methyl, bromoxynil, the octanoate ester of bromoxynil, and cypermethrin. In the RED for azinphos-methyl, the U.S. EPA/OPP (2001) uses a dermal study in rats to set a dermal absorption rate of 42% which is applied to daily exposures. This value corresponds to a first-order absorption rate coefficient of approximately 0.00227 hour^{-1} [ln(1-0.42) ÷24 hours]. The rate coefficients for bromoxynil and the octanoate ester of bromoxynil are derived from data given in the U.S. EPA/OPP (1998a) RED for bromoxynil—i.e., 1.92% absorption for a 10-hour exposure to bromoxynil and 10.32% absorption for a 10-hour exposure to bromoxynil octanoate. The absorption rate coefficients given in Table 7 are calculated as above for bromoxynil [ln(1-0.0192) ÷10 hours ≈ 0.0019 $hour^{-1}$] and bromoxynil octanoate [ln(1-0.1032) ÷10 hours ≈ 0.011 $hour^{-1}$].

The rate coefficient for cypermethrin in rats is somewhat unusual in that the estimate is based on a comparison of oral and dermal toxicity studies in rats. As detailed in the RED for cypermethrin (U.S. EPA/OPP 2006b), the EPA estimates a dermal absorption factor of 2.5%, based on subchronic oral and dermal toxicity studies in rats, and this absorption factor is applied to daily (24-hour) doses. Thus, the first-order dermal absorption rate coefficient is estimated as 0.0011 $hour^{-1}$ [ln(1-0.025) ÷ 24 hours ≈ 0.001054 $hour^{-1}$]. While this is not a typical method for estimating a dermal absorption rate coefficient, the estimate is strikingly similar to the dermal absorption rate coefficient in humans from the study by Woollen et al. (1992), as discussed above.

No experimental estimates of the dermal absorption rates for the other pesticides given in Table 7 have been encountered. All of the calculated first-order dermal absorption rate coefficients given in Table 7 are based on Equation 6, as discussed in Section 2.2 and detailed in SERA (2011a, 2014).

Figure 2 illustrates the relationship of the estimated rate coefficients to the rate coefficients based on experimental data. In Figure 2, the solid diagonal line is the line of concordance—i.e., if the estimated and experimental measurements were identical, all of the points illustrated in Figure 2 would be on the line of concordance. With the exception of picloram and azinphos-methyl, the estimates of the rate coefficients are within a factor of less than 4 of the experimental rate coefficients. This magnitude of variability is not remarkable. In studies on dermal absorption rates in humans, Feldmann and Maibach (1974) note that: … *1 person in 10 will absorb twice the mean value while 1 in 20 will absorb 3 times this amount* (Feldmann and Maibach 1974, p. 131). Similarly, the QSAR algorithm used in Forest Service risk assessments will typically have lower and upper confidence limits for the absorption rate coefficient that vary from the mean estimate by factors of about 3 to 5.

The experimental dermal absorption rate coefficient for azinphos-methyl (0.0229 $hour^{-1}$ based on a study in rats or 0.023 based on the study in humans as discussed above) is higher than the coefficient based on Equation 6 (0.0020 $hour^{-1}$) by a factor of over 11. This discordance does not have a substantial impact on the current analysis. As discussed in Section 3.3.1.3, only one worker exposure study is available on azinphos-methyl (Franklin et al. 1981). This study involves orchard airblast applications and is the only study using this application method.

The experimental rate coefficient for picloram, which is based on human data, is lower than the rate coefficient estimated using Equation 6 by a factor of about 27 [0.00134 $hour^{-1}$ ÷ 0.00005 $hour^{-1}$ = 26.8]. As discussed below, picloram is particularly important to the assessment of whether dermal absorption rates are related to occupational exposure rates because two studies (Lavy et al. 1987; Libich et al. 1984) provide information on exposures in workers involved in applying mixtures of 2,4-D and picloram. These types of studies are extremely useful in assessing the impact of dermal absorption rates on worker exposure because there are essentially no uncertainties in the relative exposures to the two chemicals. In other words, if the amounts of

2,4-D and picloram in the mixture are known, relative exposures to 2,4-D and picloram for any given worker will be identical regardless of differences in work practices among the workers.

The dermal absorption of picloram is discussed in great detail in the Forest Service risk assessment on picloram (SERA 2011d). Because of the importance of the dermal absorption of picloram to this analysis, Appendix 3 of this report reproduces the assessment of the study by Nolan et al. (1984) on the dermal absorption of picloram.

As noted above, several of the chemicals covered in the current assessment are esters of weak acids. The dermal absorption of esters of weak acids is somewhat unusual. As summarized in Table 7, estimates of dermal absorption indicate that esters should be absorbed more rapidly than weak acids. This relationship is explicitly incorporated into Equation 7, the algorithm for estimating the first-order dermal absorption rate coefficient by the positive coefficient for the octanol-water partition coefficient (K_{ow}). Esters are non-polar, and the K_{ow} for an ester will be higher than that for the corresponding weak acid or alcohol.

The expectation that esters are absorbed more rapidly than the corresponding salt, however, is not supported by experimental data. To the contrary, Moody et al. (1990) notes few substantial differences between the dermal absorption of 2,4-D salts and esters. In this study, Moody et al (1990) assayed the dermal absorption of several forms of 2,4-D in different vehicles in both humans and experimental mammals. For each of the 2,4-D compounds tested, Moody et al (1990) report the percent recovery of the compound in the urine, the half-time, as well as the dermal absorption based on the proportion of the applied dose recovered in the urine after 14 days and the assumption of first-order absorption. In the Moody et al. (1990) study, there are very substantial inconsistencies among the acid or amine versus the ester formulation. Very little difference in dermal absorption was noted when the acid, amine salt, and isooctyl ester were applied to the backs of rabbits. Nonetheless, when applied to the human forehead, the 2,4-D amine was absorbed to a much greater extent than the isooctyl ester, either in acetone or an Esteron LV96 (commercial carrier) blank. In monkeys, the absorption rates of the amine and isooctyl forms were comparable when the compounds were applied to the forehead; however, the isooctyl form was absorbed much more readily than the amine salt when applied to the forearm. Nonetheless, the difference between the absorption rate of 2,4-D acid and the isooctyl ester after application to the monkey forearm was modest. The highest cumulative absorption reported by Moody et al. (1990) is about 58% (2,4-D amine in water on the forehead of humans), which is almost the same as the 56% absorption of 2,4-D isooctyl ester in acetone applied to the forehead of monkeys (Moody et al. 1990).

Although no other studies regarding the absorption of other esters of weak acids were identified, Feldmann and Maibach (1969) did assay the absorption of hydrocortisone and testosterone as well as the esters of these compounds. These investigators report that the dermal absorption of hydrocortisone was substantially less than the dermal absorption of hydrocortisone acetate. Testosterone, however, was absorbed to a substantially greater extent than either of its esters. Thus, while the lipophilicity of the esters is greater than that of the parent compound for both testosterone and hydrocortisone, the relative dermal absorption rates of these compounds and their esters do not uniformly support the assumption that esters will be absorbed more rapidly.

The most plausible explanation for the similar dermal absorption rates of salts and esters involves skin esterases, which rapidly hydrolyze esters to the corresponding acid and alcohol (e.g., IPCS 2005, pp. 27-28). Consequently, dermal exposures to an ester of a weak acid may be functionally equivalent to exposures to the parent acid.

In the current analysis, the impact of differences or the lack of differences in the dermal absorption of acids versus esters involves the study by Lavy et al. (1987) on worker exposures to mixtures of 2,4-D and dichlorprop esters. As summarized in Table 7, structure activity relationships (Equation 6) suggests that esters of 2,4-D should be more rapidly absorbed than esters of dichlorprop but that acids of 2,4-D acid and dichlorprop should have comparable dermal absorption rates. In the application of the Lavy et al. (1987) data to assessing the impact of dermal absorption on worker exposure (Section 4.1.1), the relative dermal absorption rates for 2,4-D and dichlorprop are based on the rates for acids rather than esters based on the observations from Moody et al. (1990) as detailed above.

3.2. Directed Applications

All pesticide applications are directed in at least a general sense. In the context of the current analysis, the term "*directed applications*" refers to pesticide applications that are applied by single nozzles or wands at relatively close range—e.g., directed foliar applications using backpacks or similar devices as well as most forms of cut-surface treatments. These applications are contrasted to ground broadcast applications using heavy equipment, spray rigs or mist blowers (Section 3.3) as well as aerial broadcast applications (Section 3.4).

A summary of the available studies on directed applications is given in Table 8 and illustrated in Figure 3. Table 8 gives the pesticide, the central estimate of the worker exposure rate, a brief description of the study, and the reference to the study from which the rate is derived. For studies in which data are given for individual workers, Table 8 also specifies the 95% confidence and prediction intervals. Figure 3 illustrates the central estimate of the exposure rate from Table 8. For studies reporting data on individual workers, the bars running vertically through the mean indicate the 95% prediction interval based on a log-normal distribution, as discussed further below (Section 3.2.1). A discussion of the studies summarized in Table 8 is given in Section 3.2.2.

3.2.1. Expression of Exposure Rates

As discussed in the SERA (1998) analysis, worker exposure rates tend to fit a log-normal distribution better than they do a normal distribution. In general, log-normal distributions are typical of values based on multiplicative rather than additive models (e.g., Barnett et al. 2008; Limpert 2001; Mitzenmacher 2004; Ott 1995, p. 251ff). As indicated in Equation 1 of the current analysis, estimates of absorbed dose are based on a multiplicative model.

Lavy et al. (1987) provide the most complete and extensive data for testing the assumption of a log-normal distribution for worker exposure rates (mg/kg bw per day per lb applied). As discussed below, this study involved groups of 20 workers applying mixtures of either 2,4-D and dichlorprop (both as BEE esters) or 2,4-D and picloram (both as TIPA salts) by four directed application methods—i.e., backpack foliar, hack-and-squirt, injection bar, and hypohatchet. In addition, each group of workers was assayed in two applications, one using *normal* work practices (referred to asT1 in the Lavy study) and the other using special precautions to reduce exposure (referred to as T2 in the Lavy study). The special precautions involved the use of neoprene gloves for mixing and new leather gloves for application, improved personal hygiene, and exposure avoidance practices such as not …*walking through sprayed areas when possible* … for backpack applications. As illustrated in Figure 3 and summarized in Table 8, the special precautions did not result in marked differences between T1 and T2 backpack applications of 2,4-D and dichlorprop. As detailed in Worksheet **Lavy et al. 1987-9** of Attachment 1, analysis of variance of the worker exposure rates noted no significant differences in exposure rates among 2,4-D and dichlorprop in T1 and T2 applications ($p \approx 0.617$). Consequently, the worker exposure rates from Lavy et al. (1987) are combined and the distribution of these data is assessed in Statgraphics (Manugistics 1997). As illustrated in Figure 4, these data provide an excellent fit ($p \approx 0.75$) to the log-normal distribution.

Similar analyses on the distribution of worker exposure rates have been conducted in recent Forest Service risk assessment on triclopyr (SERA 2011d) using the studies by Middendorf (1992a,b). In all cases, the distribution of exposures are well-fit by the log-normal distribution.

While Attachment 1 to this report provides both arithmetic and geometric (i.e., log-normal) means and confidence and prediction intervals, only the log-normal values are considered further in the current analysis.

3.2.2. Backpack Foliar Applications

3.2.2.1. Atypical Applications

As illustrated in Figure 3, the studies on directed foliar applications are subdivided into two categories: atypical backpack applications and typical backpack applications. The study by Lavy et al. (1987) was sponsored by the Forest Service and, at least at the time that this study was conducted, the applications may have constituted normal Forest Service practice. This study is viewed as atypical of current standards, however, because Lavy et al. (1987) note that backpack workers would walk … *through herbicide-soaked vegetation 2 to 7 m high* (Lavy et al. 1987, p. 219). In addition, these investigators note that …*the clothing of the backpack crew members was commonly soaked with dew, perspiration and/or spray by the end of the day* (Lavy et al. 1987, p. 220). This type of application is not the current practice by the Forest Service, which does not permit backpack applications in vegetation higher than chest height.

Consistent with the assessment that this study is atypical by current standards, the mean worker exposure rates from Lavy et al. (1987) are notably higher than those from more recent studies sponsored by the Forest Service—i.e., most groups from Middendorf (1992b), Spencer (2000), and Zhang et al. (2011).

Another aspect of the Lavy et al. (1987) study which supports the notion of extreme exposures involves the use of gloves. In this study, leather gloves were used during applications and new leather gloves were supplied to each worker in the T2 (extra precautions) applications. Intuitively, leather gloves may be considered less effective in reducing pesticide exposure than more chemically resist nitrile or latex gloves. As discussed in Section 3.2.2.2, however, the backpack study by Middendorf (1992b) reports lower levels of exposures in backpack workers using leather gloves than in workers using either nitrile or latex gloves.

The other backpack application that is considered extreme in Figure 3 is Site 3 from the study by Middendorf (1992b). As discussed by Middendorf (1992b), Site 3 involved medium to tall (up to 12 feet) vegetation. The other sites included in the Middendorf (1992b) study involved vegetation of low to medium height (i.e., 2 to 8 feet). In addition, workers at Site 3 were noted to have followed poor personal hygiene practices, including not wearing gloves during application and, in at least one instance, handling concentrated formulations during mixing without wearing gloves. As detailed in Worksheet **Middendorf 1992b-1** (Attachment 1), analysis of variance indicates significant differences (p=0.048) among groups for Sites 1 through 4 but no significant differences (p=0.40) among groups when workers from Site 3 are omitted. Thus, based on the site descriptions, commentary on worker practices, as well as the analyses of variance, the data from Site 3 does not appear to be atypical of current Forest Service practice.

As discussed below, the study by Zhang et al. (2011) is not regarded as an example of extreme exposure. As with the Middendorf (1992b) and Lavy et al. (1987) studies, the study by Zhang et al. (2011) was sponsored by the Forest Service to obtain estimates of worker exposures under current practice, and a preliminary report of this study to the Forest Service (Krieger et al. 2005) was reviewed as part of the current analysis. As noted by Zhang et al. (2011, p. 290), the … *rugged terrain was uneven and slopes ranged from 10% to 50%*. As noted in Krieger et al. (2005, p. 7), the workers in this study were possibly contaminated at atypically high rates by using their feet and legs to beat a path through sprayed vegetation. This is not acceptable Forest Service practice. In contrast, Forest Service crews in the study by Middendorf (1992b) were required to walk only through untreated vegetation at all times —i.e., spraying to the left or right or spraying behind themselves. Avoiding contact with treated vegetation is a more common practice encouraged by the Forest Service. While some aspects of worker behavior as well as the inclusion of terrain with steep slopes (i.e., 50%) are not common in Forest Service applications, the worker exposure rates from Zhang et al. (2011) are quite similar to those from Spencer et al. (2000), another study sponsored by the Forest Service. As discussed further in Section 3.2.2.2.2, the backpack application study by Spencer et al. (2000) does appear to reflect current Forest Service practice.

3.2.2.2. Typical or Representative Applications

Backpack foliar applications which are considered representative of current Forest Service practice include Lavy et al. (1992), Middendorf (1992b), Spencer (2000) and Zhang et al. (2011). All of these studies were sponsored by and/or conducted in cooperation with the Forest Service. Because each of these studies is viewed as representative of current Forest Service practice in pesticide applications and because backpack applications are associated with the highest worker exposure rates, each of these studies is discussed in some detail below. The quantitative use of these studies in the derivation of worker exposure rates for backpack directed foliar applications is discussed further in Section 4.2.1.

3.2.2.2.1. Zhang et al. 2011

The recent publication by Zhang et al. (2011) is based on the report by Krieger et al. (2005) of a worker exposure study funded by the Forest Service. Zhang et al. (2011) monitored the exposure of individuals using backpack sprayers to apply a commercial formulation of triclopyr BEE and 2,4-D isooctyl ester (Garlon 4 and 2,4-D LV6) for purposes of conifer release and regeneration in Klamath National Forest in Northern California. The mixture is specified as a 1.6:1 molar ratio (Zhang et al., 2011). Based on the molecular weights of 2,4-D and triclopyr (Table 6), this corresponds to a mass ratio (w/w) of about 1.4:1::2,4-D:triclopyr [(1.6 x 221.0) ÷ (1 x 256.47) ≈ 1.37872].

At the end of the 6-day application period, workers had treated 55 acres of forest with 24 gallons each of the above triclopyr and 2,4-D formulations. Each worker applied 2 lb a.e. of triclopyr and 2.75 lb a.e. 2,4-D per day. Zhang et al. (2011) derive estimates of worker exposure rates based on curve-fitting of average urinary excretion data over the 6-day application period—i.e., 0.0147 mg/kg bw/lb applied for triclopyr BEE and 0.0062 mg/kg bw/lb applied for 2,4-D isooctyl ester. No data on individual worker exposures are provided in the report by Krieger et al. (2005) or the publication by Zhang et al. (2011).

For the current analysis, Dr. Robert Krieger (Personal Chemical Exposure Program, University of California, Riverside, California) and Dr. Xiaofei Zhang (Worker Health & Safety Branch, California Department. of Pesticide Regulation) kindly provide the individual data which are summarized in Worksheet **Zhang et al. 2011-1** of Attachment 1. Rather than adopting the curve fitting approach used by Zhang et al. (2011), the exposure rates for individual workers are calculated from the urinary excretion in the last three days of the study. As noted by Zhang et al. (2011, p. 288), the urinary data from the last 3 days of the study should reasonably approximate a steady-state dose because both of these compounds are rapidly excreted in the urine – i.e., half-lives about 17.7 hours for 2,4-D and 16.8 hours for triclopyr. As summarized in Table 8, the resulting central estimate of the worker exposure rates are 0.0113 mg/kg bw/day for triclopyr and 0.00493 mg/kg bw/day for 2,4-D. The details of these analyses are given in Worksheet **Zhang et al. 2011-2** (triclopyr) and Worksheet **Zhang et al. 2011-3** (2,4-D). The estimates of exposure rates based on the 3-day data on urinary excretion are reasonably consistent with the mean values estimated by Zhang et al. (2011) using curve-fitting.

As discussed in the previous section, this study did involve some areas with very steep slopes (up to 50%) and atypical worker exposure practices. Nonetheless, the mean worker exposure rate of 0.0113 mg/kg bw/lb applied for triclopyr BEE from the study by Zhang et al. (2011) is consistent with the mean worker exposure rate of 0.0149 mg/kg bw/lb applied for triclopyr BEE from the backpack study by Spencer et al. (2000) as detailed in the following section.

3.2.2.2.2. Spencer et al. 2000

Spencer et al. (2000) provide data on the exposure rates for individual workers involved in backpack applications of triclopyr BEE. As with the study by Zhang et al. (2011), the study by Spencer et al. (2000) was sponsored by the Forest Service, and Forest Service personnel were on-site while the study was conducted at the Eldorado National Forest (California). The study was specifically designed to assess worker exposure rates during backpack directed foliar applications of triclopyr BEE. The target vegetation was approximately 2 to 3.5 feet in height, the density of the vegetation was characterized as low to moderate, and the terrain was characterized as moderate to steeply sloping (Spencer et al., 2000 p. 11). Workers wore hard hats, leather boots with laces, one-layer shirts, socks, jeans, clean coveralls, and either commercially laundered cotton/polyester or disposable TYVEK suits. Workers also wore latex or knit gloves on either the right hand, which held the spray wand, or on both hands.

A limitation in the Spencer et al. (2000) study involves the urine sampling. While Spencer et al. (2000) attempted to obtain complete urine collections over each 24-hour period, the actual urine collections were highly variable (Spencer et al. 2000, Appendix 1, Table 4), ranging from 30 to 1400 mL. To adjust for incomplete urine collection, Spencer et al. (2000) adjusted all urine volumes to 1400 mL. In other words, urinary excretion was calculated as the pooled concentration of triclopyr in the urine multiplied by 1400 mL and divided by the volume of urine collected from the worker. While the 1400 mL urine volume is a reasonable estimate (ICRP 1975), this approach to correcting for incomplete urine collection would tend to overestimate urinary excretion if the sample were collected during a period of high excretion, such as during or shortly after work when the concentration of the herbicide in the urine would high, but could underestimate exposure if the urine was collected during a period when the concentration of the herbicide in the urine would be lower.

Another very minor limitation with this study involves an apparent reporting error. In Table IX of Spencer et al. (2000, p. 26), the amounts of triclopyr in the urine of individual workers are reported both as mg and mg/kg bw. For Day 1 of the study, the conversion from mg to mg/kg bw are correct based on the body weights for workers given in Table IV of Spencer et al. (2000, p. 17). For the results from Day 2 of the study, however, the conversion from mg to mg/kg bw does not appear to be correct. Nonetheless, the mean value and standard deviation for Day 2 (i.e., a mean of 0.067 mg/kg bw with a standard deviation of 0.044 mg/kg bw) are correct. The check of these values is given in Worksheet **Spencer et al. 2000-2** of Attachment 1. For the current analysis, the doses in units of mg/kg bw are based on the mg values for triclopyr in the urine (from Table IX) and the worker body weights given in Table IV of the Spencer report. In the preparation of the current report, Dr. Janet Spencer, the primary author of the Spencer et al. (2000) study was contacted and confirmed that the mg/kg bw values given in Attachment 1, Worksheet **Spencer et al. 2000-2**, are correct.

As noted above and illustrated in Figure 3, the mean worker exposure rates from Spencer et al. (2000) [0.0149 mg/kg bw/lb applied] are strikingly similar to the mean worker exposure rates for triclopyr BEE from the study by Zhang et al. (2011) [0.0147 mg/kg bw/lb applied]. As also illustrated in Figure 3, the worker exposure rates from Spencer et al. (2000) are only modestly higher than those reported for triclopyr BEE in the directed foliar backpack application study by Middendorf (1992b).

3.2.2.2.3. Middendorf 1992b

Middendorf (1992b) was conducted with groups of workers involved in directed foliar applications of triclopyr BEE as Garlon 4. This study is summarized in the open literature by Middendorf et al. (1992) and Tharr (1994). As detailed in Appendix 2 and Attachment 1 (Worksheets **Middendorf 1992b-1** through **Middendorf 1992b-5**), this study involves 22 workers applying Garlon 4 at four different sites with each worker handling between 1.2 and 2.2 lbs a.i. Middendorf (1992b) does not provide the body weights for the individual workers. As discussed in Section 3.2.2, Middendorf (1992a) conducted a similar study involving basal bark applications of triclopyr BEE and reported body weight data for workers—i.e., 83.1 kg. For the current analysis, 83.1 kg body weight is used for the analysis of Middendorf (1992b) rather than a default body weight of 70 kg (ICRP 1975).

The study by Middendorf (1992b) is considered particularly relevant to the current analysis because the worker practices used in this study are representative of Forest Service programs. As noted in the study,

> *The Forest Service supplied and required all volunteers to wear tightly woven, pre-washed, long-sleeved shirts and long pants. All volunteers also wore leather boots and a hard hat. Gloves were available for use at each site during applications; their use was required when handling the concentrate. The clothing met the Forest Service Guidelines.*
>
> Middendorf 1992b, p. 11

Nonetheless, not all workers used the same protective equipment. For example, polyvinyl chloride, leather, and latex gloves were used by different workers in different activities. In addition Three workers at Site 3, designated as workers NM, RH, and JJ, did not wear gloves during applications, and these three workers tended to have relatively high rates of exposure ranging from about 0.01to 0.066 mg/kg bw per lb handled. In addition, the other two workers at Site 3 also had relatively high exposure rates even though these workers wore gloves. The average exposure rate for the workers at Site 3 is about a factor of 4 higher than the average exposure rate at the other sites [$0.0236 \div 0.0058$ mg/kg bw per lb applied $\cong 4.06$]. As discussed by Middendorf (1992b), this higher exposure rate appears to be associated with the unusually high brush height at the site:

> *The brush typically ranged from four to 12 feet high on each of the stands and was very dense. The stands were described by Forest Service representatives as borderline acceptable for treatment. Subsequent discussions with Regional Forest Service Representatives suggest that the sites may not have been appropriate for directed foliar application based on the height of the brush.*
>
> Middendorf 1992b, p. 7

Consequently, as discussed in Section 4.2.1, the data from Site 3 are not viewed as representative of application conditions in Forest Service programs and are censored from the derivation of worker exposure rates.

Another interesting aspect of the results from the study by Middendorf (1992b) involves the efficacy of gloves in reducing exposures. As noted in Section 3.2.2.1, leather gloves did not appear to be effective in reducing exposures in T2 phase of the backpack study by Lavy et al. (1987). Intuitively, this might suggest that leather gloves are less effective than chemically resistant gloves. The results from Middendorf (1992b), however, do not support this supposition. As detailed in Worksheet **Middendorf 1992b-6** of Attachment 1, analysis of variance indicates no significant difference (p=0.404) among workers treating vegetation of moderate height using leather gloves (Site 1), latex gloves (Site 2), or nitrile gloves (Site 4). While the differences are not statistically significant, exposure rates in workers wearing leather gloves were the lowest; whereas, exposure rates in workers wearing latex or nitrile gloves were higher by factors of about 2.6 and 3.1, respectively.

Because of the small sample sizes (groups of 5 to 6 workers) and the lack of statistical significance among the groups, the differences should not be overly-interpreted. Nonetheless, it is notable that the type of exposure could impact the efficacy of gloves. Exposures to materials contaminating the outer surface of a glove would be expected to be less with chemically resistant gloves, relative to leather gloves. The opposite, however, would be expected if the interior of the gloves were contaminated—i.e., pesticides entering the inner surface of the glove in the area above the wrist. In this instance, a leather glove would absorb some of the chemical and reduce exposure. A latex or nitrile glove, however, would act a poultice and would lead to higher levels of exposure than with a leather glove or no glove at all. This discussion does not suggest that these types of events occurred in the Middendorf (1992b) study. Nonetheless, the Middendorf (1992b) study does indicate that the use of nitrile or latex gloves will not necessarily reduce exposure relative to the use of leather gloves.

3.2.2.2.4. Middendorf 1993

The study by Middendorf (1993) also involves backpack (directed foliar) applications of Roundup, a glyphosate/surfactant herbicide. This study was sponsored by Monsanto with support from the Forest Service. The study involved backpack directed foliar applications at three forest sites, one in Georgia and the other two in South Carolina. As summarized in Appendix 2, one of the sites contained low density vegetation at a height of 2 to 3 feet. The other two sites contained vegetation (density not specified) at a height of about 4 to 6 feet. Workers wore standard clothing required in Forest Service applications, including long-sleeved shirts, long pants, leather boots, and hard hats. Gloves (leather, latex, or cotton) were also worn by workers mixing or applying the herbicide.

Middendorf (1993) provides data (urinary excretion, pounds of glyphosate applied) on 14 workers at three different application sites as well as verbal descriptions of minor accidental events that occurred during application. As detailed in Worksheet **Middendorf 1993** of Attachment 1, exposure rates for most of the workers were in the range of 0.0002 to 0.0005 mg/kg bw per lb handled. One worker (designated as Worker Q in the study) had a substantially higher rate of exposure (i.e., about 0.0015 mg/kg bw per lb handled). As detailed in Worksheet **Middendorf 1993**, the exposure rate for Worker Q is higher than that for all other workers by factors of about 3 to 10. Middendorf (1993) is careful to note mishaps that occurred during applications in various workers as well as workers who did not wear gloves. Worker Q, however, wore cotton gloves during application, did not mix concentrated formulations, and no accidental events are noted for this worker. The only exceptional feature of Worker Q is that the worker was a female. As discussed further in Section 3.2.4, the exposure rate for Worker Q is a statistical far outlier.

Based on analysis of variance (Worksheet **Middendorf 1993**), differences in worker exposure are not significant ($p \approx 0.21$) among the sites. Based on all workers combined, the average exposure rate is about 0.00030 mg/kg bw per lb applied with a 95% prediction interval of **0.000059** to **0.0015** mg/kg bw per lb applied. As illustrated in Figure 3, these exposure rates for glyphosate are substantially below the exposure rates for backpack directed foliar applications of triclopyr BEE (Lavy et al. 1987; Middendorf 1992b; Spencer et al. 2000; Zhang et al. 2011).

3.2.2.2.4. Lavy et al. 1992

As with the Middendorf (1993) study, the Lavy et al. (1992) study involves applications of Roundup, a glyphosate/surfactant herbicide. This study was sponsored by the Forest Service and conducted at commercial seedling nurseries. The nursery workers applied Roundup to small weeds in a nursery bed by placing a 290 mL (2.5x3.5 cm) cylindrical metal shield surrounding the spray nozzle over the weed—to protect adjacent conifer seedlings—and then spraying the weeds with Roundup. While this study is included with directed foliar applications because the weeds around the seedlings were directly sprayed, the careful nature of the applications made in this study clearly differs from those made in the above studies on triclopyr and glyphosate.

Biological monitoring consisted of 5-day complete urine collections. In a total of 355 urine samples, no glyphosate was detected (limit of detection = 0.01 µg/mL). Assuming that the concentration of glyphosate in the urine was just below the limit of detection and assuming a urinary output of 1400 mL (i.e., as in the study by Spencer et al. 2000), the total absorbed dose would be 14 µg or 0.014 mg [0.01 µg/mL x 1400 mL]. The most exposed individual in this study weighed 63.5 kg and handled, on average, 0.54 kg [1.18 lbs] of glyphosate per day. Thus, the maximum absorbed dose of 0.014 mg corresponds to 0.00022 mg/kg bw [0.014 mg ÷ 63.5 kg] and 0.00019 mg/kg bw per lb applied [0.00022 mg/kg ÷ 1.18 lbs].

The rate of 0.00019 mg/kg bw per lb applied is modestly below the lower range of the value of 0.0003 mg/kg bw per lb applied used for directed foliar applications (Table 2 of the current report). The results from Lavy et al. (1992) are similar to the results from Middendorf (1993) in indicating that workers involved in glyphosate applications were subject to lower rates of exposure, compared with the workers applying triclopyr BEE in the studies discussed above (Spencer et al. 2000; Middendorf 1992b; Zhang et al. 2011).

Unlike the studies on triclopyr BEE, however, the study by Lavy et al. (1992) does not provide individual exposure rates and can be used only to estimate a plausible upper bound exposure. Consequently, this study is not included in Attachment 1.

3.2.3. Other Directed Applications

While backpack directed foliar applications are a common and important application method in Forest Service programs, other directed application methods are also used. Relatively detailed worker exposure studies are available for two of these other directed application methods: hack-and-squirt (Lavy et al. 1987) and basal bark (Middendorf 1992a).

3.2.3.1. Hack-and-squirt Applications

Hack-and-squirt applications are a form of cut surface treatment in which the bark of a standing tree is cut with a hatchet and the herbicide is applied with a squirt bottle. This treatment method is used to eliminate large trees during site preparation, conifer release operations, or rights-of-way maintenance. The hack-and-squirt application in the study by Lavy et al. (1987) is similar in design to the backpack study discussed in Section 3.2.1. Twenty workers were assayed in two separate applications, one involving normal work practice (referred to a T1) and the other involving special precautions to reduce exposure (referred to as T2). One difference, however, is that the hack-and-squirt applications involved a mixture of 2,4-D and picloram, both as the TIPA salts, rather than 2,4-D and dichlorprop esters.

As discussed in Section 3.2.2.1, the backpack applications assayed by Lavy et al. (1987) are regarded as atypical because of the height of the treated vegetation. There is no clear basis, however, for asserting that the hack-and-squirt application in Lavy et al. (1987) is atypical. Lavy et al. (1987) report several instances of equipment failure, mostly involving leaks in the spray containers. In the absence of more recent studies on hack-and-squirt applications, there is no reason to suggest that these types of events may not occur in any hack-and-squirt application.

While the hack-and-squirt applications involved a mixture of 2,4-D and picloram, Lavy et al. (1987) provide information on exposures to individual workers only for 2,4-D, because picloram was not commonly detected in the urine of the workers. Additional details on picloram exposures are discussed in Section 3.2.3.3. Unlike the backpack applications in the Lavy et al. (1987) study (Section 3.2.2.1), a significant difference (p=0.034) is apparent between the T1 (normal work practice) and T2 (extra precautions) applications with the worker exposure rates in the T2 application being lower than those in the T1 application by a factor of about 2.8 (Worksheet **`Lavy et al. 1987-7`**). Consistent with the above assessment that the hack-and-squirt applications may be viewed as typical, the effectiveness of precautionary procedures in the hack-and-squirt study suggests that the nature of the applications did not overwhelm efforts to reduce exposures in the T2 application.

One notable aspect of the Lavy et al. (1987) hack-and-squirt applications involves the width of the prediction intervals. As illustrated in Figure 3 and summarized in Table 8, the mean exposure estimate is 0.00367 mg/kg bw per lb handled, with a 95% prediction interval for the T2 application that ranges from about 0.0000288 to 0.466 mg/kg bw per lb handled. This range spans a factor of about 16,000 [0.466 ÷ 0.0000288 ≈ 16,181]. While many worker exposure rates are highly variable, this level of variability is exceptionally large.

To some extent, however, the variability in this prediction interval is partially due to the approach to missing values. As discussed in Section 2.3, the current analysis handles missing values by replacing the missing values with one-half of the minimum detected value. A more statistically correct approach is the use of the trimmed mean, in which non-detects are omitted and an equal number of the highest values are also omitted (Gilbert 1987). While the trimmed mean provides a less biased estimate of the mean, the current analysis is focused on developing worker exposure rates that will be protective. Consequently, it does not seem justified to censor data from heavily exposed workers in the absence of an indication that the data for the workers are based on atypical practices (e.g., the backpack workers in Lavy et al. 1987). For illustration, applying the trimmed mean to the T2 hack-and-squirt data (see Worksheet **`Lavy et al. 1987-6b`**) results in a mean estimate of 0.00466 mg/kg bw per lb handled with a 95% prediction interval of 0.0000996 to 0.219 mg/kg bw per lb handled. Note that this range spans a factor of about 2200 [0.219 ÷ 0.0000996 ≈ 2198.80].

In terms of statistical properties, the estimate of variance based on the use of ½ of the minimum detected value is 0.962 (Worksheet **`Lavy et al. 1987-6a`**) and the corresponding estimate of variance based on the trimmed mean is about 0.558 (Worksheet **`Lavy et al. 1987-6b`**). Thus, the approach to missing values used in the current analysis accounts increases the variance by about a factor of about 2 [0.962 ÷ 0.558 ≈ 1.72]. This increase in the estimate of variance is associated with an increase in the upper bound estimate of the prediction interval by a factor of about 2 [0.466 ÷ 0.219 ≈ 2.128]. Thus, while the approach to missing values used in the current analysis may be viewed as somewhat more conservative than the use of the trimmed mean, the differences in the upper bound estimates of the prediction interval are not substantial.

3.2.3.2. Basal Bark

Middendorf (1992a) assayed exposure in groups of backpack workers involved in basal stem applications of triclopyr BEE (as Garlon 4). Total absorption was determined by the analysis of triclopyr in the urine over a 5-day post-application collection period. A summary of relevant data from Middendorf (1992a) is given in Attachment 1, Worksheets **Middendorf 1992a-1** through **Middendorf 1992a-5**.

The Middendorf (1992a) study involved 16 workers (designated as Worker A to Worker R) who applied 4 to 5.6 kg of triclopyr at three different sites. As with most studies of worker exposure which provide individual data, exposure rates among workers varied substantially, with the lowest exposure rate of 0.00015 mg/kg bw per lb applied for Worker A at Site 1 and the highest exposure rate of 0.01428 mg/kg bw per lb applied for Worker H at Site 2. This range spans a factor of about 100 [0.01428 ÷ 0.00015 ≈ 96].

As discussed by Middendorf (1992a), a major source of variation involves the use of gloves (nitrile, latex or leather). Six of the 16 workers in the study by Middendorf (1992a) did not wear gloves during applications. As detailed in Attachment 1, Worksheet **Middendorf 1992a-4**, differences between workers wearing and not wearing gloves are significant based on a one-tailed t-test (p=0.042); moreover, the mean exposures for workers wearing gloves are a factor of about 3.4 lower than those of workers who did not wear gloves. This difference in exposure rates is similar to the factor of 2.8 for T1 (normal) versus T2 (special protection) exposures in the hack-and-squirt workers in the study by Lavy et al. (1987), as discussed in Section 3.2.3.1. In terms of the current analysis, the exposure rates for workers wearing gloves are most relevant because gloves are required in all Forest Service applications of triclopyr.

As discussed further in Section 4.2.2., this backpack basal bark study by Middendorf (1992a) was conducted at about the same time as the backpack directed foliar study by Middendorf (1992b), and these two studies by the same investigator offer a direct comparison in exposure rates for directed foliar and basal stem applications.

3.2.3.3. Applications of 2,4-D/Picloram Mixtures

In addition to backpack directed foliar (Section 3.2.2.1) and hack-and-squirt applications (Section 3.2.3.1), Lavy et al. (1987) also provide data on worker exposures associated with hypohatchet and injection bar applications. As with the hack-and-squirt applications, two sets of applications were made: normal work practice (T1) and special precautions to reduce exposures (T2).

Also as with the hack-and-squirt applications, the hypohatchet and injection bar applications involved mixtures of 2,4-D and picloram (both as the TIPA salts). The formulation used in this study is identified as *…Tordon 101-R (80% 2,4-D, 20% picloram)* (Lavy et al. 1987, p. 210). Based on more precise information given in the footnote to Table 1 in Lavy et al. (1987, p. 213), this formulation contained 2,4-D at 1 lb a.e./gallon and picloram at 0.25 lb a.e./gallon.

As discussed in Section 3.2.3.1, Lavy et al. (1987) provide individual exposure data in hack-and-squirt applications only for 2,4-D, because picloram was not detected in most of the urine samples from the workers:

> *Since for picloram only 70 of 720 samples contained more chemical than the 0.010 mg/L detection level, only summaries of the picloram excretion data are presented (Table 7, Figs. 1 and 2).*
>
> Lavy et al. 1987, p. 213

Table 7 in the Lavy et al. (1987, p. 219) study does not provide a summary of absorbed doses or dose rates. Instead, this table provides *Margins of Safety* (MOS), defined as the ratio of the exposure to the No Observed Effect Levels (NOELs), which are define in the Lavy publication as 24 mg/kg bw for 2,4-D and 50 mg/kg bw for picloram. In addition to the central estimate of the MOS, Table 7 in the Lavy et al. (1987, p. 219) study also provides 95% prediction intervals on the MOS.

Given the MOS and the NOEL, the associated doses can be calculated:

$$MOS = \frac{NOEL}{Dose},$$
$$Dose = \frac{NOEL}{MOS} \qquad \text{(Eq. 14)}$$

Lavy et al. (1987) also provide the average amount of 2,4-D and picloram applied by each group of workers. Thus, worker exposure rates can be calculated approximately by the dividing the doses by the average amount handled by each group of workers. These calculations are detailed in Worksheet **Lavy et al. 1987-8** and are illustrated in Figure 5.

As illustrated in Figure 5, the highest exposure rates for 2,4-D are associated with hypohatchet applications, followed by hack-and-squirt and then injection bar applications. For each application method, the T1 rates (normal work practice) for 2,4-D are higher than the T2 rates (extra precautions). As discussed in Section 3.2.3.1, this pattern suggests that the exposures associated with these application methods should not be viewed as extreme. Lavy et al. (1987) report several instances in which work exposures may have been augmented by equipment failure or other mishaps, which can occur during even well-conducted pesticide applications.

The pattern of exposure rates for picloram, however, does not follow the same pattern as with 2,4-D. The picloram exposures during hypohatchet and hack-and-squirt applications are comparable, with the T1 hack-and-squirt applications being somewhat higher than those for hypohatchet applications. The picloram exposures during injection bar applications are only modestly lower than those for hypohatchet applications; whereas, the exposures to 2,4-D are about an order of magnitude greater for hypohatchet applications, relative to injection bar applications.

The lack of symmetry between 2,4-D and picloram exposures is unexpected. Since 2,4-D and picloram were applied as a mixture, the relative exposure of each worker to 2,4-D and picloram would be proportional to the ratio of 2,4-D to picloram in mixture—i.e., 2,4-D:picloram::4:1 as described in the Lavy et al. (1987) publication. This does not suggest that absorbed doses would be in a 4:1 ratio. As discussed further in Section 4.1, differences in dermal absorption rates could lead to other ratios of absorbed doses. Nonetheless, in terms of relative exposures among the application methods, there is no clear explanation for the greater exposures to 2,4-D, relative to picloram in the hypohatchet application compared with the injection bar application.

One potential explanation, however, may be related to how non-detections were handled. Lavy et al. (1987) do not specifically address how missing values (i.e., non-detections) were handled in the calculation of means and confidence intervals. This factor is particularly important for the reporting of picloram. As noted above, picloram was detected in less than10% of the samples [70/720 ≈ 9.72%]. Consequently, trimmed means could not be used —i.e., the number of non-detections is so great that all of the detectable levels would need to be censored in developing trimmed means. If one-half of the minimum detected level were used, this value would be employed for more than 90% of the sample points. It does not seem likely that Lavy et al. (1987) would have used this approach but failed to note the procedure. Albeit speculative, it seems most likely that Lavy et al. (1987) simply reported the means and confidence intervals for the levels of picloram that were actually detected. As discussed by Gilbert (1987), this approach would lead to overestimates of the true mean exposures to picloram.

3.2.3.4. Other Studies

3.2.3.4.1. Brush Saw Application

The study by Jauhiainen et al. (1991) was conducted in Finland by the Kuopio Regional Institute of Occupational Health. In this study, workers applied Roundup (a formulation of glyphosate with a surfactant) by *brush saw spray*. The precise nature of the equipment is not described clearly in the publication, but the work is characterized as *physically heavy.* Brush saws are similar in design to common weed-whackers but have a rotating saw blade. Speculatively, the application method was probably a cut-surface treatment in which the brush was cut and glyphosate was sprayed onto the cut surfaces of the vegetation:

> *Although the workers' exposure to glyphosate was low with the spraying method used, some exposure may still occur, for example during pesticide dilution and administration and during repairing and servicing of the sprayer in the field.*
>
> Jauhiainen et al. (1991, p. 64)

The study does not describe the nature and height of the vegetation. Depending on the design of the brush saw, it might be used to cut moderate (1 to 3 feet) to high vegetation.

Biological monitoring was conducted on five workers applying Roundup. Each worker handled an average of 9.8 L of an 8% solution of Roundup (360 g a.i./L or 270 g a.e/L). Thus, the amount of glyphosate acid handled each day was approximately 0.211 kg [9.8 L × 0.08 × 0.270 kg/L] (Jauhiainen et al. 1991, p. 62, column one, top of page) or about 0.5 lbs. Urine samples (not total daily urine) were collected at the end of each work day for 1 week during the application period, and one sample was taken 3 weeks after the applications.

The urine samples were assayed for glyphosate using gas chromatography/electron capture with a limit of detection of 0.1 ng/µL or 0.1 mg/mL. Glyphosate was not detected in any of the urine samples using this method. One urine sample was assayed for glyphosate by gas chromatography/mass spectroscopy (GC/MS), and glyphosate was detected at a level of 0.085 ng/µL, equivalent to 0.085 µg/mL. Assuming that this urine sample was representative and using the default body weight of 70 kg and an approximate urine volume of 1400 mL/day (ICRP 1975, p. 354), the absorbed dose would be 119 µg [0.085 µg/mL × 1,400 mL] or 0.0017 mg/kg bw [0.119 mg ÷ 70 kg]. The corresponding exposure rate would be 0.0034 mg/kg bw per lb a.e. applied [0.0017 mg/kg bw ÷ 0.5 lb a.e.]. This value is similar to the central estimate of 0.003 mg/kg bw per lb applied generally used for directed foliar applications (Table 2 of the current report).

As with the study by Lavy et al. (1992), the study by Jauhiainen et al. (1991) does not provide individual exposure rates; accordingly, this study is not included in Attachment 1.

3.2.3.4.2. Greenhouse Application

The last study summarized in Figure 3 under "Other Directed Application Methods" is the greenhouse study by Cruz Marquez et al. (2001). While greenhouse applications are not a major focus in the current analysis, the Forest Service and their cooperators maintain greenhouses, and pesticide applications within greenhouses may, in some cases, be relevant to Forest Service risk assessments, environmental assessments, or environmental impact statements.

The Cruz Marquez et al. (2001) greenhouse study investigates worker exposure to semi-stationary high volume (4 L/min) spray applications of malathion to green beans, tomatoes, and cucumbers. Each of three workers applied 375 L of a solution containing 0.6 L of a 90% malathion formulation in 400 L of water. Thus, each worker applied about 0.506 kg of malathion [0.6 L formulation x 0.9 kg a.i./L formulation x 375 L/400 L = 0.506 kg a.i.], equivalent to about 1.12 lb a.i. [2.2046 lb/kg]. The absorbed dose of malathion in each worker was estimated from the total excretion of malathion monocarboxylic acid (MMA), which ranged from 133.75 to 671.24 µg per worker. The body weights of the workers are not specified in the study. Assuming a body weight of 70 kg, the absorbed doses ranged from about 0.0019 to 0.0096 mg MMA/kg bw. Based on pharmacokinetic study by Krieger and Dinoff (2000, Table 1, p. 547), the proportion of MMA excreted in urine after oral exposure to malathion is about 0.36.

As detailed in Attachment 1 (Worksheet **Cruz Marquez et al. 2001**), exposure rates can be estimated for two groups of workers: workers using PPE, specified as latex gloves, disposable coveralls (65% cotton, 35% polyester) and protective masks and one worker not using PPE The one worker who did not use PPE had an estimated exposure rate of about 0.0238 mg/kg bw per lb applied. Workers in the Cruz Marquez et al. (2001) study who used PPE had an exposure rate of 0.00474 mg/kg bw per lb applied, which is about 5 times lower than that of the worker who did not use PPE.

As summarized in Table 8, the rate of 0.00474 mg/kg bw per lb applied for workers using PPE is about a factor of two below the composite rate for backpack workers involved in typical applications of triclopyr – i.e., 0.00994 mg/kg bw per lb applied. Similarly, the rate of 0.0238 mg/kg bw per lb applied for workers not using PPE in the greenhouse study by Cruz Marquez et al. (2001) is virtually identical to the atypical backpack rate of 0.0236 mg/kg bw per lb handled for directed foliar backpack applications of triclopyr BEE in high brush from the study by Middendorf (1992b). The greenhouse study by Cruz Marquez et al. (2001) involved malathion. As summarized in Table 7, the first-order dermal absorption rate coefficient for malathion is 0.0036 $hour^{-1}$, which is comparable to the corresponding rate of 0.0021 $hour^{-1}$ for triclopyr BEE. While the study by Cruz Marquez et al. (2001) is not sufficient for the formal derivation of rates because individual data are not available, the similarities of the central estimates of the rates for malathion from Cruz Marquez et al. (2001) to rates for backpack applications for triclopyr BEE suggest that exposures to workers involved in greenhouse applications may be approximated using worker exposure rates for directed foliar backpack applications (Section 4.2.1.1).

3.2.4. Variability among Workers

As discussed previously, differences in exposure rates among workers can be highly variable. This section explicitly addresses the differences in variability, with a focus on outliers, among the worker exposure studies that provide information on groups of individual workers.

Figure 6 provides an overview of all of the directed application studies reporting individual exposure rates. Unlike Figure 3, which is based on means and prediction intervals for log transformed data, Figure 6 is given as a box-and-whisker plot showing outliers. As discussed in Section 2.3, outliers are defined as values that fall outside the first or third quartile ± 1.5 times the interquartile range and far outliers are defined as values that fall outside the first or third ± 3 times the interquartile range. As illustrated in Figure 6, the only outliers of practical concern with worker exposure rates are those beyond the third quartile.

Only four of the data sets in Figure 6 do not evidence outliers—i.e., the T1 (normal work practice) dichlorprop data from Lavy et al. (1987), the triclopyr BEE data for high bush applications from Middendorf (1992b), the triclopyr basal bark applications for workers not using gloves from Middendorf (1992a), and the triclopyr BEE data from Zhang et al. (2011). Three of the data sets contain one or more far outliers—i.e., the glyphosate applications from Middendorf (1993), the triclopyr low bush direct foliar applications from Middendorf (1992b), and the basal bark applications for all workers combined from Middendorf (1992a).

Statistical outliers, however, do not necessarily constitute data that should be excluded from analyses, and this is particularly true for the current assessment which is focused on evaluating and developing worker exposure rates for risk assessment. For example, take the four outliers in the study by Lavy et al. (1987) for backpack foliar applications of 2,4-D and dichlorprop. These four outliers are on the left side of Figure 6 under the label *Backpack Atypical*. Each of these points would be classified as a statistical outlier. These same four measurements constitute the right most data bars in the histogram and probability plot illustrated in Figure 4. Note that even though these data are outliers, they are consistent with the log-normal (left-skewed) distribution for all of the worker exposure rates. In other words, statistical outliers do not necessarily indicate a bimodal distribution.

Another interesting example of a statistical outlier which may be relevant to the assessment of worker exposure rates is Worker Q in the study by Middendorf (1993). The exposure rate for this worker is illustrated in Figure 6 as the top most circle (i.e., a far outlier) under the group labeled *Glyphosate, Middendorf*. As discussed in Section 3.2.2.2.4, the exposure rate for

Worker Q is 3 to 10 times that of the other workers but the reason for this difference cannot be identified. Worker Q wore gloves and no accidental events are noted by Middendorf (1993) for Worker Q. As also noted in Section 3.2.2.2.4, the one exceptional feature of Worker Q is that Worker Q is a female. The recent Forest Service risk assessment on glyphosate (SERA 2010a) does not contain any additional information suggesting that the kinetics of glyphosate is substantially different between males and females. Nonetheless, exposure data for worker Q in the Middendorf (1993) study might suggest that exposure rates for female workers are greater than exposure rates for male workers.

Worker Q from Middendorf (1993) is a case in which the worker may be considered an outlier potentially based on a biological trait—i.e., the worker was a woman. As summarized in Table 5 and discussed in Section 3.1, very few studies provide data on female workers. In the basal bark study by Middendorf (1992a), one worker (Worker O) is a female. This worker is one of the 10 other workers from this study who wore gloves. The exposure rate for this female worker was 0.00258 mg/kg bw per lb handled, which is a factor of about 1.4 higher than the mean exposure for male workers wearing gloves. The worker exposure rate for this female is below that for 2 of the 9 male workers in this group (Attachment 1, Worksheet **Middendorf 1992a-2**).

Given the limited information on worker exposure rates in females, the information on Worker Q from Middendorf (1993) and Worker O from Middendorf (1992a) does not justify developing different exposure rates for males and females. As discussed further in Section 4.2 (Proposed Modified Worker Rates), the approach used in the current analysis uses prediction intervals (a more protective approach) rather than confidence intervals (which are narrower than prediction intervals). With respect to Worker Q in the Middendorf (1993) study, the exposure rate for this worker is 0.0015 mg/kg bw per lb handled. As summarized in Table 8, the upper bound of the confidence interval for workers in the Middendorf (1993) study is 0.00045 mg/kg bw per lb handled. Note that this upper bound does not encompass Worker Q. As also summarized in Table 8, the upper bound of the prediction interval for workers in the Middendorf (1993) study is 0.00153 mg/kg bw per lb handled. This value does encompass the observation for Worker Q, albeit by only a slight margin [0.00153 ÷ 0.0015 ≈ 1.02].

Outliers may indicate untoward events, unidentified factors, or simply random variation. The position taken in this analysis, however, is that outliers should not be excluded from an analysis unless a compelling case can be made indicating that the events or factors causing the increase in exposure are not relevant to future exposure scenarios. Clearly, the case of Worker Q does not justify censoring this data point as an outlier, because female workers are involved in pesticide applications.

3.3. Ground Broadcast Applications

3.3.1. Overview of Studies and Pesticides

An overview of the studies from which worker exposure rates can be derived in terms of mg/kg bw per lb handled is given in Table 9 and an illustration of the data from these studies is given in Figure 7. As with the corresponding illustration of directed applications (Figure 3), most of the data in Figure 7 provide the geometric mean (large diamond) and 95% prediction intervals (thick vertical line running through the large diamond) based on data for individual workers. The only exceptions are the data for bromoxynil from the study by Cessna and Grover (2002). Cessna and

Grover (2002) do not provide data on individual workers; hence, the illustration of data from this study is based on the median values and ranges.

Of the studies summarized in Table 9, only the study by Nash et al. (1982) is used quantitatively in the 1998 analysis (SERA 1998). The study by Franklin et al. (1981) is cited in the 1998 analysis but was not considered quantitatively because of the application method—i.e., orchard airblast. In the current analysis, the study by Franklin et al. (1981) is considered quantitatively because a recent Forest Service risk assessment addresses airblast applications (SERA 2010b). The studies by Grover et al. (1986) and Dubelman and Cowell (1989) are not cited in the 1998 analysis, and the studies by Cessna and Grover (2002) and Lunchick et al. (2005) were published after the 1998 analysis. One additional study, Libich et al. (1984) is also considered. As discussed below, Libich et al. (1984) cannot be used to derive absolute exposure rates; however, the study involves applications of mixtures of 2,4-D and picloram and is useful for deriving relative exposure rates, which are discussed in Section 4.1.

As summarized in Table 9, the available studies cover five pesticides, including, 2,4-D, alachlor, azinphos-methyl, bromoxynil esters, and ethoprop. With the exception of 2,4-D, there is only one study per chemical.

3.3.1.1. Applications of 2,4-D

Grover et al. (1986) and Nash et al. (1982) involve ground broadcast applications of 2,4-D. Although these two studies provide differing levels of detail and focus on different aspects of exposure, the two studies provide remarkably consistent overall results.

Grover et al. (1986) studied a group of 12 farmers involved in mixing, loading, and applying 2,4-D (as the dimethylamine salt) to wheat. Each of the workers was involved in 1 to 7 applications over a period of several days. Grover et al. (1986) do not provide daily data but do provide information on the total amount of 2,4-D handled by each worker as well as the total urinary excretion of 2,4-D up to 7 days after the last application. Consequently, worker exposure rates may still be calculated by dividing the total urinary excretion by the total amount of 2,4-D handled by each worker. The workers did not use special PPE and wore only standard work clothing, consisting of cotton work pants, a short-sleeved, cotton T-shirt and a long-sleeved cotton overall. Notably, only one farmer wore gloves and the type of glove is not specified. The exposure rates (geometric mean and 95% prediction intervals) for these workers were about 0.00013 (0.0000094 to 0.0018) mg/kg bw per lb handled.

Nash et al. (1982) assayed the exposure of 15 workers involved in the ground application of 2,4-D (not otherwise specified). As in the study by Grover et al. (1986), the applications were made to wheat fields. The types of ground equipment used in the applications varied and are characterized only as… *4 Pull type*, *21 Self-propelled*, *10 Cab*, *and 16 No cab*. Also as in the study by Grover et al. (1986), no special PPE was used and no attempt was made to alter the work habits of the workers. Estimates of 2,4-D absorption were based on 6-day urine collections. As summarized in Table 9, Nash et al. (1982) provide separate exposure rates for applicators only (i.e., no mixing-loading), as well as mixer/loader/applicators. Based on the central estimates of the geometric means, the exposure rates for applicators only (≈0.00003 mg/kg bw per lb) were less than those for mixer/loader/applicators (≈0.00021 mg/kg bw per lb) by about a factor of 7. While this difference is substantial as well as intuitively reasonable, the differences are based on small sample sizes (i.e., 8 applicators and 7 mixer/loader/applicators), and the differences are not statistically significant using a two tailed t-test with either untransformed data (p=0.87) or log-transformed data (p=0.073) [see Attachment 1, Worksheet **Nash et al. 1982-5**].

Based on the pooled data from Nash et al. (1982) including both applicators and mixer/loader/applicators, the central estimate of the exposure rates from Nash et al. 1982 (i.e., 0.000074 mg/kg bw per lb) is similar to the central estimate of the exposure rate from Grover et al. (1986) (i.e., 0.00013 mg/kg bw per lb). Based on untransformed exposure rates, the differences in the rates from Nash et al. (1982) and Grover et al. (1986) are not significantly different (p=0.56) (Attachment 1, Worksheet **2,4-D GrndPool**).

3.3.1.2. Alachlor Application

Dubelman and Cowell (1989) provide information on worker exposures to alachlor in agricultural applications. As with many of the studies on directed foliar applications (Section 3.2.2), the study by Dubelman and Cowell (1989) is focused specifically on developing worker exposure rates in terms of mg/kg bw per lb handled. Unlike the more general studies on 2,4-D discussed in the previous section, Dubelman and Cowell (1989) derive explicit estimates of these exposure rates based on a detailed consideration of the pharmacokinetics of alachlor. Consequently, the exposure rates reported by Dubelman and Cowell (1989) can be used directly.

As summarized in Table 9, Dubelman and Cowell (1989) provide separate rates for open cab and closed cab applications. As would be expected, the closed cab applications lead to lower exposure rates, relative to open cab applications. For the open cab applications, however, the application method is described only as a *surface application*. Closed cab rates are given for both soil incorporation and ground broadcast. As summarized in Attachment 1, Worksheet **Dubelman and Cowell 1981-4**, analysis of variance indicates a significant difference (p=0.01) among the three types of applications assayed by Dubelman and Cowell (1989). The geometric means of the exposure rates for closed cab applications are lower than the corresponding rates for closed cab application by a factor of about 7.5 for soil incorporation and 38 for broadcast application. These differences between closed and open cab are much greater than the estimates from PHED (i.e., Keigwin 1998 as summarized in Table 3 of the current analysis). Nonetheless, the PHED exposure guide does indicate that enclosed cabs reduce both dermal and inhalation exposures by 98% (Keigwin 1998, p. 10), which is comparable to the factor of 38 for open and closed cab surface applications in the study by Dubelman and Cowell (1989) – i.e., 100% ÷ 2% is equivalent to a factor of 50.

3.3.1.3. Azinphos-methyl Application

Franklin et al. (1981) assayed 17 workers involved in ultra-low volume orchard airblast applications of azinphos-methyl, an organophosphate insecticide. The airblast equipment is not described in detail in the publication. The only description given of the rig set up is as follows: *The operator was located approximately 2 m in front of the spray rig nozzles* (Franklin et al. 1981, p. 717). A description of the cabs, enclosed or otherwise, is not given in the publication. While orchard airblast is a broadcast application, this application method is different from broadcast foliar applications in that airblast applications often use a finer droplet size that is essentially misted into the canopy of the treated trees.

Biomonitoring consisted of complete urine collections on the day of application and the day following application with assays for azinphos-methyl metabolites (i.e., alkyl phosphates). As detailed in Attachment 1 (Worksheet **Franklin et al. 1981**), 2 of the 17 workers (i.e., Workers 10 and 17 in Table 4 of Franklin et al. 1981) are excluded from the analysis because urine samples were incomplete. All workers in the study wore gloves (cotton, leather or rubber), boots (leather or rubber), and respirators. In the assessment of Franklin et al. (1981), the respirators were sufficient to ensure that absorption via inhalation exposures was negligible.

Data on three subgroups are reported based on differ levels of PPE use—i.e., rubber coats and pants (n=4), rubber coat only (n=4), and workers wearing no rubberized clothing (n=7). As also detailed in Attachment 1 (Worksheet **Franklin et al. 1981**) analysis of variance indicates no significant differences among these subgroups of workers based on either untransformed data (p=0.47) or log-transformed data (p=0.34). In terms of average exposures, the workers wearing both rubber coats and pants had a higher average level of exposure (by about a factor of 2) than either of the other two groups. The lack of efficacy of PPE is also noted in the discussion by Franklin et al. (1981) who indicate that patch testing noted detectable levels of azinphos-methyl under the rubberized clothing.

As summarized in Table 9 and illustrated in Figure 7, the worker exposure rates from this study are substantially higher than those from the other ground broadcast studies—i.e., by several orders of magnitude based on the central estimates of the exposure rates. As indicated in Table 3, the PHED exposure rates for airblast applications (Scenarios 11 and 12) are also substantially higher than the exposure rates for groundboom applications (Scenarios 13 and 14). While azinphos-methyl has a relatively high first-order dermal absorption rate coefficient (i.e., ≈0.023 hour^{-1} as summarized in Table 7), this rate coefficient is essentially identical to the rate coefficient for alachlor (i.e., 0.0229 hour^{-1} as also summarized in Table 7). As summarized in Table 9, the central estimates of the occupational exposure rates for alachlor (0.0000395 to 0.00000522 mg/kg bw/lb applied) are below the corresponding rate for azinphos-methyl (0.0786 mg/kg bw/lb applied)by factors of 1,990 to 15,057. Thus, the atypically high occupational exposure rates for azinphos-methyl from the study by Franklin et al. (1981) cannot be attributed to greater dermal absorption.

Given the application method used by Franklin et al. (1981) as well as the uniquely high worker exposure rates, it is apparent that worker exposure rates for orchard airblast applications are not typical of other ground broadcast application methods, as discussed in Section 4.2.3.

3.3.1.4. Bromoxynil Application

Cessna and Grover (2002) assayed worker exposures in a group of farmers applying bromoxynil (as a mixture of bromoxynil butyrate and bromoxynil octanoate) to cereal crops (i.e., wheat, barley, and oats) by tractor drawn rigs. Of the 14 rigs included in this study, 9 had enclosed cabs. Cessna and Grover (2002) provide extensive deposition data as well as concentrations of bromoxynil in air for the closed and open cabs. The biomonitoring data (Table 8 in the paper), however, are reported only in terms of workers who wore neoprene gloves (n=5) and workers who did not wear gloves (n=8). Thus, the worker exposure rates based on biomonitoring presented in Table 9 of the current analysis are reported only for workers with or without gloves.

Cessna and Grover (2002, Table 8, p. 378) report biomonitoring results in units of ng bromoxynil phenol equivalents per gram creatinine per kg body weight per kg bromoxynil handled. While not discussed in detail by Cessna and Grover (2002), excretion of a pesticide in terms of urinary creatinine is often used as a method to correct for partial urine collections because the amount of creatinine excreted per day is relatively constant (e.g., ICRP 1975, pp. 354-355). For comparisons to other exposure rates considered in the current analysis, however, the units reported by Cessna and Grover (2002) must be converted to exposure levels in units of mg bromoxynil/kg bw per lb handled. This conversion can be made because Cessna and Grover (2002, Table 8, p. 378) provide data on excretion in units of both µg bromoxynil phenol equivalents (references as µg p.e. in the paper) as well as information on µg p.e./g creatinine. Thus, in Attachment 1 (Worksheet **Cessna and Grover 2002**), the amount of creatinine excreted is calculated as µg p.e. divided by µg p.e./g creatinine. Doses of ng bromoxynil phenol equivalents per gram creatinine per kg body weight are multiplied by grams creatinine to get a dose rate in units of ng p.e./kg bw per kg handled. Other standard conversions are used to convert this rate to units of mg p.e./kg bw per lb handled.

Cessna and Grover (2002) do not correct the exposure rates for the proportion of bromoxynil that is excreted in the urine. In the Reregistration Eligibility Decision (RED) for bromoxynil, the U.S. EPA/OPP (1998a, p. 27) notes that about 75% to 90% of bromoxynil is excreted in the urine of rats. In the absence of data on humans, these data are used in Attachment 1 (Worksheet **Cessna and Grover 2002**) to adjust the exposure rates upward to account for the partial excretion of bromoxynil in the urine. Specifically, the 80% excretion (the approximate geometric mean of the range) is taken as a central estimate. Cessna and Grover (2002, Table 8) do not provide individual data but do provide the mean and range of exposure rates to bromoxynil. Thus, the mean (lower bound to upper) uncorrected values are divided by 0.8 (0.9 to 0.75) to derive the exposure rates given in Table 9 of the current analysis.

As summarized in Table 9 and illustrated in Figure 7, exposure rates for workers who wore gloves were about a factor of 8 less than exposure rates for workers who did not wear gloves [$0.0000352 \div 0.00000425 \approx 8.28$]. The central estimate for workers who did not wear gloves is about of factor of 2.6 less than the composite estimate of the exposure rates for workers applying 2,4-D [$0.0000912 \div 0.0000352 \approx 2.59$].

3.3.1.5. Ethoprop Application

Lunchick et al. (2005) provide biomonitoring data on 20 male workers involved in sweep injection boom or surface applications of ethoprop, a nematicide, to fallow fields prior to potato planting. While sweep injection boom application may be only marginally relevant to Forest Service activities, this study is included in the current analysis for the sake of completeness.

This study involved closed cabin tractor applications in which applicators wore long pants and a long-sleeved shirt inside the cab with chemical-resistant coveralls, gloves (NOS), and respirators for work done outside of the tractors. Urine collections were made prior to the start of the study and then for 12-hour intervals for 4 days after the start of applications and then for 3 additional days after applications were completed. To ensure complete urine collection, creatinine was also assayed. The absorption of ethoprop was assayed based on the urinary excretion of a well-characterized metabolite accounting for the proportion of the metabolite excreted in the urine based on pharmacokinetic studies in rats.

The only limitation in the biomonitoring data is that some of the workers continued to apply ethoprop after the termination of the study. As noted by Lunchick et al. (2005), this continued exposure may overestimate the exposure rates. Lunchick et al. (2005, Table 1, p. 86) provide information on both the total amount of ethoprop handled by the groups of workers as well as the total absorbed dose based on urinary excretion of the ethoprop metabolite. These data are used directly in Attachment 1 (Worksheet **Lunchick et al. 2005**). The only calculation of the data involves the transformation of the amount handled from kg (as reported in the publication) to pounds and the transformation of doses reported as µg/kg bw to mg/kg bw. Note that the exposure rates are not for individual workers but are the mean exposures for 18 different groups of workers with the numbers of individuals in each group ranging from 2 to 13.

As summarized in Table 9 and illustrated in Figure 7, the central estimate of the exposure rate for workers applying ethoprop is about 0.000007 mg/kg bw/lb handled. This exposure rate is similar to the central estimates of the worker exposure rates for alachlor and bromoxynil. Because of the application method used in the study by Lunchick et al. (2005), sweep injection, and the obvious efforts made to reduce worker exposures, the similarities in the rates for ground broadcast applications of alachlor and bromoxynil may be simply coincidental.

As discussed by Lunchick et al. (2005), the exposure rates for most workers are overestimates, because 13 of the 20 workers were involved in additional applications of ethoprop during the urine collection period and the additional applications are not included in the estimates of the amount of ethoprop handled. Nonetheless, Lunchick et al. (2005, p. 89) also conducted deposition based exposure assessments using PHED and note that the PHED estimates exceed the estimates based on biomonitoring by factors of 26 to 51.

Interestingly, 9 of the 17 workers in the Lunchick et al. (2005) had to perform general maintenance on the equipment and/or had to address leaks in the equipment. As detailed in Attachment 1, the mean exposure rates for groups reporting equipment issues is about a factor of 3.5 higher than groups not reporting equipment issues but the differences in exposure rates are not significant based on either untransformed rates ($p \approx 0.20$) or log-transformed rate ($p \approx 0.19$). Thus, while adverse events during application may have contributed to higher exposures, the variability in worker exposure rates cannot be attributed primarily to adverse events.

3.3.1.5. Applications of 2,4-D/Picloram Mixtures

Libich et al. (1984) studied the exposure of herbicide applicators involved in electric power transmission rights-of-way maintenance. Two types of applications were made: backpack sprays (with 2,4-D and dichlorprop or 2,4-D and picloram) and vehicle mounted spray guns (2,4-D and picloram). The data on backpack applications (Tables III and IV in the paper) cannot be used to derive relative exposure rates because data on 2,4-D are not reported separately for the 2,4-D/dichlorprop and 2,4-D/picloram applications. Thus, this paper is not considered in Section 3.2 (Directed Applications). The broadcast applications using spray guns (Tables II and VII) are reported only for mixtures of 2,4-D and picloram, and these data can be used to derive relative exposure rates. These applications used Tordon 101, a 4:1 mixture of 2,4-D and picloram (463 g/L).

A limitation in this study is that Libich et al. (1984) do not specify the amount of product handled in either the 2,4-D/picloram or 2,4-D/dichlorprop applications. In the previous analysis of worker exposure rates (SERA 1998), assumptions are made concerning the amounts of pesticides that were handled. On reexamination, these assumptions do not appear to be justified. Thus, in the current analysis, no attempt is made to derive absolute worker exposure rates.

The data on spray gun applications are summarized in Attachment 1, Worksheet **Libich et al. 1984**. While the amount of pesticide handled by each worker is not known, each worker handled some fixed amount of the 4:1 2,4-D/picloram mixture. Consequently, regardless of the amount handled, each worker handled four times more 2,4-D than picloram. While this study cannot be used to derive absolute worker exposure rates, the utility of this study in estimating and interpreting relative exposure rates is discussed further in Section 4.1.1.

3.3.2. Variability Among Workers

The variability in workers involved in ground broadcast applications of pesticides is illustrated in Figure 8. As with the corresponding plot for directed applications (Figure 6), Figure 8 is a box-and-whisker plot showing outliers (as defined in Section 2.3). Figure 8 includes all studies illustrated in Figure 7 except for the bromoxynil data from Cessna and Grover (2002) which does not provide data on individual workers.

As with the plot for directed applications, the plot for broadcast applications illustrates marked variability in worker exposure rates. The greatest variability is evident in the study by Nash et al. (1982) in which the worker exposure rates (n=15) range from 4.50×10^{-7} to 3.30×10^{-3} mg/kg bw per lb handled, spanning a factor of over 7,000 [$3.30\times10^{-3} \div 4.50\times10^{-7} \approx 7{,}343$]. This extreme variability is due to one worker (Worker 4 in Table V of Nash et al. 1982) for which no pesticide was detected in the urine. Censoring this non-detect, the variability in Nash et al. (1982) is only a factor of about 630 ($3.3\times10^{-3} \div 5.25\times10^{-6} \approx 629$). As indicated in Figure 8, however, the non-detect is not classified as a statistical outlier. While the study by Lunchick et al. (2005) on ethoprop involves a larger number of observations (n=18), the variability is less than that in the Nash et al. (1982) study—i.e., a factor of about 400 [$1.56\times10^{-4} \div 3.92\times10^{-7} \approx 397$].

The variability in exposures for workers applying alachlor (Dubelman and Cowell 1989) is much less than the variability in exposures for workers applying either 2,4-D or ethoprop. This apparent lesser variability, however, is probably an artifact of small sample sizes—i.e., the groups in the study by Dubelman and Cowell (1989) consisted of only 4 to 7 workers. As illustrated in Figure 7, which is based on prediction intervals, the prediction intervals for the workers from Dubelman and Cowell (1989) are comparable to those from the study by Nash et al. (1982). In other words, prediction intervals incorporate information on sample size; thus, prediction intervals are a more reasonable basis than ranges for quantitatively comparing variability.

As illustrated in Figure 8, the applications involving 2,4-D and ethoprop (i.e., the applications with relatively large numbers of observations) note several outliers, most of which are far outliers (i.e., points above the third quartile by greater than 3 times the inner quartile range). For the reasons discussed in Section 3.2.4, none of the points for 2,4-D applications are censored from the analysis.

As discussed further in Section 4.2.3, the data on ethoprop from the study by Lunchick et al. (2005) are not used quantitatively to develop general worker exposure rates because the application method used in this study, sweep injection boom, is not been considered in Forest Service risk assessments and is not typical of forestry applications. Nonetheless, this study provides an interesting example of a data point indicating a very high level of exposure that could be considered as both a statistical outlier as well as a data point that might be dropped in the development of worker exposure rates. This point is illustrated in Figure 8 as the only far outlier in the ethoprop applications. As indicated in Lunchick et al. (2001, p. 86, Table 1, second entry), this far outlier involved an individual mixer/loader/applicator applying 245 kg of ethoprop over a 2-day period. The total absorbed dose is reported as 84 µg/kg bw, and the worker exposure rate is calculated as 0.000156 mg/kg bw per lb handled [0.084 mg/kg bw ÷ 540.127 lb handled]. This exposure rate is higher than any other exposure rate by a factor of 4 to nearly 400. In a footnote to Table 1 of the Lunchick et al. (2001) paper, the investigators indicate… *Worker had poor work habits and removed gloves during the work period.* No similar notes are made for other groups. Thus, if this study were to be used to derive worker exposure rates, consideration could be given to excluding this data point as non-representative of expected exposures in workers following prudent handling practices. This rationale is essentially identical to the rationale for excluding the Lavy et al. (1987) backpack workers as discussed in Section 3.2.2.1.

3.4. Aerial Applications

As summarized in Table 10, worker exposure rates for aerial applications are available for pilots and mixer/loaders. In terms of risk assessments, the greatest concern is with exposures to pilots, particularly true for risk assessments of insecticides, many of which are neurotoxins. Consequently, the data in Table 10 are discussed separately for pilots and mixer/loaders.

3.4.1. Pilots

Very little information is available on worker exposure rates for aerial applications. No new studies on exposure rates for pilots based on biomonitoring have been encountered since the previous analysis (SERA 1998) which covered the study by Lavy et al. (1982) and Nash et al. (1982).

The data from these studies have been reanalyzed using the methods detailed in Section 2.3, and a summary of this reanalysis is given in Table 10 of the current report. Based on the geometric means, worker exposure rates from the study by Nash et al. (1982) (i.e., 0.00000754 mg/kg bw per lb applied) is lower than that from the study by Lavy et al. (1982) (i.e., 0.0000311 mg/kg bw per lb applied) by a factor of about 4 [0.0000311 ÷ 0.00000754 ≈ 4.12]. Given the wider variability noted in the previous discussions of other groups of workers, these estimates are remarkably consistent. As detailed in Attachment 1 (Worksheet **AerialComposite**), these differences are not statistically significant using either the untransformed data ($p \approx 0.45$) or the log-transformed data ($p \approx 0.33$). Given the small number of observations – i.e., 5 from the study by Lavy and 3 from the study by Nash – this comparison has a low statistical power.

The very small sample sizes also impact the interpretation and utility of the confidence and prediction intervals. This is strikingly evident in the confidence intervals for the T1 (normal work practice) pilots (n=3) from Lavy et al. (1982) for which the prediction interval ranges from about 2×10^{-9} to 0.5 mg/kg bw per lb applied, which spans a factor of 250 million [$0.5 \div 2\times10^{-9}$ = 250,000,000]. While the prediction interval is valid, it essentially contains no useful information, indicating only that the data are insufficient to calculate a meaningful interval. As discussed further in Section 4.2.4, the only reasonable approach to developing worker exposure rates for pilots is to pool the available data from both studies.

3.4.2. Mixer-loaders (Aerial)

In addition to the data on pilots, Lavy et al. (1982) and Nash et al. (1982) also provide data on mixer/loaders involved in aerial applications of 2,4-D.

As with the central estimates of exposure rates for pilots, the mixer/loader data are strikingly consistent ranging from about 1×10^{-5} to 4.2×10^{-5} mg/kg bw per lb handled. As with the pilot data, this range spans a factor of only about 4. Based on analysis of variance (Attachment 1, Worksheet **MxLdAerialComp**), the rates reported in these three studies are not significantly different ($p\approx0.15$). The central estimate of the composite rate for mixer/loaders is about 2.5×10^{-5} mg/kg bw per lb handled, very close to the rate for pilots ($\approx2\times10^{-5}$ mg/kg bw per lb handled). In addition, the upper bound of the 95% prediction interval for the composite rate for mixer/loaders (5.84×10^{-3} mg/kg bw per lb handled) is close to, although somewhat lower than, the corresponding value for pilots (i.e., 8.46×10^{-3} mg/kg bw per lb handled).

The previous analysis (SERA 1998) derives only a single set of exposure rates for aerial applications. Given the similarities in the exposure rates for pilots and mixer/loaders in the current reanalysis, this approach still appears to be reasonable. As discussed further in Section 4.2.4, only a single set of exposure rates is derived for aerial applications in the current analysis.

3.5. Aquatic Applications

Nigg and Stamper (1983a) is the only available study on aquatic applications that provides sufficient information to estimate worker exposure rates based on biomonitoring. This study is used in several Forest Service risk assessments involving aquatic applications (e.g., SERA 2006a, SERA 2008b,c; SERA 2010a; SERA 2011c).

Nigg and Stamper (1983a) assayed worker exposures in aquatic applications of a liquid formulation of 2,4-D amine to control water hyacinths. Absorbed doses were assayed as total urinary elimination of the compound over a 24-hour period in four workers who applied the liquid formulation by airboat handguns. Given the similarities between the occupational exposure rates for workers involved in the liquid and granular formulations of 2,4-D to turf (Harris et al. 1992), the data from Nigg and Stamper (1983) are used for exposure assessments involving both granular and liquid formulations.

As detailed in Attachment 1 (Worksheet **Nigg and Stamper 1983a**), the central estimate based on the geometric mean (i.e., the assumption of a log-normal distribution) is 8.75×10^{-4} mg/kg bw per lb applied with 95% confidence intervals of 4.09×10^{-4} to 1.87×10^{-3} and 95% confidence prediction intervals of 1.6×10^{-4} to 4.79×10^{-3}. These intervals, which are based on a sample size of only 4, may be very conservative. Nonetheless, the prediction interval spans a factor of about 30, which is not substantially different from other prediction intervals for other application methods. As discussed in Section 4.2.5, the central estimate and prediction intervals from Nigg and Stamper (1983a) serve as the basis for recommending worker exposure rates for aquatic applications.

4. DISCUSSION AND CONCLUSIONS

4.1. Impact of Dermal Absorption

A major focus of the current analysis is to assess whether or not dermal absorption rates have an impact on occupational exposure rates (Section 1.2). As illustrated in Figure 1, the previous analysis (SERA 1998) fails to note a significant relationship between relative dermal absorption rates and relative occupational exposure rates using 2,4-D as the reference compound. Given that dermal exposures predominate over inhalation exposure in workers applying pesticides (e.g., van Hemmen 1992), it seems sensible that dermal absorption rates should correlate with applicator exposure rates. In discussing the failure to detect a significant correlation, SERA (1998) notes:

> *Based on the information that has been gathered to date, it appears that worker exposure rates are reasonably consistent across compounds. Confidence in this generalization, however, is tempered both by the limitations in the currently available studies as well as the substantial variability in exposure rates among individuals.*
>
> SERA 1998, p. 1

4.1.1. Mixture Studies

As discussed in Section 3.1, mixture studies are useful for assessing the impact of dermal absorption rates on occupational exposure rates because there are essentially no uncertainties in relative exposures to the components in the mixture so long as the composition of the mixture is known. Three mixture studies, each of which includes 2,4-D in the mixture, are available that meet this criterion: picloram from Libich et al. (1984), picloram and dichlorprop from Lavy et al. (1987), and triclopyr from Zhang et al. 2011. The relative occupational exposure rates and dermal absorption rates from these studies are summarized in Table 11, and the results of the analyses are illustrated in Figure 9. Details of the analyses are given in Attachment 1 (Worksheet **RelRatesMixAnal**).

Exploratory linear regression analyses were conducted with the relative dermal absorption rates as the independent variable and relative worker exposure rates as the dependent variable (Eq. 15). Equation 15 may be viewed as an elaboration of Equation 4 in the current analysis. In other words, Equation 4 may be viewed as a standard linear equation:

$$\frac{ExpRt_P}{ExpRt_{2,4-D}} = a + b\frac{ka_P}{ka_{2,4-D}} \qquad \text{(Eq. 15)}$$

in which the intercept, ***a***, is assumed to be zero and the slope, ***b***, is assumed to be 1.

As illustrated in Figure 9, two types of regressions are conducted: one constraining the intercept to zero and the other allowing the intercept to be estimated from the data. In Figure 9, the dotted line (referred to as the line of concordance, represents Equation 4 (i.e., ***a*** = 0, ***b*** = 1). The dashed line represents the constrained regression (***a*** = 0 with the slope estimated from the data), and the solid line represents the unconstrained regression (with both the intercept, ***a***, and slope, ***b***, estimated from the data).

Both regressions indicate highly significant associations between relative absorption rates and relative occupational exposure rates (i.e., $p \approx 0.00003$ for the constrained regression and $p \approx 0.00002$for the unconstrained regression). Both analyses indicate a slope that is less than 1.

For the unconstrained analysis, the regression equation is:

$$\frac{ExpRt_P}{ExpRt_{2,4-D}} = 0.38 + 0.58 \frac{ka_P}{ka_{2,4-D}} \; (r^2 = 0.88) \qquad \text{(Eq. 16)}$$

where the 95% confidence limits for the intercept range from 0.22 to 0.56 and the 95% confidence limits for the slope range from 0.38 to 0.77.

The corresponding equation for the constrained analysis is:

$$\frac{ExpRt_P}{ExpRt_{2,4-D}} = 0.77 \frac{ka_P}{ka_{2,4-D}} \; (r^2 = 0.88) \qquad \text{(Eq. 17)}$$

where the 95% confidence limits for the slope range from 0.50 to 1.03. In that the upper bound of the slope for the constrained analysis encompasses 1, the constrained analysis (Eq. 17) supports the use of Equation 4. The support, however, may be viewed as tenuous if not marginal in that the upper bound of the slope barely encompasses 1.

4.1.2. Backpack Directed Foliar Studies

As summarized in Table 8, there are five studies involving backpack directed foliar applications which appear to be typical of Forest Service application practices: Middendorf (1993) and Lavy et al. 1993, both of which involve applications of glyphosate; Middendorf (1992b) and Spencer et al. (2000), both of which involve applications of triclopyr BEE; and Zhang et al. (2011) which involves applications of a mixture of triclopyr BEE (butoxyethyl ester) and an octyl ester of 2,4-D (2-ethylhexyl). In each of these studies, absolute worker exposure rates can be estimated; consequently, there is no need to analyze these studies using either relative dermal rates or relative exposure rates. In other words, the regression analysis can be conducted using the dermal absorption rate coefficient as the independent variable and the absolute occupational exposure rate as the dependent variable. Another benefit to this group of studies is that all of the dermal absorption rate coefficients are based on human data (Table 7).

Two sets of regressions were conducted, one using a constrained model (i.e., the intercept set to zero) and the other using a standard unconstrained model (i.e., the intercept estimated from the data). These analyses are detailed in Attachment 1, **`Worksheet BackpackTypFolDerm1a-1`** for the constrained analysis and **`BackpackTypFolDerm1a-2`** for the unconstrained analysis.

The unconstrained analysis yields a low value for the intercept (-0.0011) that was not significantly different from zero (p=0.71). In both analyses, the regression equations indicate a significant association between the dermal absorption rate coefficient and the worker exposure rate—i.e., p=0.0041 with an r^2=0.94 for the constrained analysis and p=0.033 with an r^2=0.85 for the unconstrained analysis.

For comparison with the analyses on mixtures (Section 4.1.1), a regression analysis was also conducted with the backpack directed foliar studies using relative dermal absorption rates and relative occupational exposure rates with 2,4-D as the reference chemical. Only the constrained model is discussed because, as noted above, the intercept for the unconstrained analysis (Worksheet **BackpackTypFolDerm1a-2**) is not significantly different from zero.

The constrained analysis is detailed in Attachment 1 (Worksheet **BackpackTypFolDerm1c**). Since this analysis involves simple scaling of both axes, the fit statistics are identical to that of the analysis discussed above – i.e., p=0.0041 with an r^2=0.94. The data fit the following equation:

$$\frac{ExpRt_P}{ExpRt_{2,4-D}} = 0.67\frac{ka_P}{ka_{2,4-D}}\ (r^2 = 0.94) \qquad \text{(Eq. 18)}$$

Unlike the analysis of the mixture studies (Section 4.1.1), the 95% confidence limits for the slope in the constrained analysis does not encompass 1, ranging from 0.38 to 0.97. As illustrated in Figure 10, the slope is shallower than that noted in the analysis of the mixture studies (a slope of 0.77 as indicated in Equation 17).

4.1.3. Combined Analysis of Directed Foliar Data

In order to increase the power of the analysis, data from the mixture studies (Section 4.1.1) and backpack directed foliar studies (Section 4.1.2) were combined and an analysis of relative dermal absorption rates and relative worker exposure rates was conducted. Only the constrained model (intercept=0) was used.

Unlike the mixture analysis, the individual data points from Lavy et al. (1987) and Libich et al. (1984) were composited. This approach with Lavy et al. (1987) is taken because the T1 (normal practice) and T2 (special precautions) data on injection bar, hypohatchet, and hack-and-squirt applications are all clustered in a narrow region. The data from Libich et al. (1984) are combined because these data consist of observations on individuals rather than groups of workers. In both cases, geometric means were used, and details of these calculations are given in Attachment 1 (Worksheet **RelRatesMixData**). This approach is intended to avoid artificially inflating the number of points in the combined analysis.

The only other atypical aspect of the combined analysis involves the relative dermal absorption rate for dichlorprop. As summarized in Table 7, no experimental data are available on the dermal absorption of dichlorprop. As detailed in Section 3.1.2 and discussed by Lavy et al. (1987), dichlorprop is structurally similar to 2,4-D and the two compounds should have similar rates of dermal absorption. Consequently, the dermal absorption rate of dichlorprop relative to 2,4-D is based on the QSAR estimates for both compounds [0.0013 $hour^{-1}$÷0.0012 $hour^{-1}$ ≈

1.083] rather than using the somewhat lower experimental dermal absorption rate for 2,4-D (i.e., 0.00066 $hour^{-1}$).

The data for this analysis are summarized in Table 12 and illustrated in Figure 11. Details of the analysis are given in Attachment 1 (Worksheet **RelRatesComposite**). The regression yields the following relationship:

$$\frac{ExpRt_P}{ExpRt_{2,4-D}} = 0.69\frac{ka_P}{ka_{2,4-D}} \ (r^2 = 0.93) \qquad \text{(Eq. 19)}$$

and the fit of the regression model is clearly significant ($p \approx 4.9\text{x}10^{-5}$). The confidence limit on the slope does not encompass a value of 1 (i.e., a 95% confidence interval ranging from 0.49 to 0.89).

4.1.4. Ground Broadcast Applications

As summarized in Table 9 and discussed in Section 3.3.1, six studies on five pesticides are available involving broadcast applications from which absolute worker exposure rates can be derived. As noted in Section 3.3.1.1, two studies are available on 2,4-D (Grover et al. 1986; Nash et al. 1982) and these studies yield remarkably concordant estimates of worker exposure rates. Consequently, the worker exposure rates from Grover et al. (1986) and Nash et al. (1982) were combined to derive a single composite worker exposure rate for 2,4-D (Attachment 1, Worksheet **GrndComposite**). A summary of the data used to assess the relationship of worker exposure rates to dermal absorption rates is given in Table 13, and these data are illustrated in Figure 12. Details of the statistical analyses of these data are included in Attachment 1 (Worksheets **BroadcastAnal-1a** to **BroadcastAnal-1c**) as discussed below.

Unlike the case for mixture studies (Sections 4.1.1) and directed foliar applications (Section 4.1.2), no significant correlations are apparent between dermal absorption rates and occupational exposure rates for broadcast applications. Based on the data summarized in Table 9, the regression based on dermal absorption rates and worker exposure rates yields the following relationship:

$$ExpRt = -0.11 + 1.43k_a \qquad \text{(Eq. 20)}$$

While the regression yields a positive slope (i.e., a direct relation between the dermal absorption rate and occupational exposure rate), the squared correlation coefficient is low (r^2=0.30) and the regression model is not statistically significant (p=0.33) [Worksheet **BroadcastAnal-1a**].

As illustrated in Figure 12, the estimate of a positive slope is dominated by the high occupational exposure rate for azinphos-methyl from the study by Franklin et al. (1981). As discussed in Section 3.3.1.3, the Franklin et al. (1981) study involves orchard air blast applications, which are not comparable to the methods used in the other broadcast application studies.

Censoring the Franklin et al. (1981) data point from the regression does not substantially improve the correlation (r^2=0.64) and results in a negative slope (i.e., -0.0035 with a 95% confidence interval of -1.9 to 0.0019). As with the analysis including the data on Azinphos-methyl, the model fit is not statistically significant (*p*=0.20) [Worksheet **BroadcastAnal-1b**]. The plot of the data points in Figure 12 is suggestive of a log-log correlation censoring the data on azinphos-methyl. Using a natural log transformation of both the dermal absorption rate and occupational exposure rate improves the correlation (r^2=0.80) but the model fit remains statistically insignificant (p=0.10) [Worksheet **BroadcastAnal-1c**].

The failure to note a significant or even apparent relationship between dermal absorption and worker exposure rates in the broadcast application studies may be associated with at least two factors, differences in how the pesticides were applied and differences in the source of the estimates of the dermal absorption rate coefficients. As noted in Table 13 and discussed in Section 3.3.1, the studies on 2,4-D (Grover et al. 1986; Nash et al. 1982) and bromoxynil (Cessna and Grover 2002) involve broadcast foliar applications. The other studies, however, involve soil incorporation, sweep injection boom, surface applications, and orchard airblast. It seems likely that worker application rates would vary with these different types of application methods and that these differences may obscure any underlying relationships between dermal absorption rates and worker exposure rates.

As also noted in Table 13, the estimates of the dermal absorption rates for the chemicals used in the broadcast application studies are based on different sources—i.e., human data, studies in rats, studies in monkeys, and QSAR estimates (Equation 6). As discussed in Section 3.1 and illustrated in the Figure 2, differences in experimental measures of dermal absorption rates vary among species and differences in dermal absorption rates based on structure-activity relationships differ from experimental measurements.

Notwithstanding the above discussion, the studies on 2,4-D (Grover et al. 1986; Nash et al. 1982) and bromoxynil (Cessna and Grover 2002) both involve foliar broadcast applications to agricultural crops. Bromoxynil ester should be absorbed more rapidly than 2,4-D by a factor of about 27 [$0.011\ \text{hour}^{-1} \div 0.00041\ \text{hour}^{-1} \approx 26.83$] based on the best available data—i.e., human data on 2,4-D and data on rats for bromoxynil. Thus, if dermal absorption rates are assumed to be directly related to worker exposure rates, it is expected that worker rates for bromoxynil will be higher than those for 2,4-D and probably substantially higher. As summarized in Table 13, however, this does not appear to be the case, with the worker exposure rates for 2,4-D exceeding the corresponding rate for bromoxynil by a factor of about 4 [$0.0000912 \div 0.0000234 \approx 3.897$].

While the data on broadcast applications are not as extensive as the data on directed foliar applications (Sections 4.1.1 through 4.1.3), the data on broadcast applications are consistent with the SERA (1998) analysis, indicating no apparent association between dermal absorption rates and worker exposure rates.

4.1.5. Other Application Methods

In addition to directed applications and broadcast ground applications of pesticides, the current analysis is also concerned with aerial broadcast applications and aquatic applications. As discussed in Section 3.4 (aerial applications) and Section 3.5 (aquatic applications), data are available only on applications of 2,4-D. Consequently, information on aerial and aquatic applications cannot be used to assess the potential impact of dermal absorption rates on worker exposure rates.

4.1.6. Conclusions

4.1.6.1. Directed Applications

Given the data on directed foliar backpack applications (Section 4.1.2) and the consistency of these data with the available studies on directed applications of mixtures (Section 4.1.3), the relationship between dermal absorption rates and worker exposure rates for directed applications of pesticides is clear and compelling. The significant association between dermal absorption rates and worker exposure rates supports the use of Equation 3 in estimating worker exposure rates for pesticides on which no data are available using a reference pesticide on which a worker exposure study is available as well as estimates of the dermal absorption rate coefficients for the pesticide under consideration and the reference pesticide.

As discussed in Sections 4.1.1 through 4.1.3, however, the implicit slope of 1 in Equation 3 is not supported by the available studies on directed foliar applications. Based on the available information, a more general form of Equation 3 is indicated,

$$ExpRt_P = F \times \frac{ka_P}{ka_{2,4-D}} \times ExpRt_{2,4-D} \qquad \text{(Eq. 21)}$$

where F is an empirical adjustment factor in the range of about 0.7 (slope of 0.67 in Equation 18) to 0.8 (slope of 0.77 in Equation 17). In other words, Equation 3 may underestimate or overestimate exposures by factors of about 1.3 [1÷0.77≈1.2987] to 1.5 [1÷0.67≈1.4925]. Nonetheless, given the wide variability in worker exposure rates which generally encompass factors of 10 to 100 (e.g., Figure 6), a correction for F in the range of 1.3 to 1.5 is essentially inconsequential.

The only substantial modification to Equation 3 is to note that the use of 2,4-D as the reference pesticide is not necessary, and, in some cases, may not be desirable. When Equation 3 was developed (e.g., USDA/FS 1989a,b,c), the best worker exposure studies were those conducted on 2,4-D, and the pharmacokinetics of 2,4-D were better characterized than the pharmacokinetics of most other pesticides. As discussed in Section 3.2, studies representing current Forest Service practice are available on triclopyr (Middendorf 1992a,b; Spencer et al. 2000; Zhang et al. 2011), glyphosate (Middendorf 1993), as well as 2,4-D (Zhang et al. 2011). Over time, additional studies on additional pesticides are likely to become available.

In selecting a reference pesticide, the preferred approach is to minimize extrapolation. For example, selecting glyphosate as the reference chemical for a poorly absorbed pesticide would be generally preferred over selecting triclopyr as a reference pesticide, because triclopyr is absorbed more quickly than glyphosate. Conversely, selecting data on 2,4-D or triclopyr would be preferred in developing worker exposure estimates for a weak acid with a dermal absorption rate comparable to 2,4-D or triclopyr.

Consequently, a more general form of Equation 3 is proposed:

$$ExpRt_P = \frac{ka_P}{ka_{\text{Ref}}} \times ExpRt_{\text{Ref}} \qquad \text{(Eq. 22)}$$

where the subscript *Ref* indicates the reference pesticide and subscript *P* indicated the pesticide of concern.

The selection of the reference chemical is left as a matter of judgment that must be articulated in any application of Equation 22. In general and as noted above, the selection of a reference pesticide should be dominated by an attempt to minimize extrapolation. Nonetheless, other factors involving the relationship of the reference pesticide to the pesticide of concern could supersede or augment selections based solely on minimizing extrapolation. The nature of these relationships could include but would not be limited to chemical structure, chemical properties (e.g., lipophilicity) and mode of action.

Related to the selection of the reference pesticide is the set of reference pesticides that should be considered. As discussed in Section 4.2 and summarized in Table 14, the reference pesticides covered in the current report include 2,4-D, glyphosate, and triclopyr BEE. Over time, additional worker exposure studies on other pesticides suitable for the development of worker exposure rates will become available. In such cases, it may be appropriate and preferable to use pesticides other than those included in Table 14 in the application of Equation 22.

4.1.6.2. Ground Broadcast Applications

Unlike the case for directed applications, the available data on ground broadcast applications do not support the use of dermal absorption rates to adjust worker exposure rates. As with the previous analysis (SERA 1998), this assessment is neither intuitive nor satisfying. As discussed in Section 1.1, skin contamination is the predominant route of exposure for pesticide applicators. There is no basis for asserting that this observation does not apply to ground broadcast applications. Consequently, it is sensible to assert that exposure rates to pesticides (in units of absorbed dose) should be directly correlated with the dermal absorption rates of the pesticides.

No such correlation, however, is apparent in the available studies on ground broadcast applications (Section 4.1.4). As discussed in Section 4.1.4, the available data on ground broadcast applications are more diverse than the corresponding data on directed applications, particularly in terms of the different types of ground broadcast applications (e.g., broadcast foliar, soil incorporation, sweep injection boom, surface applications, and orchard airblast). Given this diversity, consideration could be given to using Equation 22 with worker exposure rates from a study on ground broadcast applications. Such an approach would implicitly assume that a true underlying relationship between worker exposure rates and dermal absorption rates exists but that this relationship is obscured by the diversity in the application methods used in the available studies.

As also discussed in Section 4.1.4, the limited available data do not support the use of dermal absorption rates to estimate or adjust worker exposure rates. Specifically, the studies on the broadcast foliar applications of 2,4-D (Grover et al. 1986; Nash et al. 1982) and bromoxynil

(Cessna and Grover 2002) are comparable. Based on Equation 22 and using 2,4-D as the reference chemical, the central estimated of the occupational exposure rate for bromoxynil would be about 0.0025 mg/kg bw per lb [0.0000912 mg/kg bw per lb x (0.011 $hour^{-1}$ ÷ 0.00041 $hour^{-1}$) ≈ 0.00245 mg/kg bw per lb]. As summarized in Table 9, the observed exposure rate for bromoxynil (combining all workers) is 0.0000234 mg/kg bw per lb. Thus, the application of Equation 22 would overestimate the exposure rate for bromoxynil by a factor of about 100 [0.00245 ÷ 0.0000234 ≈ 104.7]. While a modest degree of conservative bias is, in some respects, desirable in risk assessments, overestimates at a magnitude approaching 100 distort the risk assessment.

Given the above considerations, the application of Equation 22 to estimating worker exposure rates for ground broadcast applications is not recommended at this time. The cautionary language in the previous assessment (SERA 1998), which is quoted in Section 4.1, continues to apply to ground broadcast exposures. As additional data become available, particularly data on ground broadcast applications in forestry programs, the approach to estimating worker exposure rates associated with ground broadcast applications should be reexamined.

4.1.6.3. Aerial and Aquatic Applications

Unlike the case with ground broadcast applications, no data are available for assessing the applicability of Equation 22 to either aquatic or aerial applications (Section 4.1.5). Consequently, the application of Equation 22 to aquatic or aerial applications cannot be supported or refuted by the available data.

In the absence of information, it seems sensible to neither recommend nor exclude the application of Equation 22. For aerial and aquatic applications, Equation 22 should be considered, and the rationale for using or not using Equation 22 should be made on a case-by-case basis.

4.2. Modified Worker Rates

The revised exposure rates for workers are summarized in Table 14. For directed ground applications, worker exposure rates are derived for backpack directed foliar, hack-and-squirt, and basal bark applications. For directed foliar applications, three sets of exposure rates are derived for three reference pesticides: glyphosate, 2,4-D, and triclopyr BEE. For ground broadcast applications, separate rates are derived for broadcast foliar applications (using 2,4-D as the reference pesticide) and orchard airblast applications (using azinphos-methyl as the reference pesticide). Single worker exposure rates are given for aerial applications and aquatic application and both rates use 2,4-D as the reference pesticide. The derivations of the worker exposure rates summarized in Table 14 are discussed below.

4.2.1. Directed Ground Applications

4.2.1.1. Directed Foliar Application

Three sets of worker exposure rates are derived for backpack directed foliar application based on glyphosate, 2,4-D, and triclopyr BEE as reference pesticides. All worker exposure rates are based directly on worker studies.

For glyphosate, the worker exposure rates are taken from the study by Middendorf (1993). As discussed in Section 3.2.2.2.4, this study was sponsored by the Forest Service and appears to reflect current Forest Service practice. Details of the calculations of the worker exposure rates are given in Worksheet **`Middendorf et al. 1993`**.

For 2,4-D, the worker exposure rates are taken from the study by Zhang et al. (2011). This study was also sponsored by the Forest Service and appears to reflect current Forest Service practice. Details of the calculations of the worker exposure rates are given in Worksheet **`Zhang et al. 2011-3 2,4-D`**.

For triclopyr, the worker exposure rates are based on a composite of the studies by Spencer et al. (2000), Zhang et al. (2011), and Middendorf (1992b), excluding the data from Middendorf (1992b) on Site 3 (i.e., the site with very high vegetation). As discussed in 3.2.2.1, Site 3 from Middendorf (1992b) is considered atypical of current Forest Service practice. Details of the calculations of the worker exposure rates are given in Worksheet **`BkPkComposite`**. As also detailed in this worksheet, an analysis of variance of the data from these three studies indicates that differences among the studies are not statistically significant (p=0.14) As indicated in Table 14, the upper bound of the prediction interval for the composite rate is 0.06 mg/kg bw per lb handled. This upper bound rate encompasses the maximum individual exposure rates from the Middendorf (1992b) study (i.e., 0.037 mg/kg bw per lb), the Spencer et al. (2000) study (i.e., 0.041 mg/kg bw per lb), as well as the Zhang et al. (2011) study (i.e., 0.023 mg/kg bw per lb).

4.2.1.2. Hack-and-Squirt Application

The worker exposure rate for hack-and-squirt applications is taken directly from the Lavy et al. (1987) for T2 (special precaution) applications. As discussed in Section 3.2.2.1, the backpack directed foliar applications from Lavy et al. (1987) are considered atypical. Nonetheless, as discussed in Section 3.2.3.1, there is no basis for asserting that the hack-and-squirt applications from Lavy et al. (1987) are atypical. Unlike the case with the directed foliar applications in which no substantial differences were noted between T1 (normal practice) and T2 (special precautions) applications, the mean exposure rate for the T2 hack-and-squirt applications are less than the T1 applications by a factor of about 3 [$0.0173 \div 0.0062 \approx 2.79$].

It worth noting that the central estimate of the rate for hack-and-squirt applications, 0.004 mg/kg bw per lb, is identical to the rate for backpack applications using 2,4-D as the reference pesticide. The upper bound of the worker exposure rate for hack-and-squirt applications, however, is 0.5 mg/kg bw per lb handled. This upper bound rate is higher than that for backpack applications – i.e., 0.01 mg/kg bw per lb handled – by a factor of 50. This marked difference is not intuitive. Lavy et al. (1987) report several instances in which hack-and-squirt bottles leaked in both T1 and T2 applications. Nonetheless, hack-and-squirt applications are, by nature, physically demanding applications in which the vegetation is hacked with a cutting tool in one hand and the herbicide is applied to the cut surface with a squirt bottle in the other hand. It seems reasonable to assert that instances of worker contamination could occur commonly. As illustrated in Figure 6, the T2 hack-and-squirt application from Lavy et al. (1987) involves only one outlier (out of 20 workers). This indicates that the statistics from these data are not heavily skewed by outliers. As a further demonstration of this, Worksheet **`Lavy et al. 1987-2`** provides an analysis of this data set using the trimmed mean – i.e., censoring the highest and lowest values to remove the outlier. As calculated in this worksheet, the mean and prediction interval are about 0.005 (0.0001 to 0.2) mg/kg bw per lb handled. The upper bound of 0.2 mg/kg bw per lb handled from the trimmed dataset is only modestly below the upper bound of 0.5 mg/kg bw per lb handled from the full dataset. Consequently, while the upper bound rate of 0.5 mg/kg bw per day may seem extreme, this rate is consistent with the only available study on hack-and-squirt applications, the estimate does not appear to be substantially impacted by statistical outliers, and there is no apparent basis for judgmentally lowering this upper bound rate.

4.2.1.3. Basal Bark Application

The recommended worker rate for basal bark application using triclopyr BEE is based on the study by Middendorf (1992a), using data from workers wearing gloves (nitrile, latex or leather). As with the other studies by Middendorf, this study was sponsored by the Forest Service and appears to represent current Forest Service practice (i.e., workers must wear gloves). The central estimate of basal bark rates from this study are about a factor of 10 less than the central estimate for backpack applications of triclopyr BEE based on the composite from Middendorf (1992b) and Spencer et al. (2000). The upper bound rate for basal bark is identical to the corresponding rate for backpack foliar. Given the nature of basal bark applications (relatively clean) to backpack foliar applications (somewhat less clean and more strenuous), the lower central estimate for basal bark applications relative to backpack foliar applications appear to be reasonable.

4.2.3. Ground Broadcast Applications

4.2.3.1. Broadcast Foliar Application

As discussed in some detail in Section 4.1.4, ground broadcast applications are problematic. As illustrated in Figure 8, two studies (Grover et al. 1986; Nash et al. 1982) involving ground foliar broadcast applications of 2,4-D lead to remarkably similar worker exposure rates that are somewhat higher than worker exposure rates for alachlor and ethoprop involving somewhat different application methods. The only clear outlier involves orchard airblast applications of azinphos-methyl, which is discussed in the following section.

For the current analysis, worker exposure rates from the studies by Grover et al. (1986) and Nash et al. (1982) are combined and worker exposure rates of 0.0001 (0.000002-0.005) mg/kg bw per lb applied are derived. The central estimate is very similar to the rate of 0.0002 mg/kg bw per lb applied which was used previously in Forest Service risk assessments (Table 2). The upper bound rate of 0.005 mg/kg bw per lb is a factor of about 5 higher than the previous rate of 0.0009 mg/kg bw per day (Table 2). As summarized in Table 9, this difference is attributable to the use of prediction intervals rather than confidence intervals. If confidence intervals were used, the upper bound rate would be 0.0002 mg/kg bw per lb, only modestly greater (about a factor of 2) from the previous rate of 0.0009 mg/kg bw per day.

4.2.3.2. Orchard Airblast Application

Given the substantially higher worker exposure rates in the orchard airblast study of azinphos-methyl from the study by Franklin et al. (1981) relative to the exposure rates for other broadcast ground applications (Figure 7), separate and much higher exposure rates can be derived for orchard airblast applications—i.e., 0.08 (0.02 to 0.3) mg/kg bw per lb—as summarized in Table 7. These rates, however, are derived with substantial reservation and solely for the sake of transparency. As detailed below, these worker exposure rates are not recommended for use in Forest Service risk assessments.

As summarized in Table 7, the dermal absorption rate for azinphos-methyl is higher than that of 2,4-D by a factor of over 30 [0.0227 $hour^{-1}$ ÷ 0.00066 $hour^{-1}$ ≈ 34.39]. Thus, if there is an underlying relationship between worker exposure rates and dermal absorption rates, it would be reasonable to expect that an application of azinphos-methyl would be associated with higher worker exposure rates. Conversely, the dermal absorption rate of alachlor (0.0229 $hour^{-1}$) is comparable to that of azinphos-methyl. As illustrated in Figure 8 and summarized in Table 9, the exposure rates for alachlor following surface application and soil incorporation are much lower than those for orchard airblast applications of azinphos-methyl. Thus, there does not appear to be a basis for asserting that high exposure rates from orchard airblast applications of azinphos-methyl are due solely to the high dermal absorption rate for this pesticide.

A reservation with the worker exposure rates derived for orchard airblast applications using biomonitoring data on azinphos-methyl involves exposure rates from PHED (Table 3). Based on the PHED dermal deposition rates for open cab groundboom applications (i.e., 0.014 mg/lb) and the corresponding scenario for orchard airblast applications (i.e., 0.24 mg/lb) orchard airblast exposures are about a factor of 17 greater than rates for groundboom applications [0.24 mg/lb ÷ 0.014 mg/lb ≈ 17.1]. Based on the rates from biomonitoring given in Table 14, the central estimate of the exposure rate for airblast applications is greater than the corresponding rate for broadcast foliar applications by a factor of 800 [0.08 ÷ 0.0001].

The worker exposure rates based on the biomonitoring study by Franklin et al. (1981) do not seem sufficient, in the absence of additional supporting data, to propose using the very high worker exposure rates from Franklin et al. (1981) in risk assessments on other pesticides. As discussed in Section 1.1, both the current analysis as well as some U.S. EPA documents (e.g., U.S. EPA/OPP 1998b) generally take the position that biomonitoring is preferable to deposition-based exposure assessments, at least when data are available on the pesticide under analysis. In the case of orchard airblast applications, however, the single study by Franklin et al. (1981) on azinphos-methyl does not appear to be sufficient to warrant the application of the exposure rates from this study to estimating exposure rates for orchard airblast applications of other pesticides.

Given the above considerations, the current analysis recommends that worker exposures associated with orchard airblast applications should be assessed using PHED rather than the available single study involving biomonitoring.

4.2.4. Aerial Applications

No new information is available on exposure rates in workers involved in aerial applications. Consequently, the data used for recommending rates is identical to that used in the previous analysis (SERA 1998).

As summarized in Table 14, the recommended rates for workers involved in aerial applications are 0.00002 (5×10^{-7} – 0.0008) mg/kg bw per lb. The central estimate is modestly lower than the previous estimate of 0.00003 mg/kg bw per lb. In the previous analysis, the central estimate was based on pilots from the study by Lavy et al. (1982). The revised estimate is based on a composite of pilots in the studies from Lavy et al. (1982) and Nash et al. (1982). As discussed in

Section 3.4.1, this compositing of the rates is justified because the rates from these two studies are not significantly different. In addition, combining the rates increases the degrees of freedom in the calculation of prediction intervals.

The upper bound rate of 0.0008 mg/kg bw per lb is a factor of 8 higher than the previous rate of 0.0001 mg/kg bw per lb. As indicated in Table 10, this increase is due entirely to the use of prediction intervals rather than confidence intervals. If confidence intervals were used in the current analysis, the upper bound rate would be 0.00007 mg/kg bw per lb which is not substantially different from the previous rate [0.0001 mg/kg bw per lb ÷ 0.00007 mg/kg bw per lb ≈ 1.42].

The revised lower bound rate of $5x10^{-7}$ is lower than the previous rate of $1x10^{-6}$ by a factor of 2. Again, this difference is attributable solely to the use of prediction intervals rather than confidence intervals.

4.2.5. Aquatic Applications

As discussed in Section 3.5, aquatic applications had not been covered in the previous assessment of worker exposure rates (SERA 1998) but this application method has been addressed in several more recent Forest Service risk assessments (e.g., SERA 2006a, SERA 2008b,c; SERA 2010a; SERA 2011c). In these assessments, worker exposure rates of 0.0009 (0.0004-0.002) mg/kg bw per lb are based on the data from Nigg and Stamper (1983a). A reanalysis of these data (Attachment 1, Worksheet **Nigg and Stamper 1983a**) yields a central estimate of $8.75x10^{-4}$ mg/kg bw per lb with 95% confidence intervals of $4.09x10^{-4}$ to $1.87x10^{-3}$ and 95% prediction intervals of $1.60x10^{-4}$ to $4.79x10^{-3}$.

For the current analysis, the central estimate of the worker exposure rate remains at 0.0009 mg/kg bw per lb (i.e., $8.75x10^{-4}$ mg/kg bw per lb rounded to one significant decimal). Consistent with the other rates derived in the current analysis, the upper and lower bounds are based on prediction intervals rather than confidence intervals. As indicated in Table 14, the bounds are rounded to one significant digit (i.e., 0.0002 to 0.005 mg/kg bw per lb).

4.3. Implementation Notes

4.3.1. Utility of Both Deposition and Absorption Based Models

While the current report is focused on the reevaluation of worker exposure rates based on absorption data (biomonitoring), this focus is not intended to imply that deposition based models are not or should not be used. Both the deposition method used by the U.S. EPA (PHED Task Force 1995) as well as the estimates of worker exposure rates based on absorbed doses derived in the current analysis should be viewed as relatively crude approximations. As better data become available and methods to use these data are refined, additional methods may be employed in refining exposure assessments for workers. For example, Durkin et al. (2004) developed a physiologically based pharmacokinetic model for 2,4-D and demonstrated that the model can be used to fit the variability in worker exposure to 2,4-D from the study by Lavy et al. (1982). This analysis involved a combination of both deposition data from PHED and measurements of dermal absorption rates. As pharmacokinetic models are developed for other pesticides, these models sometimes may be preferable to current methods based on either the deposition-based or biomonitoring-based methods.

As detailed in this analysis, the use of biomonitoring studies to estimate exposures in workers applying pesticides is most fully supported by data from directed pesticides applications, particularly directed foliar backpack applications. Few studies are available for other types of pesticide applications. Consequently, Forest Service risk assessments often compare worker exposure estimates based on biomonitoring with worker exposure estimates using PHED either from the scenarios summarized in Table 3 or from EPA risk assessments. Particularly for aerial and ground broadcast applications, PHED may provide a more fully supported basis for conducting exposure assessments. A limitation with most PHED-based exposure assessments is that estimates of variability (e.g., confidence or prediction intervals) are not provided. In such cases, it seems prudent to use PHED to derive the central estimate for the exposure assessment but use scaled variability from a comparable biomonitoring data set summarized in Table 14 of this report.

4.3.2. Data on Female Workers

As discussed in Section 3.1, the lack of studies on female workers is another limitation in the development of worker exposure rates. The anecdotal observations from the available biomonitoring studies (i.e., Middendorf 1992a and 1993, particularly Worker Q from Middendorf 1993) suggest that exposure rates in female workers may not be well approximated, at least for some pesticides, by exposure rates in male workers.

It is beyond the scope of the current effort to extensively review studies on differences in dermal absorption rates between males and females. Nonetheless, a cursory review of the literature does not suggest that clear and substantial differences in dermal absorption rates between males and females have been documented. Bronaugh et al. (1983) does note that the back skin of female rats is more permeable than the back skin of male rats and this difference is correlated with differences in skin thickness. Differences in skin permeability between sexes, however, have not been noted in humans (e.g., Reed et al. 1995; Singh and Morris 2011). In addition, a relatively recent review by the International Programme on Chemical Safety, a branch of the World Health Organization, specifically notes that gender does not appear to be a significant source of variation in dermal absorption rates (IPCS 2005, p. 1); however, the discussion of differences between males and females is not detailed or well documented. The most recent dermal exposure assessment guidelines from the U.S. EPA do not specifically address differences in dermal absorption rates between males and females (U.S. EPA/ORD 2007).

While there is no basis for suggesting that female workers, relative to male workers, are likely to be subject to substantially greater exposure levels, the anecdotal observations from Middendorf (1992a; 1993) are sources of residual concern. Most forestry workers, including most pesticide applicators, are males and it does not appear likely that the available data on female forestry workers will increase substantially in the foreseeable future. Regardless, a clearer resolution of concerns for potential differences in exposure rates between male and female workers would be best resolved by focused and systematic studies on difference between male and female workers involved in pesticide applications.

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NOTE: The initial entry for each reference in braces {} simply specifies how the reference is cited in the text. The final entry for each reference in brackets [] indicates the source for identifying the reference.

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Set02	**Additional references from follow-up literature search.**
Set03	**Supplemental references from December 2011 search.**
Set04	**Additional references primarily on greenhouse exposures.**
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PeerRev	**Studies recommended during peer review.**
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Table 1: Overview of Worker Exposure Methods

Factor	Forest Service	U.S. EPA
General Approach	Absorption based	Deposition based
Database	Worker exposure studies measuring absorbed dose covering all routes of exposure (SERA 1998).	Worker exposure studies on deposition from Pesticide Handlers Exposure Database (PHED Task Force 1995).
Worker groups	Aerial, boom spray, and backpack applicators.	37 different groups are defined in database – e.g., mixing, loading, application, flaggers) for different application methods.
Absorption rate coefficients	Not explicitly used – i.e., incorporated into studies in database.	Uses estimates of daily absorption rates for dermal and inhalation exposures.
Personal Protective Equipment	Chemical specific study or taken from PHED	Taken from PHED

See Section 1 for discussion.

Table 2: Worker Exposure Rates for Standard Terrestrial Application Methods

Absorbed Dose Rates in mg/kg bw/day per lb applied

Worker Group	Central	Lower	Upper
Directed foliar	0.003	0.0003	0.01
Broadcast foliar	0.0002	0.00001	0.0009
Aerial	0.00003	0.000001	0.0001

Treatment Rates in Acres per Day

Worker Group	Central	Lower	Upper
Directed foliar	4.4	1.5	8.0
Broadcast foliar	112	66	168
Aerial	490	240	800

See Section 1 for discussion.

Table 3: Summary of Exposure Rates from PHED

All values in mg/lb handled

Scenario	No clothing	Single Layer, No gloves	Single layer, Gloves	Inhalation
1. Dry flowable, open mixing and loading	1.1	0.066	0.066	0.00077
2. Granular, open mixing and loading	0.032	0.0084	0.0069	0.0017
3. All liquids, open mixing and loading	3.1	2.9	0.023	0.0012
4. Wettable powder, open mixing and loading	6.7	3.7	0.17	0.04342
5. Wettable powder, water soluble bags	0.039	0.021	0.0098	0.00024
6. All liquids, closed mixing and loading			0.0086	0.000083
7. Aerial-fixed wing, enclosed cockpit/liquid	0.0050	0.0050	0.0022	0.000068
8. Aerial-fixed wing, enclosed cockpit/granular	0.0044	0.0017	0.0017	0.0013
9. Helicopter application, enclosed cockpit		0.0019	0.0019	0.0000018
10. Aerosol application	480	190	81	1.3
11. Airblast application, open cockpit	2.2	0.36	0.24	0.0045
12. Airblast application, enclosed cockpit			0.019	0.00045
13. Groundboom applications, open cab	0.046	0.014	0.014	0.00074
14. Groundboom applications, enclosed cab	0.010	0.0050	0.0051	0.000043
15. Solid broadcast spreader, open cab, AG	0.039	0.0099		0.0012
16. Solid broadcast spreader, enclosed cab, AG	0.0021	0.0021	0.0020	0.00022
17. Granular bait dispersed by hand			71	0.47
18. Low pressure handwand	25	12	7.1	0.94
19. High pressure handwand	13	1.8	0.64	0.079
20. Backpack applications	680			0.33
21. Hand gun (lawn) sprayer			0.34	0.0014
22. Paintbrush applications	260	180		0.280
23. Airless sprayer (exterior house stain)	110	38		0.830
24. Right-of-way sprayer	1.9	1.3	0.39	0.0039
25. Flagger/Liquid	0.053	0.011	0.012	0.00035
26. Flagger/Granular	0.0050			0.00015
27. WP or liquid/open pour/airblast/open cab	26			0.021
28. WP or liquid/open pour/airblast/closed cab	0.88	0.37	0.057	0.0013
29. Liquid or DF /open pour/ground boom/closed cab	0.22	0.089	0.029	0.00035
30. Granule/open pour/belly grinder	210	10	9.3	0.062
31. Push type granular spreader		2.9		0.0063
32. Liquid/open pour/low pressure handwand	110	100	0.43	0.030
33. WP/open pour/low pressure handwand			8.6	1.1
34. Liquid/open pour/backpack			2.5	0.03
35. Liquid/open pour/high pressure handwand			2.5	0.12
36. Liquid/open pour/garden hose end sprayer	34			0.0095
37. Liquid/open pour/termiticide injection			0.36	0.0022

Note that the above values are in mg a.i./lb handled and not in mg/kg bw per lb handled.

Source: Keigwin (1998)
See Section 1 for discussion.

Table 4: Dermal Absorption Rates and Absorbed Dose Rates Used in SERA (1998) Analysis

Code	Chemical	Relative Dermal Absorption Rate [1]	Relative Occupational Exposure Rate [1]
A	Dichlorprop	0.82	1.3846
B	Picloram	0.77	0.3846
C	Dichlorprop	0.82	3.2258
D	Picloram	0.77	0.1613
E	Picloram	0.77	0.4286
F	Dichlorprop	0.82	1.0313
G	Dichlorprop	0.82	0.8857
H	Picloram	0.77	0.4487
I	Picloram	0.77	0.7321
J	Picloram	0.77	0.1125
K	Picloram	0.77	0.1526
L	Picloram	0.77	0.6286
M	Picloram	0.77	0.7260
N	Glyphosate	0.62	1.1818
O	Glyphosate	0.62	0.4286
P	Cypermethrin	3.85	1.0000
Q	Dithiopyr	1.90	0.1086
R	Triclopyr, BEE	2.21	0.1212
S	Triclopyr, BEE	2.21	0.4396
T	Dicamba	0.97	1.0000

[1] All dermal absorption rates and occupational exposure rates are relative to 2,4-D.

Source: SERA (1998)
See Section 1 for discussion
See Figure 1 for illustration

Table 5: Studies (n=20) Used Quantitatively in Current Analysis

Study[1]	Application Method(s)	Pesticides(s)	Includes Females
Cessna and Grover 2002	Tracker rigs	Bromoxynil (esters)	No
Chester et al. 1987	Aerial, mixer-loaders	Cypermethrin	Not specified
Cowell et al. 1991	Lawn spray applications	Dithiopyr	Not specified
Cruz Márquez et al. 2001	Greenhouse	Malathion	Not specified
Dubelman and Cowell 1989	Ground broadcast, Agricultural	Alachlor	No
Franklin et al. 1981	Orchard airblast	Azinphos-methyl	No
Grover et al. 1986	Ground broadcast, Agricultural	2,4-D (amine salt)	No
Jauhiainen et al. 1991	Backpack	Glyphosate	No
Lavy et al. 1982	Aerial, pilots and mixer-loaders	2,4-D (ester)	Not specified
Lavy et al. 1987	Directed foliar, hack-and-squirt	2,4-D (ester and salt), dichlorprop (ester), picloram (salt)	Not specified
Lavy et al. 1992	Directed foliar	Glyphosate	Not specified
Libich et al. 1984 [2]	Directed foliar	2,4-D/Picloram Mixture (amines)	Not specified
Lunchick et al. 2005	Tracker rigs	Ethoprop	No
Middendorf 1992a	Streamline Bark	Triclopyr BEE	1/16 Worker O
Middendorf 1992b	Directed foliar	Triclopyr BEE	Not specified
Middendorf 1993	Directed foliar	Glyphosate	1/16 Worker Q
Nash et al. 1982	Aerial and Ground Broadcast, mixer-loaders	2,4-D (NOS)	1/19 (aerial) 1/26 (ground)
Nigg and Stamper 1983a	Aquatic	2,4-D (salt)	No
Spencer et al. 2000	Backpack foliar	Triclopyr BEE	No
Zhang et al. 2011 (Krieger et al. 2005[3])	Backpack foliar	2,4-D (ester) and Triclopyr BEE	Not specified

[1] Studies in shaded cells were included in SERA (1998) analysis.
[2] Study used only to assess relative occupational exposure rates.
[3] Pre-publication report submitted to the Forest Service.

Table 6: Pesticides Covered in Current Analysis

Pesticide (CAS No)	CAS No.	MW	Log_{10} Kow	References
2,4-D acid[1]	94-75-7	221.0	-0.75 (pH 7)	SERA 2006a
2,4-D isooctyl ester[1]	25168-26-7	333.3	6.73	SERA 2006a
Alachlor	15972-60-8	269.77	3.52	EPI Suite 2011
Azinphos-methyl	86-50-0	317.32	2.5315	EPI Suite 2011
Bromoxynil alcohol	1689-84-5	276.92	3.39	EPI Suite 2011
Bromoxynil butyrate	3861-41-4	347.01	3.94	EPI Suite 2011
Bromoxynil octanoate	1689-99-2	403.12	5.40	EPI Suite 2011
Cypermethrin	52315-07-8	416.31	6.05	EPI Suite 2011
Dichlorprop acid[1]	120-36-5	235.07	-0.25 (pH 7)	EPI Suite 2011
Dichlorprop BEE[1]	53404-31-2	335.23	4.52	EPI Suite 2011
Dithiopyr	97886-45-8	401.41	4.75	EPI Suite 2011
Ethoprop	13194-48-4	242.33	3.59	EPI Suite 2011
Glyphosate (acid)	1071-83-6	169.07	-2.90	SERA 2010a
Malathion	121-75-5	330.4	2.75	SERA 2008a
Picloram (acid) [1]	1918-02-1	241.5	-0.05	SERA 2011d
Triclopyr acid[1]	55335-06-3	256.47	-0.45 (pH 7)	SERA 2011c
Triclopyr BEE[1]	64700-56-7	356.63	4.30	SERA 2011c

[1] Parent compound is a weak acid.

See Section 3.1 for discussion.

Table 7: Dermal Absorption Data for Pesticides Covered in Current Analysis

Chemical	Measured (k_a, hour^{-1})	Estimated (95% C.I.) [1] (k_a, hour^{-1})	Species	Ratio of Measured to Est. [2]	Reference for Measured k_a
2,4-D acid	0.00066	0.0012 (0.00039-0.0037)	Humans	1.82	Feldmann and Maibach 1974[3]
2,4-D ester	N/A	0.015 (0.0032-0.075)	N/A	N/A	N/A
Alachlor	0.0229	0.0063 (0.0026-0.015)	Monkeys	3.64	U.S. EPA/OPP 1998b
Azinphos-methyl	0.0230 0.0227	0.0020 (0.001-0.0041)	Humans Rats	11.5 11.4	Feldmann and Maibach 1974[4] U.S. EPA/OPP 2001a
Bromoxynil (alcohol)	0.0019	0.0054 (0.0023-0.012)	Rats	2.82	U.S. EPA/OPP 1998a
Bromoxynil octanoate	0.011	0.0030 (0.00086-0.011)	Rats	3.62	U.S. EPA/OPP 1998a
Cypermethrin	0.0015 0.0011	0.0036 (0.00088-0.015)	Humans Rats	2.40 2.76	Woollen et al. 1992 (see text) U.S. EPA/OPP 2006b
Dichlorprop acid	N/A	0.0013 (0.00048-0.0036)	N/A	N/A	N/A
Dichlorprop ester	N/A	0.0046 (0.0017-0.012)	N/A	N/A	N/A
Dithiopyr	N/A	0.00222 (0.00069-0.0069)	N/A	N/A	N/A
Ethoprop	N/A	0.0093 (0.0035-0.025)	N/A	N/A	N/A
Glyphosate	0.00041	0.00074 (0.00014-0.0039)	Monkeys	1.32	Wester et al. 1991[5]
Malathion	0.0036	0.0019 (0.00088-0.0041)	Humans	1.90	Feldmann and Maibach 1974[4]
Picloram acid	0.00005	0.0013 (0.00051-0.0035)	Humans	26.80	Nolan et al. 1984/SERA 2011a
Triclopyr acid	N/A	0.00088 (0.00030-0.0026)	N/A	N/A	N/A
Triclopyr BEE	0.0021	0.0031 (0.0012-0.0081)	Humans	1.47	Carmichael et al. 1989[6]

[1] Based on Equation 6 as discussed in Section 3.1.
[2] The ratio of the measured to estimated values (if measured>estimated) or estimated to measured (if estimated > measured.
[3] Based on k_a estimates from SERA 2006a.
[4] Based on k_a estimates from SERA 2008a.
[5] Based on k_a estimates from SERA 2010a.
[6] Based on k_a estimates from SERA 2011d.

See Section 3.1 for discussion.
See Figure 2 for illustration.

Table 8: Worker Exposure Rates for Directed Applications

All values in units of mg/kg bw per lb applied [1]

Pesticide	Central	Lower CI	Upper CI	Lower PI	Upper PI	Note [number of data points]	Reference/ Worksheet[2]
Backpack	**Atypical**						**Section 3.2.2.1**
Dichlorprop BEE	3.36E-2	2.86E-2	3.97E-2	1.58E-2	7.17E-2	Backpack, T1 [20]	Lavy et al. 1987-1
Dichlorprop BEE	3.09E-2	2.49E-2	3.83E-2	1.15E-2	8.27E-2	Backpack, T2 [20]	Lavy et al. 1987-2
Dichlorprop BEE	3.22E-2	2.84E-2	3.66E-2	1.44E-2	7.21E-2	Backpack, T1&T2	Lavy et al. 1987-1&2
2,4-D BEE	3.19E-2	2.63E-2	3.87E-2	1.32E-2	7.70E-2	Backpack, T1 [20]	Lavy et al. 1987-3
2,4-D BEE	3.54E-2	2.75E-2	4.54E-2	1.12E-2	1.11E-1	Backpack, T2 [20]	Lavy et al. 1987-4
2,4-D BEE	3.36E-2	2.90E-2	3.89E-2	1.31E-2	8.60E-2	Backpack, T1 & T2	Lavy et al. 1987-3&4
Triclopyr BEE	2.36E-2	6.99E-3	7.94E-2	1.20E-3	4.62E-1	Backpack, hi bush [5]	Middendorf 1992b-3
Backpack	**Typical**						**Section 3.2.2.2**
Glyphosate	**3.00E-4**	**2.00E-4**	**4.51E-4**	**5.90E-5**	**1.53E-3**	**Backpack [15]**	**Middendorf 1993**
Glyphosate	1.9E-4					Backpack [N/A]	Lavy et al. 1993
Triclopyr BEE	8.00E-3	4.86E-3	1.32E-2	7.31E-4	8.76E-2	Backpack, all [22]	Middendorf 1992b-1
Triclopyr BEE	5.82E-3	3.53E-3	9.62E-3	6.76E-4	6.15E-2	Backpack, low-med bush [18]	Middendorf 1992b-2
Triclopyr BEE	3.25E-3	1.26E-3	8.4E-3	3.18E-4	3.33E-2	Backpack, leather gloves (Site 1) [5].	Middendorf 1992b-4
Triclopyr BEE	7.43E-3	4.00E-3	1.38E-2	7.95E-4	6.94E-2	Backpack, latex or nitrile gloves (Sites 2 and 4). [12]	Middendorf 1992b-5
Triclopyr BEE	1.49E-2	1.10E-2	2.00E-2	3.79E-3	5.82E-2	Backpack, Max=0.041 [20]	Spencer et al. 2000-1
Triclopyr BEE	**9.94E-3**	**7.70E-3**	**1.28E-2**	**1.75E-3**	**5.63E-2**	**Middendorf (except high bush), Spencer, and Zhang [45]**	**BkPkComposite**
Triclopyr BEE	1.13E-2	6.83E-3	1.88E-2	2.47E-3	5.18E-2	Backpack [8]	Zhang et al. 2011-2
2,4-D octyl ester	**4.93E-3**	**3.08E-3**	**7.90E-3**	**1.20E-3**	**2.02E-2**	**Backpack** [8]	**Zhang et al. 2011-3**
Other	**Directed**						**Section 3.2.3**
Dithiopyr	4.34E-5	3.17E-5	5.94E-5	1.11E-5	1.70E-4	Lawn care [18]	Cowell et al. 1991
2,4-D TIPA	1.73E-2	8.69E-2	3.47E-2	7.27E-4	4.15E-1	Hack&Squirt T1[20]	Lavy et al. 1987-5
2,4-D TIPA	**3.67E-3**	**1.27E-3**	**1.06E-2**	**2.88E-5**	**4.66E-1**	**Hack&Squirt T2**[20]	**Lavy et al. 1987-6a**
Glyphosate	3.4E-3					Backpack [5]	Jauhiainen et al. 1991
Malathion	4.47E-3					Greenhouse, PPE [3]	Cruz Marquez et al. 2001
Malathion	2.38E-2					Greenhouse, no PPE [3]	Cruz Marquez et al. 2001
Triclopyr BEE	2.07E-3	1.11E-3	3.87E-3	1.56E-4	2.74E-2	Basal Bark, all [16]	Middendorf 1992a-1
Triclopyr BEE	**1.24E-3**	**5.71E-4**	**2.69E-3**	**1.26E-4**	**1.64E-2**	**Basal Bark, gloves [12]**	**Middendorf 1992a-2**
Triclopyr BEE	4.87E-3	2.11E-3	1.12E-2	5.35E-4	4.43E-2	Basal Bark, no gloves [6]	Middendorf 1992a-3

[1] Confidence intervals (CI) and prediction intervals (PI) are calculated for the 95th percentile.

[2] Worksheets are included in Attachment 1 for all references to studies for which confidence and prediction intervals are given. Studies that are considered in more than one worksheet are designative by a dash followed by an integer (e.g., Lavy et al. 1987-5). This corresponds to the name of the worksheet in Attachment 1 for the data set from the study.

Note: In Lavy et al. (1987), T1 refers to normal work practice and T2 refers to special precautions.

See Section 3.2 for discussion.
See Figure 3 for an illustration of these data.

Table 9: Worker Exposure Rates for Ground Broadcast Applications

All values in units of mg/kg bw per lb applied [1]

Central	Lower CI	Upper CI	Lower PI	Upper PI	Chemical Note	Reference/ Worksheet
					2,4-D	
1.30E-4	5.65E-5	2.98E-4	9.36E-6	1.80E-3	Open cab (n=9).	Grover et al. 1986-1
2.89E-5	3.29E-6	2.53E-4	4.23E-8	1.95E-2	Applicators only. Form N.S. (n=8)	Nash et al. 1982-3 [2]
2.15E-4	7.84E-5	5.91E-4	1.24E-5	3.75E-3	Mixer/loader/applicators (n=7)	Nash et al. 1982-4 [2]
7.38E-5	2.15E-5	2.53E-4	5.31E-7	1.02E-2	Applicators and M/L/A (n=15)	Nash et al. 1982-5 [2]
9.12E-5	**4.14E-5**	**2.01E-4**	**1.75E-6**	**4.75E-3**	**All from Grover and Nash (n=24)**	**GrndComposite**
					Alachlor	
3.95E-5	1.19E-5	1.31E-4	2.71E-6	5.76E-4	Open cab, surface application (n=4)	Dubelman and Cowell 1989-1
5.23E-6	1.69E-6	1.62E-5	2.13E-7	1.28E-4	Closed cab, soil incorporation (n=7)	Dubelman and Cowell 1989-2
1.03E-6	5.82E-7	1.83E-6	2.54E-7	4.19E-6	Closed cab, ground broadcast (n=5)	Dubelman and Cowell 1989-3
5.22E-6	2.16E-6	1.26E-5	1.38E-7	1.88E-4	All data combined (n=16)	Dubelman and Cowell 1989-5
					Azinphos-methyl	
7.86E-2	**5.61E-2**	**1.10E-1**	**2.04E-2**	**3.03E-1**	**Orchard airblast. PPE not effective. Cabs not described. (n=15)**	**Franklin et al. 1981**
					Bromoxynil ester [3]	
3.52E-5	8.56E-6	1.50E-4	N/A[3]	N/A[3]	Ground broadcast. No gloves. (n=8)	Cessna and Grover 2002 [3]
4.25E-6	1.37E-6	2.61E-5	N/A[3]	N/A[3]	Ground broadcast. Gloves. (n=5)	Cessna and Grover 2002 [3]
2.34E-5	5.80E-6	1.04E-4	N/A[3]	N/A[3]	Weighted average of gloves and no gloves (n=8+5=13)	Cessna and Grover 2002 [3]
					Ethoprop	
6.76E-6	3.01E-6	1.57E-5	2.00E-7	2.29E-4	Injection boom (soil injection) (n=18)	Lunchick et al. 2005-1

[1] Confidence intervals (CI) and prediction intervals (PI) are calculated for the 95th percentile.
[2] At total of 26 rigs, 10 with cabs and 16 without cabs. Ground broadcast.
[3] Individual data not provided. The 'confidence limits' are based on the median and range.

NB: The study by Libich et al. (1984) is not included in the above table because absolute worker exposure rates cannot be derived. This study involved applications of 2,4-D and picloram (TIPA) and relative exposure rates are discussed in Section 3.3.

See Section 3.3 for discussion.
See Figure 7 for illustration.

Table 10: Exposure Rates for Aerial Broadcast

All values in units of mg/kg bw per lb applied [1]

Central	**Lower CI**	**Upper CI**	**Lower PI**	**Upper PI**	**Group** / **Note**	**Reference/ Worksheet[2]**
					Pilots -- All studies involve applications of 2,4-D	
3.11E-5	4.07E-6	2.38E-4	2.13E-7	4.55E-3	Pilots, T1 (n=3) and T2 (n=2)	Lavy et al. 1982-1
2.95E-5	2.35E-7	3.71E-3	1.87E-9	4.66E-1	Pilots, T1 (n=3)	Lavy et al. 1982-2
7.54E-6	3.23E-6	1.76E-5	6.86E-7	8.28E-5	Pilots (n=3)	Nash et al. 1982-2
2.03E-5	**5.87E-6**	**7.05E-5**	**4.89E-7**	**8.46E-4**	**Composite of Nash and Lavy (n=8)**	**PilotComposite**
					Mixer/Loaders	
2.37E-5	1.23E-5	4.56E-5	6.36E-6	8.79E-5	Cypermethrin (n=3)	Chester et al. 1987
4.19E-5	7.22E-6	2.44E-4	4.00E-7	4.40E-3	2,4-D (n=6)	Lavy et al. 1982-3
1.00E-5	6.97E-7	1.44E-4	4.85E-8	2.06E-3	2,4-D (n=3)	Nash et al. 1982-1
2.54E-5	1.06E-5	6.06E-5	1.10E-7	5.84E-3	Composite of above (n=12)	MxLdAerialComp

[1] Confidence and prediction intervals are calculated for the 95th percentile.
[2] The worksheet names refer to Attachment 1.
Note: In Lavy et al. (1987), T1 refers to normal work practice and T2 refers to special precautions.

See Section 3.4 for discussion.

Table 11: Mixture Data on Relative Dermal and Exposure Rates

Study	Other Chemical	Subgroup	Relative Exposure Rate	Relative Dermal Absorption Rate
Libich et al. 1984	Picloram	Kapuskasing	0.337	0.076
		North Bay	0.329	0.076
		Applicator 1	0.165	0.076
		Applicator 2	0.236	0.076
		Driver 1	0.813	0.076
		Driver 2	0.262	0.076
Lavy et al. 1987	Picloram	Injection Bar, T1	0.521	0.076
		Injection Bar, T2	1.108	0.076
		Hypohatchet, T1	0.126	0.076
		Hypohatchet, T2	0.157	0.076
		Hack-and-squirt, T1	0.514	0.076
		Hack-and-squirt, T2	0.601	0.076
Lavy et al. 1987	Dichlorprop	Backpack, T1	1.056	1.083
		Backpack, T2	0.873	1.083
Zhang et al. 2011	Triclopyr	Backpack	2.245	3.182

Note: 2,4-D is the reference pesticide for relative rates. The absolute exposure rates and dermal rates are divided by the corresponding values for 2,4-D. In Lavy et al. (1987), T1 refers to normal work practice and T2 refers to special precautions.

See Section 4.1 for discussion.
See Figure 9 for illustration.
Details of analysis in Attachment 1, Worksheet **RelRatesMixAnal1**.

Table 12: Relative Dermal and Exposure Rates for Combined Mixture/Backpack Analysis

Study	Pesticide	Relative Exposure Rate (mg/kg bw per lb)	Relative Dermal Absorption Rate ($hour^{-1}$)	Source of Dermal Absorption Rate
Middendorf 1993	Glyphosate	0.06085	0.62121	Humans
Lavy et al. 1987, T1	Dichlorprop	1.05557	1.08333	QSAR
Lavy et al. 1987, T2	Dichlorprop	0.87316	1.08333	QSAR
Lavy et al. 1987 [1]	Picloram	0.39010	0.07576	Humans
Lavy et al. 1993	Glyphosate	0.03854	0.62121	Humans
Libich et al. 1984	Picloram	0.31171	0.07576	Humans
Middendorf 1992b, low bush	Triclopyr	1.18053	3.18182	Humans
Spencer et al. 2000	Triclopyr	3.02231	3.18182	Humans
Zhang et al. 2011	2,4-D	1.00000	1.00000	Humans
Zhang et al. 2011	Triclopyr	2.29209	3.18182	Humans

Note: 2,4-D is the reference pesticide for relative rates. The absolute exposure rates and dermal rates are divided by the corresponding values for 2,4-D.

[1] Includes T1 and T2 groups for injection bar, hypohatchet, and hack-and-squirt. In Lavy et al. (1987), T1 refers to normal work practice and T2 refers to special precautions.

See Section 4.1.3 for discussion.
See Figure 11 for illustration.
Details of analysis in Attachment 1, Worksheet **RelRatesComposite**

Table 13: Dermal Absorption and Worker Exposure Rates for Ground Broadcast Applications

Study/Studies	Pesticide (Application Method)	Exposure Rate (mg/kg bw per lb)	Dermal Absorption Rate ($hour^{-1}$)	Source of Dermal Absorption Rate
Grover et al. 1986 and Nash et al. 1982 Combined	2,4-D (Foliar Broadcast)	0.0000912	0.00041	Humans
Dubelman and Cowell 1989, all	Alachlor (Soil Incorporation and Surface Application)	0.00000522	0.0229	Monkeys
Franklin et al. 1981	Azinphos-methyl (Orchard Airblast)	0.0786	0.0227	Rats
Cessna and Grover 2002, all	Bromoxynil ester (Foliar Broadcast)	0.0000234	0.011	Rats
Lunchick et al. 2005	Ethoprop (Sweep injection boom or surface application)	0.00000676	0.0093	QSAR (Equation 6)

See Section 4.1.4 for discussion.
See Figure 12 for illustration.
Details of analysis in Attachment 1, Worksheet **BroadcastAnal-1a**.

Table 14: Revised Recommendations for Worker Exposure Rates

Application Method	Reference Chemical [Dermal k_a]	Worker Exposure Rate (mg/kg bw per lb) [Confidence Intervals] (Prediction Intervals)[1]	Eq. 22[2]	Note; Detail Table [4]
Directed Ground				
Backpack Directed Foliar and Greenhouse Applications [5]	Glyphosate [0.00041 hour^{-1}]	0.0003 [0.0002-0.0005] (0.00006-0.002)	Yes	Middendorf, 1993; Table 8
	2,4-D [0.00066 hour^{-1}]	0.005 [0.003-0.008] (0.001-0.02)	Yes	Zhang et al. 2011; Table 8
	Triclopyr BEE [0.0031 hour^{-1}]	0.01 [0.008-0.01] (0.002-0.06)	Yes	Composite of Middendorf 1992b, Spencer et al. 2000 and Zhang et al. 2011; Table 8
Hack-and-squirt	2,4-D [0.00066 hour^{-1}]	0.004 [0.001-0.01] (0.00003-0.5)	Yes	Lavy et al. 1987, T2; Table 8
Basal Bark	Triclopyr BEE [0.0031 hour^{-1}]	0.001 [0.0006-0.003] (0.0001-0.02)	Yes	Middendorf 1992a, workers with gloves; Table 8
Ground Broadcast				
Broadcast foliar	2,4-D [0.00066 hour^{-1}]	0.0001 [0.00004-0.0002] ($2x10^{-6}$-0.005)	Opt.	Composite of Grover et al. 1986 and Nash et al. 1982, Table 9
Orchard Airblast	Azinphos-methyl [0.023 hour^{-1}]	0.08 [0.06-0.1] (0.02-0.3)	No	Franklin et al. 1981, Table 9. **Not recommended for use in risk assessments.[3]**
Aerial				
All aerial broadcast	2,4-D [0.00066 hour^{-1}]	0.00002 [0.000006-0.00007] ($5x10^{-7}$-0.0008)	Opt.	Composite of pilots from Lavy et al. 1982 and Nash et al. 1982, Table 10
Aquatic				
Aquatic broadcast	2,4-D [0.00066 hour^{-1}]	0.0009 [0.0004-0.002] (0.0002-0.005)	Opt.	Nigg and Stamper 1983a. No detail table. See Section 4.2.5.

[1] Central estimate and bounds are given as the geometric mean and 95% confidence and prediction intervals based on a log-transformation of the data except for backpack foliar applications of 2,4-D for which is set by analogy to triclopyr BEE. See text for discussion.

[2] Equation 22 (the adjustment of exposure rates based on relative dermal rate coefficients) should be applied to all directed ground applications but not to broadcast ground applications. For other application methods, the adjustment for dermal absorption is optional. See Section 4.2 for discussion.

[3] This rate is derived for the sake of transparency but is not recommended for use. See Section 4.2.3.2 for discussion.

[4] The detail tables are Table 8 (directed ground applications), Table 9 (ground broadcast applications), and Table 10 (aerial applications). The entries in the detail tables corresponding to the entries above are given in bold type face.

[5] See Section 3.2.3.4.2 for a discussion of the rationale for using directed foliar as a surrogate for greenhouse applications.

See Section 4.2 for discussion

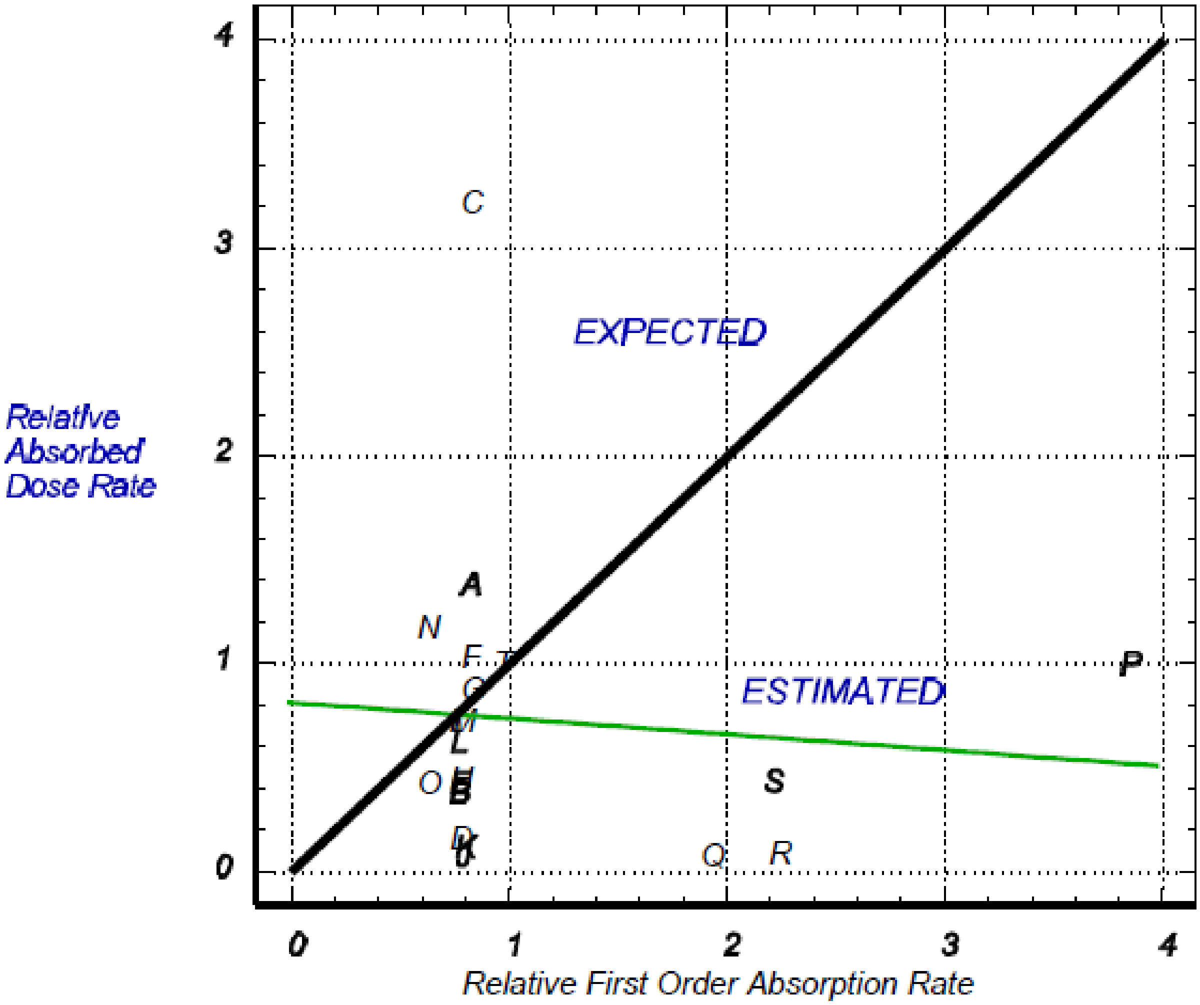

Figure 1: Exposure Rates and Dermal Absorption Rates Relative to 2,4-D

Note: 2,4-D is the reference pesticide for both relative absorbed dose rate and relative first order absorption rate. Each point represents a different chemical, the key for which is given in Table 4. See Section 1.2 for a discussion of the analysis. Additional details are given in SERA (1998).

Source: SERA (1998).
See Section 1 for discussion.
See Table 4 for data.

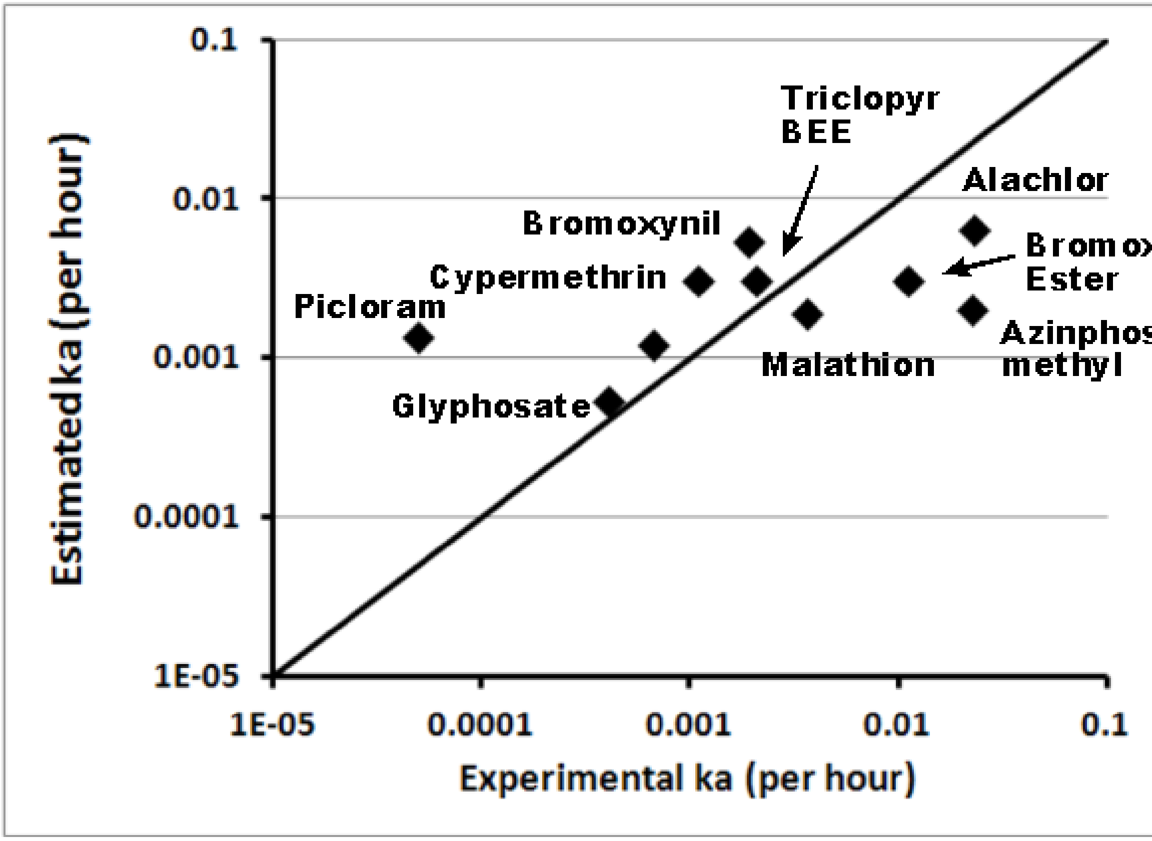

Figure 2: Observed vs Predicted Dermal Absorption

Note: This figure plots the experimental first-order dermal absorption rate coefficients (k_a) on the x-axis against the corresponding estimate of k_a using the algorithm given in Equation 6 which is taken from SERA (2014). The solid diagonal line is the line of concordance—i.e., if the estimated and experimental measurements were identical, all of the points would be on the line of concordance.

See Section 3.1 for discussion.
See Table 7 for data.

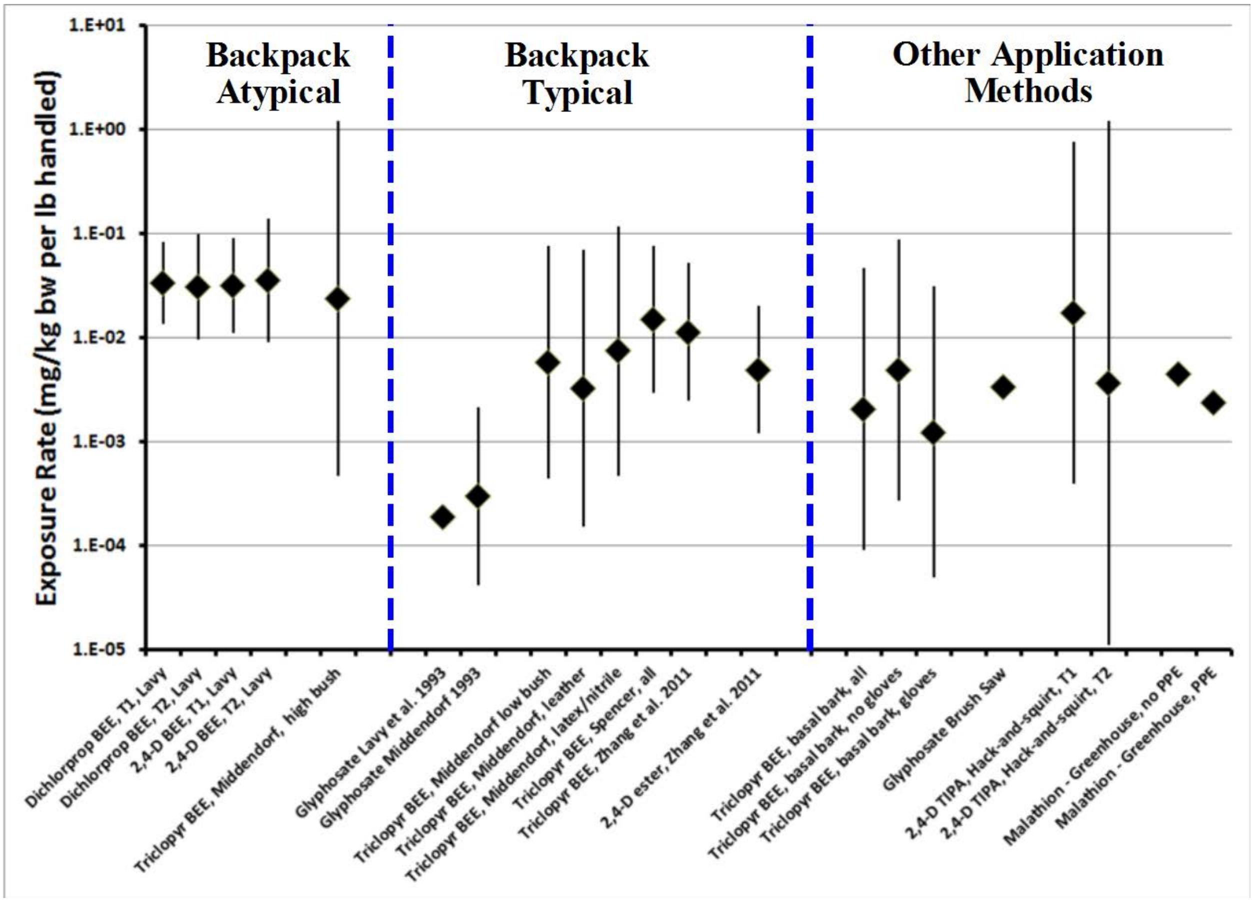

Figure 3: Worker Exposure Rates for Directed Applications

Note: The large diamonds indicate the geometric mean. The bars running vertically through the diamonds indicate the 95% prediction intervals based on a log-normal distribution.

See Section 3.2 for discussion.
See Table 8 for data.

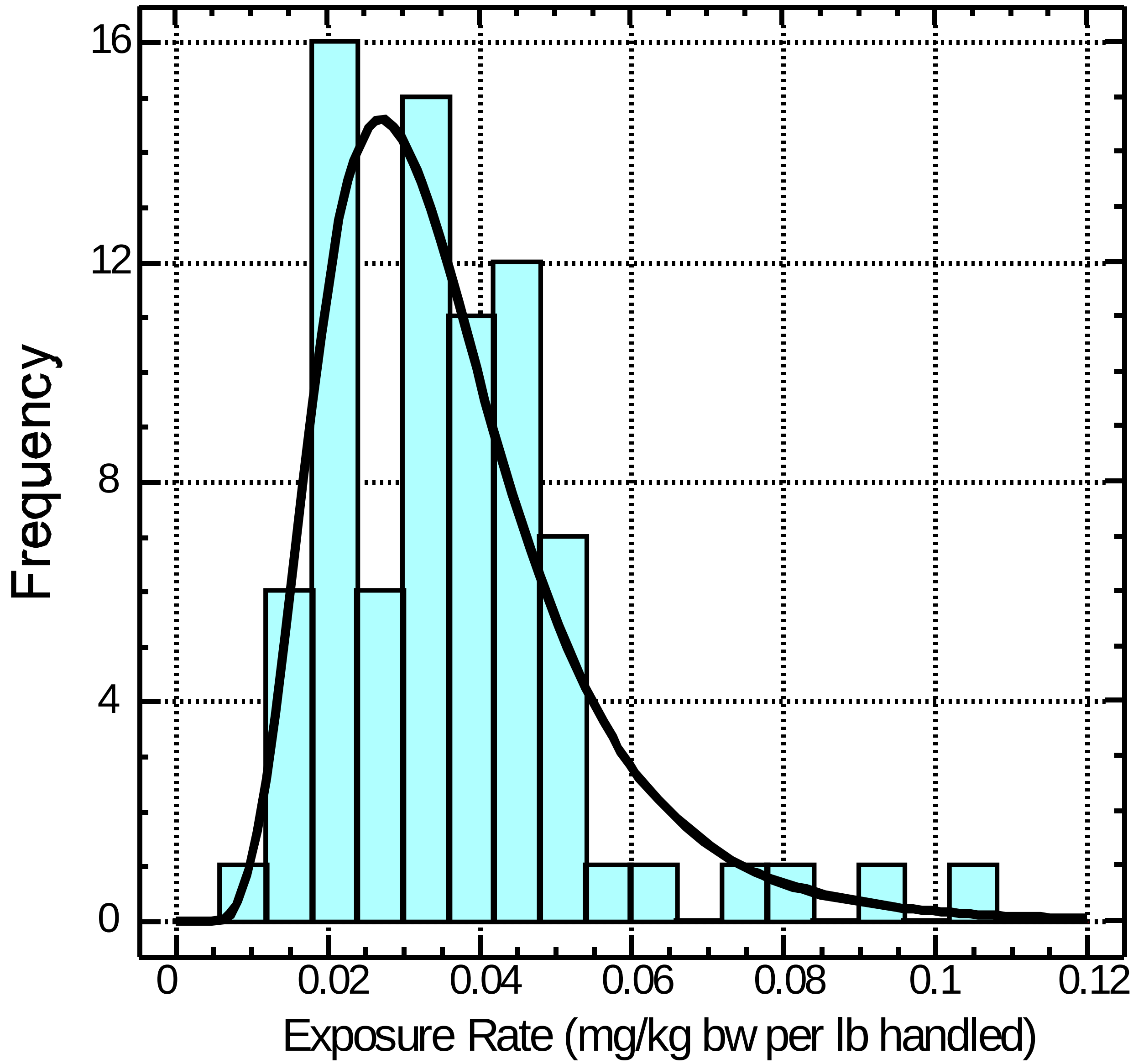

Figure 4: Distribution of Backpack Worker Exposure Rates from Lavy et al. 1987

Note: Data fit a log-normal distribution with a p-value of 0.747 using the Kolmogorov–Smirnov test. As discussed in Section 2.3, this *p*-value indicates that these data well fit the log-normal distribution.

See Worksheet **Lavy et al. 1987-9** for data.
See Section 3.2 for discussion.

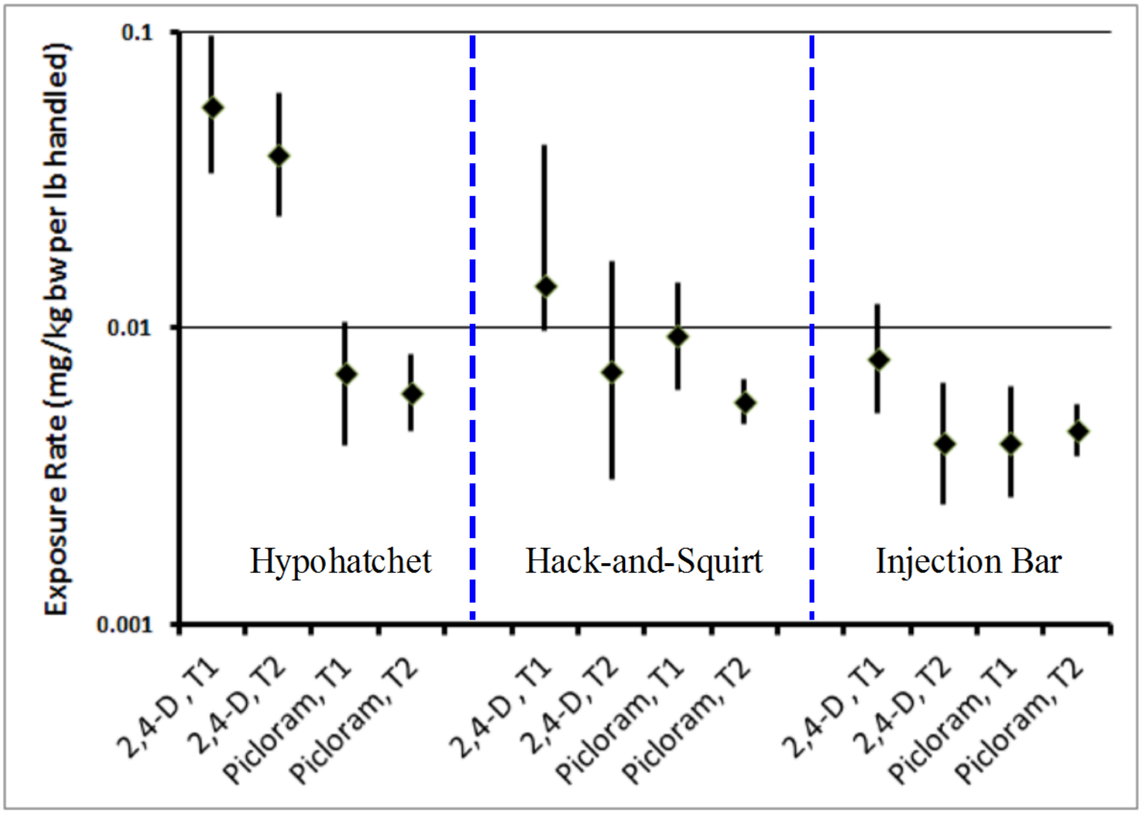

Figure 5: Exposure Rates for 2,4-D/Picloram Mixtures

Note: In Lavy et al. (1987), T1 refers to normal work practice and T2 refers to special precautions.

Data estimated from Lavy et al. 1987.
See Attachment 1, Worksheet **Lavy et al. 1987-8** for details of calculations.
See Section 3.2.3.3 for discussion.

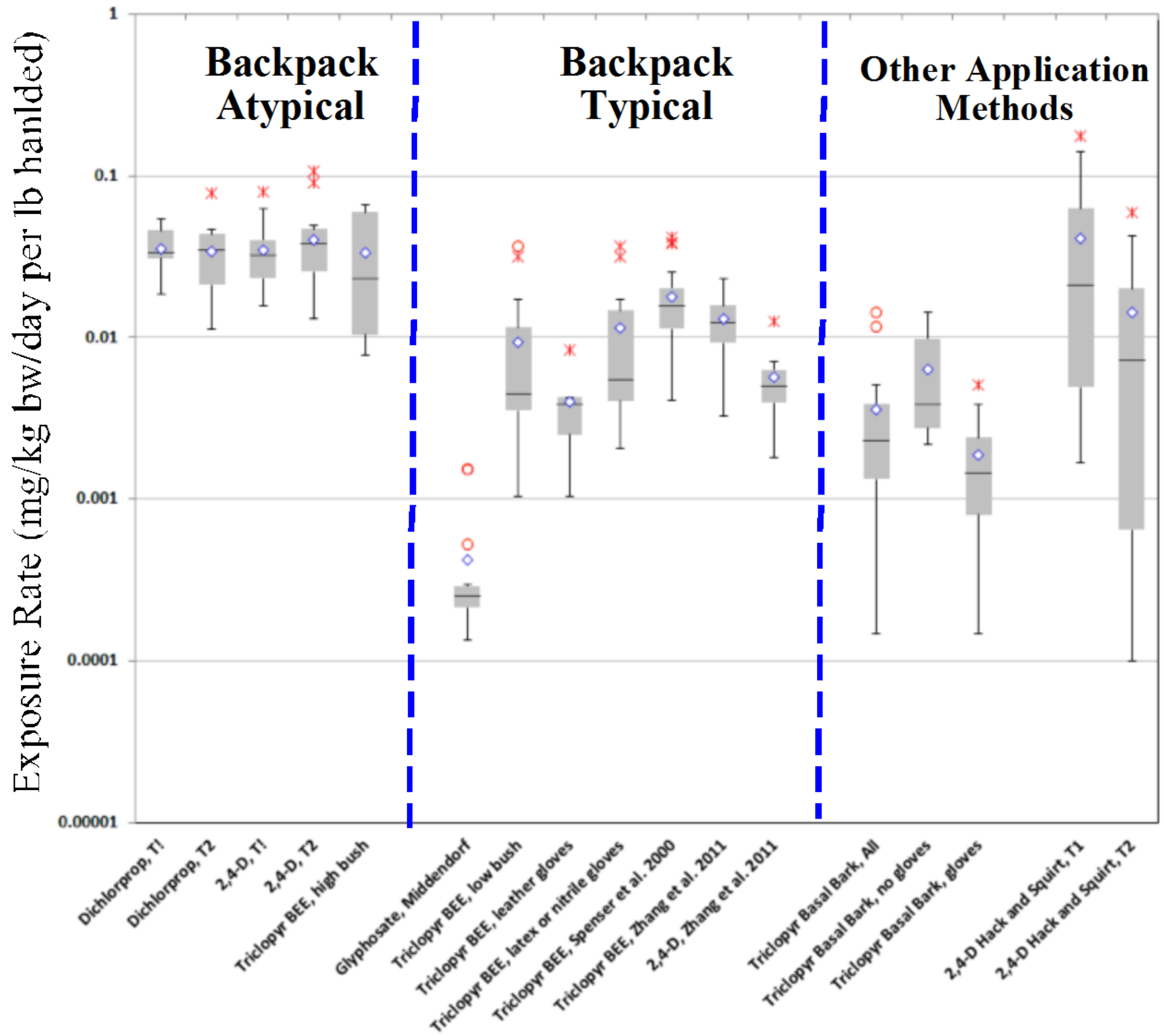

Figure 6: Box-and-Whisker Plot for Directed Applications (mg/kg bw per lb applied)

See Section 3.2.2 for discussion.

Note on Box-and-Whisker Plot: The large diamond is the arithmetic mean. The shaded box defines the first and third quartiles – i.e., regions encompassing 25% to 75% of the observations. The line running through the shaded box is the median. Points indicated by x marks denote statistical outliers – i.e., points that are greater than 1.5 times the inner quartile range (the distance between the first and third quartile) from the third quartile. The circles represent far outliers – i.e., points that are greater than 3 times the inner quartile range from the third quartile. The capped lines extending from the shaded box represent the range of values, excluding statistical outliers.

T1 refers to normal work practice and T2 refers to special precautions in the study by Lavy et al. 1987..

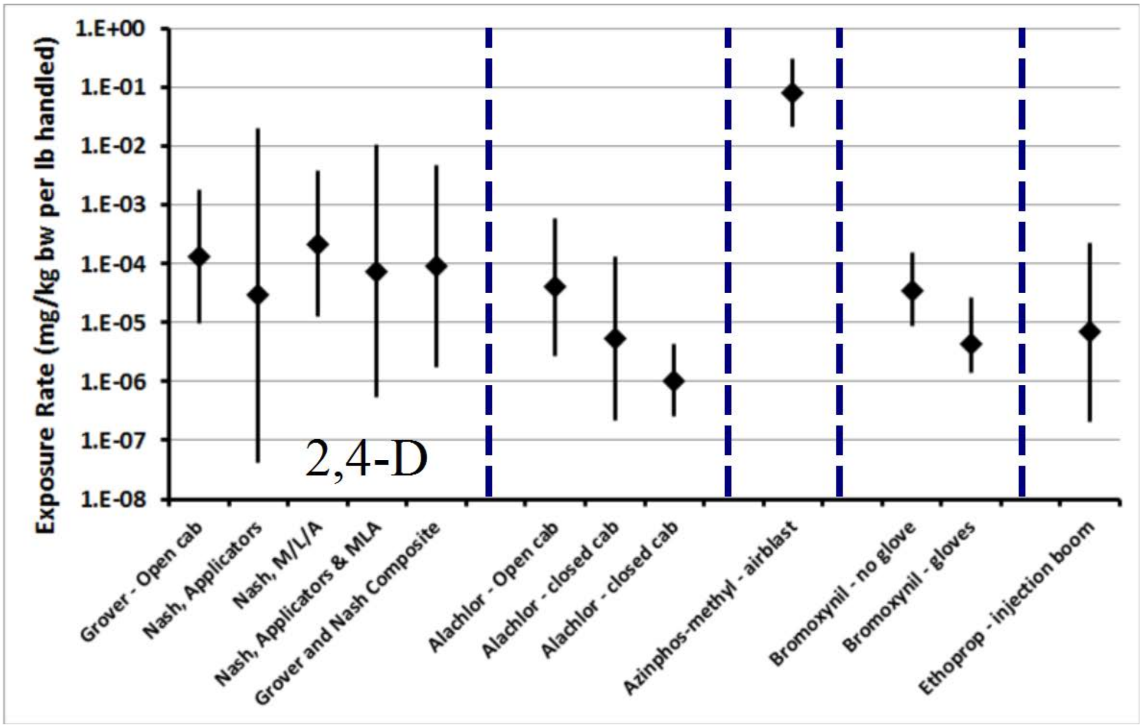

Figure 7: Ground Broadcast Exposure Rates

See Section 3.3 for discussion.
See Table 9 for data.

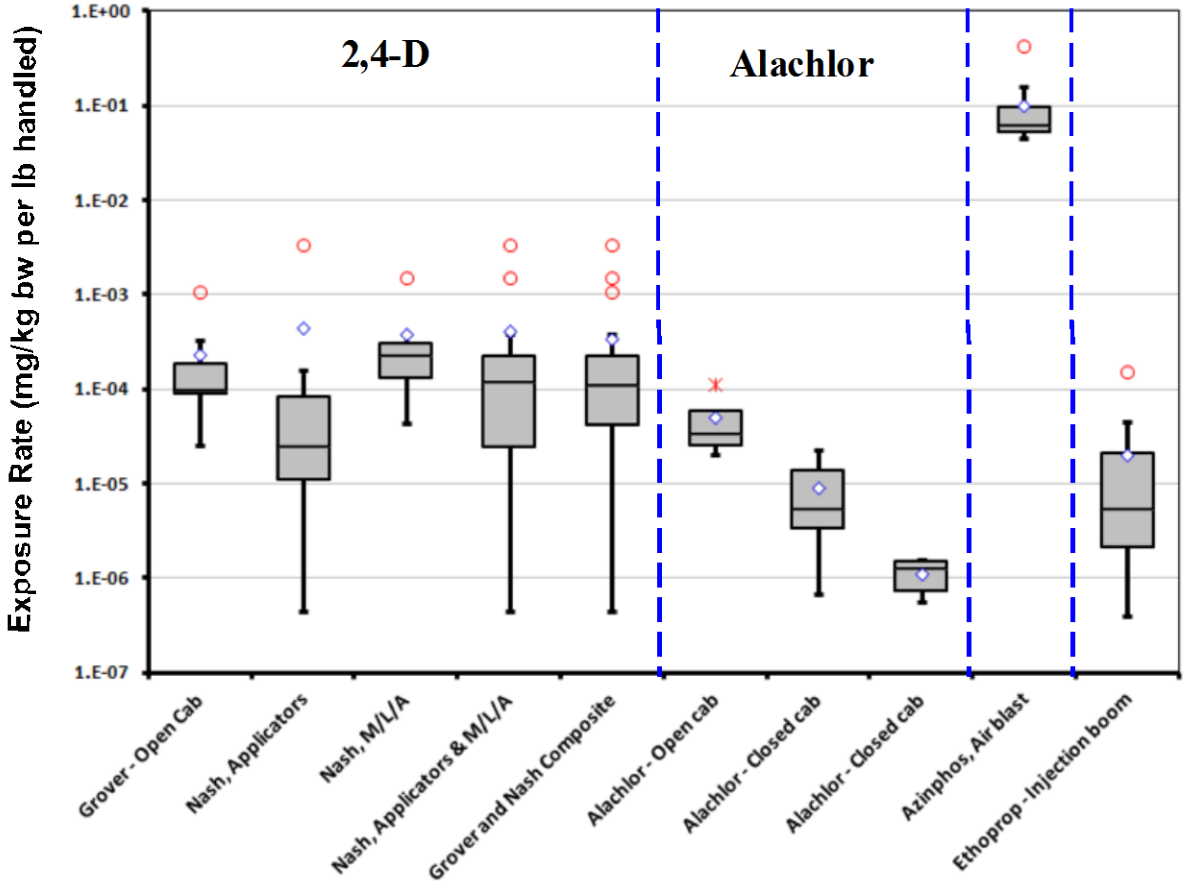

Figure 8: Box-and-Whisker Plot, Ground Broadcast

See Section 3.3 for discussion.

Note on Box-and-Whisker Plot: The large diamond is the arithmetic mean. The shaded box defines the first and third quartiles – i.e., regions encompassing 25% to 75% of the observations. The line running through the shaded box is the median. Points indicated by x marks denote statistical outliers – i.e., points that are greater than 1.5 times the inner quartile range (the distance between the first and third quartile) from the third quartile. The circles represent far outliers – i.e., points that are greater than 3 times the inner quartile range from the third quartile. The capped lines extending from the shaded box represent the range of values, excluding statistical outliers.

M/L/A = mixer/loader/applicator.

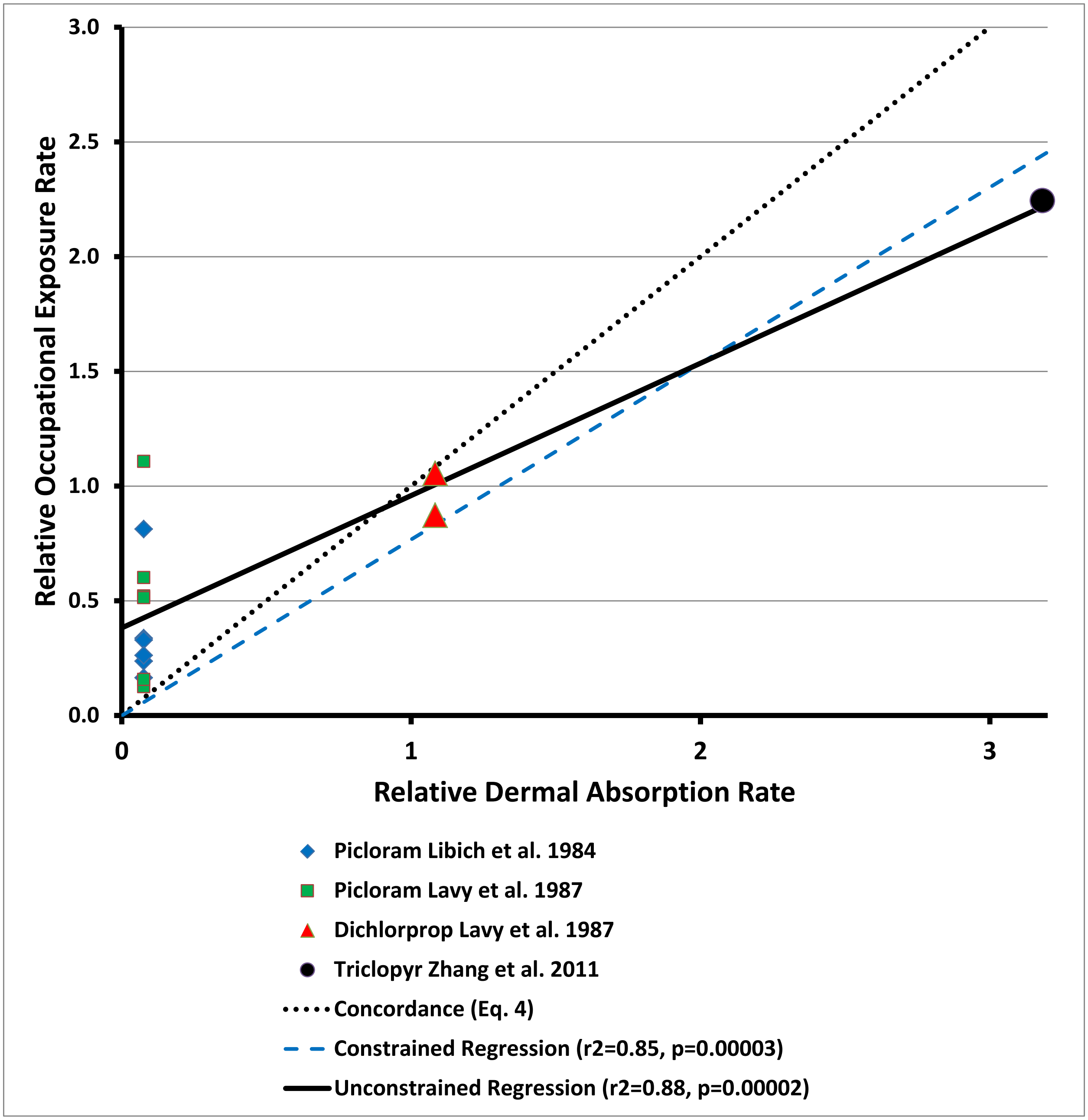

Figure 9: Relative Dermal and Exposure Rates from Mixture Studies

Note: Both the occupational exposure rates and dermal absorption rates are relative to 2,4-D. The analyses are detailed in Section 4.1.1 and the data used in the plot are given in Table 11.

See Section 4.1.1 for discussion.
See Table 11 for data.
Details of analysis in Attachment 1, Worksheet **RelRatesMixAnal**.

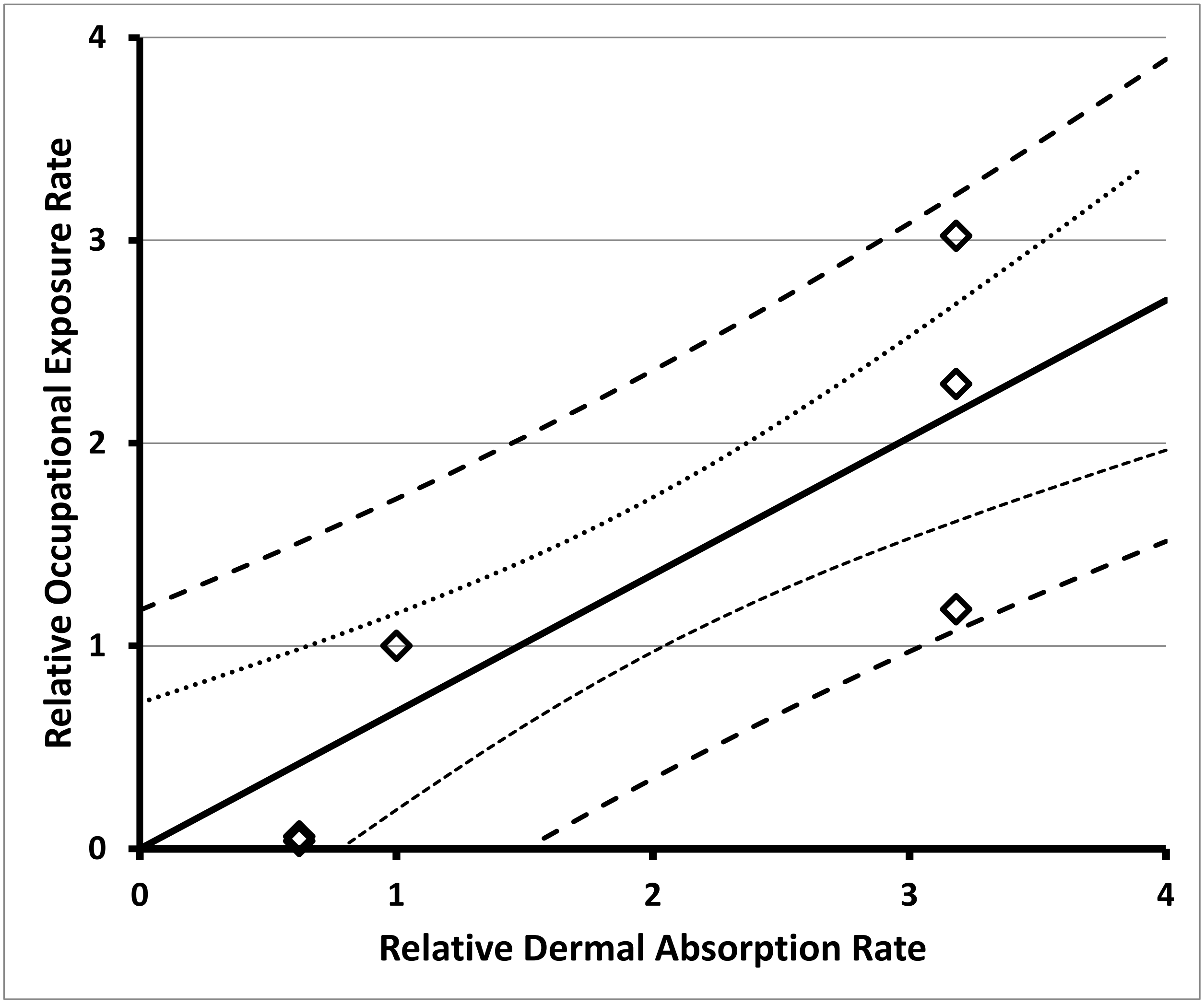

Figure 10: Relative Dermal and Exposure Rates for Backpack Directed Foliar Applications

Note: 2,4-D is the reference pesticide for relative rates. The absolute exposure rates and dermal rates are divided by the corresponding values for 2,4-D. The dotted line illustrates the confidence interval and the dashed line illustrates the prediction interval. See Section 4.1.2. for a detailed discussion of this figure.

See Section 4.1.2 for discussion.
Data and Details of analysis in Attachment 1, Worksheet **BackpackTypFolDerm1c**.

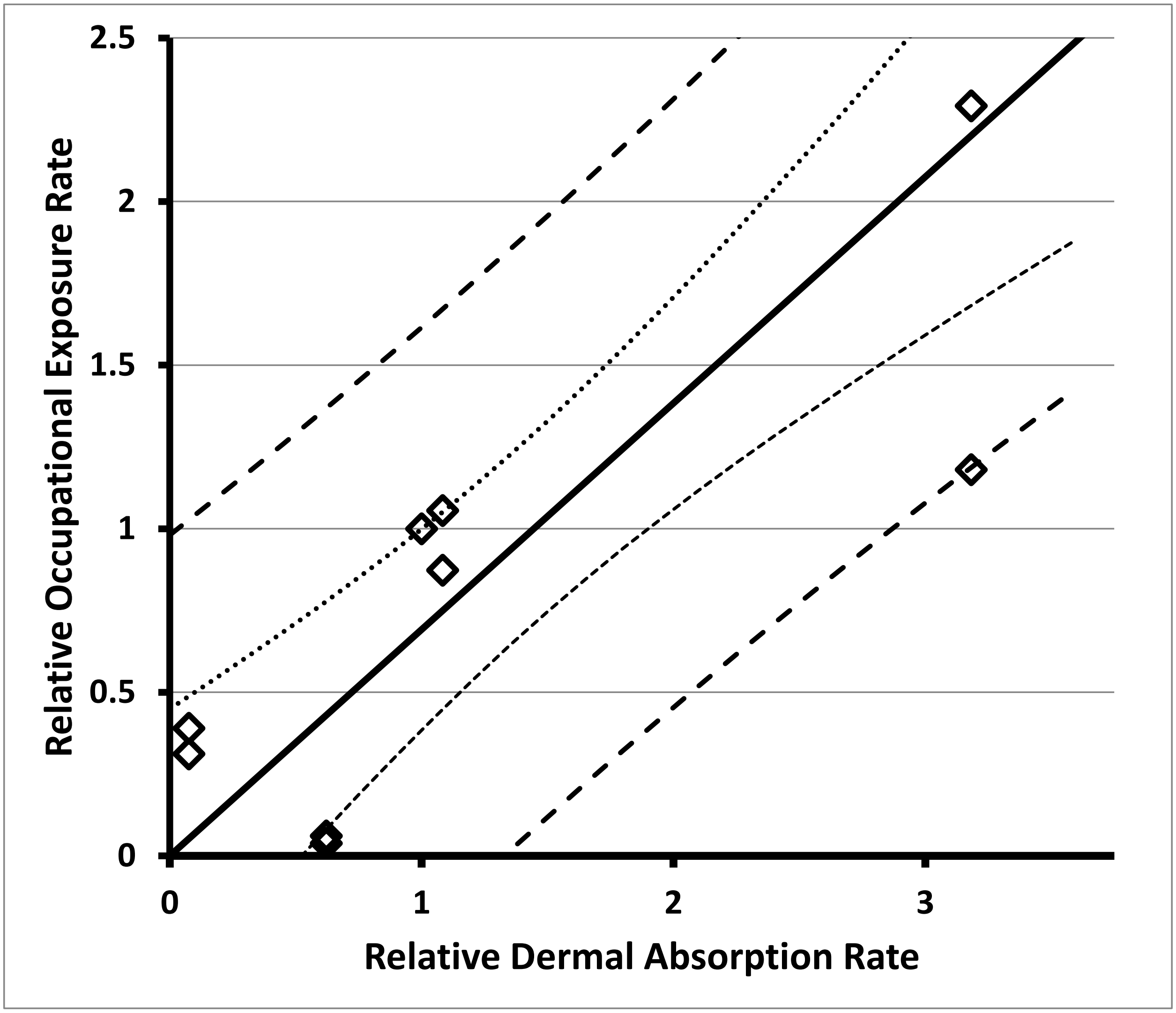

Figure 11: Composite Analysis for Backpack and Mixture Studies

Note: 2,4-D is the reference pesticide for relative rates. The absolute exposure rates and dermal rates are divided by the corresponding values for 2,4-D. The dotted line illustrates the confidence interval and the dashed line illustrates the prediction interval. The analyses are detailed in Section 4.1.3 and the data used in the plot are given in Table 12.

See Section 4.1.3 for discussion.
See Table 12 for data.
Details of analysis in Attachment 1, Worksheet **RelRatesComposite**

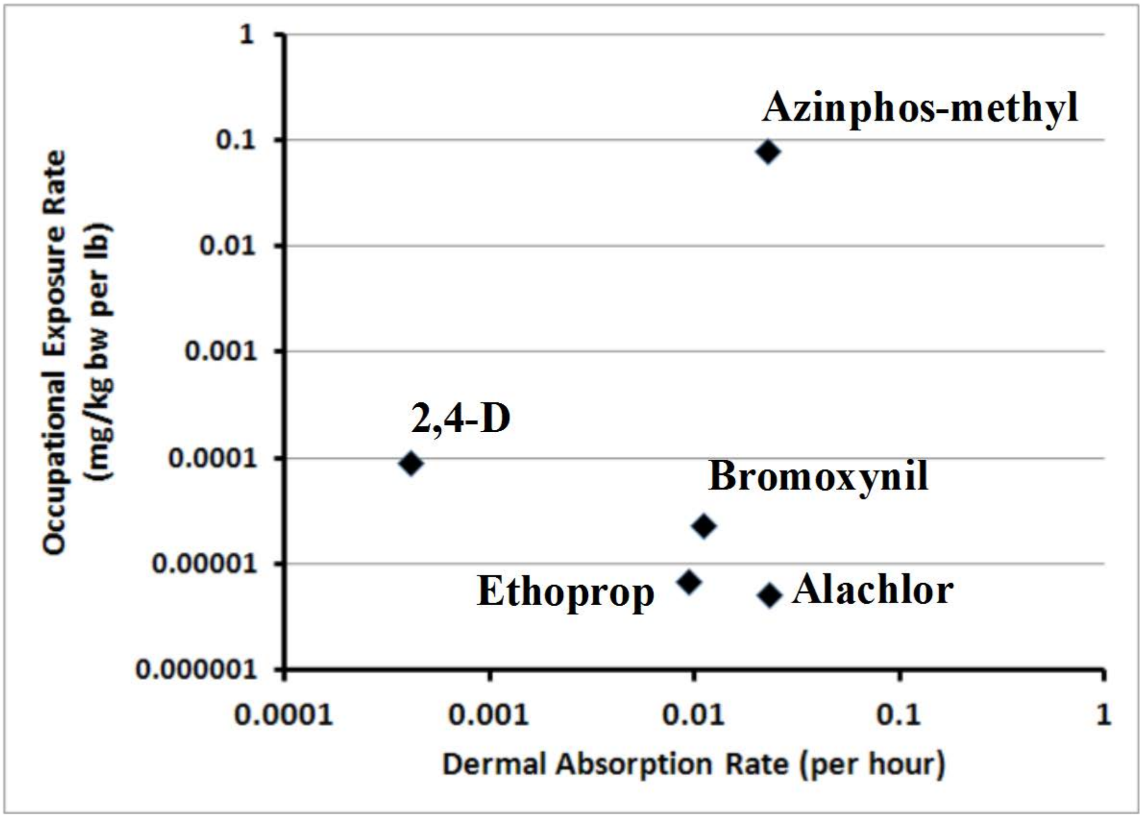

Figure 12: Relationship Exposure Rate to Dermal Absorption for Ground Broadcast Applications

See Section 4.1.4 for discussion.
See Table 13 for data.
Details of analysis in Attachment 1, Worksheet **`BroadcastAnal-1a`**

Note: The pesticide labels in the above figure do not appear in Worksheet **`BroadcastAnal-1a`** but the plot is taken from this worksheet.