OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

July XX, 2024

MEMORANDUM

SUBJECT: Review of *"Operator dermal exposure and protective factors provided by personal protective equipment during foliar application using backpack sprayer in vineyards"* (I. Thouvenin, et al., 2016).

PC Code: --
Decision No.: --
Petition No.: --
Risk Assessment Type: --
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FROM: Matthew Zampariello, MPH, Biologist
Brent Davis, Biologist
Risk Assessment Branch 3 (RAB3)
Health Effects Division (HED) (7509T)

THRU: Matthew Crowley, Branch Supervisor
Chemistry and Exposure Branch (CEB)
Health Effects Division (HED) (7509T)

And

Briana Lee, ExpoSAC Reviewer
Brian VanDeusen, ExpoSAC Reviewer
Exposure Science Advisory Committee (ExpoSAC) / HED

TO: --
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Pesticide Re-evaluation Division (7508M)

The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: EPA's Scientific Integrity Policy. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: Approaches for Expressing and Resolving Differing Scientific Opinions | US EPA

Note: This memorandum was reviewed by the Exposure Science Advisory Committee (ExpoSAC) on 12/7/2023.

Executive Summary

This document represents EPA's Office of Pesticide Programs Health Effects Division (HED) review of a publication by the French agency for food, environmental and occupational health and safety (ANSES: Agence nationale de sécurité sanitaire de l'alimentation) "*Operator dermal exposure and individual protection provided by personal protective equipment during application using a backpack sprayer in vineyards.*" (I. Thouvenin, et al., 2016)[1]. The publication reports dermal monitoring for workers who mixed, loaded and applied a pesticide (active ingredient (ai) cymoxanil) to grape vineyards using a handheld motorized backpack fogger/mister. As the study was not conducted nor submitted for the purposes of supporting U.S. pesticide registrations, the study does not meet all criteria listed in the Series 875 - Occupational and Residential Exposure Test Guidelines (875.1100)[2]; however, EPA currently does not have dermal exposure monitoring data to quantitatively assess the safety of applying pesticides with a handheld fogger/mister. It is HED policy to use the best available data to assess pesticide handler exposure; and the data in the publication being considered is currently the most reliable data for assessing exposure and risk to individuals mixing/loading/applying (M/L/A) any formulation using handheld fogger/mister equipment in agricultural settings. Despite study limitations, the publication and resulting data are considered acceptable and appropriate for use in regulatory assessments of occupational pesticide exposure.[3]

This memorandum additionally references review of the same publication by the Pest Management Regulatory Agency (PMRA) of Canada as a supporting source for EPA's use of the study data. PMRA's review of this study is attached, however, HED's analysis of the study differs from PMRA in the following aspects (further detailed below in this review): (1) the levels of work clothing and PPE represented by the exposure measurements, (2) estimated head exposure and incorporation of head surface area extrapolation, and (3) the application of field fortification recovery adjustments.

The exposure study was designed to quantify dermal exposure for workers applying the ai, cymoxanil, to grape vineyards using a motorized backpack fogger/mister. Inhalation exposure was not measured. Dermal exposure monitoring was conducted on 10 professional farm employees or contractors at three sites on the same vineyard in south-eastern France. The exposure monitoring data was collected from workers wearing chemical-resistant gloves (nitrile), a full-length cotton undergarment that covered the arms, legs, and torso, a full body Tyvek® coverall, and a half-mask respirator (covering the mouth and nose). For U.S. purposes, the results of the study will be used to assess exposure and risk to individuals mixing/loading/applying liquid solutions using handheld fogger equipment while wearing the following attire: long-sleeved shirts, long pants, shoes, and socks and chemical resistant gloves (also referred to as "single layer + gloves"). In addition, if applicable for a given regulatory

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[1] Publication available: https://link.springer.com/article/10.1007/s00003-016-1047-z
[2] http://www.regulations.gov/document/EPA-HQ-OPPT-2009-0157-0003
[3] [Placeholder for ethics/HSRB review statement]

action, the monitoring data collected allow for representation of other clothing configurations (e.g., no chemical-resistant gloves, or a second layer of clothing).

Dermal dosimetry methods in monitoring studies like these are intended to capture "what might land on the skin" during the monitoring period. In this study, all materials worn by the workers were analyzed, including their Tyvek coverall and nitrile gloves. Compared to the cotton undergarment, Tyvek® coveralls and nitrile gloves are materials that can repel, rather than retain, the liquid pesticide solution. Thus, the study's use of a Tyvek® coverall and nitrile gloves as a collection media introduces uncertainty regarding the worker's total "potential" exposure, because those media may not retain residues on the surface of the Tyvek and nitrile gloves during the worker's exposure duration. For clarity, measurements using media *underneath* those the Tyvek and gloves will adequately represent exposure while wearing such garments; uncertainty is introduced when using measurements of those garments to represent total "potential" exposure or as a surrogate for other clothing materials or configurations. While we recognize the resulting uncertainty involved with estimating the total "potential" amount of residue that workers were in contact with during monitoring periods, the study's dermal measurements collected from all monitoring matrices are currently the best available data to use to assess pesticide handler exposure for this application scenario.

HED estimated dermal exposure for workers wearing standard-fabric (e.g., cotton, polyester, etc.) long-sleeved shirt and pants by, first, totaling the residues collected from each worker's full-length cotton undergarment and full body Tyvek® coverall then dividing that sum by 2, representing HED's standard default 50% exposure reduction offered by regular standard-fabric work clothing. This body exposure is then summed with each worker's head and hand exposure (underneath chemical-resistant gloves). HED has also presented results for additional clothing configurations (e.g., a second layer of clothing or coveralls) via an additional application of default/standard protection factors (i.e., standard 50% protection factor for second layer of standard-fabric clothing).

The data are recommended for generic exposure assessment use to support regulatory decisions for any pesticidal active ingredient where workers are expected to mix/load/apply liquid pesticide solutions using handheld fogger/mister equipment. Exposure assessors should consult HED policy for additional exposure scenarios where this study is applicable as a surrogate dataset, since other studies monitoring handheld equipment used in other scenarios (e.g., forestry, indoors, etc.) may be more appropriate.

Select summary statistics for the handheld portable fogger/mister, liquid spray application scenario "unit exposures" (i.e., exposures normalized by the amount of active ingredient handled (AaiH)) are presented in Table 1 below. Parametric exposure estimates based on a lognormal distribution are included.[4] Generally, the arithmetic mean is recommended for standard short-/intermediate-/long-term pesticide handler exposure assessments.

[4] Fitting exposure monitoring data to a lognormal distribution is standard practice given the typical nature of such data. Alternative distributions are possible with sufficient statistical justification.

Additionally, solely for the purpose of comparison with the results from the publication, summary statics of the residues monitored during the study – representing workers wearing Tyvek coveralls and chemical-resistant gloves - are presented in Table 1.

Table 1. Unit Exposures (µg/lb ai handled): Mixer/Loader/Applicator Handheld Fogger/Mister.[1]

Exposure Route	PPE[2]	Geometric Mean	Arithmetic Mean[3]	95th Percentile[4]
Dermal	Single layer, no gloves	362,208	399,790	752,274
	Single layer, gloves	312,208	344,593	648,367
	Double layer, gloves	187,886	213,986	434,763
	Tyvek Single layer, gloves[5]	31,262	57,085	190,081

[1] Statistics are estimated assuming a lognormal distribution assuming independent measurements. At this time correlations were not considered, but statistics can also be estimated using a variance component model accounting for correlation between measurements conducted within the same field study (i.e., measurements collected for the same individual or the same location).
[2] Single layer (long pants, long sleeve-shirt, shoes, and socks) – sum of measurements of Tyvek and inner dosimeter, then assuming 50% reduction/protection of that sum to represent standard-fabric work clothing
No gloves – sum of direct measurements of chemical-resistant gloves and hand washes
Gloves – direct from hand washes
Double layer (e.g., coveralls, long pants, long sleeve-shirt, shoes, and socks): derived from "Single layer" plus an additional 50% reduction/protection to represent a second layer of standard-fabric work clothing.
[3] Arithmetic Mean (AM) = GM * $e^{\{0.5*[(\ln GSD)^{\wedge}2]\}}$
[4] 95th percentile = GM * $GSD^{1.645}$
[5] Tyvek Single layer (Tyvek Coverall) – raw sum of measurements of the inner dosimeter (i.e., whole body cotton undergarment), bandana/coverall hood, and direct measurements from hand washes. No adjustments including field fortification or head extrapolation were made.

Study Details

The study was conducted in France and funded by ANSES (Agence nationale de sécurité sanitaire de l'alimentation), the French agency for food, environmental and occupational health and safety. The study design, operator details, exposure monitoring methodologies, LOQ/LODs, and laboratory fortification results are summarized in Tables 2-7 and additional details can be found in PMRA's review in the Attachment.

Table 2. Study Design.

Item	Details	
Chemical	Cymoxanil; 1-[(EZ)-2-cyano-2-methoxyiminoacetyl]-3-ethylurea	
Formulation	Suspension concentrate (SC); cymoxanil 30 g/L (2.14% w/w)	
Packaging	2.64-gallon container (10 L)	
Application Equipment	Motorized backpack fogger/mister (models unknown)	
Spray Tank Capacity	12 to 15 L (3.17 to 3.96 gallon), varying by model	
Loads Applied	3 to 10, varying by worker	
Amount of Active Ingredient Handled (AaiH)	0.019 – 0.072 kg (0.048 kg, average)	0.042 – 0.16 lb (0.11 lb, average)

Concentration of Spray Solution	0.0006 – 0.001 kg ai/L	0.005 – 0.083 lb ai/gal
Volume of Solution Sprayed	32 – 91 L (66 L, average)	8.45 – 24 gal (17.44 gal, average)
Area Treated	1.5 – 3.8 ha (3.7 – 9.4 A), varying by worker team	
Location	Grape vineyards; Ardèche and Drôme, France (south-eastern)	
Crop	Grapes	
Clothing/PPE Worn	Long-sleeve shirt, long pants, shoes, socks, chemical-resistant (nitrile) gloves, chemical-resistant coveralls (Tyvek®, Model CHA5a DuPont®), half-mask respirator (covering mouth and nose)	
# of monitored workers	10 workers	
Monitoring Time	114 – 206 minutes (165 minutes, average)	

Notes:
- Work duration range of 114 – 206 minutes (approximately 3 hours, on average) is considered sufficiently representative of a typical workday making fogger applications in vineyards.
- Face and neck wipes were not used during this study to measure head exposure, only bandanas and coverall hoods were collected and analyzed for the purpose of measuring head exposure.

Table 3. Operator Details.

Operator Number	Sex	Age (years)	Weight (lbs)	Height (ft)	Activity
1	Male	55	143	5’6”	Loading/applying
2	Male	27	192	5’11”	Loading/applying
3	Male	34	141	6’1”	Loading/applying
4	Male	21	207	6’1”	Mixing/loading/applying[1]
5	Male	29	181	6’0”	Mixing/loading/applying
6	Male	37	137	5’7”	Loading/applying
7	Male	22	150	5’6”	Loading/applying
8	Male	38	265	6’0”	applicator
9	Male	35	161	5’11”	applicator
10	Male	27	170	5’7”	Loading/applying

[1] Protective gloves and coveralls during the mixing activity for worker number 4 was not collected and analyzed; however, worker number 4 was given new coveralls and gloves for loading and application activities that was measured during specimen collection.

Dermal Exposure Measurements

The publication successfully validated and confirmed the stability of cymoxanil residues in all specimens collected during the operator exposure study. Additionally, PMRA found the analytical methods used in the publication to be acceptable and HED agrees with such conclusion. Dermal exposure was measured by analyzing residues in/on the following:

- Fully body Tyvek® coverall (i.e., “outer dosimeter”)
- 100% cotton “inner dosimeters” worn underneath the full body Tyvek® coverall; sectioned and analyzed by body part (i.e., upper and lower arms, upper and lower legs, etc)
- Chemical-resistant gloves (nitrile gloves; Gants Ansell Sol-Vex 37-675, Cat.III, EN-374-3), shaken in acetone and analyzed for residues in rinsate solution.
- Hand washes were performed to measure dermal hand exposure.

- Head exposure was measured via the Tyvek® coverall hood on the outer dosimeter or a cotton bandana.
    - Workers 1-4, 8, and 10 wore cotton bandanas over their head (in lieu of coverall hood), and workers 5, 6, 7, and 9 wore the coverall hood attached to the full body Tyvek® coverall.
    - When workers chose to use the bandana instead of the coverall hood, the hood was analyzed along with the torso subsection of the outer dosimeter (i.e., coverall).

Table 4. Exposure Monitoring Methodology.

Matrix	Details
Inner Dosimeters (full-length undergarment)	One-piece, 100% cotton, union suit covering arms, legs, and torso (no underwear worn); sectioned into three parts (arms, legs, and torso).[1]
Outer Dosimeters (coveralls)	One-piece Tyvek® coverall suit with hood, covering arms, legs, and torso (over cotton inner dosimeter); sectioned into three or four parts (arms, legs, and torso, and hood when worn by worker over the head).[1]
Head/Face/Neck	Head exposure monitored via hood (chemical-resistant Tyvek® coverall material), or via bandana (100% cotton).[1] Face exposure not monitored; all workers wore half-face respirators (covering mouth and nose), several workers wore protective goggles.
Gloves	Nitrile gloves worn by all workers during loading and application activities; removed and collected at end of monitoring period. Protective glove specimens were shaken in acetone for extraction. Aliquots were then diluted with acetonitrile/formic acid solution 6.7 mM (25/75, v/v).
Hand Washes	Fixed volume (1000 mL) of detergent solution (0.01% dioctyl sulfosuccinate sodium and water solution); poured over workers' bare hands while mimicking hand washing.[2]
Inhalation	Not monitored during study.
Biological Monitoring	Not conducted during study.

[1] All inner and outer dosimeter (coverall) samples and glove samples were wrapped in aluminum foil and stored in labelled plastic bags in deep freezers (and coolers with dry ice when in transport).

[2] Two aliquots of 500 mL each collected as final specimens. Samples stored in labeled plastic bottles in deep freezers (and coolers with dry ice when in transport).

Table 5. Limits of Quantification (LOQ) and Detection (LOD).[1]

Matrix[2]	LOQ (µg/specimen)	LOD (µg/specimen)
Coveralls (outer dosimeter)	10	3
Full-length undergarment (inner dosimeter)	0.25	0.075
Chemical-resistant gloves	10	3
Hand Wash	0.5	0.15
Bandana (same material as full-length undergarment)	0.25	0.075
Hood (extension of, and therefore same as, Coveralls)	10	3

[1] No residue levels were measured below LOQ.
[2] Specimen sizes = 1,000 cm^2 cloth for dosimeters, 1,000 mL for hand washes, and pair of gloves.

Table 6. Summary of Laboratory Fortification Results.				
Matrix	**Fortification Levels (µg)**	**Sample size**	**Average Recovery (%± SD)**	**Overall Recovery (% ± SD)**
Coveralls (outer dosimeter)	10	8	93 ± 5	97 ± 9
	5,000	8	100 ± 9	
	20,000	1	109	
Full-length undergarment (inner dosimeter)	0.25	10	94 ± 10	97 ± 10
	125	10	98 ± 7	
	5,000	1	102	
Chemical-resistant gloves	10	7	90 ± 12	88 ± 11
	5,000	7	85 ± 10	
	20,000	1	94	
Hand Washes	0.5	7	105 ± 7	102 ± 6
	250	7	99 ± 3	
	1,000	1	98	
Bandana	0.25	10	94 ± 10	97 ± 10
	125	10	98 ± 7	
	5,000	1	102	
Hood	10	8	93 ± 5	97 ± 9
	5,000	8	100 ± 9	
	20,000	1	109	

SD = Arithmetic Standard Deviation

Quality Control / Field Fortifications

Results of field fortifications (Table 7) were considered acceptable as average recoveries ranged from 93% to 104% across all matrices. Correction of inner dosimeter and hand wash field samples were not conducted as recovery of the corresponding field fortifications were greater than 95%,[5] however, field fortifications for coveralls, hood, and chemical-resistant glove samples were less than 95% (only at the 5,000 µg/specimen level) and were adjusted accordingly. Notably, none of the field samples were below the method limit of quantification (LOQ) for any matrix.

Table 7. Summary of Field Fortification Recovery Results.							
Matrix	**Fortification level (µg/specimen)[1]**	**n**	**Arithmetic Mean (%)[2]**	**SD (%)**	**CV (%)**	**Min. (%)**	**Max. (%)**
Coveralls (outer dosimeter)	10	3	95	4	4	91	99
	5,000	3	**93**	2	2	91	94
Full-length undergarment (inner dosimeter)	0.25	3	96	4	4	92	100
	125	3	100	3	3	96	103
Chemical-resistant gloves	10	3	104	6	6	97	110
	5,000	3	**94**	1	2	93	96
Hand wash	0.5	3	97	8	8	88	102

[5] Typically for HED, correction of measured residues using mean fortifications are conducted regardless of spiking levels selected for an exposure study. However, to remain consistent with the study report and PMRA's primary review, HED did not make any adjustment to residues corresponding to a mean fortification recovery greater than 95%; in terms of overall results, this is an insignificant departure from standard practice.

Table 7. Summary of Field Fortification Recovery Results.							
Matrix	**Fortification level (µg/specimen)[1]**	**n**	**Arithmetic Mean (%)[2]**	**SD (%)**	**CV (%)**	**Min. (%)**	**Max. (%)**
	250	3	95	6	6	92	102
Bandana	0.25	3	96	4	4	92	100
	125	3	100	3	3	96	103
Hood	10	3	95	4	4	91	99
	5,000	3	**93**	2	2	91	94

n = sample size, SD = Arithmetic Standard Deviation, CV = coefficient of variation, Min. = minimum, Max. = maximum

[1] Specimen sizes = 1,000 cm^2 cloth for dosimeters, 1,000 mL for hand washes, and pair of gloves

[2] Figures in **bold font** indicate dermal exposure monitoring matrices adjusted for recoveries <95%.

Data Analyses

Dermal monitoring exposure was conducted on 10 professional farm employees or contractors at three sites on the same vineyard in south-eastern France. Inhalation exposure was not monitored. There was no repeat sampling of the same worker. In typical occupational pesticide exposure monitoring studies, dermal exposure is measured using an inner dosimeter underneath standard work clothing (e.g., cotton, denim, twill, polyester shirts and pants). In this study, however, operators wore Tyvek coveralls rather than standard work clothing. Additionally, the researchers analyzed the Tyvek coveralls for pesticide residue, as well as the cotton inner whole-body dosimeter, thereby providing results in terms of an “outer dosimeter” and “inner dosimeter”. Based on a comparison of the results for the outer dosimeter (Tyvek coverall) and the inner dosimeter (cotton whole body dosimeter), the Tyvek coveralls provided significant protection, preventing approximately 95% of residues from reaching the inner dosimeter (see Table 9). These results indicate protection far greater than the standard 50% reduction assumed for regular work clothing (e.g., cotton twill or denim). Therefore, estimating dermal exposures based on the inner dosimeter alone would not be representative of standard work clothing. In other words, use of the inner dosimeter alone would assume the Tyvek coverall provides the same level of protection as regular clothing – with resulting exposure estimates *underestimating* exposures while wearing regular work clothing. Thus, total dermal body exposure (e.g., micrograms active ingredient) is being calculated by first, totaling the residues collected from each worker’s full-length cotton undergarment and full body Tyvek® coverall then dividing that sum by 2, representing the standard default 50% exposure reduction offered by regular standard-fabric work clothing (e.g., cotton, polyester, etc.), then summing with each worker’s head and hand exposure. As previously stated, monitoring studies are typically conducted to represent standard work clothing with dermal exposure measured by way of the inner dosimeter only. Additionally, there is some level of uncertainty relating to the amount of residue that workers were in contact with during monitoring periods, i.e., the potential loss of residue that dripped off the surface of the gloves and Tyvek coverall during the worker’s exposure duration. However, as no other data is available for handheld foggers/misters, HED is making best use of the data despite the limitations presented with the use of Tyvek coveralls. Dermal “unit exposures” (i.e., µg/lb ai handled) were then calculated by dividing the summed total exposure by the AaiH.

A summary of the 10 monitoring units (MUs) and their dermal unit exposures for the motorized backpack fogger/mister exposure scenario are presented in Table 9 below. Additionally, HED has presented dermal unit exposure results for both no PPE (i.e., single layer with no chemical-resistant gloves) and extra/additional clothing and PPE; see Table 10.

Method Efficiency Adjustment (MEA): As presented at a June 2007 Human Studies Review Board (HSRB) meeting to account for potential residue collection method inefficiencies, adjustments are made to hand and face/neck field study measurements according to EPA directions as follows:

- If measured exposures from hands, face and neck contribute less than 20% as an average across all workers, no action is required;
- If measured exposure contribution from hands and face/neck represents between 20% and 60% of total exposure, the measurements shall be adjusted upward by 50%, or submission of a validation study to support the residue collection method;
- If measured exposure contribution from hands and face/neck represents is greater than 60%, a validation study demonstrating the efficiency of the residue collection methods is required.

For the dermal unit exposures in this study, MEA was considered for hand washes only; MEA is inapplicable for residues collected from the head as head exposure was measured in this study via bandana and coverall hood, matrices that are not considered to have the same methodological uncertainty in collecting expected exposure. Hand residue measurements were considered for MEA, but since contribution of the hands averaged only 0.3% to the total dermal exposure (for the “single-layer, with gloves” monitoring scenario), MEA was not included in overall dermal unit exposure calculations.

Head Exposure – Surface Area Extrapolation

Head exposure sample values collected from workers wearing a bandana or coverall hood were extrapolated to account for any potential residues that may have deposited on the face and neck during the exposure monitoring period but were not measured by the hood or bandana.[6] The extrapolation for total head exposure is based on relative surface areas of the non-face/non-neck parts of the head represented or captured by the bandana or coverall hood. Residue sample results from the bandana and coverall hood were extrapolated to account for the remainder of the head not measured (e.g., face/neck), based on the following simple formula:

$$\mathit{Total\ Head\ Exposure} = \mathit{Measured\ Residue}\ (\mu\mathrm{g}) + [\mathit{Measured\ Residue}\ (\mu\mathrm{g}) \times \mathit{Extrapolation\ Factor}]$$

[6] Note: the primary review by PMRA used the head monitoring sample results unadjusted, without conducting calculations for surface area extrapolation (Thouvenin, I., 2016).

Extrapolation Factors

The coverall hood and bandana each covered different amounts of the total surface area of the workers' head available for exposure during the monitoring period. Therefore, separate extrapolation factors were considered for use in calculating total head exposure.

Workers pictured wearing coverall hood (left) and bandanas (right) to measure head, face, and neck from pesticide exposure during handling activities (Thouvenin, 2016).

Coverall Hood: Since the coverall hood captured pesticide spray residue on the head and neck, but not the face, of each worker (i.e., "head, non-face"), the extrapolation for coverall hood samples accounts for any potential exposure to the head not captured by the coverall hood (i.e., "face, only"). The extrapolation factor for coverall hoods is represented as:

$$EF_{hood} = \left(\frac{SA_F}{SA_{HNF}}\right)$$

where:

EF_{hood} = extrapolation factor for coverall hood measurements
SA_F = surface area of the face, only
SA_{HNF} = surface area of the head, non-face

Bandana: Since the bandana captured residue on the head, but not the face or neck, of each worker (i.e., "head, non-face/non-neck"), the extrapolation for bandana samples accounts for any potential exposure to the head not captured by the bandana (i.e., "face/neck"). The extrapolation factor for bandanas is represented as:

$$EF_{bandana} = \left(\frac{SA_{FN}}{SA_{HNFN}}\right)$$

where:

$EF_{bandana}$ = extrapolation factor for bandana measurements
SA_{FN} = surface area of the face and neck

SA_{HNFN} = surface area of the head, non-face and non-neck

Each part/area of the head (e.g., face, neck) are represented by standard percentages of total body surface area (of adult males, representing study participants), presented in Table 8 below. The percent of total body surface area represented by the head for adult males is not meaningfully different than percentages for females, therefore, no additional adjustments are needed.

Table 8: Percent Surface Areas of Body Parts/Sections of Adult Male Head Relative to Total Body Surface Area (Exposure Factors Handbook: 2011 Edition).[1]

Body Part/Sections of Head		% of Total Body Surface Area
Surface Area	Description	
SA_{HT}	Head, total (head, face, neck)	7.79%
SA_{F}	Face, only	3.46%
SA_{N}	Neck, only	1.39%
SA_{FN}	Face and neck[2]	4.85%
SA_{HNFN}	Head, non-face/non-neck[3]	2.95%
SA_{HNF}	Head, non-face[4]	4.33%

[1] Source: U.S. EPA. Exposure Factors Handbook 2011 Edition (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F, 2011.

[2] $SA_F + SA_N$ = (3.46% + 1.39%) = 4.84%.

[3] $SA_{HT} – SA_{FN}$ = (7.79% – 4.84%) = 2.95%. Representative of exposure measured by bandana.

[4] $SA_{HT} – SA_F$ =(7.79% – 3.46%) = 4.34%. Representative of exposure measured by coverall hood.

Therefore, the extrapolation factors used in calculating total head exposure for coverall hood and bandana samples, respectively, are:

$$EF_{hood} = \left(\frac{SA_F}{SA_{HNF}}\right) = \frac{3.46\%}{4.34\%} = \mathbf{0.797}$$

and,

$$EF_{bandana} = \left(\frac{SA_{FN}}{SA_{HNFN}}\right) = \frac{4.84\%}{2.95\%} = \mathbf{1.641}$$

<u>Total Head Exposure Algorithms</u>

The full algorithms used to extrapolate coverall hood and bandana sample residues to total head exposure values are provided below. Example calculations are provided in Appendix A.

$$Total\ Head\ Exposure_{hood} = Measured\ Residue_{hood}\ (\mu g) + [Measured\ Residue_{hood}\ (\mu g) \times EF_{hood}]$$

and,

$$Total\ Head\ Exposure_{bandana} = Measured\ Residue_{bandana}\ (\mu g) + [Measured\ Residue_{bandana}\ (\mu g) \times EF_{bandana}]$$

<u>Confidence Intervals</u>

Accuracy of the estimated dermal unit exposures are addressed by presenting the 95th percentile confidence intervals (Results, Table 10). The 95% confidence intervals were estimated for parametric estimates of the geometric mean (GM), arithmetic mean (AM), and the 95th percentile using the methods outlined below.

The 95% CI of GM was calculated using the formula[7]:

$$95\%\ CI = \exp\left(\bar{X} \pm t_{1-\frac{\alpha}{2},\ N-1} S/\sqrt{N}\right),$$

where $\bar{X}$, S, and N are the sample mean, standard deviation, and sample size of the log-transformed data.

The 95% CI of AM was calculated using the modified version of Cox method[8]:

$$95\%\ CI = \exp\left(\bar{X} + \frac{S^2}{2} \pm t_{1-\frac{\alpha}{2},\ N-1}\sqrt{\frac{S^2}{N} + \frac{S^4}{2(N-1)}}\right)$$

The 95% CI of the 95%-tile was calculated using the Lawless method[9]:

$$95\%\ CI = \exp\left[\ \bar{X} - t'_{\frac{\alpha}{2},\ N-1,\ -\sqrt{N}Z_p}\frac{S}{\sqrt{N}},\ \ \bar{X} - t'_{1-\frac{\alpha}{2},\ N-1,\ -\sqrt{N}Z_p}\frac{S}{\sqrt{N}}\ \right]$$

Results

<u>Summary of Dermal Exposure Monitoring Results and Unit Exposures</u>

Dermal exposure monitoring sample results for each matrix were combined [i.e., (outer dosimeter + inner dosimeter) x 50% clothing protection factor) + hand exposure (i.e., handwashes, after removing gloves) + extrapolated head exposure)] to estimate total dermal exposure for each worker. Total dermal exposure values were then normalized by the AaiH for each worker, resulting in a final dermal unit exposure value.[10] Dermal exposure monitoring results and unit exposures for each individual worker are presented in Table 9.

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[7] https://www.itl.nist.gov/div898/handbook/eda/section3/eda352.htm

[8] https://jse.amstat.org/v13n1/olsson.html#Zhou1997

[9] https://www.ncss.com/wp-content/themes/ncss/pdf/Procedures/PASS/Confidence_Intervals_for_a_Percentile_of_a_Normal_Distribution.pdf

[10] The study report and PMRA's primary review reported amount of active ingredient handled (AaiH) values in kilograms (kg). HED converted the AaiH values from kg to pounds (lbs) using conversion factor 1 kg = 2.205 lbs. Unlike the study report and PMRA's primary review reporting final dermal unit exposures as ug/kg ai/day, HED reported the normalized unit exposures as ug/lb ai/day.

Table 9. Summary of Dermal Exposure Monitoring Sample Results (Single Layer/Gloves).							
MU #	AaiH (lbs)	Dermal Exposure[1,2]					Unit Exposure (µg/lb ai)[7]
		Inner Dosimeter Residue (µg)[3]	Outer Dosimeter Residue (µg)[4]	Total Head (Extrapolated) (µg)[5]	Total Hand Washes Residue (µg)	Total Dermal Residue (µg)[6]	
1	0.107	120.09	34,681	1,761.33	4.7	19,166	178,853
2	0.062	1,677.8	55,039	1,962.02	60.9	30,381	488,593
3	0.086	137.8	45,067	1,676.83	5.1	24,284	282,390
4	0.042	79.27	46,883	2,041.24	6.4	25,529	603,002
5	0.097	400	44,473	17,611.11	130	41,503	427,780
6	0.128	288.47	53,925	7,798.20	183	35,675	278,949
7	0.133	387.5	36,585	16,238.02	147	36,093	271,458
8	0.164	719.7	43,990	1,581.77	67.8	24,005	146,127
9[8]	0.101	4,516.9	32,060	23,845.71	54.1	43,983	433,631
10	0.163	5,381	84,871	1,573.84	308	47,008	288,091

[1] Monitoring represents workers wearing long-sleeve shirt, long pants, shoes/socks, and chemical-resistant gloves. See Table 10 for results representative of alternative PPE.

[2] Coverall and samples (at 5,000 µg/specimen level) corrected for field fortification recovery results; all other sample types were not adjusted, including recoveries above 100%. See Table 7.

[3] Inner dosimeter is the sum of four sections (arms, chest, back, legs).

[4] Outer dosimeter = full body Tyvek® coverall. The coverall is the sum of four sections (arms, chest, back, legs). Residues from the coverall hood were only included for monitoring units 1-4, 8, and 10 due to the operators opting to wear a bandana over their head vs. coverall hood. Unworn coverall hoods were not separated from the coverall torso at specimen preparation.

[5] Total head exposure was measured either with a bandana or coverall hood as the dosimeter methods. Because neither covered the head completely, surface area-based extrapolations were conducted to estimate the exposure of the non-measured portions of the head not covered by the bandana or the hood (e.g., face and neck).

[6] Single layer, gloves, Total Dermal Exposure = ((inner dosimeter + outer dosimeter) x 0.50) + hand exposure + extrapolated head exposure.

[7] The data are recommended for generic use in exposure assessments of workers mixing/loading/applying liquid solutions using handheld fogger/mister equipment.

[8] The study authors excluded results for Worker 9 due to a potential data reporting error, where the inner dosimeter torso appeared to be incongruently larger than the outer dosimeter torso. While EPA agrees that a data reporting error was likely, our approach of summing the outer and inner dosimeters obviates this concern.

Summary statistics for the dermal unit exposures calculated are presented in Table 10.

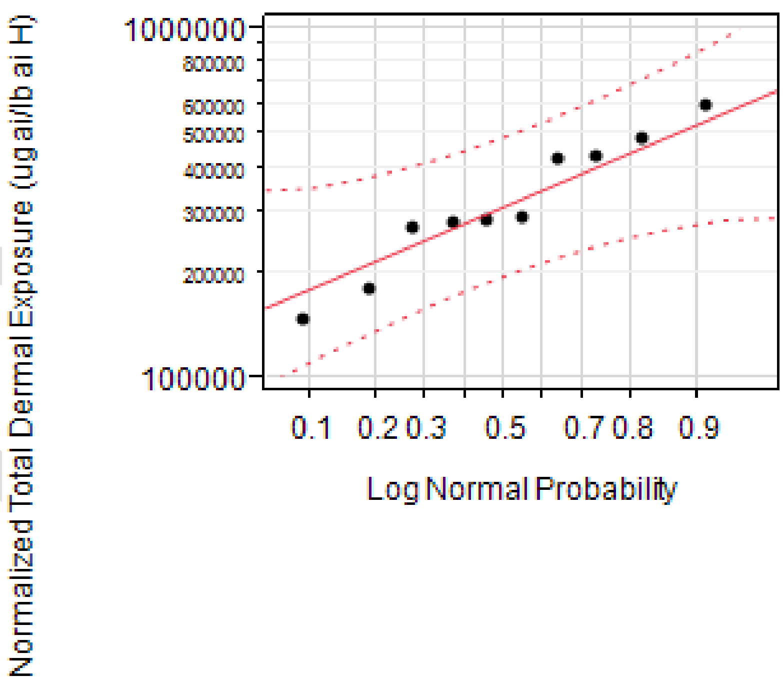
Table 10. Summary of Dermal Unit Exposures (µg/lb ai handled).					
Statistic[1]		Dermal			
		Single layer, no gloves	Single layer, gloves	Double layer, gloves	Tyvek Single layer, gloves[5]
GM (95% CI)		362,208 (263,579, 497,743)	312,208 (227,203, 429,016)	187,886 (130,446, 270,617)	31,262 (14,259, 68,541)
GSD		1.56	1.56	1.67	3.0
AM	Empirical[2]	395,220	339,887	209,333	51,551
	Parametric[3] (95% CI)	399,790 (286,030, 558,796)	344,593 (246,551, 481,623)	213,986 (144,830, 316,164)	57,085 (20,704, 157,389)

95th Percentile	Empirical[4]	671,929	551,518	335,471	144,639
	Parametric[5] (95% CI)	752,274 (484,815, 1,149,095)	648,367 (417,874, 990,325)	434,763 (262,565, 707,035)	190,081 (64,228, 541,142)

[1] GM = geometric mean; GSD = geometric standard deviation; AM = arithmetic mean. CI = confidence interval All statistics (except "empirical") are based on a lognormal distribution.
[2] Simple average of the 10 unit exposures.
[3] Arithmetic Mean (AM) = GM * $e^{\{0.5*[(\ln GSD)^2]\}}$
[4] Based on the rank ordering of the 10 unit exposures.
[5] 95th percentile = GM * $GSD^{1.645}$
"No glove" estimates calculated by summing hand washes and residues measured on the chemical-resistant gloves. "Double layer" estimates calculated assuming 75% protection to the torso, arms, and legs by an additional layer of clothing, applied to the inner and outer dosimeter measurements (50% assumed to represent single-layer regular work clothing, then another 50% reduction to "add" a second layer of regular work clothing). "Tyvek Single layer" estimates calculated from the raw sum of measurements of the inner dosimeter (i.e., whole body cotton undergarment), bandana/coverall hood, and direct measurements from hand washes.

Figure 1: Dermal Unit Exposure Lognormal Probability Plot

The probability plot below, Figure 1, provides a visual representation of the distribution and lognormal fit of the dermal unit exposures calculated for each worker. The relatively straight-line fit indicates lognormality of the data.



Limitations of the Study

Partly due to the observational nature of this study, some of the recommendations of the Series 875.1100 Guidelines for occupational exposure monitoring were not met and therefore, limitations of the study were identified. Despite these limitations, listed below, the results of the study are the only reliable data available to HED, therefore, the data is still considered acceptable for use in exposure and risk assessment. If contemporary handler studies were generated for the handheld fogger/mister exposure scenario, and included multiple monitoring units, geographic locations, and field replicates, HED would consider such data to assess pesticide handler exposure from handheld fogger/mister equipment instead of Thouvenin, 2016.

1. 10 workers were monitored all on the same farm and any pre-study sampling design is unknown. In addition to the Series 875 Guidelines which require a sample size of 15, more recent contemporary handler monitoring studies (e.g., those conducted by the Agricultural Handler Exposure Task Force, AHETF) have included at least 15 workers when monitoring is done in separate/independent locations or a clustered design when monitoring multiple workers in the same location (e.g., typically 5 workers each in 5 locations totaling 25 monitored workers).
2. Face and neck wipe was not the method used in this study to measure head exposure. Head exposure was measured via cotton bandana or coverall hood, and these results were extrapolated to the rest of the head to account for unmeasured residues that might have been deposited on the face and neck. Extrapolating to unmeasured parts of the face/head/neck resulted in almost a 2-fold increase (on average) to the hood or bandana measurements.
3. Field fortification levels for coveralls did not bracket the range of residues observed in the field samples; some of the observed coverall worker samples were greater than the highest spike level selected. However, this is not considered to be a major limitation as recovery at the highest laboratory fortification level is acceptable (109%). Results of this matrix's field samples were adjusted and used in the review's calculations for total dermal exposure.
4. The data are recommended for generic use in exposure assessments of workers mixing/loading/applying liquid solutions using handheld fogger/mister equipment. However, not all workers performed the same mixer/loader/applicator activities. Only dermal exposure from worker number 5 successfully captures dermal residues collected during the mixing/loading and application tasks (i.e., worker 5 wore the same protective equipment during mixing/loading and application).

Appendix A. Sample Calculations – Head Exposure Surface Area Extrapolation

<u>Total Head Exposure/Extrapolation Example Calculations</u>
Example calculations for each algorithm are presented below.

a) Measured hood residue = 9799 µg (MU#5):

$$Total\ Head\ Exposure_{hood} = Measured\ Residue_{hood}\ (\mu g) + Extrapolated\ Residue\ Value$$

$$\begin{aligned} Total\ Head\ Exposure_{hood} &\\ &= Measured\ Residue_{hood}\ (\mu g) + [Measured\ Residue_{hood}\ (\mu g) \times\ EF_{hood}] \\ &= 9799\ \mu g + [9799\ \mu g \times\ 0.797] \\ &= 9799\ \mu g + [7812\ \mu g] \\ &= \mathbf{17,611}\ \mu g \end{aligned}$$

b) Measured bandana residue = 743 µg (MU#2):

$$Total\ Head\ Exposure_{bandana} = Measured\ Residue_{bandana}\ (\mu g) + Extrapolated\ Residue\ Value$$

$$\begin{aligned} Total\ Head\ Exposure_{bandana} &\\ &= Measured\ Residue_{bandana}\ (\mu g) + [Measured\ Residue_{bandana}\ (\mu g) \times\ EF_{bandana}] \\ &= 743\ \mu g + [743\ \mu g \times\ 1.641] \\ &= 743\ \mu g + [1219\ \mu g] \\ &= \mathbf{1,962}\ \mu g \end{aligned}$$

Attachment
Primary Data Review
PMRA, (4/4/19)

Officer Number: __2577 ___ __________ Date_April 4, 2019____ _____

STUDY TYPE: Mixer/Loader/Applicator Passive Dosimetry Study using whole body dosimeters, and hand washes.

TEST MATERIAL: Selva containing cymoxanil (30 g a.i. /L)

SYNONYMS: Cymoxanil; 1-[(EZ)-2-cyano-2-methoxyiminoacetyl]-3-ethylurea

CITATION: Thouvenin, I. (2015). Determination of operator dermal exposure and protective factors provided by personal protective equipment during foliar application using backpack sprayer in vineyards. ANSES. STAPHYT study No. ChR-15-19603, 10 July 2015. Unpublished. PMRA# 2873196

Thouvenin, I., Bouneb, F., Mercier, T. (2016). Operator dermal exposure and individual protection provided by personal protective equipment during application using a backpack sprayer in vineyards. Journal of Consumer Protection and Food Safety. Vol 11, Pg. 325-336. 30 August 2016. Published. PMRA#2847175

SPONSOR: The French Agency for Food, Environment and Occupational Health and Safety (ANSES)

EXECUTIVE SUMMARY:

This study was designed to quantify exposure for workers applying cymoxanil to vine growing farms in France using handheld motorized mist-blower power sprayer (hereinafter referred to as backpack sprayers); these are considered to be representative of handheld airblast/mistblowers. Workers applied the cymoxanil end use product Selva (guarantee 30 g/L). Although the active ingredient copper oxychloride is also present in the Selva end-use product, it was not examined in this study.

Ten different workers (operators) were monitored at 3 sites on the same vine growing farm in the south of France. They were all professional farm employees or contractors. The test area comprised vine growing fields that were 1.5 – 3.8 ha. The test item, Selva, was applied in a manner that is typical of a normal treatment day using backpack sprayers in vineyards. The conditions and practices monitored at the test sties are intended to be representative of conditions in other vine growing areas in Europe.

Workers were monitored for dermal exposure while loading and application of Selva in vine growing farms; mixing activities was also monitored for two workers. All workers wore chemical resistant coveralls with a chemical-resistant hood or cotton bandana, chemical resistant gloves, face mask and a respirator when performing these tasks. Workers were monitored throughout the work day, which was approximately 165 minutes in duration (114-206 minutes), and handled an average of 48 g a.i (19-72 g a.i). Approximately 78 minutes (43-104 minutes) of this time was dedicated to spraying/application of Selva.

Dermal exposure was monitored using the whole body dosimetry method. A full-length cotton undergarment (inner dosimeter) was worn underneath the chemical-resistant coveralls (outer dosimeter). Hand washes were also performed to measure hand exposure. Face/neck exposure was not monitored. Total dermal exposure was determined by measuring the residues on the inner dosimeter and the hand washes. Inhalation exposure was not measured.

Average field fortification recoveries ranged from 93%-104% across the various matrices and spike levels. Correction of inner dosimeter and hand wash field samples was not required as recovery of the corresponding field fortifications were greater than 95%. Limitations were noted for this study, including that face and inhalation exposure were not monitored, not all workers wore hoods, and that the chemical-resistant coverall was used as the outer dosimeter.

Although there were limitations with this study, it was considered to be acceptable to be used generically across a range of active ingredients to assess exposure for workers during application with backpack sprayer equipment. The dermal unit exposure value and associated PPE is presented in Table 1. A parametric arithmetic mean was calculated as it fits the data to a lognormal distribution which is typical of exposure data and is similar to how other generic unit exposures (e.g. AHETF) have been calculated. As exposure from the hands represents less than 20% of the total dermal exposure and neck exposure was collected using a dosimeter, rather than a wipe, a method efficiency adjustment (MEA) factor for hand wash and face /neck wipes was not required for this study (PMRA, 2010).

Table 1: Dermal unit exposure value for workers applying using airblast/mistblower handheld sprayers wearing maximum PPE

	Dermal Unit Exposure	PPE[a]
Parametric arithmetic mean (AMu)[b]	32, 561 µg/kg ai handled	Chemical-resistant coveralls with chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant gloves and a respirator[c]

PPE = personal protective equipment

[a] Clothing that was worn by workers in the study and must be included in the risk assessment.

[b] Calculated assuming that the data has a log-normal distribution using the following equation: Mean = geometric mean x exp(0.5 x [(ln Geometric mean standard deviation)^2]). Values have been corrected for field fortifications <95%.

[c] A respirator is required as part of the dermal clothing scenario as it was worn by all workers in the study. It is not possible to calculate a scenario excluding the respirator as face exposure was not monitored.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

- OECD Series on Principles of GLP and Compliance Monitoring No. 1 (revised) "OECD Principles on Good Laboratory Practice." Paris 1998
- OECD Series on Principles of GLP and Compliance Monitoring No. 6 (revised) "The application of GLP Principles to Field Studies." Paris 1999
- OECD Series on Principles of GLP and Compliance Monitoring No. 13 (revised) "The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site." Paris 2002

GUIDELINE OR PROTOCOL FOLLOWED: OECD OR Eurofins Agroscience Services Chem SAS

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material:

End-Use Product Name: Selva

Active Ingredient(s): Cymoxanil (30g/L), copper oxychloride (300 g/L)
Formulation: Suspension concentrate
Lot/Batch # technical: Not mentioned
Lot/Batch # formulation: 2407316, 891303140
Purity: 99.9% a.i. in technical
CAS #(s): 57966-95-7

2. Relevance of Test Material to Proposed Formulation(s):

This study was submitted to generically assess exposure to workers when conducting applications using backpack sprayers across multiple active ingredients. Cymoxanil is non-volatile (vapour pressure of approximately 1.1 x 10^{-6} mmHg at 20ºC), and is considered relevant to model exposure for other non-volatile active ingredients.

3. Packaging:

Selva (cymoxanil) Fungicide is packaged into 10 L containers which were obtained from local distributors.

B. STUDY DESIGN

1. Number and type of workers and sites:

The field portion of the study was conducted from July 9-16, 2015 in the surroundings along the Rhone River in the south of France. The test area was a vine-growing farm. The area treated ranged from 1.5 – 3.8 ha. In July, the vineyards had reached their maximum foliage development. The vineyards where treatment was done often had a steep slope. It was only possible to use a backpack sprayer to enter and treat such types of vineyards. Each plant was attached to an individual stake. There were no wires between the stakes.

Air temperature, relative humidity, and wind speed and direction were monitored at approximately one to two-hour intervals at each site during each day of treatment. The air temperature ranged from 21.1 to 27.8°C and the relative humidity ranged from 23 to 50% over all sites. On the first day of monitoring, it was raining on the morning and the treatment was delayed to the afternoon. During the afternoon, a light rain started to fall at the end of the monitoring period. On one occasion, a wind speed higher than 3 m/s was registered during field monitoring of the second team (workers 5 to 7). This happened at the end of the monitoring period, late in the morning.

Ten workers were monitored at three separate sites on the same farm. All the workers monitored for this study were farm employees or contractors, with about 2 months to 38 years of experience.

2. Replicates:

The dermal exposure of workers applying cymoxanil was measured for the duration of a typical working day; some mixing and loading activities were also monitored. The average duration of the exposure activities in the study was 165 minutes (114-206 minutes). During this time, workers were actively applying cymoxanil for an average of 78 minutes (43-104 minutes). The monitored working duration was considered by study authors to be representative of the usual duration of a normal treatment day using a backpack sprayer in vineyards. The combination of a heavy backpack sprayer to carry on the shoulders/back under warm conditions with mandatory individual protective equipment requires that the workday be as short as possible. Every effort is done in a team organization to optimise the time to spend for this type of treatment.

As detailed in Table 6, all ten workers applied cymoxanil to the crop. Some of the workers were also responsible for other tasks such as spray tank loading, tank rinsing, and mixing in the big tank (large tank that is fix to a truck which allows for loading of Selva in the field). Exposure during mixing was only monitored for two workers (4 and 5). Worker 4, who was on the first team (workers 1-4), wore dedicated protective gloves and coveralls during mixture preparation carried out at the farm. These gloves and coveralls were not collected or analyzed. He was given new coveralls and gloves for loading and application activities, which were subsequently collected and analysed. Worker 5, who was on the second team (workers 5-7), wore the same coveralls and gloves for mixing/loading and application because the mixing/loading event was conducted in the field. For the third team (workers 8-10), only exposure due to loading and application was monitored as mixing was conducted by another, unmonitored, worker. All mixing/loading/application activities were conducted on the same farm.

Loading activities were performed in the field as necessary. Workers would load backpack sprayers either directly from the spray tank or by filling a 10 L can, which was filled from the spray tank. The loading of the sprayer tank was done by the worker themselves, by another worker who was already filling their own sprayer tank or by another person who was not monitored.

During application, workers walked at a brisk pace, along a path perpendicularly to the slope. Given the steep slope they sometimes needed to grip the stakes to ensure their stability. Vineyards were at maximum foliage and the path between the stakes was sometimes narrow. Repeated contact with the treated foliage was unavoidable while they were walking forward during application. As noted in Table 6, workers applied between 6-10 loads of spray solution, except for worker 4 who predominantly performed mixer/loader tasks and only applied 4 loads of spray. The area treated by each 3-4 person team was 1.5 ha (team 1), 2.8 ha (team 2) and 3.8 ha (team 3). Area treated per day values for individual workers were not reported.

The study authors noted that several times during application, workers tended to spray other workers or themselves and the product persisted in the air as workers sprayed near each other. See Table 6 for more details. Spray drift was observed on several occasions during the application phase. Workers were sometimes applying against wind. Even in the absence of wind, they were usually walking through the spray mist (due to their own movement ahead while the mist was still in the air).

3. <u>Protective clothing:</u>

Workers wore protective chemical resistant gloves (nitrile gloves; Gants Ansell Sol-Vex 37-675, Cat.III, EN-374-3), chemical-resistant coveralls (Tyvek® Classic Plus, Model CHA5a DuPont®) and half-mask respirators (covering the mouth and nose). Respirators were either 3M dust mask respirators with a brown cartridge against organic vapors (protection level A2P3D[11]) or Moldex dust mask respirators equipped with two cartridges (brown, grey, yellow and green) against gas and vapors (protection level P3RD[a]). Workers also wore a hood that covered their neck and partial face, which was part of the coveralls or they wore a cotton bandana that covered their head and part of their face. Some workers also wore protective goggles and/or ear protection. For footwear, workers wore walking shoes up to the ankle. This protective clothing is considered by the study authors as representative of what workers would normally wear while applying pesticides in vine farms in Europe.

Typically in exposure studies, workers wear an inner and outer dosimeter under chemical-resistant clothing, as this is representative of what is included in the risk assessment. However, due to excessive heat during the testing month (July), it was decided that workers would not be expected to wear a clothing layer between their protective chemical-resistant layer and their full-length undergarment inner dosimeter layer. As a result, the residue levels measured on the inner dosimeter does not represent actual exposure (i.e. what would be found on the skin) but what would pass through the chemical-resistant coverall and would be found on the long-sleeved shirt and long pants worn by the worker. As such, the dermal exposure determined from this study is expected to overestimate what would be found on the skin of workers when using this application equipment.

<u>4. Mixing/loading/application method:</u>

One mix/load event was performed for each of the three work teams, as discussed in Section B.2, above. Details regarding how the product was mixed (e.g. poured from jug) were not included in the study report.

[11] Source of protection level was not reported by the study authors. It is likely from the European Union legislation (EU EN405).

Workers applied cymoxinal via backpack (motorized mist blower power) sprayer. The tank capacity of each sprayer was either 12 or 15 L. When they were filled, this was not always done up to the maximum capacity and loading was also done sometimes when the tank was not empty. The sprayers used by workers 8 to 10 had been used on the day before by workers 5 to 7. The sprayers used by workers 1 to 4 sprayers were cleaned with a brush and water on the day before monitoring. This was not done for the sprayers used by the other workers. However, as noted by the study authors, this was representative of the usual situation for equipment cleanliness with each monitored team as the sprayers which were not cleaned are not usually cleaned after each day of use whereas the sprayers which were cleaned are usually cleaned after each use. Clean up activities were not monitored in the study.

5. Application Rate/Amount Handled:

The study authors (Thouvenin, *et al*, 2016) report an average application rate of 66 g a.i./ha (51-90 g a.i./ha). Since area treated per day values per worker were not reported, it is not possible to confirm this application rate.

The spray solutions reported by the study authors had concentrations of 0.6-1.0 g a.i./L. However, this seems to be based on the volume of water used when diluting the pesticide product, rather than the total water and pesticide product volumes. Spray concentration values in this review vary slightly from those reported by the study authors (32-91 L of product), which corresponds to an average of 48 g a.i. per day (19-72 g a.i.). The calculated amounts handled per day vary slightly from those in the study report, due to differences in the calculated spray concentrations.

Exposure monitoring methodology:

Dermal: Dermal exposure was measured using inner and outer whole body dosimeters. The outer layer was the Tyvek® coverall that was worn over a full-length cotton undergarment that covered the arms, legs, and torso. These dosimeters were worn throughout the monitoring period and were removed at the end of the working day. As there were no real break during the monitoring period (e.g. lunch), there was no need to cover or remove these dosimeters during the monitoring period. It was noted that during short breaks, the workers sometimes took the gloves, coverall hood and respirator off; however, this is considered to be consistent with typical practice.

Exposure of the head was measured via the hood on the outer dosimeter or a cotton bandana (same fabric as the inner dosimeter). Six of the workers chose to wear a bandana in the place of the coverall hood, the bandana was used to measure potential dermal exposure to the head and the coverall hood, which was not worn over the head, was included in the torso subsection of the outer dosimeter. When workers chose to use the coverall hood, the hood was separated from the rest of the outer dosimeter, and used to measure potential dermal exposure of the head. Although both were measures of head exposure, the bandana did not cover the neck or the circumference of the face that the coverall hood did.

At the end of the monitoring period, the dosimeters were sectioned into three or four parts (arms, legs, and torso, and hood when worn over the head by the worker). Each part was wrapped in aluminum foil.

Face and Neck: Face exposure was not monitored. However, head and neck exposure were monitored using the dosimeters, as described above. The study authors mentioned that all of the workers had half of their faces protected by a respirator and some workers also wore protective goggles. Due to this, the face surface area available for exposure was small.

Hand: Potential hand exposure was monitored using nitrile gloves and hand washes. Protective gloves were worn by all workers during loading and application activities. At the end of the monitoring period gloves were removed by the study team, and the pair was wrapped in aluminum foil.

The hand wash procedure was conducted as follows: a fixed volume (1000 mL) of an appropriate detergent solution (0.01% dioctyl sulfosuccinate sodium solution in Evian water) was continuously poured by a team member over the worker's hands over a metal bowl while the worker mimicked the action of hand washing. Acidification of the hand washes was done by emptying two tubes each containing 5 mL of 0.1 M hydrochloric acid to obtain a pH of 3. Two aliquots of approximately 500 mL each were obtained as final specimens. The second aliquot was identified as a repeat specimen. Both specimens were stored and sent to the analytical laboratory. Hand washes were conducted at times when the worker would normally be required to remove their gloves and wash their hands (bathroom breaks, lunch breaks, etc.). Each hand wash sample collected during and at the end of the day were treated as a separate specimen. All hand wash specimens were pooled together in the analytical facility after thawing and treated as one sample per worker.

Inhalation: Inhalation exposure was not monitored.

Biological Monitoring: Biological monitoring samples were not collected.

Each specimen (wrapped in aluminum foil or filled in a plastic bottle) was placed in a labelled plastic bag and gathered in a grouping bag (one per worker) and placed in the freezer. The date and time each packed specimen was placed in the freezer was noted. Specimens were deep-frozen in a freezer during storage (~ ≤ -18°C) at the field site and at the analytical site. During transport, such as shipment from field to analytical site, specimens were kept in dry ice. The temperature in the deep freezer was monitored at regular intervals and noted in the raw data. There was a deviation where the freezer temperature was above -18°C for a short period of time when some specimens were placed into the freezer. However, field fortification results for these samples were acceptable, so this deviation was considered by the study authors to have no impact on the study results.

7. <u>**Analytical Methodology:**</u>

Extraction method(s): Outer dosimeter specimens were wetted with ultra-pure water by shaking for 30 minutes. Residues of cymoxanil were extracted from coverall specimens via shaking in acetone. Aliquots were then diluted with acetonitrile/formic acid solution 6.7 mM (25/75, v/v).

Inner dosimeter specimens were wetted with ultra-pure water by shaking for 30 minutes. Residues of cymoxanil were extracted from full-length undergarment specimens via shaking in acetone. After shaking, aliquots were evaporated to dryness and then dissolved in acetonitrile/formic acid solution 6.7 mM (25/75, v/v).

Protective gloves specimens were shaken in acetone for extraction. Aliquots were then diluted with acetonitrile/formic acid solution 6.7 mM (25/75, v/v).

Hand wash aliquot specimens were acidified with formic acid.

Detection method(s): Cymoxanil residues were quantified using liquid chromatography/mass spectrometry (LC-MS/MS) using an API 400 (Sciex). Refer to page 133 of the study report for the chromatographic conditions.

Method validation: The analytical method Eurofins Agroscience Services Chem SAS method AGR/MOA/CYMO-3 was developed and validated during the course of the study. The method is considered to be valid as average laboratory recovery, as discussed below, was between 70-120% with a coefficient of variation less than 20%. Limits of Quantification (LOQ) and Limits of Detection (LOD) are included below in Table 2. The LOQ of the method is defined as the lowest analyzed concentration in a specimen at which the methodology was validated. The LOD was set as 30% of the limit of quantification.

Table 2. Limits of Quantification and Detection

Matrices[a]	LOQ (µg/specimen)	LOD (µg/specimen)
Coveralls	10	3
Full-length undergarment	0.25	0.075
Protective gloves	10	3
Hand Wash	0.5	0.15

[a] Specimen sizes = 1000 cm^2cloth for dosimeters, 1000 mL for hand washes, and pair of gloves

Instrument performance and calibration:

Specimens were analyzed using appropriate analytical method using a calibration curve prepared with eight cymoxanil external standards injected prior to the samples analysis and covering the calibration range of 0.0125 ng/mL to 2.5 ng/mL. The calibration curve consisted of at least 5 points. The range extended from 30% of the LOQ to 20% above the highest level. A linear calibration curve was calculated using the method of least squares (1/x weighting). $R^2 \geq 0.990$. No residue levels were measured below LOQ. One quality control was injected every four injections to check the absence of signal deviation.

8. <u>Quality Control:</u>

Lab Recovery: Prior to analysis of the field samples, blank and fortified controls were spiked in the lab at levels corresponded to LOQ, 500x LOQ, and 2000-80000 LOQ for each matrix. Samples were analyzed immediately after fortification. It was not mentioned if samples were allowed to dry prior to analysis, as applicable. For each matrix, at each fortification/spike level, the average recovery was 70-120% and the relative standard deviation was less than or equal to 20%. The average recoveries for the different matrices are presented in Table 3 below. It was not mentioned if concurrent laboratory fortifications were run with field samples.

The tested spike levels bracketed the residue levels in the field samples for the inner dosimeter, gloves, and hand washes. For coveralls, 11 of the 34 samples were greater than the highest spike level (20,000 µg/sample) and included all leg sections and one torso section. This is a limitation of the study, as it is unknown if recovery would be acceptable at levels greater than the highest spike level used in the laboratory fortification samples or the analytical methodology development. However, given that recovery at the highest fortification levels is good (109%), it is likely that recovery would continue to be acceptable at greater concentrations.

Table 3. Summary of Laboratory Fortification Results

Matrix	Fortification Levels (µg)	Sample size	Average Recovery (%± SD)	Overall Recovery (% ± SD)
Coveralls	10	8	93 ± 5	97 ± 9
	5 000	8	100 ± 9	
	20 000	1	109	
Inner Dosimeter	0.25	10	94 ± 10	97 ± 10
	125	10	98 ± 7	
	5 000	1	102	
Protective Gloves	10	7	90 ± 12	88 ± 11
	5 000	7	85 ± 10	
	20 000	1	94	

Matrix	Fortification Levels (µg)	Sample size	Average Recovery (%± SD)	Overall Recovery (% ± SD)
Hand Washes	0.5	7	105 ± 7	102 ± 6
	250	7	99 ± 3	
	1 000	1	98	

SD = Arithmetic Standard Deviation

Field blanks: Two blank specimens for each matrix were prepared for each day of the study and included with field fortifications. Residues were below the LOD for all blank samples. A blank specimen was also included with the travel fortifications; however, these were not analyzed, as discussed below.

Field recovery: Field recovery samples were prepared on each day of exposure monitoring. Triplicate samples of each media were fortified at two spike levels (LOQ and 500x LOQ for each matrix). The fortified whole body dosimetry specimens were kept at ambient conditions for the duration of the monitoring period. Coveralls and protective gloves were left uncovered during exposure to ambient conditions. Undergarment specimens were covered with a single layer of coverall material during exposure to ambient conditions. Hand wash specimens were fortified during the exposure monitoring period. After aliquots were taken, acidification was done and collection bottles were closed and kept under ambient conditions for about four hours after fortification. They were then frozen for transport. Packaging, storage and shipment of these specimens were the same as for the worker specimens.

The first series of field recovery hand wash specimens from the first day of monitoring (9th of July, 2014) was analysed on the 10th of November, 2014 and was re-analysed on the 10th of February, 2015. The reason for this re-analysis was to cover the analysis of the hand wash specimens from the workers, which could not have been done properly before February 2015. The recoveries were similar at the two dates (reported in Appendix 3 of the analytical phase report). Only the recoveries from the first analysis of this first series were considered in further calculations.

The mean recovery of field fortification specimens was 93-104% (± 1-8%) with a coefficient of variation lower than 20% at each fortification level for all matrices and deemed acceptable. See Table 4 for results of the field fortification samples.

Table 4. Summary of Field Recovery Results

Specimen	Fortification level (µg/specimen)[a]	n	Arithmetic Mean (%)	SD (%)	CV(%)	Min. (%)	Max. (%)
Coveralls	10	3	95	4	4	91	99
	5000	3	93	2	2	91	94
Undergarment	0.25	3	96	4	4	92	100
	125	3	100	3	3	96	103
Chemical resistant gloves	10	3	104	6	6	97	110
	5000	3	94	1	2	93	96
Hand wash	0.5	3	97	8	8	88	102
	250	3	95	6	6	92	102

SD = Arithmetic Standard Deviation, CV = coefficient of variation, min = minimum, max = maximum

[a] Specimen sizes = 1000 cm^2 cloth for dosimeters, 1000 mL for hand washes, and pair of gloves

Formulation: Samples of the formulated product were not taken.

Travel Recovery: Three travel specimens for each matrix were fortified at one spike level on two days. The procedure for fortification was the same as for the field fortification samples, except that samples were immediately frozen and not exposed to ambient conditions. As field recoveries were acceptable for all matrices, travel recovery samples were not analysed.

Storage Stability: The storage stability of test samples was verified using field fortification samples. The field recovery samples were stored under the same conditions as the test samples and therefore will adequately reflect the field storage, transport and frozen storage period prior to and following extraction prior to analysis. Samples were stored for 96-212 days between collection and extraction and for 0-21 days between extraction and analysis.

II. RESULTS AND CALCULATIONS:

A. EXPOSURE CALCULATIONS:

See Table 7 for a summary of the results.

Overall the field fortification results were considered acceptable. Field fortification recoveries from all three days were pooled together for each matrix and fortification level in order to calculate an average recovery value. Since the % CV for each matrix was low across all 3 days (≤ 20%), it is likely that the daily conditions were similar and the data were pooled together. Mean field fortification recoveries per sample matrix were 93%-104% with a CV lower than 20%. Correction of inner dosimeter and hand wash field samples was not required as recovery of the corresponding field fortifications were greater than 95%. None of the field samples were below the method LOQ for any matrix.

Inhalation exposure was not monitored. Total dermal exposure was calculated as the sum of the inner dosimeter (arms, leg, torso), and handwash. Face exposure was not monitored; therefore, it was not possible to estimate exposure for workers not wearing a hood or a half-mask respirator. As such, a chemical-resistant hood and a respirator will be required as part of the clothing scenario when the unit exposure from this study is used. Although respirators are typically required based on the outcome of the inhalation risk assessment or acute inhalation toxicity study, they will be included to reduce the available face surface area that would be exposed when using this application equipment.

All workers monitored in this study were included in the analysis. Although worker 4 applied fewer loads (3 loads) of cymoxanil solution compared to other workers (6-10 loads), he conducted other activities (e.g. mixing/loading, repairing sprayers, moving trucks) which could also result in exposure. When normalized by amount handled, his exposure was within the range calculated for the other workers. Study authors excluded worker 9 as the residue level in the coverall torso was considered to be unlikely and suspected an inversion with the coverall hood. This worker was not excluded in this analysis, as only the inner dosimeters were included in the calculation of dermal exposure.

As exposure from the hands represents less than 20% of the total dermal exposure and neck exposure was collected using a dosimeter, rather than a wipe, a method efficiency adjustment (MEA) factor for hand wash and face /neck wipes was not required for this study (PMRA, 2010).

The study was considered to be appropriate for estimating exposure for workers applying using handheld airblast/mistblower equipment. Although some workers also mixed/loaded, it was not performed by all workers. Dermal exposure during application of cymoxanil resulted in an average (parametric) exposure of 32,561 µg/kg a.i. applied. The calculation of a parametric arithmetic mean was considered to be appropriate as it fits the data to a lognormal distribution which is typical of exposure data and is similar to how other generic unit exposures (e.g. AHETF) have been calculated. This dermal unit exposure value is conservative as the inner dosimeter was worn directly under the chemical-resistant coverall; typically, workers would wear a single layer of clothing underneath their chemical resistant coveralls which provides an additional layer of protection for the worker and another barrier that chemicals would need to pass through to reach the skin.

Dermal exposure in this study is considered to be on the high-end, as workers contacted treated foliage as they walked down the rows, walked into spray clouds created by themselves or others, and were also sprayed by other workers. Given this, the exposure in this study is considered to be appropriate for other scenarios, such as indoor space sprays and outdoor mosquito control, where workers may walk through spray clouds during application, or contact treated foliage during application.

III DISCUSSION

A. LIMITATIONS OF THE STUDY:

5. Inhalation exposure was not measured. As inhalation is considered to be a significant route of exposure, this is a major limitation of the study.
6. Only 10 workers were monitored. The test guidelines recommend at least 15.
7. Face and neck exposure was not monitored in this study (e.g. face/neck wipes). To address this, the PPE worn in this study will be required when using the unit exposure value from this study.
8. Some of the workers wore bandannas over their heads instead of hoods. As face/neck wipes were not conducted, residues that fell on the neck and face for these workers were not accounted for. This is considered to be a limitation as it would result in an underestimate of exposure.
9. Not all workers performed the same mixer/loader/applicator tasks, which may represent different levels of exposure per worker
10. Tyvek coveralls were used as the outer dosimeter. As Tyvek coveralls are considered to be chemical-resistant, the results of this study could not be extrapolated to another clothing scenario.
11. The inner dosimeter was worn directly under the chemical-resistant coverall. This is a limitation in that it is not representative of what workers typically wear when using chemical-resistant coveralls, nor what will be required on the label. As this would result in an overestimate of exposure, this is not considered to be a major limitation.
12. Field fortification levels for coveralls did not bracket the range of residues observed in the field samples. However, this is not considered to be a major limitation as recovery at the highest laboratory fortification level is acceptable (109%) and this matrix was not used in the dermal exposure calculation.

B. CONCLUSIONS:

Overall, this study was well conducted and considered to be acceptable for estimating dermal exposure for workers applying with handheld airblast/mistblowers equipment generically for other active ingredients and scenarios. However, the inhalation exposure for workers using this equipment will need to be addressed by another study, as it is unlikely to be insignificant. The calculated dermal unit exposure value from this study is representative of a worker wearing chemical resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical resistant gloves, socks, chemical-resistant footwear, and a respirator. These unit exposures are conservative in that they are representative of chemical-resistant coveralls worn as a single layer, while two layers will be required when using these unit exposure values.

References:

PMRA. 2010. PMRA position on the use of method efficiency adjustment factors for skin wash and face/neck wipes. Sept 2, 2010. PMRA#2340675.

Table 5. Mixing Parameters and Determination of Spray Concentration

Team	Worker No.	Mixing/Loading Events.	Volume of formulation handled (L)	Volume of water used (L)	Amount a.i. handled (g)	Concentration a.i. in spray (g/L)[b]	Duration of mixing/loading (min)
1	4[a]	1	6	300	180	0.59	16
2	5[a]	1	10	450	300	0.65	5
3	Performed by unmonitored worker	1	10	300	300	0.97	Not recorded

M/L = Mixing/Loading, a.i. = active ingredient

[a] These workers performed the mixing/loading of the product in the big tank, for their respective teams. For the third team, a fourth person, who was not monitored for exposure, performed the mixing/loading of the product in the big tank.

[b] Determined using the following equation: Concentration in spray = (volume of formulation handled x guarantee (30 g/L)/ (volume of water used+ volume of formulation handled)

Table 6: Applicator Details and Field Observations

Worker	BW (kg)	Application Method	Application Loading Events	Total Spray Volume Applied (L)	Amount applied (kg)[a]	Total Spray Duration (min)	Duration of Working Day (min)	PPE and Clothing Worn	Observations
1	65	Solo - Port 423	9	81	0.0476	73	124	Coverall, full-length cotton undergarment, chemical resistant gloves, respirator, bandana, leather shoes	- Sprayer broke and worker had to travel back to get a new one - Worker sprayed two rows at once. - Worker rinsed sprayer after working day.
2	87		10	47	0.0276	86	116	Coverall, full-length cotton undergarment, chemical resistant gloves, respirator, protective glasses, bandana, leather shoes	- Worker filled sprayer (big tank)/applied 10 times. - Sprayer tank overflowed, with liquid formulation spilling onto the back of the worker. - Worked sprayed from one side to the other. - Worker removed gloves and respirator between transiting between sites.

									- Worker rinsed sprayer after working day.
3	64		8	65	0.0382	73	117	Coverall, full-length cotton undergarment, chemical resistant gloves, respirator, ear plugs, bandana, walking shoes.	- Worker filled sprayer (big tank)/applied 8 times. - Worked sprayed from one side to the other. - Worker rinsed sprayer after working day.
4	94		3	32	0.0188	43	114	Coverall, full-length cotton undergarment, chemical resistant gloves, respirator, ear plugs, bandana, leather shoes.	- Worker was in charge of mixing/loading for the big tank. PPE used for mixing was not collected, worker was issued new PPE before application. - Worker drove the truck (big tank) from site to site, and helping other team members fill spray tanks. - Worker filled their sprayer/applied 3 times. - Big spray tank was not rinsed at the end of the working day.
5	82	Stihl - SR 420	7	66	0.0430	63	195	Coverall (with hood), full-length cotton undergarment, chemical resistant gloves; respirator, walking shoes.	- Worker was in charge of mixing/loading for the big tank - Worker filled sprayer/applied 7 times. - Worker filled sprayer tank from back of truck and used a 10 L can to help colleagues fill up their sprayers. - U movement spraying technique
6	62		10	87	0.0567	88	194	Coverall (with hood), full-length cotton undergarment chemical resistant gloves; respirator, walking shoes	- Worker filled sprayer/applied 10 times. - Worker went into the field carrying a 10 L can full of solution - Sprayed between 1-2 rows at a time - Took breaks which involved taking mask and gloves off
7	68	Stihl - SR 450	9	90.5	0.0590	104	190	Coverall (with hood), full-length cotton undergarment chemical resistant gloves; respirator, walking shoes	- Worker filled sprayer/applied 9 times. - Some spilling occurred
8	120	Stihl - SR 450	6	74.5	0.0721	76	206	Coverall, full-length cotton undergarment, chemical resistant gloves, respirator, bandana, sport shoes, ear plugs, sunglasses	- Worker filled sprayer/applied 9 times. - Carried spare 10 L can filled with solution
9	73	Stihl - SR 420	7	46	0.0445	90	198	Coverall (with hood), full-length cotton undergarment chemical resistant gloves; respirator, protective goggles, ear plugs, walking shoes	- Did not load own spray tank (7 loads)
10	77	Stihl - SR 420/450	8	74	0.0716	80	193	Coverall, full-length cotton undergarment, chemical resistant gloves, respirator, bandana, canvas	- Loaded spray tank 8 times from back of truck - Alternated between spraying one row at a time and spraying two at a time

BW = body weight; PPE = personal protective equipment

[a] The amount handled for workers differs slightly from the study report, due to differences in the spray concentration (Table 5).

Table 7. Individual results for workers

Worker	1	2	3	4	5	6	7	8	9	10
Amount a.i. handled (kg)	0.0476	0.0276	0.0382	0.0188	0.0430	0.0567	0.0590	0.0721	0.0445	0.0716
Inner dosimeter (µg/sample)										
Arms	10.35	94.83	19.30	1.67	40.64	5.37	16.24	15.70	20.34	11.00
Legs	6.69	101.46	77.94	12.53	29.40	79.12	35.29	39.99	86.56	1152.62
Torso	102.77	1 482.32	40.60	65.12	329.87	203.99	335.81	663.67	4409.62	4217.47
Inner dosimeter (µg/kg ai handled)										
Arms	217.22	3 430.02	504.77	88.72	944.16	94.64	275.15	217.76	456.91	153.60
Legs	140.41	3 669.83	2 038.438	665.668	683.03	1 394.45	597.92	554.67	1 944.46	16 095.14
Torso	2 156.90	53 615.83	1 061.85	3 459.50	7 663.65	3 595.23	5 689.60	9 205.27	99 056.68	58 892.60
Total Inner dosimeter (µg/kg ai handled)	2 514.53	60 715.68	3 605.05	4 213.88	9 290.84	5 084.32	6 562.67	9 977.70	101 458.06	75 141.35
Hand washes (µg/sample)	4.70	60.90	5.10	6.40	129.80	182.80	147.10	67.80	54.10	308.30
Hand washes (µg/kg ai handled)	98.64	2 202.77	133.38	340.00	3 015.56	3 221.76	2 492.30	940.40	1 215.29	4 305.09
Normalized Dermal exposure (µg/kg ai handled)[b]	2 514.53	60 715.68	3 605.05	4 213.88	9290.84	5 084.32	6 562.67	9 977.70	10 1458.06	75 141.35
AM (µg/kg ai handled)	29 652.93									
SD	37 241.71									
GM (µg/kg ai handled)	13 687.09									
GSD	3.73									

Parametric AM[c] (µg/kg ai handled)	32 561.16

a.i, = active ingredient; AM = arithmetic mean; SD = arithmetic mean standard deviation; GM = geometric mean; GSD = geometric standard deviation

[a] Dermal exposure = undergarment + hand washes

[b] Calculated as dermal exposure/amount of a.i. handled.

[c] Calculated using the following equation: Mean = GM x exp(0.5 x [(ln GSD)^2])

Signature Page

Officer Number:2577
Evaluator
Exposure Re-evaluation Section - 2

August 19/2019
Date

Officer Number: 1153
Peer-Reviewer
Exposure Re-evaluation Section - 1

Aug. 19, 2019.
Date

Officer Number: 1143
Head,
Exposure Re-evaluation Section - 1

2019 Aug 19
Date