STUDY TITLE

The Conservative Nature of the Current Practice in Estimating Pesticide Handler and Reentry Dermal Exposures and Doses

REPORT DATE

December 7, 2006

SUBMITTED BY

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1.0 SUMMARY

Pesticide registrations are licenses for use that are issued to registrants. They may be issued, re-issued, or revoked, depending on whether regulatory agencies have made a determination that the risks to humans, non-target organisms and the environment are acceptable or unacceptable. A critical part of the process is the modeling of human exposure while handling pesticides (mixing/loading and applying) and when reentering treated areas (e.g., harvesting fruit or playing on treated turf). Several parameters comprise the exposure models:

--Handler model parameters: Rate of dermal transfer in mg per pound active ingredient (Lb AI) handled; Lb AI per acre; acres treated per day; dermal absorption; and, kg bodyweight.

--Reentry model parameters: Dermal transfer coefficient (TC, cm^2/hr); dislodgeable foliar residue (DFR, $\mu g/cm^2$); hours exposed per day; dermal absorption; and, kg bodyweight.

--Reentry onto residential turf model parameters: Dermal ug/hr; transferable turf residue (TTR, $\mu g/cm^2$); hours exposed per day; dermal absorption; and, kg bodyweight.

--Note: For non-volatile compounds, dermal exposure is usually the route of concern. We will discuss only the dermal route, but many of the same considerations apply to the inhalation route.

Currently, the models are deterministic—all parameters are point estimates. However, each parameter has “measurement uncertainties” and “lack of knowledge” uncertainties associated with it. Regulatory agencies address these uncertainties by requiring better measurements or by applying precautionary default assumptions. The first parameter of each model is considered to be amenable to measurement uncertainty reduction and to be generic: a study with one formulation can serve as a surrogate for a similar formulation of another active ingredient. Rates of exposure for handlers are derived from the Pesticide Handlers Exposure Database (PHED), a collaborative effort of the U.S. Environmental Protection Agency, Health Canada, and the National Agricultural Chemicals Association, the industry trade association now known as Crop Life America. Three industry-sponsored task forces are currently developing additional data on the first parameter in each model: Agricultural Handler Exposure Task Force (AHETF); Agricultural Reentry Task Force (ARTF), and

Outdoor Residential Exposure Task Force (ORETF). Although PHED and the task forces provide the highest quality and best available information on the rates of exposure, there is disagreement by some stakeholders as to whether exposure assessments with generic data are sufficiently protective. In the following sections we therefore examine the measurement biases, exposure calculation biases, and model biases that result in biased risk characterizations. We here use "bias" as a neutral term. A bias can result in an increase or decrease in calculated exposure. We conclude that the current practice of using central tendency measures of rates of exposure from the databases is biased toward overestimating exposure, and that other parameters of the models also bias estimates toward overestimating exposure—a classic case of compounding conservatisms with deterministic parameter estimates. Using new "upper bound" estimates for the exposure model parameters would be a *de facto* implementation of the precautionary principle. This practice not necessary and is not supported by legislation or regulation and is not in the best interest of the public. Unrealistic overestimates of risk can lead to denial of new pesticide registrations, revocation of existing registrations, and the public's consequent loss of benefit from tools to manage noxious pests. For more reliable estimates of central tendency and upper bound risks, we recommend probabilistic assessments with the best available distributions for each model parameter.

2.0 BACKGROUND AND INTRODUCTION

Pesticides are widely used in agricultural, residential, and many other settings. Human exposures to pesticides when handling the products during application or when reentering treated sites are unavoidable. Congress has therefore charged the U.S. Environmental Protection Agency (EPA) with reviewing the toxicology, potential human exposure, and potential risk of adverse health effects when determining whether to issue registrations (licenses) for product uses. Other North American regulatory agencies make similar determinations: e.g. Canada's Pest Management Regulatory Agency (PMRA) in Health Canada and California's Department of Pesticide Regulation (DPR) in the California EPA. The process involves four major steps:

- Hazard Evaluation. Toxicity studies in laboratory animals are reviewed and the "no observed effect level" (NOEL), "no observed adverse effect level" (NOAEL), and "lowest observed adverse effect level" (LOAEL) doses associated with acute, intermediate-term, long-term, and lifetime exposures are determined. Oncogenic potential is also evaluated and quantified, if appropriate. NOTE: There are many uncertainties concerning the use of animal toxicity studies to quantitatively predict adverse effects in humans.

The animal studies are generally used conservatively, but these issues are beyond the scope of this report.

- Exposure Assessment. Rates of exposure are determined for each method of pesticide application, site of use, and route: dermal; inhalation; and, oral. The rates of application, amount of product handled, residues dislodgeable from treated surfaces, frequency, and duration of exposure are characterized, and the magnitudes of handler and reentry exposures are estimated.

- Risk Characterization. The hazard evaluation and exposure assessment are synthesized into a risk characterization. Typically, the NOAELs (mg/kg) from the most sensitive sex of the most sensitive species are selected as reference doses against which to compare human exposures/doses. The NOAEL is divided by the estimated human exposure/dose to yield a margin of exposure (MOE), formerly known as a margin of safety (MOS). Margins of exposure are calculated for all scenarios of interest.

- Risk Management. The hazard evaluations, exposure assessments, and risk characterizations are considered in conjunction with public policies to ensure safety. For occupational exposures, the standard under the Federal Insecticide, Rodenticide, and Fungicide Act (FIFRA) is no “unreasonable risk” after balancing risks and benefits. For non-occupational residential exposures, the standard under the Food Quality Protection Act (FQPA) is “reasonable certainty of no harm” with no consideration of benefits except in public health cases. In general, human exposures are considered acceptable when the MOE is equal to or greater than 100. “Acceptability” is based on a 10X uncertainty factor (UF) for intraspecies sensitivity and a 10X UF for inter-species extrapolation. Stated another way, human exposure/dose is acceptable when it is 100 times less than the exposure/dose that caused no adverse effect in the most sensitive relevant animal toxicity study. Based on a weight of evidence, and a consideration of risks and benefits when allowed, MOEs less than 100 may also be acceptable. Uncertainty factors may be added, increased, or decreased on a case-by-case basis. When the toxicity database is incomplete, or NOAELs have not been firmly established, a third UF is usually added. When the dose-response slope is steep or the toxic effect is severe, the sensitivity UF may be increased or a toxicity UF added. When non-human primate data are available, the interspecies UF may be reduced to 3X. When human data are available, the 10X interspecies UF may be unnecessary. An example is organophosphate-induced acetylcholinesterase inhibition that is known to be similar in humans and test animals (NAS, 2004).

In order for risk managers to make informed decisions, it is imperative that the hazard evaluations, exposure assessments, and risk characterizations be presented without bias or systematic error. Biases and errors quantitatively cascade through the assessments in a multiplicative fashion. In most cases, the biases err on the side of safety and, when taken together, the multiple biased values result in “compounding conservatisms” that overestimate risk. Unjustified and unrealistic overestimates of exposure and risk are detrimental to society because costs are associated with over-protection: denial of new pesticide registrations, revocation of existing registrations, and the public’s consequent loss of benefit from tools to manage noxious pests. As a committee convened by the National Academy of Sciences (2004) recently stated,

> "The committee concluded that improving the accuracy of the science employed in regulatory decisions, whichever direction (i.e., lower or higher) it moves...constitutes a societal benefit...."

In the following sections we address the exposure assessment and risk characterization elements of the process and attempt to identify biases in current practices. We discuss only dermal exposure, the route of primary concern.

3.0 BACKGROUND ON EXPOSURE TASK FORCES

The Agricultural Reentry Task Force, L.L.C (ARTF) is a consortium of agricultural chemical companies that was formed in December of 1994 to collectively satisfy data requirements for a Data Call-In (DCI) issued by the U.S. Environmental Protection Agency (EPA). The DCI was issued to all pesticide registrants, requiring data on dislodgeable foliar residues (DFR), inhalation exposure, and dermal transfer coefficients (TC) on virtually all pesticides applied to agricultural crops. The data are used in assessing potential post-application exposure to agricultural workers upon entering treated areas and in calculating safe reentry intervals. To fulfill the DCI, the member companies of the ARTF conducted a series of studies and purchased other studies, from which a comprehensive generic database was constructed that will be used to calculate dermal exposure TCs for all pesticides, crops, and reentry activities.

The Outdoor Residential Exposure Task Force, L.L.C (ORETF) is a consortium of agricultural chemical companies that was formed in December of 1994 to collectively satisfy data requirements for a Data Call-In (DCI) issued by the U.S. Environmental Protection Agency (EPA). The DCI was issued to all pesticide registrants requiring data on inhalation and dermal exposure to professional lawn care operators and homeowners who mix, load and apply pesticides to

residential turf; and post-application exposure to children and adults who reenter a treated turf area following application of a pesticide. To fulfill the DCI, the member companies of the ORETF conducted a series of studies, which, in conjunction with data from other purchased studies, was used to construct a comprehensive generic database that will be used by ORETF members in making exposure and risk assessments applicable to all of their pesticides used in residential settings.

The Agricultural Handlers Exposure Task Force, L.L.C (AHETF) was formed in December of 2001 to develop a generic exposure database for use by its member companies in assessing potential exposure to workers who mix, load, and/or apply pesticides. The generic database will contain representative data of worker activities and methods used in the handling of pesticides in North America. The studies conducted and planned by the three exposure task forces have been designed to fulfill the requirements of the US EPA Series 875: "Occupational and Residential Exposure Test Guidelines" in accordance with EPA FIFRA Good Laboratory Practice Standards, 40 CFR 160.

4.0 PESTICIDE HANDLER EXPOSURE

Pesticide handlers are people who mix and load product into application equipment, apply the product (usually diluted into water), make minor repairs to equipment during application, and clean equipment after application, usually by simply washing with a garden-type hose. The current model for quantifying pesticide handler exposure follows:

Equation 1

UE * AR * AT * DA / BW = Exposure (mg/kg BW/day)

Where:

UE	=	Unit exposure (mg/Lb AI handled),
AR	=	Application rate (Lb AI/A or LB AI/gal),
AT	=	Area treated (A/day or gal/day),
DA	=	Dermal absorption (%), and
BW	=	Body weight (70 kg for males, 60 kg for females).

The calculated mg/kg BW/day is referenced to the NOAEL to calculate the MOE. When the NOAEL is a dermal endpoint, dermal absorption is not considered. Dermal absorption is only included when It is necessary to calculate an absorbed dermal dose to assess against an oral toxicity endpoint.

Unit exposures are typically determined using passive dermal dosimetry, but they may also be based on monitoring of body fluids for residues, metabolites, or clinical chemistry changes. This report is limited to passive dermal dosimetry—the collection of residues on absorbent media placed on different handler body regions or the collection of residues from skin of the hands, face, and neck by washing or swabbing.

In the early 1980's, registrants began conducting handler and reentry exposure studies. Formal analytical method validations, complete body dosimetry, and extensive quality control programs evolved, adding to the quality and cost of studies. Registrants soon concluded that there was expensive duplication of effort in studying similar handler scenarios again and again. Registrants and regulatory authorities concurred that exposure during mixing/loading was related primarily to the pesticide formulation. For example, dumping a dusty wettable powder from a bag into a tank was different from pouring a liquid from a jug. Likewise, exposure during application was related to equipment. For example, an airblast sprayer would produce exposures different from a groundboom sprayer. Dilution of the formulation into hundreds of gallons of water to concentrations of less than 5% (typically) made the equipment the primary variable influencing application exposure. Hence, the concept was developed that rates of exposure measured from one product could serve as a surrogate for others of similar formulation (mixing/loading) or application method. Additionally, combining similar surrogate studies would increase the representativeness and statistical power for handler scenarios as compared to the limited number of replicates in a registrant's single exposure study. At that time, the EPA could not consider a study done by registrant A when reviewing a product belonging to registrant B. The use of aggregated anonymous surrogate data alleviated that problem. The creation of a surrogate database provided better exposure estimates, consistency, and transparency in calculating exposure, as well as cost efficiencies to registrants, regulators, and the public. A collaborative EPA/NACA/PMRA effort compiled existing studies and produced the Pesticide Handlers Exposure Database (PHED), a personal computer application released to the public in 1992 and still used today.

In PHED, exposures are calculated for the head/face, front of neck, back of neck, upper arms, forearms, chest/stomach, back, thighs, lower legs, feet, and hands. There are usually a different number of replicates for each body part and the algorithm determines the arithmetic mean, geometric mean, and median value for each. The algorithm then determines whether the distribution is normal, lognormal, or "other" and selects the respective measure of central tendency as a best estimate for each body part. The rate of dermal exposure is the sum of the best estimates of central tendency for each body part, normalized to Lb AI

handled. Standard central tendency rates of exposure (mg/Lb AI) for common handler scenarios have been developed by EPA (1998) and used in regulatory exposure assessments.

Recently, however, California's DPR (Powell, 2003) has concluded that unit exposures should be calculated from PHED by determining the 95th percentile using an assumed lognormal distribution and an assumed coefficient of variation of 100%. Powell concluded that due to the "uncertainty added by use of surrogate data", the 90% upper confidence limit (UCL) on the 95th percentile should be used as the unit exposure for acute and short-term assessments. Similarly, for exposure durations greater than 7 days, the 90% UCL on the arithmetic mean should be used. DPR (Powell, 2003) has estimated that these policies result in acute and short-term exposure estimates 5 to 12 times above the arithmetic mean for n<20, and intermediate- and long-term exposure estimates 2 to 3 times above the arithmetic mean for n <15.

Selection and justification of a central tendency or upper bound unit exposure is a critical science policy decision. For example, we know of no quantitative uncertainties associated with the use of surrogate data and DPR provided no justification or relevant citation for its "uncertainty" statement. Any bias at this level will cascade through the exposure assessment (see Eq. 1) and risk characterization, thus ill-informing risk managers. However, the selection of a policy, and the need for conservatism at this level of the assessment, can be informed by examining the database for "measurement biases".

4.1 Measurement Biases

Most of the bodily dermal exposure estimates in PHED are derived from pads or patches placed at the above-mentioned body parts. Exposure of the hands is usually estimated from handwashes and occasionally from woven fabric gloves. In the following section, we identify each element of a PHED exposure estimate and attempt to identify fundamental measurement biases.

Adjustments for field-fortified controls—general.

> All measured residues are adjusted for recoveries from field-fortified media to account for degradation during the monitoring period, transport to the laboratory, and storage before analysis. For example, a measured residue of 10 micrograms (µg) with field-fortified media averaging 70% recovery would be adjusted to 14.3 µg (10 µg / 70%)—a 43% increase. Samples are not adjusted for recoveries >100%. This practice of not

adjusting for >100% recovery yields reported residues that are higher than actual residues due to an analytical artifact.

Adjustments to handwash residues for field fortification recoveries.

There is no bias when these are true travel and stability spikes (i.e., samples are fortified and immediately frozen). If fortified and exposed to the environment during the entire monitoring period (as was often the case in early studies), adjusting residues for degradation during the monitoring period will bias the exposure values upward when there is similar degradation on the hands of the worker. The "adjusted" residues would be greater than the "degraded" residues on the handler.

Adjustments to residues on patches/pads/woven fabric gloves for field fortification recoveries.

Accounting for degradation during transport and storage has no impact. Adjusting dosimeter residues for degradation during the monitoring period biases the values upward because one would also expect degradation of residues on the worker. The "adjusted" residues would be greater than the "degraded" residues on the handler.

Extrapolation from patch/pad surface areas to body region surface areas.

Dosimeters typically are ~100 cm^2. The adjusted residue per cm^2 is extrapolated to the corresponding larger body region surface area. That surface area in PHED is 2.11 m^2—a value that approximates the 85th percentile for males and the 100th percentile for females (EPA, 1997). As shown in Eq. 1, exposures are normalized to bodyweight using EPA defaults of 70 kg for males and 60 kg for females. However, the 85th percentile male bodyweight (mean of ages 18-64 years) is 91 kg and the 95th percentile female bodyweight (mean of ages 18-64 years) is 93 kg (EPA, 1997). The mismatch of the PHED body surface area to the EPA default bodyweights results in mg/kg BW extrapolation errors of 1.3X and 1.55X for males and females, respectively.

Extrapolation of residues in small patch dosimeters to larger body regions has been an issue. It is not known with certainty whether the extrapolations underestimate, overestimate, or reliably estimate true dermal exposures. It is generally believed that dermal exposures are overestimated. A recent comparison of exposures predicted by PHED and measured by biological monitoring confirms this belief (Ross, 2005).

Residues less than the limit of quantitation (LOQ) or detection (LOD).

The default approach is to assume 50% of the limit value and to extrapolate to the relevant body surfaces. When monitoring the

effectiveness of a full ensemble of personal protective equipment (PPE), the exposure estimate may be dominated by less than limit values that are likely to be true “zeroes”. In some PHED scenarios, the measurements are dominated by less than limit values. Dermal exposures extrapolated from those values are calculation artifacts that overestimate likely near-zero exposures. This convention increases exposure estimates.

Handwash and woven fabric glove dosimetry.

Depending on the solvent system, handwashes may be less than 100% efficient in removing residues. The typical solvent system is a detergent water solution. Woven fabric gloves are considered to be more efficient than skin at acquiring and retaining residues. Most hand dosimetry is by washing. However, almost all pesticide labels require the wearing of chemical-resistant gloves: exposure of the hands is often a minor component and residue collection inefficiencies would have little impact.

Handwash frequency.

When the monitoring period is a full day, washes are collected at the lunch break and any other break a worker takes to eat, to smoke, or to use the bathroom. The samples are pooled for analysis or for calculating exposure. Including residues removed by hygiene early in the day and throughout the day in the calculation of exposure is a conservative bias. Those residues simply are not available for dermal absorption. Extrapolating exposures from short monitoring periods to a full day has the same bias in that it does not account for residues removed by customary hygiene.

Bodily residues.

The total residue accumulated over many hours is assumed to have deposited at initiation of monitoring (as in dermal dosing of test animals) and to have resided on the skin for 8-12 hours. This approach ignores the time factor in loading of pesticide residues on the skin. Therefore, the effective daily human dose will be much less than the calculated total daily dose.

Head patches.

Exposure of the head, face, and neck is usually estimated from head patches extrapolated to those surfaces. No adjustment is made for the observation that most handlers wear a protective hat or cap. Only recently has adjustment been allowed for the use of protective rain hats based on an AHETF airblast applicator exposure study.

Penetration of woven fabric coveralls as a second layer of clothing.

EPA assumes 50% penetration of deposited residues. For non-volatile compounds, penetration of residues is likely to approximate 10%. Dermal exposures for this PPE will be overestimated.

Glove protection factor.

EPA assumes 90% exposure reduction, a factor supported by field studies with chemical-resistant gloves.

Other PPE.

Respirators cover a substantial portion of the face. Chemical-resistant coveralls or aprons provide more protection than woven fabric coveralls. These PPE are not quantitatively accounted for by EPA, and so, dermal exposures are overestimated with these PPE.

Engineering controls.

The default estimates for exposure reduction associated with enclosed cabs and closed mixing/loading systems may be close approximations to the true values, but data are needed for refinement of these values.

We conclude that the first parameter in Eq. 1, mg/Lb AI handled, is estimated with considerable conservative bias in PHED. The systematic biases discussed above serve to inflate the fundamental rate of exposure. Calculating upper limits on an inflated estimate will adversely affect the objectivity of the exposure assessment and risk characterization. This will be especially true when other elements of the exposure model are conservatively biased.

4.2 Biases In The Pesticide Handlers Exposure Model

The EPA currently uses the central tendency mg / Lb AI as the “unit exposure” value. As discussed above, it is conservatively biased and is actually a higher percentile. In addition to unit exposure measurement biases, there are model biases that tend to be conservative. The second parameter in Eq. 1 is the rate of application in terms of Lb AI / A. Regulatory agencies generally assume the highest rate on the pesticide label. For most products, the lowest and highest label rates will be used rarely. Examination of National Agricultural Statistics Service pesticide use surveys confirms a commonsense observation. Pesticides and their application are expensive, so handlers typically use the lowest rate that is efficacious. The maximum label rate is often 2-3X greater than the typical use rate. Selection of the maximum rate is in most situations a conservative bias.

The third parameter in Eq. 1 is the acreage treated per day: A / day. EPA, DPR, and PMRA cooperated to produce a policy document on this issue (Haskell, 1998) and EPA has issued Policy Number 9.1 (EPA, 2001). The acreage defaults are the high-end values for each type of crop and equipment, and are another conservative bias.

The fourth parameter in Eq. 1 is dermal absorption. When the reference toxic endpoint is dermal, no adjustment is made for dermal absorption. However, the reference dermal toxicity studies are typically based on a test substance residence time of 8-12 hours on skin followed by washing, 5-6 days of dosing per week, and 3-4 weeks of dosing. As discussed above, assuming 8-12 hours residence time for residues removed by normal hygiene overestimates exposure. With normal hygiene washings, the effective residence time is considerably shorter. Likewise, in animal toxicity studies, the entire dose is applied at the beginning of the daily exposure period, but workers acquire the dermal dose over the course of a day: absorbed doses will be lower in the workers. Additionally, handlers are not likely to have the frequency or duration of exposure similar to the reference toxicity studies; handler exposures will typically be less frequent and of shorter duration. Since toxicity is a function of dose, frequency of dosing, and duration of dosing, the animal study NOAELs will be conservatively biased toward lower mg/kg BW/day while the estimates of human doses will be biased toward greater mg/kg/day—another conservative bias. When the reference toxicity endpoint is oral, doses are calculated from dermal exposure and percent dermal absorption. When dermal absorption data are unavailable, the EPA default is 100% (Zendzian, 1994), a generally acknowledged overestimate. Occasionally, regulatory agencies consider the ratios of oral to dermal NOAELs or LOAELs to estimate dermal absorption, which is a refinement over the 100% assumption, but is still based on non-human test animals. After a review of 40 pesticide dermal absorption studies in rats, the typical test animal, DPR found a mean of 19+/-14% and a 95th percentile of 42%, supporting a recommended conservative default of 50% (Donahue, 1996). DPR also noted that dermal absorption in the rat is likely to exceed human dermal absorption by 2-10X (Wester and Maibach, 1993) and that ethical human dermal absorption studies were preferred. As with dermal toxicity studies, dermal absorption studies are typically based on 8-12 hours of test substance residence time on skin, followed by washing. Again, assuming 8-12 hours residence time for residues removed by normal hygiene, and loading of the entire dermal dose at the beginning of the day, overestimate exposure. Additionally, residues bound in skin in dermal absorption studies are considered to be absorbed, even if not bioavailable, thus increasing the calculated rate of exposure and dose. As discussed by Ross et al (2000), the simple comparison of dose calculated from percent dermal absorption to an oral dose NOEL (assuming 100% absorption) is incorrect. Peak plasma concentrations from the oral dose will be higher and occur earlier than peak

plasma concentrations from a similar calculated dermal absorbed dose due to slower absorption. Examples of the differences in peak concentration ranged from 3X to 8X.

The fifth parameter in Eq. 1 is bodyweight. As noted above, the mismatch between body surface area and the EPA default weights of 70 kg and 60 kg for males and females injects substantial conservative bias. A recent inter-agency document (Thongsinthusak, 1998) proposes using median bodyweights from the EPA Exposure Factors Handbook (1997): 77, 62, and 70 kg for males, females, and combined genders, respectively. While this somewhat reduces bias, it is still incongruent with two observations:

--Occupational handlers are almost exclusively males.

--The mean bodyweight of handlers in studies reviewed for inclusion in the new Agricultural Handlers Exposure Task Force database is approximately 85 kg.

Unless actual or corresponding body surface areas and bodyweights are used, the dose metric will be conservatively biased.

A sixth parameter is not included in the current regulatory model but should be considered. The current regulatory model assumes serial daily exposure in a use season, an assumption that generally will not be true. The days of exposure per year will generally be intermittent and distributed over the use season, so actual handler doses over the period will be smaller than calculated doses. An “area under the curve” estimate of dose would be more appropriate and should be considered along with expected pharmacokinetics and toxic kinetics of specific products when estimating doses.

Almost every element of the current PHED-based pesticide handler exposure model is conservatively biased. Adding further conservatisms (e.g. 90th UCL on the 95th percentile rate of exposure) will result in risk characterizations that ill serve risk managers or the public. For example, consider the current EPA model for applicator exposure to orchard airblast equipment (long pants, long-sleeved shirt, and chemical-resistant gloves at 2.0 Lb AI/A, and DPR default dermal absorption):

[0.24 central tendency dermal mg/Lb AI] * [2 Lb AI/A] * [40 A/day] * [50% dermal absorption] / [70 kg BW] = 0.14 mg/kg BW.

The 90th UCL on the 95th percentile rate of exposure would be calculated by DPR as:

[0.843 arithmetic mean dermal mg/Lb AI] * [4, percentile multiplier] * [2 Lb AI/A] * [40 A/day] * [50% dermal absorption] / [70 kg BW] = 1.93 mg/kg BW.

The difference is approximately 14X. A product that was considered safe (MOE=100) at an oral NOAEL of 14 mg/kg BW would now require a NOAEL of 193 mg/kg BW for the same safety determination. Yet many products with a NOAEL of 14 would be frankly toxic at a dose of 193. Therefore, if the more precautionary approach is warranted, airblast pesticides regulated under the current approach should be causing significant numbers of illnesses when used as labeled. That is not been the case. In our opinion, the more conservative precautionary exposure characterization does not properly inform risk managers.

4.3 Agricultural Handlers Exposure Task Force (AHETF)

Although the PHED has utility, it is based for the most part on "patch dosimetry" of the 1980's. Passive dermal dosimetry has evolved and matured and a standard approach has been used since the 1990s:

--The face and neck are sampled by swabbing the entire face and neck with a multilayer gauze pad moistened with detergent water, usually 0.01% Aerosol OT in water.
--The hands are sampled by washing with the same concentration detergent water.
--The body under normal work clothing or PPE is sampled by a whole-body dosimeter: long underwear.
--The feet may be sampled by lightweight socks under work socks and footwear.

The AHETF, a consortium of registrants organized in 2001, is compiling existing agricultural pesticide use exposure studies that meet stringent quality criteria and include complete body dosimetry (although feet are optional). That database will be supplemented by new passive dermal dosimetry replicates to fill data gaps or to increase the statistical robustness of important handler scenarios. It is anticipated that this database will not have all of the conservative biases associated with the PHED (e.g., mismatch of bodyweights and body surface areas, see further discussion under reentry, below) and will be amenable to probabilistic analyses, thus better informing risk managers as to the magnitudes and distributions of rates of exposure.

The ARTF has developed agricultural reentry exposure data by the mature approach, as discussed below. The ORETF has developed "homeowner" and "lawn care operator" handler data by the mature approach and has developed "home garden" and turf reentry data, as discussed below.

5.0 AGRICULTURAL REENTRY EXPOSURE

After a site has been treated with a pesticide, people who reenter it may be exposed to vapors, dusts, and residues dislodged from treated surfaces. The primary concern is dermal exposure to residues dislodgeable from treated surfaces; other routes of exposure will not be discussed here. The typical scenario involves working in a treated crop, resulting in exposure to treated produce and/or foliage. The current model for quantifying most agricultural reentry dermal exposures is:

Equation 2.0

TDE / (DFR * 1 mg/1,000 µg) = TC

Where:

TDE = Total dermal exposure (mg/hr),
DFR = Dislodgeable foliar residue (µg/cm^2), and
` TC = Transfer coefficient (cm^2/hr).

Equation 2.1

DFR * 1 mg/1,000 µg * TC * ET * DA / BW = Exposure (mg/kg BW/day)

Where:

DFR = Dislodgeable foliar residue (µg/cm^2),
TC = Transfer coefficient (cm^2/hr),
ET = Exposure time (hr/day),
DA = Dermal absorption (%), and
BW = Body weight (70 kg for males, 60 kg for females).

A residue is quantified as “dislodgeable” by reference to a standard measurement technique based on the technique of Iwata et al (1977). Typically, 40 leaf disks, 2.5 cm in diameter, are punched into a collection jar and then shaken twice with 100 mL detergent water (0.01% Aerosol OT), 10 minutes each. The DFR is the residue in the pooled rinsates normalized to the leaf surface area (400 cm^2, both sides). The purpose is not to extract 100% of the residue from the leaf, but to use this method as an index method to assess transferability of different products to workers. When dermal exposure has been determined by passive dosimetry, and the DFR has been measured, a dermal Transfer Coefficient (TC) may be calculated (Eq. 2.0). The TC is considered to be generic to a crop/activity scenario (ARTF “cluster”). To estimate dermal exposure to another product, one has only to measure the product-specific DFRs on the days of concern and to apply them to the established crop/activity TCs. Since residues decline with time, a “restricted entry interval” (REI) may be determined;

i.e., the post-application day when exposure and risk are acceptable. Reentry prior to the REI is presumed to be a concern to regulatory agencies.

The measurement of agricultural worker reentry exposure co-evolved with the measurement of handler exposure in the 1980's and 1990's. The passive dermal dosimetry techniques were identical, along with many of the same conservative biases discussed for pesticide handlers. However, there was no collaboration between registrants and regulators to compile a reentry exposure database similar to the PHED. Realizing that there were gaps in the representativeness and quality of the existing reentry data, the EPA issued a sweeping data call-in (DCI) in 1995. No single registrant had the resources to meet the DCI. Hence, the formation of the Agricultural Reentry Task Force (ARTF) was established in 1997. Based on experiences with the development of PHED, the ARTF focused on:

--Identifying crop groupings and tasks and representative crop/task scenarios.
--Soliciting and purchasing high quality reentry studies from member registrants.
--Conducting new passive dosimetry studies using the mature techniques to fill data gaps.

Crop clusters and generic TCs have been developed after extensive statistical evaluation (Korpalski et al, 2006) and are available to ARTF members, regulators, and the public.

Again, one must ask whether there are dermal exposure measurement biases or model biases that affect risk characterizations. In terms of measurement biases, the same conservatisms discussed under "Pesticide Handlers" obtain here for the TC calculated in Eq. 2.0:

--Adjustments for field-fortified controls. ARTF and ORETF do adjust for recoveries >100%, thus making this a neutral issue.
--Adjustments to handwash residues for field fortification recoveries.
--Adjustments to residues on patches/pads/[long underwear] for field fortification recoveries.
--Handwash dosimetry.
In the case of reentry exposure, a significant portion of dermal exposure may occur on unprotected hands. Currently used reentry studies do not rely on glove dosimetry.
--Handwash frequency.
--Face/neck swabbing. The same considerations as washing hands.
--Bodily residues.

In addition to unit exposure measurement biases, there are model or scenario biases that tend to be conservative.

The first parameter in Eq. 2.1 is DFR in μg/cm^2. A registrant will usually conduct 3 or more DFR studies in a representative crop (e.g. apples representing deciduous tree fruits) in major growing regions. By EPA guidelines, the studies must be done at the highest labeled rate per acre, the maximum labeled frequency of application, and the minimum re-treatment interval in order to maximize the DFR. Normal rainfall at a site may disqualify it from consideration, depending on the timing of applications and the precipitation. As discussed under handlers, this use-scenario is rare. Regulators typically select the site with the greatest DFR for calculating exposure, which is another conservative bias. When studies are conducted at less than the maximum label rate, DFRs are linearly extrapolated to the highest label rate—probably a neutral issue.

The second parameter of Eq. 2.1 is the TC in cm^2/hr. Regulators currently use EPA Policy 003.1, a compilation of TCs for many crops and tasks. The TCs are referenced to old defaults, published studies, best guesses, and some ARTF TCs. In cases of lack of agreement between ARTF-proposed TCs and Policy 003.1, the usually higher policy TC is usually used to calculate exposure. This is another conservative bias. The Agency recently disclosed that it intends to use the highest quality available data (that will usually be ARTF and ORETF data)—this bias may diminish.

The third parameter in Eq. 2.1 is duration of exposure in hr/day. The regulatory default is 8 hr/day and is reasonable for most scenarios.

The fourth parameter in Eq. 2.1 is dermal absorption. See the detailed discussion of the conservatisms under “Pesticide Handlers”.

The fifth parameter in Eq. 2.1 is bodyweight: kg BW--70 for males; 60 for females. The ARTF and ORETF studies are generally based on whole-body dosimetry. There are no mismatches between calculated exposure, body surface area, and bodyweight when the monitored subjects’ bodyweights are used. However, the bodyweights of monitored workers averaged XX kg. Thus, the use of 70 or 60 kg BW would result in a conservative mismatch of X.X to X.X.

Again, as discussed under “Pesticide Handlers”, the frequency and duration of exposure during a season should be considered more thoroughly.

Although the dermal dosimetry has fewer biases than handler dosimetry in PHED, almost every element of the current agricultural reentry exposure model is conservatively biased. Adding further conservatisms will result in risk characterizations that ill-serve risk managers and the public. Such conservatisms could include upper bound DFRs, upper bound TCs, comparison

of single day or short-term exposures to longer-term NOAELs, and failure to account for DFR dissipation at a work site.

6.0 REENTRY EXPOSURE—RESIDENTIAL TURF

The Outdoor Residential Exposure Task Force (ORETF) has developed "homeowner" and "lawn care operator" handler data by the mature approach and has also developed turf reentry data, as discussed below.

Turf transferable residues (TTR) are measured by pinning a cotton cloth to treated turf, pressing it into the turf with a weighted roller, and analyzing the cloth for residues expressed as ug/cm^2. TTR are the turf equivalent of DFR and are used in the same manner to calculate dermal exposure from standard whole-body dermal dosimetry as described in the "AHETF" section, above. Volunteers perform a Jazzercise routine (Ross et al, 19XX) or simulated children's activities on treated turf. Jazzercise is a 20-minute choreographed exercise routine involving moves from prone and sitting positions. The ORETF developed CHAPS—children's activity patterns—a standard 2-hour routine involving running, walking, playing games, and resting on turf. CHAPS yields higher TCs than Jazzercise and will probably become the default index activity for calculating exposure.

6.1 Measurement Biases

ORETF developed the CHAPS routine from the National Human Activity Patterns Survey (NHAPS) categorization of activities obtained from the 24-hour diaries of Outdoor Playing, Active Sports, and Outdoor Recreation. Potential contact with turf was categorized as passive (low exposure potential), active (high exposure potential), and as hard direct contact (very high exposure potential). From the NHAPS survey, the ratio of time spent by children (infants through 12 years) averaged 60:33:7 for passive, active and hard direct activities, respectively. The CHAPS routine has a ratio of 50:35:15 that diminishes passive activity, increases active activities somewhat, and more than doubles hard direct activities. Additionally, the number of turf contacts per body part in the CHAPS routine exceed the target values from Stanford University videography of children by a factor of 2 to 10 and provide a worst case, upper-bound limit for representative children's activities. The rates of dermal exposure based on CHAPS and Jazzercise are from choreographed routines that are designed to maximize exposure and that would rarely, if ever, be found among free-living people.

The passive dermal dosimetry biases are the same as discussed in the section "AGRICULTURAL REENTRY EXPOSURE", above.

The rates of dermal exposure for the person wearing short pants/T-shirt are also biased by the dermal dosimetry method. Residues in lower leg and lower arm outer dosimeters are added to the inner dosimeter residues for the short pants/T-shirt scenario. However, woven fabrics are known to collect dislodgeable residues more efficiently than skin, as measured by detergent-water handwashes; i.e., cloth has a greater loading capacity than skin. Smith et al, (1991) found that nylon gloves collected 9.5X more residue than handwashes from grape leaf-pruners and harvesters. Baugher (2004) found that cotton inspectors' gloves and brown jersey work gloves collected 16X more residue than handwashes from apple harvesters. We would therefore expect dermal exposure estimates from residues in the woven fabric (cotton) outer dosimeters to be similarly overestimated.

6.2 Model Biases

As is the case for agricultural reentry, the TTR used to calculate the dermal µg/hr will be derived from the site with the largest magnitude measured. Additionally, the immediate post-application TTR is used because it is assumed that people will not respect a restricted entry interval and will allow their children to play on freshly treated lawns in short pants and T-shirts.

Toddlers are the usual focus of residential turf reentry risk assessments. The regulatory default exposure duration of 2 hours is a conservative estimate approximating the 75th percentile for toddlers (Reference).

See the previous comments regarding dermal absorption.

It has been confirmed that the measurement biases and model biases for reentry onto treated turf produce compounding conservatisms. When exposure estimates from situational biomonitoring (i.e., unsupervised people) were compared to passive dosimetry, dermal exposure was overestimated by 17—18,000X by passive dosimetry. (See discussion in ORETF turf reentry for details, Baugher et al, 2004).

7.0 CONCLUSIONS

The distributions of rates of exposure are generally skewed such that the geometric mean or median is the best estimate of central tendency. Some advocacy groups and regulators have questioned whether these central tendency rates of exposure from surrogate/generic databases are sufficiently protective when used in risk characterizations, and have suggested using arithmetic means or upper bound estimates in exposure models. However, rates of dermal exposure, as measured by passive dosimetry, are measured with considerable conservative bias. The estimated geometric mean or median rate dermal exposure is likely to be much greater than the true 50th percentile, although it is not possible to quantify the actual upper percentile it represents. When inflated central tendency rates of exposure are incorporated into dermal exposure models, the conservative bias is compounded by the conservative biases in the model parameters. The final estimate of dermal exposure will be at an upper bound, although it is not possible to quantify that percentile. Other elements of the hazard evaluation and exposure assessment, such as the lack of concordance between dosing regimens in animal dermal toxicity or dermal absorption studies and the patterns of human dermal exposure, further compound the conservatisms in the risk characterization. In short, risk managers are today presented with risk characterizations that are upper bound and, except in cases of accident or misuse of pesticides, have been shown by experience to protect the public. Altering the current practice by substituting upper bound estimates for the central tendency rates of exposure, or by substituting increased upper bound estimates for other model parameters, will produce exposure estimates that vastly overestimate likely upper bound exposures and will result in characterizations of excess risk. Such biased risk characterizations will not allow risk managers to fulfill their ethical and statutory obligations to determine which pesticides have acceptable risks and which do not. Denying or revoking registrations based on fundamentally flawed and biased risk characterizations would deny the public the benefit of necessary pest management tools.

A qualitative summary of the measurement biases and model biases are presented in Table 1.

Currently, the models are deterministic—all parameters are point estimates. Where possible, the known biases should be re-examined and modified to be more realistic. For reliable estimates of central tendency and upper bound exposures and risks, we also recommend probabilistic assessments with the best

available distributions for each model parameter. As the EPA Scientific Advisory Panel has stated (1997):

> "The problem of compounding conservatism may be avoided using probabilistic methods. They provide a more accurate image of the likelihood of exposure at different levels. Generally, we conclude that it would be most desirable for the Agency to estimate exposure probabilistically, if credible distributions of data exist."

We believe that credible distributions can be created for most if not all model parameters. Although there would be uncertainties associated with the distributions, the resulting exposure estimates would be better than the current estimates based on compounded conservatisms with unknown aggregate impact on the estimates.

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Table 1—Elements of a dermal exposure assessment and introduction of biases

Qualitative assessment of the current practice for estimating dermal exposure.	
Measurement or Model Parameter	Effect on
PHED Measurements	Conservative Bias
Adjustments for field-fortified controls.	None/Increases
Adjustments to handwash residues for field fortification recoveries.	None/Increases
Adjustments to residues on patches/pads/woven fabric gloves for field fortification recoveries.	None/Increases
Extrapolation from patch/pad surface areas to body region surface areas.	Increases
Residues less than the limit of quantitation (LOQ) or detection (LOD).	Increases
Handwash dosimetry. Residue collection efficiency and reference toxicology.	Decreases/None/Increases
Glove dosimetry. Residue collection efficiency.	None/Increases
Handwash frequency. Removal of residues by hygiene, including as exposure.	Increases
Face/neck swabbing. Removal of residues by hygiene, including as exposure.	Increases
Accumulating body residues as if acquired at beginning of day.	Increases
Head patches. Extrapolation as if head not protected.	Increases
Penetration of woven fabric coveralls: 50% protection rather than documented higher rate.	Increases
Glove protection factors.	None
Other PPE. Not quantitatively factored.	Increases
Engineering controls.	None
Agricultural and Residential Reentry Measurements by ORETF and ARTF	
Adjustments for field-fortified controls.	None
Adjustments to handwash residues for field fortification recoveries.	None
Adjustments to residues on inner and outer dosimeters for field fortification recoveries.	None/Increases
Extrapolation from whole body dosimeters to body	None
Residues less than the limit of quantitation (LOQ) or detection (LOD).	Increases
Handwash dosimetry. Residue collection efficiency and reference toxicology.	Decreases/None/Increases
Handwash frequency. Removal of residues by hygiene, including as exposure.	Increases
Face/neck swabbing. Removal of residues by hygiene, including as exposure.	Increases
Accumulating body residues as if acquired at beginning of day.	Increases
Other PPE. Not quantitatively factored.	Increases
Collection efficiency of cloth dosimeters representing skin (9.5-16X)	Increases
Jazzercise and CHAPS: intense contact with turf	Increases
Model Parameters	
Application rate per acre: highest, not typical	Increases
Acres treated per day: high end, not typical.	Increases
DFR and TTR studies: conduct at highest label rate and frequency of application, atypical	Increases
DFR and TTR values: select highest from all sites	Increases
Selection of default TCs from EPA policy, publications, or Task Forces	None/Increases
Hours per day: agricultural reentry at 8/day at restricted entry interval	None
Hours per day: residential reentry onto turf at 2/day--75th percentile	Increases
Residential reentry onto turf assumed immediately postapplication	Increases
Bodyweight: PHED handler BW and surface areas mismatch 1.3 to 1,55X	Increases
Bodyweight: defaults are smaller than reentry subjects resulting in surface area mismatch	Increases
Dermal absorption: defaults of 50% to 100% usually very high	Increases