REPORT TITLE

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

Validation of Exposure Monitoring Methodologies

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Summary of Exposure Monitoring Methodologies

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Summary of Exposure Monitoring Methodologies

I. SUMMARY

Human exposure to pesticides is usually measured by passive dermal and inhalation dosimetry and less frequently by biomonitoring. Passive dosimetry typically consists of a partial or whole body dosimeter (usually underwear) on the skin under clothing; washes of the hands; swabbing of the face and neck with moistened gauze pads, or absorbent hat patches; and, collecting air samples in the breathing zone with a personal pump and sampling train. The passive dosimetry methods have never been formally validated and no validation protocol exists. There is concern among some people that passive dosimetry may not be valid for its purpose: estimating exposure and absorbed dose in safety assessments. The task forces compared the absorbed doses calculated from passive dosimetry (PD) with the urinary metabolite biomonitoring (BM) of 290 people in 24 studies over a wide range of products and uses. The absorbed dose (AD) estimates may be compared as the ratio, PD_{AD}/BM_{AD}. When the ratio is ~1, the two methods are equivalent. In this report, biomonitoring is the collection of urine and analysis for residues of parent compound or known human metabolites. Over the range of BM doses of ~0.02 to ~200 ug/kg bodyweight, the ratio was 1.18, indicating that the two methods produced equivalent results. No single study or group of studies biased the ratios. The ratios were not influenced by the human dermal absorption over the range of 0.3% to 8%. The task forces conclude, as confirmed by comparison with biomonitoring, that passive dosimetry estimates of dermal and inhalation exposure, and subsequent absorbed dose, are valid and useful for the intended purpose in the current regulatory paradigm. There is no need to develop validation protocols or to adjust passive dosimetry estimates.

II. INTRODUCTION

The exposure of people handling pesticides or reentering pesticide-treated areas may be estimated from passive dosimetry or biomonitoring. Passive dosimetry, as practiced since the late 1980s, typically consists of a partial or whole body dosimeter (usually underwear) on the skin under the clothing of interest; washes of the hands with detergent water; swabbing of the face and neck with gauze pads moistened with the detergent water, or absorbent hat patches; and, collecting air samples in the breathing zone with a personal pump and sampling train. The sum of the residues in the dermal dosimeters is considered to represent dermal deposition. Absorbed dermal dose is estimated by applying a dermal absorption rate (percent), usually from an *in vivo* rat study but preferably from an *in vivo* human or *in vitro* human study. Exposures from the inhalation route are usually assumed to be 100% absorbed and are simply calculated from the pump flow rate and an appropriate task-related ventilation rate (L/min). Exposures are seldom fractionated by particle size to separate true inhalation exposure from oral exposure for low volatility compounds. Although long practiced and used for safety determinations, concerns have been expressed recently regarding the validity of passive dosimetry, particularly dermal dosimetry (HSRB, 2006).

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Passive dermal dosimetry methods have not been formally validated. Note that validation is not simply determining residue retention or removal efficiencies. A validation protocol would have to account for exposure to the concentrated active ingredient (AI) in neat formulation; exposure to the AI over a range of concentrations in carrier (usually relatively high volumes of water); fresh and aged residues on the skin; heterogeneous distribution and concentrations over the body regions; partial dermal absorption during the sampling period; and, mass balance. There are no known validated protocols and it is doubtful that a consensus could be reached on a proposed protocol. Additionally, there would be no justification for intentional human dosing studies for validating passive dosimetry if it is already useful for its intended purpose.

Given that each of the different passive dosimetry methods may not be validated, the issue is properly framed as follows:

> Is passive dosimetry, in the aggregate, useful for its intended purpose of estimating dose in the current exposure assessment and risk assessment paradigm?

Framed in this more holistic manner, the issue can be addressed by comparing exposure and absorbed dose estimates from passive dosimetry with biomonitoring.

In the context of this paper, biomonitoring is the collection of urine and analysis for residues of parent compound or known human metabolites. Based on appropriate supporting human pharmacokinetic and dermal absorption studies, absorbed dose can be calculated from dermal exposure. Based on concurrent, sequential, or parallel group passive dosimetry (PD) and biomonitoring (BM), the absorbed dose (AD) estimates may be compared as the ratio, PD_{AD}/BM_{AD}. When the ratio is ~1, the two methods are equivalent. When the ratio is greater than one, doses estimated from PD are greater than those measured from BM and passive dosimetry would be overestimating exposure. When the ratio is less than one, doses estimated from PD are lower than those measured from BM and passive dosimetry would be underestimating exposure. In the following sections of this report, the summary analyses of comparative studies are presented. Additional documentation may be found in Ross *et al*. (2006a).

III. BIOMONITORING AND PASSIVE DOSIMETRY STUDIES

Selection criteria for an <u>ideal</u> biomonitoring study have been summarized in Ross et al., 2001. For comparison with passive dosimetry, a biomonitoring study should ideally be conducted concurrently to capture the same exposure conditions. Concurrent passive dosimetry requires that there be no additional layers of clothing that would not normally be worn under the prevailing conditions and would therefore be unrepresentative.

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The basic method for calculating an absorbed dose from biomonitoring data is shown in equation [1].

BM_{AD} (μg) = (((μg metabolite/L urine) x (L urine) x (MW Parent / MW metabolite)) / Fraction excreted) + ((μg parent/L urine) x (L urine)) / Fraction excreted)

Where, BM_{AD} = Absorbed Dose calculated from biomonitoring,
and MW = molecular weight.

For passive dosimetry, the absorbed dose is estimated as shown in equation [2].

PD_{AD} = (dermal exposure x % dermal absorption) + (inhalation exposure x % inhalation absorption)

Where, PD_{AD} = Absorbed Dose calculated from passive dosimetry.

Twenty-four studies were identified with concurrent, parallel or sequential group passive dosimetry and urinary biomonitoring of sufficient quality to make comparisons. In the concurrent studies, passive dosimetry typically consisted of outer clothing; a tee-shirt and shorts (briefs); handwashes with detergent water; and, face/neck swabs or head patches; and breathing zone air sampling. Dermal exposure of body areas covered by clothing but not by inner dosimeters was estimated from residues on the corresponding sections of outer clothing and a clothing penetration factor obtained from body regions with both outer and inner dosimeters. Tee-shirts and briefs are typically worn and were considered not to compromise the biomonitoring. In parallel group studies one group was monitored by whole-body passive dosimetry while another group wore typical or minimal clothing. In sequential monitoring studies, a group was monitored by typical whole-body passive dosimetry and, after sufficient time for clearance of metabolites, by biomonitoring. As shown in Table 1, the studies covered a broad range of products, activities, and locations. It is noted that different investigators have used different dermal absorption values for the pesticide “B”. After careful consideration, all of the dermal dosimetry values for B were normalized to the 3% value historically used by EPA for regulating B.

Table 1: Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring

Study Reference[a]	Scenario[b]	Pesticide/Rat/ Human Dermal Absorption[c] (%)	Number of Replicates[d]	Dermal Dosage (µg/kg)[e] Human	Inhalation Dosage (µg/kg)[f]	Estimated Absorbed Dosage (µg/kg)[g]	Fraction Dermal of Total[h]	Biomon. Dosage (µg/kg)[i]
Honeycutt, 1994	ML	B/66/3.0	12/15	2.0	0.13	2.2	0.91	5.4
Honeycutt, 1994	Applicator	B/66/3.0	11/14	2.9	0.33	3.5	0.83	6.7
Honeycutt, 1994	Cleanup	B/66/3.0	10/15	0.37	0.010	0.38	0.97	0.55
Knuteson, 1994	ML	B/66/3.0	11/15	0.34	0.23	0.68	0.50	0.71
Shurdut, 1993	ML	B/66/3.0	9/9	3.9	0.34	4.9	0.80	7.5
Shurdut, 1993	Applicator	B/66/3.0	8/9	0.61	0.84	1.5	0.41	1.9
Shurdut, 1993	Scout	B/66/3.0	8/10	0.48	0.17	0.67	0.72	1.3
Murphy, 1998	MLA	B/66/3.0	12/16	0.027	0.10	0.14	0.19	0.30
Honeycutt, 1993	Citrus harvester	B/66/3.0	5/5	0.053	0.18	0.17	0.31	0.36
Honeycutt, 1993	Citrus pruner, dry	B/66/3.0	5/5	0.29	0.50	0.79	0.37	6.3
Honeycutt, 1993	Citrus pruner, wet	B/66/3.0	5/5	1.3	0.80	2.1	0.62	2.8
Rosenheck, 2000	Hose end sprayer	D/31/3.6	12/12	1.0	0.070	1.2	0.83	1.0
Rosenheck, 2000	RTU hose end	D/31/3.6	11/11	0.32	0.26	0.63	0.51	0.84
Rosenheck, 2000	Hand pump	D/31/3.6	10/10	0.11	0.039	0.17	0.65	0.40

Table 1 (cont.): Study Results for Estimated Absorbed Dosage from Passive Dosimetry and Biomonitoring

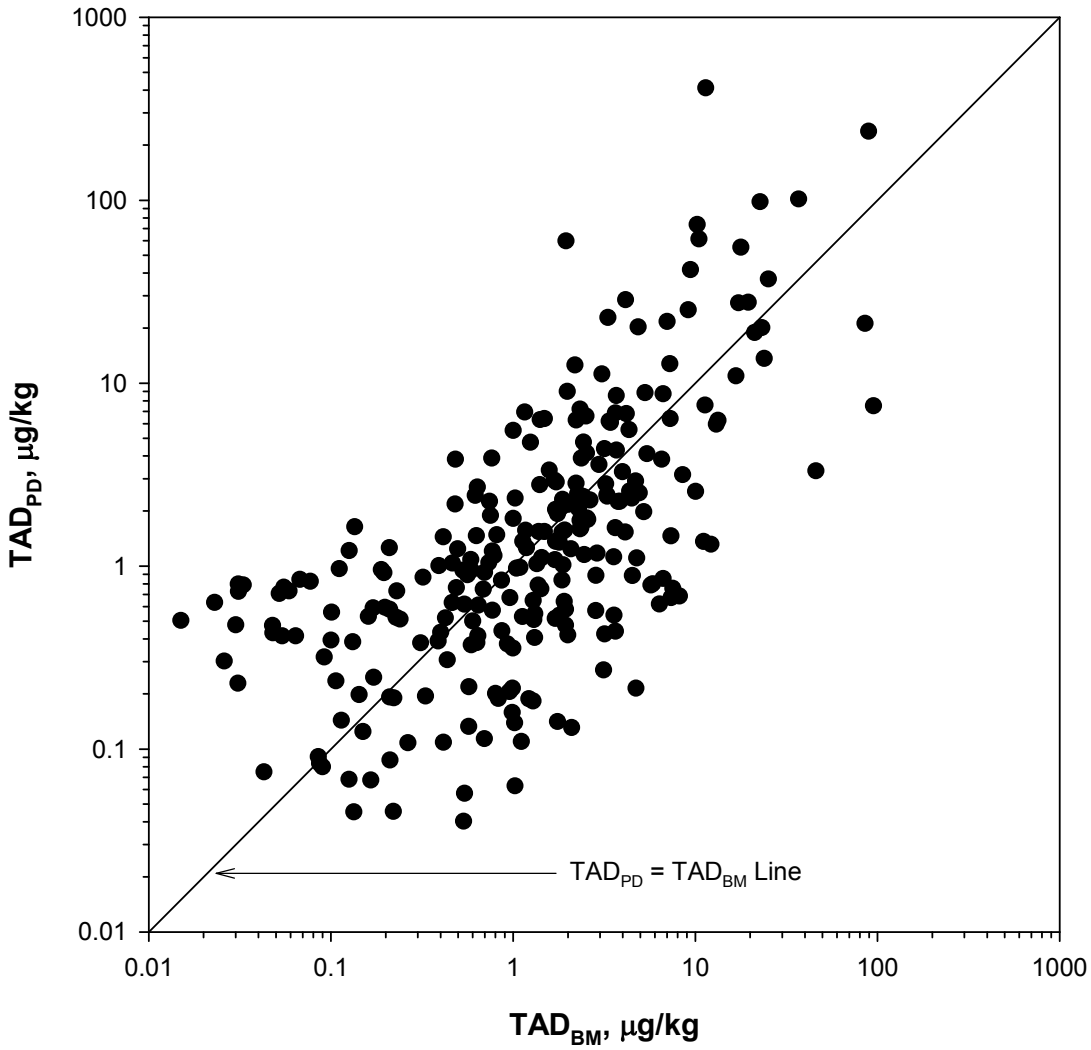
Study Reference	Scenario	Pesticide/Rat/ Human Dermal Absorption (%)	Number[a] of Replicates	Dermal Dosage (µg/kg)[b] Human	Inhalation Dosage (µg/kg)[c]	Estimated Absorbed Dosage (µg/kg)[d]	Fraction Dermal of Total	Biomon. Dosage (µg/kg)[e]
Chester, 1989	Groundboom MLA,	F/73/8.0	14/14	5.3	NA[h]	5.3	1.0	3.1
Findlay, 1998	Backpack MLA	E/3.0/0.3	20/20	0.55	0.070	0.65	0.85	0.08
Selman, 1996	groundboom ML	A/8.0/5.6	7/7	1.3	0.054	1.4	0.93	0.81
Selman, 1996	groundboom MLT	A/8.0/5.6	7/7	2.5	0.13	2.8	0.89	0.77
Selman, 1996	groundboom MLA	A/8.0/5.6	4/4	5.1	0.12	5.3	0.96	1.6
Grover, 1986	Open pour groundboom M/L/A	2,4-D/17/5.7	7/8	33.8	NA	33.8	1.00	14.3
Chester, 1986	Open pour groundboom M/L/A, ML	F/73/8.0	10 M/L/A; 3 M/L[h]	7.9	NA	7.9	1.00	5.8
Williams, 2003	Jazzercise	C/11/1.2	7/7	42	NA	0.51	1.00	0.094
Krieger, 2000	Jazzercise	B/66/3.0	11/13	110	NA	0.34	1.00	0.80
Williams, 2004	Jazzercise	B/66/3.0	41/41	69	NA	2.1	1.00	1.8

[a] Reference citations use only the first authors last name to conserve space
[b] Scenario refers to the work task being performed during exposure monitoring
[c] Most of the rat/human dermal absorption measurements are compiled in Ross et al., 2001. The rat dermal absorption for diazinon was estimated from the ratio of oral to dermal LD_{50}.
[d] Proprietary studies use letter code to identify pesticide. Only replicates where post application exposures were greater than pre-application based on biomonitoring were used. The first number indicates the number of replicates used, the second is the number of replicates actually monitored.
[e] Geometric mean absorbed dermal dosage derived by applying dermal absorption factor from third column.
[f] Geometric mean inhalation dosage based on respiratory protection (if used) and assuming 100% uptake and retention.
[g] Total of dermal + inhalation absorbed dose by replicate, then averaged as geometric mean.
[h] Fraction dermal = Dermal dosage/Estimated Absorbed Dosage
[i] Excluding replicates where post-exposure excretion was less than pre-exposure or with aberrant excretion patterns.
ABBREVIATIONS: ML=Mixer/Loader; MLA=Mixer/Loader/Applicator; MLT=Mixer/Loader/Truck Driver; RTU=Ready to Use Liquid.

IV. RESULTS AND DISCUSSION

As shown in Figure 1, the total absorbed dose estimated from passive dosimetry (TAD_{PD}) is similar to total absorbed dose estimated from the biomonitoring (TAD_{BM}) of 290 people in 24 studies. Without any statistical analysis, it is obvious that the data support a ratio (slope) of one and equivalence. The variance in the ratios is not out of the ordinary for exposure monitoring studies. The line shown depicts a perfect 1:1 correlation.

Figure 1.—The relationship of passive dosimetry and biomonitoring total absorbed doses.



The current regulatory paradigm for calculating exposures, absorbed doses, and risks involves central tendency passive dosimetry dermal and inhalation rates of exposure combined with high-end defaults for amount of active ingredient handled (or residue generated), duration of exposure, dermal absorption, and less-than-central-tendency default bodyweights (Ross et al., 2006b). Without data the dermal absorption default is 50-100%, which is usually replaced by

the highest value from a rat dermal study if available. Rat skin, in common with many animal species' skin, is not a good model for human dermal absorption. It has been shown to overestimate human dermal absorption by an average of approximately 5-fold for pesticides (Ross *et al.*, 2001).

An excellent example of the conservatism associated with use of passive dosimetry data is illustrated with calculation of absorbed dosage using rat data. The fraction of total absorbed dosage attributed to the dermal route in the studies reviewed falls in the range of 19-100%, with an average of 73%. Rat dermal absorption data are the most commonly available for pesticides. For the test substances utilized in the summarized studies, the ratio of rat to human dermal absorption ranges from 2.7 to 22-fold with an average of 5-fold. Thus, use of the rat data would increase apparent total exposure on average by 5 x 0.73 = 3.7-fold. Likewise, the application of a single human dermal absorption rate to residues on all monitored humans and all parts of the human body may be improper for some people and some parts, but it appears to work on the whole.

While there is, and always has been, large variance in the estimates of rates of exposure, other parameters in the model (paradigm) assure a compounding conservatism that has been considered protective of health (Ross et al., 2006b). It is concluded, as confirmed by comparison with biomonitoring, that passive dosimetry to estimate dermal and inhalation exposure is valid and useful for its intended purpose in the current regulatory paradigm. There is no need to develop validation protocols or to adjust passive dosimetry estimates.

V. REFERENCES

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

Chester, G. et al (1989). Compound F: dermal exposure of and absorption by workers using tractor sprayers in the Netherlands. ICI Agrochemicals Report No TMF 3487.

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

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

Honeycutt RC and Day EW (1993). Worker re-entry exposure to Compound B in citrus treated with 'Compound B 4E' insecticide. DowElanco Study ID 91-102HE.

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

HSRB (2006). Human Studies Review Board letter from Celia Fisher, Chair to George Gray, dated August 28, 2006.

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

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

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

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

Ross, J., Chester, G., Driver, J., Lunchick, C., Holden, L., Rosenheck, L., and Barnekow, D. (2006a). Comparative Evaluation Of Absorbed Dose Estimates Derived From Passive Dosimetry Measurements With Those Derived From Biological Monitoring: Validation Of Exposure Monitoring Methodologies. Report prepared for the Agricultural Handlers Exposure Task Force, L.L.C.

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

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

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