



SUMITHRIN®

Exposure & Risk Analysis of Indoor Residential Uses

March 5, 2008

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AGENDA

- Introduction
- Sumithrin Toxicology Benchmarks – Key Considerations
- Overview of Residential Exposure Scenarios Evaluated for Sumithrin
- Hand to Mouth Exposure Pathway Considerations
 - General refinements
 - Surface to hand transferability
 - Scenario-specific refinements
 - Product wt% and application rates
 - Indoor crack & crevice treatment
- Results of Sumithrin Deterministic and Probabilistic Modeling
 - Comparison SOP screening-level and alternative deterministic calculations
 - Results of stochastic modeling
- Discussion & Next Steps

TOXICOLOGY BENCHMARKS

Summary of EPA-Selected Toxicological Endpoints for Phenothrin			
Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Short-Term (1 - 30 days)	Systemic toxicity NOAEL = 9.3 mg/kg/d UF _A = 10 UF _H = 10 UF _{DB} = 10	Residential LOC for MOE = 1000 Occupational - N/A	26 week oral toxicity study in dogs LOAEL = 32 mg/kg/d based on increased alkaline phosphatase and increased liver weight (absolute and relative) in both sexes
Dermal Short/Intermediate - Term (1 - 30 days/1-6 months)	Dermal toxicity systemic LOAEL = not established 21/28 Dermal toxicity study in rats dermal toxicity systemic LOAEL not established up to 1000 mg/kg/d (HDT)		
Inhalation Short/Intermediate -Term (1 - 30 days/1-6 months)	Systemic toxicity NOAEL = 9.3 mg/kg/d UF _A = 10 UF _H = 10 UF _{DB} = 10	Residential LOC for MOE = 1000 Occupational LOC for MOE = 1000	26 week oral toxicity study in dogs LOAEL = 32 mg/kg/d based on increased alkaline phosphatase and increased liver weight (absolute and relative) in both sexes
Cancer (oral, dermal, inhalation)	Classification: not likely to be carcinogenic to humans		

TOXICOLOGY BENCHMARKS (cont.)

Summary of EPA-Selected Toxicological Endpoints			
Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
■ Acute Dietary (general population)	An acute RfD for the general population or any population subgroups was not selected because no effect attributable to a single (or few) day(s) oral exposure was observed in animal studies.		
Acute Dietary (females 13-49)	Dose for risk assessment = 30 mg/kg $UF_A = 10$ $UF_H = 10$ $UF_{DB} = 10$ Acute RfD = 0.30 mg/kg	aPAD = <u>acute RfD</u> FQPA SF = 0.030 mg/kg/day	Developmental Toxicity Study – rabbit Developmental LOAEL = 100 mg/kg/day based on spina bifida
Chronic Dietary (all populations)	Dose for risk assessment = 7.1 mg/kg/day $UF_A = 10$ $UF_H = 10$ $UF_{DB} = 10$ Chronic RfD = 0.007 mg/kg	cPAD = <u>chronic RfD</u> FQPA SF = 0.007 mg/kg/d	Chronic Toxicity study in dogs Chronic toxicity LOAEL = 26.7 mg/kg/d based on hepatocellular enlargement in the liver and focal degeneration in the adrenal cortex in both sexes.

TOXICOLOGY ENDPOINT – Incidental Oral, Short-Term

The incidental oral endpoint was selected from a 6-month dog feeding study in which groups of 6 pure-bred beagle dogs/sex/dose were fed diets containing 0, 100, 300, or 1000 ppm (3.02/3.14, 9.28/9.31, 31.87/32.90 mg/kg/day (M/F) phenothrin technical (93.1% purity) for 26 weeks (MRID 00148558)

- No effects in behavioral and clinical signs, body weight, food consumption and hematology. Alkaline phosphatase and liver weight (absolute and relative) were both significantly elevated in both sexes at the high dose of 1000 ppm. All other parameters were within normal limits.
- **NOAEL is 300 ppm (9.3 mg/kg/day)** and the LOAEL is 1000 ppm (32 mg/kg/day) based on increased alkaline phosphatase and liver weight (absolute and relative) in both sexes.
- **Increased alkaline phosphatase in the 6-month dog study achieved statistical significance at weeks 8, 17, and 21.** The duration of the dog study (6 months) is the same as an intermediate scenario (1-6 months)

TOXICOLOGY ENDPOINT – Acute RfD

The acute RfD was selected from a developmental toxicity study in rabbits (MRID 41230003) in which groups of 20 pregnant does were administered by gavage technical phenothrin at doses of 0, 30, 100, 300, or 500 mg/kg/day during gestation days 7-19.

- Maternal toxicity was manifested as an increased incidence of clinical signs (decreased urinary and fecal excretion, and urogenital staining) and abortions at 500 mg/kg/day and decreased body weight gain and food consumption at 300 and 500 mg/kg/day.
 - **The maternal toxicity NOAEL is 100 mg/kg/day** and the maternal toxicity LOAEL is 300 mg/kg/day based on decreased body weight gain and food consumption.
- Developmental toxicity was indicated at 100 mg/kg/day based on the presence of spina bifida in one fetus. While only a single fetus exhibited spina bifida, this effect was considered by EPA to be an indicator of potential neurotoxicity. Additionally, it was noted that this effect may have greater significance due to the use of the methylcellulose as the vehicle for the study. Available data suggest that methylcellulose may decrease oral absorption of pyrethroids (Crofton et al. (1995). Developmental toxicity was also observed as the presence of microphthalmia in one fetus at 300 mg/kg/day and increased incidence of fetuses (4) and litters (3) with hydrocephalus (with or without dome head) at 500 mg/kg/day.
 - **The developmental NOAEL is 30 mg/kg/day** and the developmental LOAEL is 100 mg/kg/day based on the presence of spina bifida, which was considered to be an indicator of neurotoxicity.

Considerations Regarding EPA-Selected NOAELs and Additional UF_{DB}

- Use of NOAEL from the rabbit developmental toxicology (DT) study is conservative:
 - No treatment-related dose-response in the rabbit (DT) study
 - Rabbits are coprophagous, and reduced food intake or reduced defecation could result in effects unrelated to a.i.
 - No developmental effects in the rat (2-gen repro) study
- Additional 10x UF_{DB} for neurotoxicity data is questionable
- Applying UF_{DB} for incidental oral short term exposure based on subchronic dog study (oral route) is unjustified; the adaptive liver-related effect does not occur until 8 weeks
- UF_{DB} only potentially relevant to maternal NOAEL (100 mg/kg/day) from rabbit developmental toxicity study

Incidental Oral, Short-Term Toxicology Endpoint Considerations

- An 8-week time-averaging period for exposure estimates is appropriate based on time-to-effect in the 26-week oral dog study
 - i.e., comparison of NOAEL of 9.3 mg/kg/day to 8-week time-averaged incidental oral exposures derived from temporal incidental oral / HtM exposure estimation (e.g., via CARES) that addresses:
 - per day transferability decline post-application of product based on NDETF temporal data
 - frequency of product use (e.g., once per month for foggers; once per 2-weeks for crack & crevice aerosols) based on label and/or REJV data
- Alternatively, the maternal NOAEL of 100 mg/kg/day, could be used to compare to single-day (day of application) incidental oral / HtM exposure estimates

Residential Uses and Associated Maximum Wt% & Application Rates Addressed in EPA RED / ORE

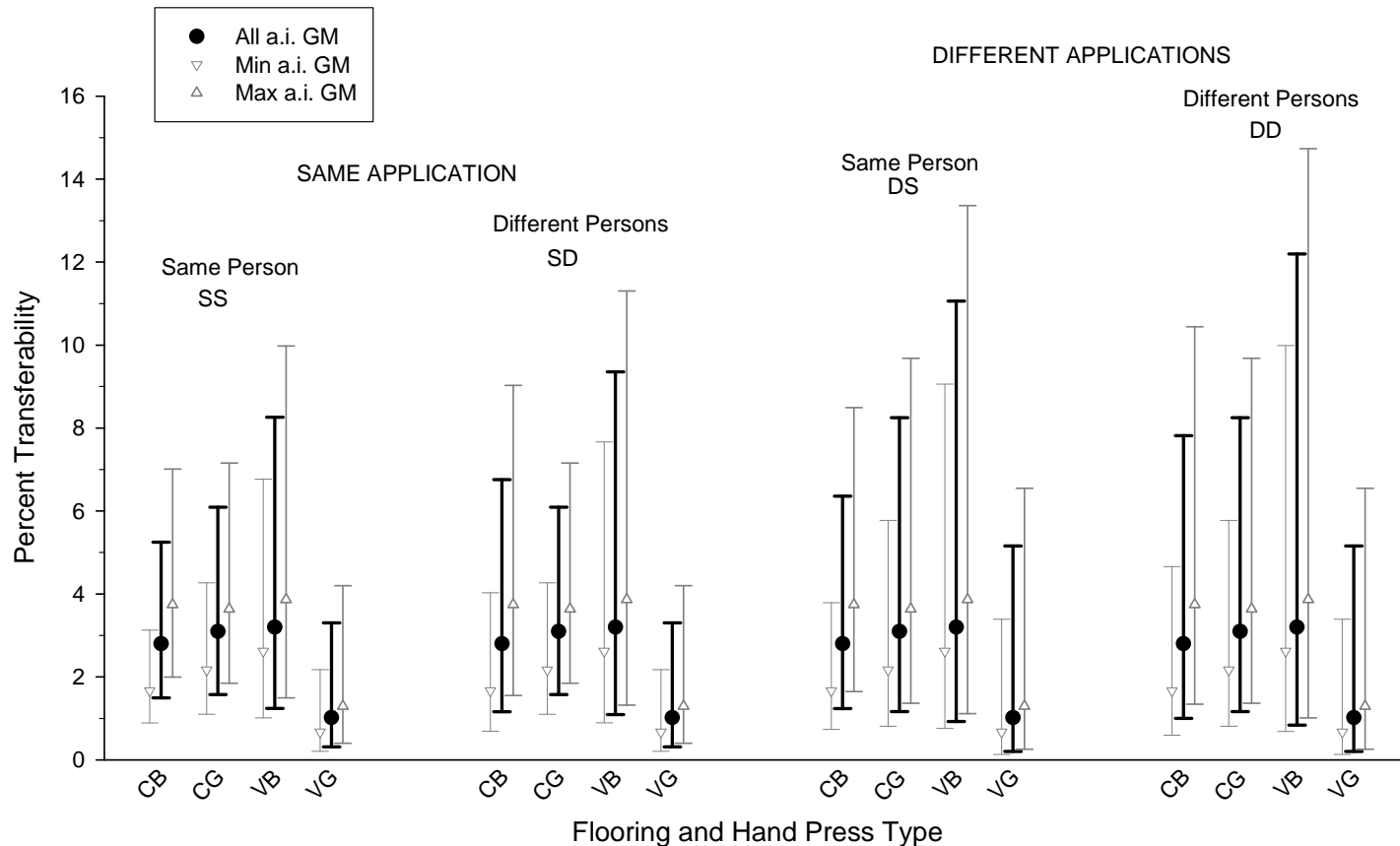
SCENARIO	Wt%	Application Rate	EPA Reg No
Indoor Household Sprays – Space Spray	3	10 sec spray 1.5 g/sec (0.002 lb ai/application)	44446-66
Indoor Household Sprays – Surface/Crack and Crevice Spray	3	1 16 oz can (0.03 lb ai/16 oz can)	44446-66
Indoor Household Carpet Powder	0.5	1 lb/108 sq ft (0.000046 lb ai/sq ft)	2596-132
Total Release Fogger	2	1 5 oz can/8000 cu ft (0.0008 lb ai cu ft)	68543-2
Outdoor House and Garden Sprays	0.2	3 sec/cu yd; 1.5 g/sec	1021-1588
Direct Application to Pets	0.3	½ 16 oz can per animal (680 mg ai/animal)	4822-404

Incidental Ingestion via Hand-to-Mouth Exposure Pathway: Transferability – A Key Input Variable

- Surface to hand residue transferability
 - Human hand generic transferability from treated surfaces as a function of single and repeat contact, surface type and time post-application
 - saturation transfer efficiency (TE; per press) approx. 3% across multiple a.i.s
 - temporal decline in transferability
 - see NDETF Vol. 43: MRID 464937-01
 - Transferability resultant from frequency and pattern of hand to treated surface versus hand to mouth contact
 - Weighted average wet/dry hand TE likely to be 8% or less; more realistic saturation TE approx. 3%
 - see NDETF Vol. 46: MRID 466147-01

Predicted Distributions of Transferability with Single Hand Press at 4 hours Post Application (NDETF Vol 43)

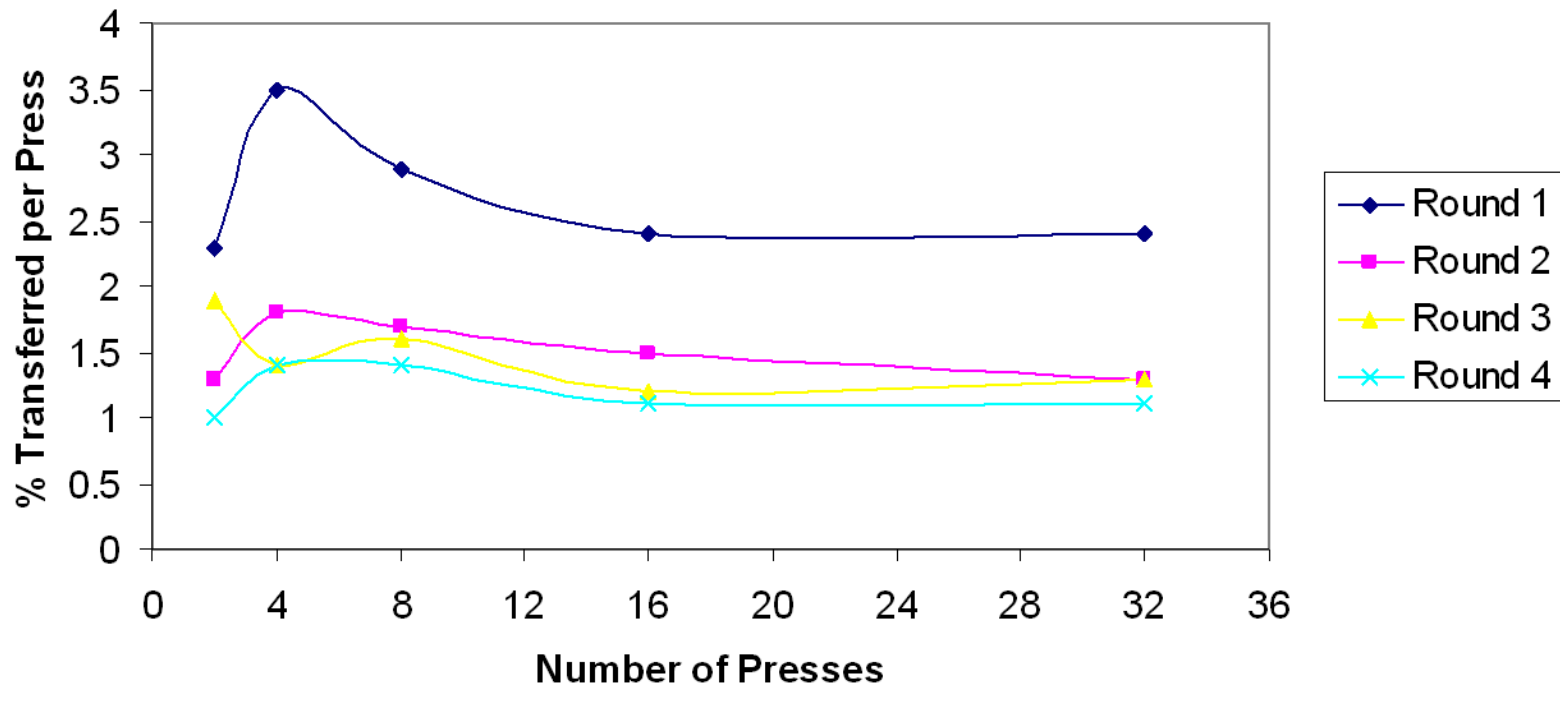
(CB = carpet-to-bare hands, CG = carpet-to-gloves, VB = vinyl-to-bare hands, VG = vinyl-to-gloves)



Saturation of Transferability: Example

Measurement of Transfer of Pyrethrin and Piperonyl Butoxide Residues from Carpet Flooring Treated with a Fogger Formulation to Bare and Gloved Hands Following Multiple Hand Presses (NDETF Study 01-025-PY01)

Figure 4:
PERCENT OF PBO TRANSFERRED FROM CARPET SURFACE TO THE BARE HAND PER PRESS FOLLOWING MULTIPLE HAND PRESSES



Published Reports Supporting Surface Transfer Equilibrium

Situation	Body Region	Sample Method	n	Reference
Hand press	Hand	Sequential presses	10, 50	Lu & Fenske, 1999
Hand press	Hand	Sequential presses	6, 12	Brouwer et al., 1999
Harvesters	Hand	Timed hand washes	~ 20	Spencer et al., 1995
Adult crawling	Hand	Glove extraction	1	Versar, 1997
Harvesters	Hand	Timed hand washes	15	Smith et al., 1991
Modeling children	Hand, Foot	SHEDS model	-----	Zartarian et al., 2000
Mousercise	Knee	Fluorescent tracer	12	Black et al., 1993

Transferability Resultant from Frequency and Pattern of Hand to Treated Surface Versus Hand to Mouth Contact

Ratio of Hand-to-Surface and HTM Contact (per Hr) Frequencies

Variable	Reed et al. 1999 (2 - 6 yrs)			Freeman et al. 2001			
				3 - 4 yrs		5 - 6 yrs	
	Mean	Median	Max	Mean	Median	Mean	Median
Mouth (HTM)	9.5	8.5	26	4	3.5	8	2.5
Surfaces (Hand-to-Textured and Smooth Surfaces)	106	96	259	203	174	152	131
Ratio of Hand-to-Surface / HTM Contacts	11.2	11.3	10.0	50.8	49.7	19.0	52.4

This implies that the HTM incidental exposure scenario would be more realistically yet very conservatively estimated by the weighted average transfer observed with an initially wetted hand due to a mouthing event (likely to involve <1% of the SA of the hand; see HESI 2004; Chapter 5) *and* the transfer observed from repeat dry hand presses (e.g., 10 to 50) each from a previously un-contacted treated surface. This method assumes the hand only contacts treated surfaces before going into the mouth.

Child #755 Hand Touches

00:01:25:12
00:29:24:24



00:32:24:26
00:58:33:27



01:00:10:24
01:30:55:20



01:31:20:20
02:08:07:01



- | Head/Face
- | Mouth Out/Mouth In
- | Turf

Predicted Change in Transferability with Time Relative to the Level at 4 hours Post-Application (NDETF Vol 43)

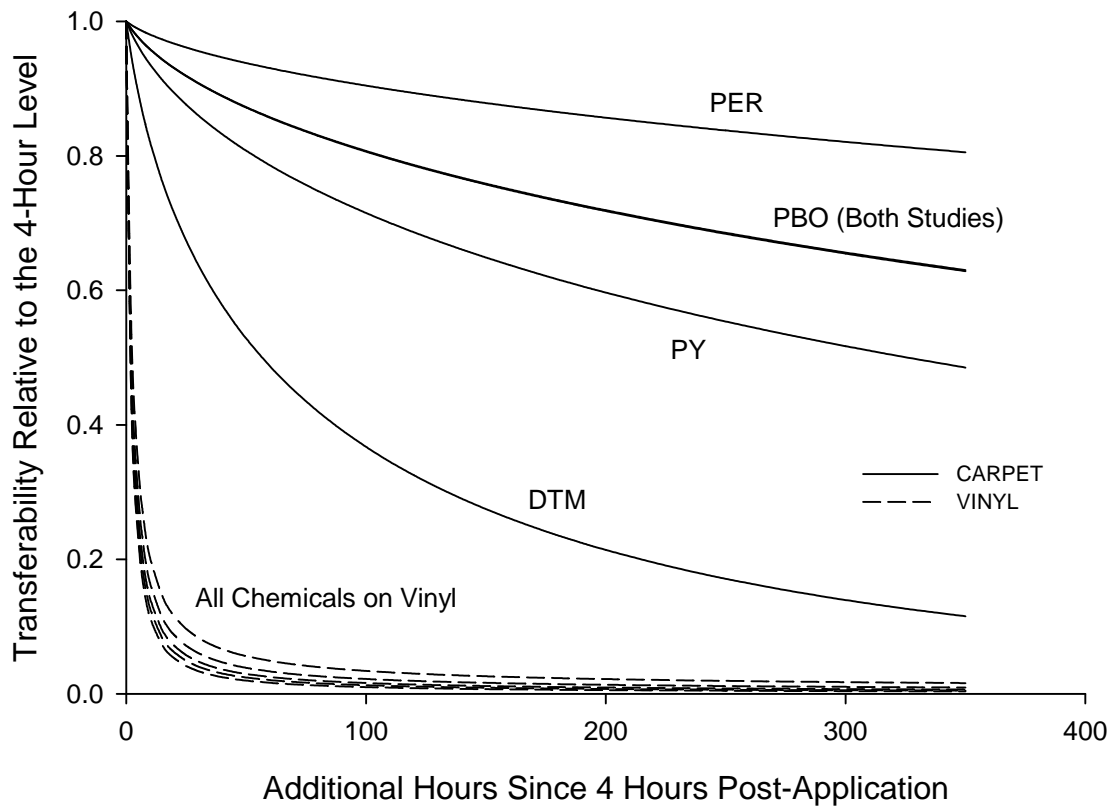


TABLE 1. NHAPS* Duration Statistics for Time Spent by Children in Selected Activities and Indoor Microenvironments Relevant to Potential Contact with Indoor Treated Surfaces and Hand-to-Mouth Based Incidental Ingestion Exposure.

Age Group	Activity	Duration		Statistical Metric	Assumed Flooring Surface Type
		mins/day	hrs/day		
3 to 5 yrs	Time spent "playing" on weekdays	218	3.6	mean value	Soft and/or Hard
3 to 5 yrs	Time spent "playing" on weekends	267	4.5	mean value	Soft and/or Hard
3 to 5 yrs (boys)	Time spent in "recreation"	311	5.2	mean value	Soft and/or Hard
3 to 5 yrs (girls)	Time spent in "recreation"	255	4.3	mean value	Soft and/or Hard
1 - 4 yrs	Time spent "indoors playing"	130	2.2	mean value	Soft and/or Hard
5 to 11 yrs	Time spent "indoors playing"	93.6	1.6	mean value	Soft and/or Hard
1 - 4 yrs	Time spent "indoors playing"	255	4.3	90th percentile	Soft and/or Hard
5 to 11 yrs	Time spent "indoors playing"	180	3.0	90th percentile	Soft and/or Hard
1 - 4 yrs	Time spent in "kitchen"	73.7	1.2	mean value	Hard
5 to 11 yrs	Time spent in "kitchen"	60.5	1.0	mean value	Hard
1 - 4 yrs	Time spent in "kitchen"	140	2.3	90th percentile	Hard
5 to 11 yrs	Time spent in "kitchen"	120	2.0	90th percentile	Hard
1 - 4 yrs	Time spent in "bathroom"	35.9	0.6	mean value	Hard
5 to 11 yrs	Time spent in "bathroom"	31	0.5	mean value	Hard
1 - 4 yrs	Time spent in "bathroom"	60	1.0	90th percentile	Hard
5 to 11 yrs	Time spent in "bathroom"	52.5	0.9	90th percentile	Hard
1 - 4 yrs	Time spent in "basement"	94.8	1.6	mean value	Soft and/or Hard
5 to 11 yrs	Time spent in "basement"	135.4	2.3	mean value	Soft and/or Hard
1 - 4 yrs	Time spent in "basement"	180	3.0	90th percentile	Soft and/or Hard
5 to 11 yrs	Time spent in "basement"	270	4.5	90th percentile	Soft and/or Hard

Source: EPA EFH

Hrs/Day	Statistical Metric
2.4	Overall Average of Mean Values
2.8	Overall Average of 90th Percentile Values
0.5 to 5.2	Range (Min to Max) of Mean Values
0.9 to 4.5	Range (Min to Max) of 90th Percentile Values

Summary of Variables for Estimating Hand to Mouth Exposure Used by EPA

Variable	Tier I (SOP 12)	Stochastic
Transferable Res.	5% of appl'n rate	1-13% uniform
Wet hand incr.	N/A	1.5-3; 2.3 avg; triangular
Finger tip SA	20 cm²	0-20 cm² uniform
Saliva removal efficiency	50%	10-50% uniform
Events/hr	20	0.4, 8.5, 25.7 triangular
Hours/day	4 (hard surf.) or 8 (soft surf.)	1 to 5 uniform
Body Weight (kg)	15	11-20 uniform

Comparison of Normalized Exposure Metrics from Studies Involving Crack & Crevice versus Broadcast Pesticide Chlorpyrifos Applications.

Study	Number of replicates	g Chlorpyrifos /m ² Applied	Air Conc. ($\mu\text{g}/\text{m}^3$)	Surface Conc. (ng/cm^2)	Time in House (hr/day)	Dosage ($\mu\text{g}/\text{kg}$)	Normalized Metrics		C&C vs Broadcast - FOLD DIFFERENCE (indoor broadcast / crack & crevice)	
							Based on Body Wt., Application Rate, and Exposure Duration	Based on Body Wt.		
							($\mu\text{g}/\text{kg}$)/(g/m^2)/hr	$\mu\text{g}/\text{kg}$	Based on ($\mu\text{g}/\text{kg}$)/(g/m^2)/hr)	Based on $\mu\text{g}/\text{kg}$ **
Indoor Crack & Crevice										
Byrne, 1998	6	0.026-0.037	0.76-2.3	3.2-8.7	12+	0.049±0.042 (0.009-0.09)	0.1	0.049	166	222
Krieger, 2001	5	0.042	NA	NA	14-24	1.3±1.1 (0.4-3.2)	1.63	1.3	13	8
Hore, 2003*	7	0.002-0.022*	0.032-0.82	8.5-10	21±2	0.62±0.33 (0.04-4.8)	1.34	0.62	16	18
Summary	18	0.002-0.042	0.032-2.3	3.2-10	>16	0.61 (0.009-4.8)	1.73	0.61	12.4	17.9
Indoor Broadcast										
Vaccaro 1991	6	0.127	12.4-23	11,000	4	10.9±5.1	21.46	10.9		

*Homes with application rates of approx. 0.002 g/m² were excluded

**If a central tendency value is used from Vaccaro 1991, Krieger 2000, and Krieger 2001, i.e., weighted average of 10.9, 1.7, 1.2, 1.3, 6 and 8 $\mu\text{g}/\text{kg}$, the fold-difference is approximately 9.4 (5.75 / 0.61), rather than 17.9 as presented in the table above - see "Summary" value based on $\mu\text{g}/\text{kg}$.

Broadcast vs C&C Post-Application Exposures

- Submitted report supporting re: refinement of C&C exposure estimates (MRID 470129-01)
 - Crack and crevices exposures are approx 10-fold lower than broadcast (10x increase in oral MOEs)
 - default assumption is that they are only 2-fold lower
 - Confirmatory data can be developed, when necessary, e.g., comparative deposition measurements from target (e.g., baseboard perimeter) versus accessible surface areas post application (C&C and broadcast)

Sumithrin - Total Release Indoor Fogger			
Parameter	Unit	EPA	MGK
Amount of Formulation (NDETF)	lb	0.37	0.37
Weight Fraction of AI (NDETF)		0.005	0.005
Volume of Room (NDETF)	ft ³	2048	2048
Surface Residue (NDETF)	μg/cm ²	3.6	3.6
Amount of Formulation	lb	0.3125	0.375
Weight Fraction of AI		0.02	0.004
Volume of Room	ft ³	8000	5000
Surface Residue	μg/cm ²	3.114	1.196
Hand Transfer Efficiency		0.13	0.08
Saliva Extraction Factor		0.5	0.5
Surface Area of 2 Fingers	cm ²	20	20
Hand-to-Mouth Frequency	events/hr	20	20
Exposure Duration	hr	8	8
Body Weight	kg	15	15
Oral NOAEL	mg/kg/day	9.3	9.3
Oral Dose	mg/kg/day	0.0432	0.0102
Oral MOE		215	912

Oral doses and MOEs shown do not consider time-averaging or the use of alternative single day NOAEL of 100 mg/kg/day

Sumithrin - Carpet Powder							
Parameter	Unit	EPA			MGK		
Amount of Formulation	lb	1	1	1	1	1	1
Weight Fraction of AI		0.005	0.005	0.005	0.004	0.004	0.004
Area Treated	ft ²	108	108	108	108	108	108
Surface Residue	mg/cm ²	0.023	0.023	0.023	0.018	0.018	0.018
Vacuum Efficiency		0	0.36	0.8	0	0.36	0.8
Hand Transfer Efficiency		0.05	0.05	0.05	0.05	0.05	0.05
Saliva Extraction Factor		0.5	0.5	0.5	0.5	0.5	0.5
Surface Area of 2 Fingers	cm ²	20	20	20	20	20	20
Hand-to-Mouth Frequency	events/hr	20	20	20	20	20	20
Exposure Duration	hr	8	8	8	8	8	8
Body Weight	kg	15	15	15	15	15	15
Oral NOAEL	mg/kg/day	9.3	9.3	9.3	9.3	9.3	9.3
Oral Dose	mg/kg/day	0.1206	0.0772	0.0241	0.0964	0.0617	0.0193
Oral MOE		77	121	386	96	151	482

Oral doses and MOEs shown do not consider time-averaging or the use of alternative single day NOAEL of 100 mg/kg/day

Sumithrin - Pet Care			
Parameter	Unit	EPA (Spray)	MGK (Shampoo)
Amount of Formulation	lb	0.5	0.75
Weight Fraction of AI		0.003	0.00075
Area Treated	cm ²	6000	6000
Surface Residue	mg/cm ²	0.113	0.043
Shampoo Efficiency		0	0.7
Hand Transfer Efficiency		0.02	0.02
Saliva Extraction Factor		0.5	0.5
Surface Area of 2 Fingers	cm ²	20	20
Hand-to-Mouth Frequency	events/hr	20	20
Exposure Duration	hr	2	2
Body Weight	kg	15	15
Oral NOAEL	mg/kg/day	9.3	9.3
Oral Dose	mg/kg/day	0.0605	0.0068
Oral MOE		154	1367

Oral doses and MOEs shown do not consider time-averaging or the use of alternative single day NOAEL of 100 mg/kg/day

Sumithrin - Carpet Powder, 0.4% ai, 1 lb can

Parameter	Unit	Low	High
Amount of Formulation	<i>lb</i>	0.5	1
Weight Fraction of AI		0.004	0.004
Area Treated	<i>ft²</i>	108	216
Vacuum Efficiency		0	0.8
Hand Transfer Efficiency		0.01	0.08
Saliva Extraction Factor		0.1	0.5
Surface Area of 2 Fingers	<i>cm²</i>	1	20
Hand-to-Mouth Frequency	<i>events/hr</i>	1	20
Exposure Duration	<i>hr</i>	1	8
Body Weight	<i>kg</i>	15	15
Oral NOAEL	<i>mg/kg/day</i>	9.3	9.3
Surface Residue	<i>mg/cm²</i>	9.04E-03	1.81E-03
Oral Dose	<i>mg/kg/day</i>	6.03E-07	1.54E-02
Oral MOE		15428635	603

Assumption

All parameters are distributed uniformly

MOE (based on N = 10,000)

Minimum	232
99.9th percentile	234
99th percentile	391
90th percentile	1087
Median	6268
Average	20109
Maximum	900762

Oral doses and MOEs shown do not consider time-averaging or the use of alternative single day NOAEL of 100 mg/kg/day

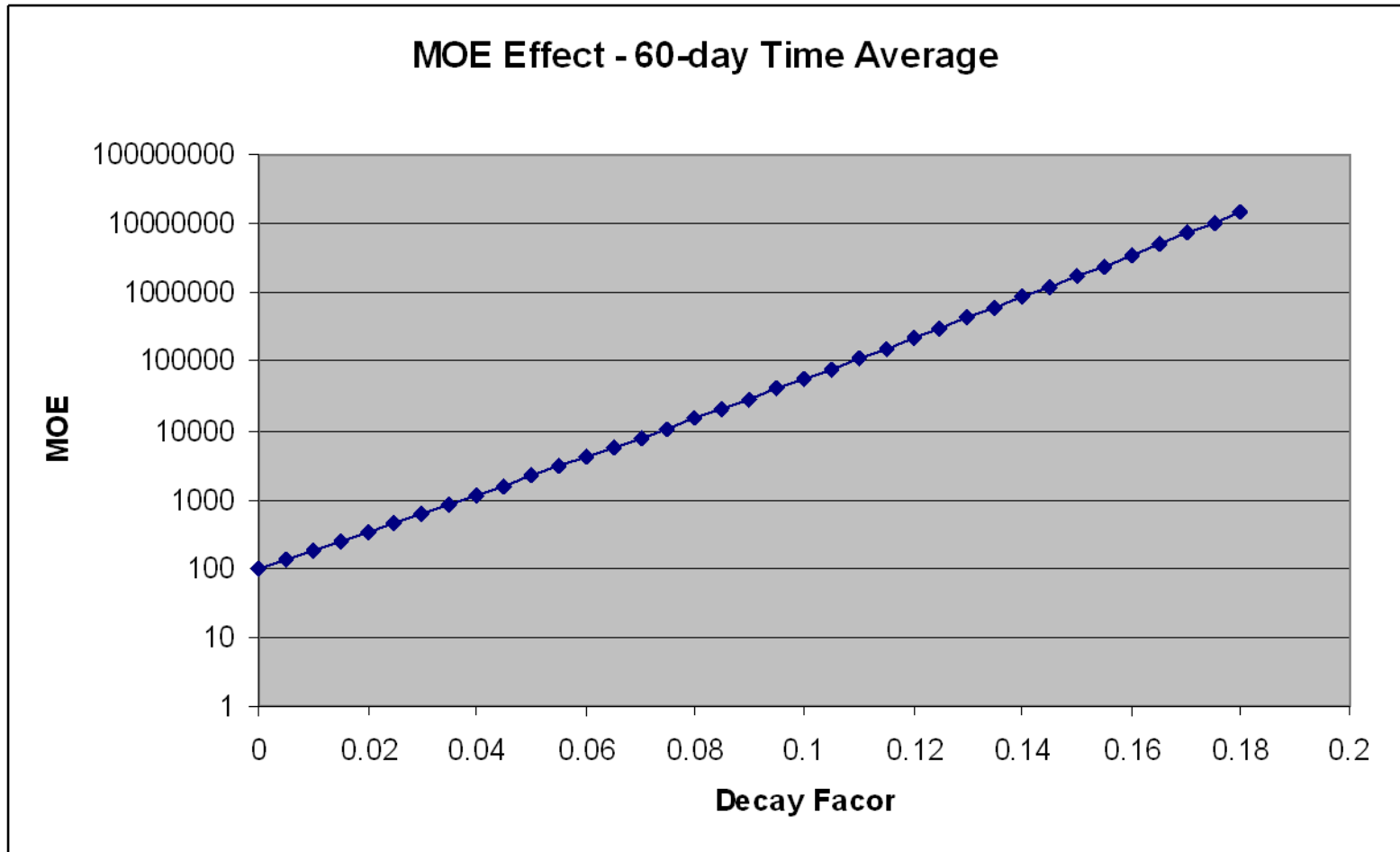
REJV Data – Households

Parameter	Number
12-Month Households	1217
Sumithrin Households	269 (22.1%)
Application Records	1691

REJV Data – Application Methods

Application Method	# of Applications
Spray, Aerosol	1458
Spot-on	47
Spray, Hand trigger	39
Granular/Dust/Powder	21
Sprayer, Spritz	14

EFFECT of TIME-AVERAGING



CONCLUSIONS

- Toxicology endpoint for oral route
 - Time-averaged (8-week) oral exposures should be compared to the 26-day dog study NOAEL
 - Day 0 oral exposures should be compared to the rat maternal NOAEL
- General refinements to the exposure assessment
 - Use of a transferability value (or distribution) to estimate hand loading that addresses, wet and dry hand surfaces, repeat contact saturation and a realistic pattern of surface to hand and hand to mouth activity
- Scenario-specific refinements
 - Wt% of a.i.
 - Exposures following crack & crevice versus broadcast
- Deterministic versus stochastic modeling demonstrates conservative bias in screening-level calculations
- Residential scenario MOEs are acceptable
 - Reasonable certainty of no harm can be substantiated via refined assessments, and where necessary confirmatory data (including toxicology studies and Sumithrin deposition and transferability measurements)
- Continued registration is appropriate

THANK YOU

