M E M O R A N D U M

To:	Timothy Leighton, EPA; Bob Ross, Summitec Inc.; Andrew Yin, Summitec Inc.
From:	Jonathan Cohen, ICF International, Inc.
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Re:	Contract No.: EP-W-11-014 TAF 1-6-3: Liquid Pour AEATF Study Statistical Review for HSRB

Introduction and Summary

In August 2012, AEATF submitted the final report for their study "A Study for Measurement of Potential Dermal and Inhalation Exposure during Application of a Liquid Antimicrobial Pesticide Product During Manual Pouring of a Liquid Containing an AntiMicrobial." ICF International, Inc. (ICF) was asked by EPA through Summitec Inc. to analyze the data from this study to investigate the relationship between dermal and inhalation exposures and the pesticide product usage. Note that much of the SAS code used for these analyses and some of the following description was adapted from Sarkar's SAS code (which, in turn, was based on code provided by the AHETF) and his June 2010 Statistical Review "Review of Statistical Analyses in Agricultural Handler Exposure Task Force (AHETF) Monographs."

The study report describes the experimental study methodology and the measurements in detail. Briefly, the study was carried out at an indoor test site in Concord, Ohio. Each of 18 volunteer subjects performed both the following scripted Conventional Pour study and the following scripted Reduced Splash, in a randomly selected order.

For the Conventional Pour (CP) study, 18 volunteer subjects, referred to here as "workers," were randomly assigned into three groups of six subjects, numbered 1, 2 and 3, and the workers in group 1 were randomly assigned into two groups of three subjects, referred to as groups 1a and 1b. The workers in group 1a were assigned a task of pouring a liquid containing the active ingredient DDAC from a set of 10 conventional small source containers of sizes 24, 32, and 64 fl oz into 32 fl oz trigger spray bottles. The workers in group 1b were assigned a task of pouring a liquid containing the active ingredient DDAC from a set of 10 conventional small source containers of sizes 24, 32, and 64 fl oz into 2 gallon buckets. The workers in group 2 were assigned a task of pouring a liquid containing the active ingredient DDAC from a set of 10 conventional medium source containers of sizes 128, 202, and 256 fl oz into either 2 gallon buckets, 4 gallon buckets, or 50 gallon low-walled troughs, where the three receiver container types were each randomly assigned to two of the group 1 workers. The workers in group 3 were assigned a task of pouring a liquid containing the active ingredient DDAC from a set of conventional large source containers of sizes 640 fl oz (5 gallon buckets) with standard flat lids into 50 gallon low-walled troughs. All subjects in group 1 and 4 randomly selected subjects in group 2 used a measuring cup. For each subject in groups 1 and 2, it was randomly determined whether the receiving containers would be placed on the floor or on a table (at waist to chest height). For all subjects in group 3, the receiving containers were on the floor.

For the Reduced Splash (RS) study, the same 18 volunteer subjects, referred to here as "workers," were randomly assigned into three groups of six subjects, numbered 1, 2 and 3, and the workers in group 1 were randomly assigned into two groups of three subjects, referred to as groups 1a and 1b. All these assignments were independent of the Conventional Pour study assignments, so that a worker might not be in the same groups for the CP and RS studies. The workers in group 1a were assigned a task of pouring a liquid containing the active ingredient C14 ADBAC from a set of 10 reduced splash small source containers of size 64 fl oz into 32 fl oz trigger spray bottles. The workers in group 1b were assigned a task of pouring a liquid containing the active ingredient C14 ADBAC from a set of 10 reduced splash small source containers of size 64 fl oz into 2 gallon buckets. The workers in group 2 were assigned a task of pouring a liquid containing the active ingredient C14 ADBAC from a set of 10 reduced splash medium source containers of sizes 96, 128 and 180 fl oz into either 2 gallon buckets, 4 gallon buckets, or 50 gallon low-walled troughs, where the three receiver container types were each randomly assigned to two of the group 1 workers. The workers in group 3 were assigned a task of pouring a liquid containing the active ingredient C14 ADBAC from a set of large source containers of sizes 640 fl oz (5 gallon buckets) that had lids with a pull-out pour spout into 50 gallon low-walled troughs. All subjects in group 1, and 4 randomly selected subjects in group 2, used a measuring cup. For each subject in groups 1 and 2, it was randomly determined whether the receiving containers would be placed on the floor or on a table (at waist to chest height). For all subjects in group 3, the receiving containers were on the floor.

Each subject was given inner and outer dosimeters to wear and was also given a personal air-sampling pump attached to an OVS air sampling tube. The air sampling pump was switched on at the beginning of the first monitoring experiment (ME) and turned off once the pouring was completed. The subject sat on a chair covered with plastic sheeting until the preparation of the containers for the second ME was completed. Then the air sampling pump was switched on again for the second ME and turned off once the pouring was completed. The air sampling tubes, hand wash, face/neck wipes, outer dosimeters, and inner dosimeters, were collected by a researcher and were later analyzed by the laboratory to measure the mass of DDAC (attributable to the Conventional Pour active ingredient) and the mass of C14 ADBAC (attributable to the Reduced Splash active ingredient).

The exposure measurements in the report were corrected for the average percentage recovery of field fortification samples and for the removal efficiency of hand wash (90%) and face and neck (89%) wipe samples. These analyses used the corrected measurements. An Excel spreadsheet containing the data in the report was supplied by the Study Director and used for these analyses. This included the units conversion of the amounts of active ingredient from mg into pounds and of the mass from µg to mg. The report data for inhalation exposure were unchanged other than the units conversions and some corrections to the tabulated air sampling durations in the original study report that were noted by the Study Director in September 2012. The dermal exposure data were used to develop exposure measurements for four dermal exposure routes, as follows:

- **Long Dermal**. This case represents the dermal exposure for a subject wearing long pants and long-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

- **Short Dermal**. This case represents the dermal exposure for a subject wearing short pants and short-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, the outer dosimeters for the lower arm and lower leg, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

- **Long Short Dermal**. This case represents the dermal exposure for a subject wearing long pants and short-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, the outer dosimeter for the lower arm, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

- **Hands Only**. This case represents the dermal exposure to the hands only and is the mass from hand wash. This case is used for comparison purposes.

The report only considered the dermal exposure for the "Long Dermal" case, and used the same definition. However for our analyses we chose a more consistent, and more conservative (i.e., more health protective) approach to deal with values reported as being below the level of quantitation (LOQ):

Several of the measured values were below the level of quantitation (LOQ). Such values are called "non-detects." The experimental protocol also required that measurements of the inner dosimeters were not taken if the outer dosimeter was below the LOQ, although this did not in fact apply for any of the outer dosimeter measurements made in this study. As a slightly more conservative (i.e., more health protective) approach than the method used in the report, we replaced any value that was either a non-detect or was not measured by one half the LOQ. If any inner or outer dosimeter value was below the LOQ, 3 μg, each such value was replaced by 1.5 μg = 0.0015 mg. For example, if all the inner dosimeters were below the LOQ, then the total would be replaced by 0.009 mg. If the face and neck measurement was below the LOQ, 50 ng, it was replaced by 25 ng = 0.000025 mg. If the inhalation mass OVS measurement (mg) was below the LOQ, 10 ng, it was replaced by 5 ng = 0.000005 mg. All the hand wash measurements in the study were above the LOQ. For the Conventional Pour, 4 of the 18 face and neck measurements, 67 of the 108 outer dosimeter measurements, 107 of the 108 inner dosimeter measurements, and 6 of the 18 OVS measurements were below the LOQ. For the Reduced Splash, 0 of the 18 face and neck measurements, 41 of the 108 outer dosimeter measurements, 105 of the 108 inner dosimeter measurements, and 9 of the 18 OVS measurements were below the LOQ. In Tables 10 and 11 below, we present the results of alternative analyses of values below the LOQ that demonstrate that the impact of the method for analyzing non-detect samples is negligible.

For three subjects and MEs (Reduced Splash ME 1 in group 1a, Reduced Splash ME 7 in group 2, and Conventional Pour ME 6 in group 1b), the hand exposure measurements were much higher than values for all other subjects in the same group. The liquid pour scenario is one in which unusually large hand exposures can occur through random dripping and spilling events that may be poorly associated with the total amount of active ingredient used. No adjustments were made in these analyses for these potential outliers. In Table 10 below, we analyze the impact of removing these outliers.

Inhalation exposure was measured using the air sampling OVS tubes. The inhalation exposure concentration (mg/m^3) was calculated by dividing the corrected residue mass by the volume of air drawn. The following exposure concentrations are analyzed in this memorandum:

- **Inhalation Concentration (mg/m^3).** Concentration measured by the OVS tube.

- **Inhalation Dose (mg).** Inhalation Concentration (mg/m^3) × Air Sampling Duration (hr) × Breathing Rate for Light Activity (m^3/hr). A breathing rate of 1 m^3/hr is assumed.

- **8-Hour Time Weighted Average (TWA) Concentration (mg/m^3).** Average concentration over eight hours that includes this period of liquid pouring activity.
  Inhalation Concentration (mg/m^3) × Air Sampling Duration (hr) / 8 (hr).

In this memorandum we present the analysis of the unit or normalized exposure defined as the dermal or inhalation exposure divided by the pounds of active ingredient handled. Estimates of the arithmetic and geometric means and standard deviation as well as the 95th percentile are computed using the empirical data for each group as well as two statistical models: the lognormal simple random sampling model for each group and the lognormal mixed model with groups. Because the study design used predetermined groups of containers, these analyses take into account the possibility that the mean exposure depends upon the group, which in statistical terminology represents a fixed effect rather than a random effect. Unlike the previously analyzed mop, wipe, and aerosol studies, this study does not have a

random cluster effect and so the statistical models used here are very different. The empirical model calculates statistics for all the unit exposure measurements on a group of subjects assuming the data are statistically independent with a possibly different distribution for each group. The lognormal simple random sampling model calculates statistics for all the unit exposure measurements on a group of subjects assuming the unit exposure measurements are statistically independent with a lognormal distribution that can be different for each group. The lognormal mixed model is fitted to the entire set of 36 exposure measurements, from both studies, and assumes that the logarithm of the exposure has a normal distribution with a mean that varies between groups, a random worker effect, and a residual error. The random worker effect is a random value associated with each of the 18 workers that represents the possibility of clustering or association between the two measurements made for that worker (one for conventional pour and one for reduced splash), expressing the possibility that some workers have a tendency for getting more highly exposed to antimicrobials than other workers.

Although the experimental design randomized for the effects of whether a measuring cup was used and whether the receiving container was placed on the floor or on a table, we treated these effects as part of the random error and did not directly include those effects in the statistical models. However, in many cases we found a strong worker effect, and so this effect is specifically included in the mixed model so that correlations between consecutive measurements on the same worker (e.g., for the conventional pour and reduced splash MEs) can be adjusted for.

As discussed below, we considered various groupings. Initially we separately considered the six groups of container sizes 1, 2 and 3 separately for CP and RS. Since groups 1a and 1b represent very different scenarios of pouring into trigger sprays versus pouring into a larger container, with much higher observed exposures for trigger sprays due to the more complex nature of that task, we also considered separating group 1 into groups 1a and 1b. We also considered combining the data for the CP and RS for each of these container size groups. For the final lognormal mixed model we used three groups: 1a with CP and RS combined; 1b, 2 and 3 for CP only, and 1b, 2 and 3 for RS only. Separation of the 1a group is justified due to the large difference between scenarios of pouring into larger containers and scenarios of pouring into small trigger spray bottles. For the pouring into trigger spray bottles, the CP and RS unit exposure values were not statistically significantly different and so could be combined. Although the remaining groups 1b, 2 and 3 have large differences in unit exposure, it is appropriate to combine these data into a single group of container sizes because of the difficulties in creating different regulations for pouring liquids from containers of different sizes. However for the pouring into non-trigger spray bottles, the unit exposure values were significantly different between CP and RS and so those scenarios were also separated. In summary we present results for the following groupings:

Initial groupings:

- 1aCP. Pouring from small conventional pour containers into trigger spray bottles
- 1aRS. Pouring from small reduced splash containers into trigger spray bottles
- 1a. Pouring from small containers into trigger spray bottles
- 1bCP. Pouring from small conventional pour containers not into trigger spray bottles
- 1bRS. Pouring from small reduced splash containers not into trigger spray bottles
- 1b. Pouring from small containers not into trigger spray bottles
- 2CP. Pouring from medium conventional pour containers
- 2RS. Pouring from medium reduced splash containers
- 2. Pouring from medium containers

- 3CP. Pouring from large conventional pour containers
- 3RS. Pouring from large reduced splash containers
- 3. Pouring from large containers

Final groupings used in lognormal mixed model:

- Bottle. Pouring from CP and RS containers into trigger spray bottles
- Conventional. Pouring from conventional containers not into trigger spray bottles
- Reduced Splash. Pouring from reduced splash containers not into trigger spray bottles

For each summary statistic we present confidence intervals. We also compute the fold relative accuracy of the summary statistics and compare with the study design benchmark of 3-fold accuracy, which was met for the mixed model used for the main statistical analyses for all the dermal and inhalation exposures except for dermal exposures in the Bottle grouping. To evaluate the statistical models we present quantile-quantile plots to compare the fit of normal and lognormal distributions to the data.

The statistical models for the normalized exposure assume that the mean value of the logarithm of the exposure is equal to an intercept plus the slope times the logarithm of the amount of active ingredient used, where the slope equals 1. To test this "log-log-linearity" assumption, the mixed model with a slope term was fitted to the data and a 95% confidence interval for the slope was calculated. A statistical test was used to determine if the slope was 1 or 0, corresponding either to a valid normalized exposure model or to a case where the exposure is independent of the amount of active ingredient used. We applied this test to the three dermal exposures and to the three inhalation exposures using the statistical mixed model. For dermal exposures it is reasonable to assume on physical grounds that the same patterns ought to apply to any type of dermal exposure, so that the slope should either be one for all types of dermal exposure or not one for all types of dermal exposure. To evaluate this issue we applied the same log-log-linearity test to a hypothetical all dermal exposure case representing a janitor with no clothing, using a dermal exposure estimated as the sum of the exposures measured on the face and neck, hands, and all the inner and outer dosimeters. We also developed a statistical repeated measures model to analyze the three main types of dermal exposure (excluding hands only) in a single statistical model, accounting for within-worker correlations and within-location clustering. We also evaluated quadratic regression models.

The results for all the dermal concentration exposure routes show that the estimated intra-cluster correlation (ICC) coefficient for the worker effect is between 0.2 and 0.4, which implies that there are some worker effects, and therefore, in particular, differences between exposures for different workers, as might be expected. The results for the inhalation exposures show an ICC of zero, showing no worker effects.

The mixed model results for the four dermal exposure routes show small positive or negative slopes of between -0.3 and 0.2. These dermal exposure models consistently reject log-log-linearity (slope equals one) at the 5% significance level. These dermal exposure models also consistently do not reject independence (slope equals zero) at the 5% significance level. The finding that the dermal exposure could be independent of the amount of active ingredient may be due to the fact that the dermal exposure is primarily caused by accidental splashes and spills which may be related to the shape and volume of the source container but otherwise not very strongly to the volume poured. The experimental design did not allow the concentrations to be varied within the Conventional or Reduced Splash experiments since using much higher concentrations would require the need for protective gloves. For this scenario a stronger log-log-linearity between exposure and concentration can be expected than between exposure and volume poured. For the inhalation exposures, the estimated slopes are close to one, log-log-linearity is not rejected, and independence is rejected.

Summary statistics of exposure per pounds of active ingredient handled

Tables 1 to 7 summarize the normalized exposure data (per lb active ingredient handled) with the summary statistics from the 18 measurements for each dermal and inhalation exposure route, for the various container groups described above. These analyses assume that the exposure measurements within each group come from some unspecified distribution for that group.

Table 1. Summary statistics for normalized long dermal exposure (mg/lb AI) using empirical sampling model.

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Arithmetic Mean	155	111	200	11	20	3	7	7	7	2	4	0	155	8	4
Arithmetic Standard Deviation	152	14	227	13	14	3	9	6	12	4	5	0	152	9	8
Geometric Mean	116	110	123	6	17	2	4	4	4	1	2	0	116	4	1
Geometric Standard Deviation	2	1	3	4	2	3	4	5	3	4	3	2	2	4	4
Min	40	95	40	1	10	1	0	0	1	0	1	0	40	0	0
5%	40	95	40	1	10	1	0	0	1	0	1	0	40	0	0
10%	40	95	40	1	10	1	1	0	1	0	1	0	40	1	0
25%	95	95	40	1	10	1	2	2	2	0	1	0	95	1	0
50%	107	115	99	8	14	1	4	7	3	1	1	0	107	6	1
75%	122	122	459	14	35	7	10	14	4	1	4	1	122	14	3
90%	459	122	459	35	35	7	15	15	31	4	14	1	459	15	7
95%	459	122	459	35	35	7	31	15	31	14	14	1	459	35	31
Max	459	122	459	35	35	7	31	15	31	14	14	1	459	35	31

Table 2. Summary statistics for normalized short dermal exposure (mg/lb AI) using empirical sampling model.

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Arithmetic Mean	158	114	202	13	22	3	8	8	8	3	4	1	158	9	4
Arithmetic Standard Deviation	153	11	229	14	16	3	9	6	12	4	6	1	153	10	8
Geometric Mean	119	113	124	7	18	3	4	5	4	1	2	1	119	5	2
Geometric Standard Deviation	2	1	3	3	2	2	3	4	3	3	3	2	2	4	3

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Min	41	102	41	2	11	2	1	1	1	0	1	0	41	1	0
5%	41	102	41	2	11	2	1	1	1	0	1	0	41	1	0
10%	41	102	41	2	11	2	1	1	1	1	1	0	41	1	1
25%	100	102	41	2	11	2	2	2	2	1	1	1	100	1	1
50%	109	116	100	9	14	2	4	7	4	1	2	1	109	6	2
75%	123	123	465	14	40	7	11	14	4	2	4	1	123	14	4
90%	465	123	465	40	40	7	15	15	32	4	16	2	465	16	7
95%	465	123	465	40	40	7	32	15	32	16	16	2	465	40	32
Max	465	123	465	40	40	7	32	15	32	16	16	2	465	40	32

Table 3. Summary statistics for normalized long short dermal exposure (mg/lb AI) using empirical sampling model.

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Arithmetic Mean	156	111	201	11	20	3	8	8	7	2	4	0	156	8	4
Arithmetic Standard Deviation	152	14	228	13	13	3	9	6	12	4	5	0	152	9	8
Geometric Mean	117	110	123	6	17	2	4	5	4	1	2	0	117	4	1
Geometric Standard Deviation	2	1	3	4	2	2	3	4	3	4	3	2	2	4	4
Min	41	95	41	1	10	1	1	1	1	0	1	0	41	1	0
5%	41	95	41	1	10	1	1	1	1	0	1	0	41	1	0
10%	41	95	41	1	10	1	1	1	1	0	1	0	41	1	0
25%	95	95	41	2	10	1	2	2	2	0	1	0	95	1	0
50%	108	116	100	8	14	2	4	7	3	1	1	0	108	6	1
75%	123	123	461	14	35	7	11	14	4	1	4	1	123	14	3
90%	461	123	461	35	35	7	15	15	31	4	14	1	461	15	7
95%	461	123	461	35	35	7	31	15	31	14	14	1	461	35	31
Max	461	123	461	35	35	7	31	15	31	14	14	1	461	35	31

Table 4. Summary statistics for normalized hands only dermal exposure (mg/lb AI) using empirical sampling model.

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Arithmetic Mean	153	109	197	11	20	3	7	7	7	2	4	0	153	8	4
Arithmetic Standard Deviation	152	14	227	13	14	3	9	6	12	4	5	0	152	9	8
Geometric Mean	114	108	119	6	17	2	4	4	3	1	2	0	114	4	1
Geometric Standard Deviation	2	1	3	4	2	3	4	5	3	4	3	2	2	4	5
Min	38	93	38	1	10	1	0	0	1	0	1	0	38	0	0
5%	38	93	38	1	10	1	0	0	1	0	1	0	38	0	0
10%	38	93	38	1	10	1	1	0	1	0	1	0	38	1	0
25%	93	93	38	1	10	1	2	2	2	0	1	0	93	1	0
50%	105	113	97	8	14	1	4	7	3	1	1	0	105	6	1
75%	120	120	457	14	35	6	10	14	4	1	4	1	120	14	3
90%	457	120	457	35	35	6	15	15	31	4	13	1	457	15	6
95%	457	120	457	35	35	6	31	15	31	13	13	1	457	35	31
Max	457	120	457	35	35	6	31	15	31	13	13	1	457	35	31

Table 5. Summary statistics for normalized inhalation concentration ((mg/m^3)/lb AI) using empirical sampling model.

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Arithmetic Mean	0.0347	0.0388	0.0305	0.0076	0.0121	0.0030	0.0106	0.0175	0.0037	0.0124	0.0189	0.0058	0.0347	0.0170	0.0044
Arithmetic Standard Deviation	0.0058	0.0041	0.0038	0.0090	0.0119	0.0005	0.0117	0.0132	0.0034	0.0151	0.0197	0.0033	0.0058	0.0151	0.0031
Geometric Mean	0.0343	0.0387	0.0303	0.0052	0.0089	0.0030	0.0057	0.0121	0.0027	0.0078	0.0120	0.0051	0.0343	0.0113	0.0035
Geometric Standard Deviation	1.1858	1.1138	1.1376	2.3129	2.5264	1.1635	3.4127	3.0232	2.3450	2.6313	3.0588	1.8229	1.1858	2.7484	2.0072
Min	0.0262	0.0343	0.0262	0.0027	0.0051	0.0027	0.0010	0.0017	0.0010	0.0019	0.0019	0.0022	0.0262	0.0017	0.0010
5%	0.0262	0.0343	0.0262	0.0027	0.0051	0.0027	0.0010	0.0017	0.0010	0.0019	0.0019	0.0022	0.0262	0.0017	0.0010
10%	0.0262	0.0343	0.0262	0.0027	0.0051	0.0027	0.0013	0.0017	0.0010	0.0022	0.0019	0.0022	0.0262	0.0019	0.0013
25%	0.0322	0.0343	0.0262	0.0028	0.0051	0.0027	0.0018	0.0076	0.0013	0.0035	0.0081	0.0035	0.0322	0.0053	0.0022
50%	0.0337	0.0399	0.0322	0.0043	0.0053	0.0028	0.0059	0.0146	0.0027	0.0080	0.0130	0.0053	0.0337	0.0131	0.0035
75%	0.0399	0.0423	0.0331	0.0053	0.0259	0.0036	0.0146	0.0331	0.0042	0.0130	0.0202	0.0079	0.0399	0.0259	0.0071

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
90%	0.0423	0.0423	0.0331	0.0259	0.0259	0.0036	0.0331	0.0337	0.0101	0.0202	0.0571	0.0107	0.0423	0.0337	0.0101
95%	0.0423	0.0423	0.0331	0.0259	0.0259	0.0036	0.0337	0.0337	0.0101	0.0571	0.0571	0.0107	0.0423	0.0571	0.0107
Max	0.0423	0.0423	0.0331	0.0259	0.0259	0.0036	0.0337	0.0337	0.0101	0.0571	0.0571	0.0107	0.0423	0.0571	0.0107

Table 6. Summary statistics for normalized inhalation dose (mg/lb AI) using empirical sampling model.

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Arithmetic Mean	0.0093	0.0086	0.0099	0.0011	0.0016	0.0006	0.0017	0.0027	0.0008	0.0011	0.0013	0.0009	0.0093	0.0019	0.0008
Arithmetic Standard Deviation	0.0009	0.0006	0.0007	0.0009	0.0012	0.0000	0.0018	0.0022	0.0007	0.0010	0.0013	0.0006	0.0009	0.0017	0.0005
Geometric Mean	0.0092	0.0086	0.0099	0.0009	0.0013	0.0006	0.0011	0.0019	0.0006	0.0008	0.0008	0.0008	0.0092	0.0013	0.0007
Geometric Standard Deviation	1.1045	1.0700	1.0757	1.8321	2.0497	1.0161	2.9094	2.6705	2.3240	2.3476	2.9358	1.9434	1.1045	2.6982	1.9286
Min	0.0080	0.0080	0.0094	0.0006	0.0008	0.0006	0.0003	0.0003	0.0003	0.0002	0.0002	0.0004	0.0080	0.0002	0.0003
5%	0.0080	0.0080	0.0094	0.0006	0.0008	0.0006	0.0003	0.0003	0.0003	0.0002	0.0002	0.0004	0.0080	0.0002	0.0003
10%	0.0080	0.0080	0.0094	0.0006	0.0008	0.0006	0.0003	0.0003	0.0003	0.0004	0.0002	0.0004	0.0080	0.0003	0.0003
25%	0.0086	0.0080	0.0094	0.0007	0.0008	0.0006	0.0003	0.0015	0.0003	0.0005	0.0005	0.0005	0.0086	0.0006	0.0004
50%	0.0093	0.0086	0.0096	0.0007	0.0011	0.0007	0.0014	0.0023	0.0005	0.0008	0.0008	0.0009	0.0093	0.0015	0.0007
75%	0.0096	0.0092	0.0107	0.0011	0.0030	0.0007	0.0024	0.0028	0.0012	0.0015	0.0017	0.0014	0.0096	0.0028	0.0013
90%	0.0107	0.0092	0.0107	0.0030	0.0030	0.0007	0.0028	0.0067	0.0020	0.0017	0.0038	0.0016	0.0107	0.0038	0.0016
95%	0.0107	0.0092	0.0107	0.0030	0.0030	0.0007	0.0067	0.0067	0.0020	0.0038	0.0038	0.0016	0.0107	0.0067	0.0020
Max	0.0107	0.0092	0.0107	0.0030	0.0030	0.0007	0.0067	0.0067	0.0020	0.0038	0.0038	0.0016	0.0107	0.0067	0.0020

Table 7. Summary statistics for normalized inhalation 8-hour time weighted average concentration ((mg/m^3)/lb AI) using empirical sampling model.

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Arithmetic Mean	0.0012	0.0011	0.0012	0.0001	0.0002	0.0001	0.0002	0.0003	0.0001	0.0001	0.0002	0.0001	0.0012	0.0002	0.0001
Arithmetic Standard Deviation	0.0001	0.0001	0.0001	0.0001	0.0002	0.0000	0.0002	0.0003	0.0001	0.0001	0.0002	0.0001	0.0001	0.0002	0.0001

Statistic	1a	1aCP	1aRS	1b	1bCP	1bRS	2	2CP	2RS	3	3CP	3RS	Bottle	Conventional	Reduced Splash
Geometric Mean	0.0012	0.0011	0.0012	0.0001	0.0002	0.0001	0.0001	0.0002	0.0001	0.0001	0.0001	0.0001	0.0012	0.0002	0.0001
Geometric Standard Deviation	1.1045	1.0700	1.0757	1.8321	2.0497	1.0161	2.9094	2.6705	2.3240	2.3476	2.9358	1.9434	1.1045	2.6982	1.9286
Min	0.0010	0.0010	0.0012	0.0001	0.0001	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010	0.0000	0.0000
5%	0.0010	0.0010	0.0012	0.0001	0.0001	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010	0.0000	0.0000
10%	0.0010	0.0010	0.0012	0.0001	0.0001	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010	0.0000	0.0000
25%	0.0011	0.0010	0.0012	0.0001	0.0001	0.0001	0.0000	0.0002	0.0000	0.0001	0.0001	0.0001	0.0011	0.0001	0.0000
50%	0.0012	0.0011	0.0012	0.0001	0.0001	0.0001	0.0002	0.0003	0.0001	0.0001	0.0001	0.0001	0.0012	0.0002	0.0001
75%	0.0012	0.0011	0.0013	0.0001	0.0004	0.0001	0.0003	0.0003	0.0001	0.0002	0.0002	0.0002	0.0012	0.0003	0.0002
90%	0.0013	0.0011	0.0013	0.0004	0.0004	0.0001	0.0003	0.0008	0.0003	0.0002	0.0005	0.0002	0.0013	0.0005	0.0002
95%	0.0013	0.0011	0.0013	0.0004	0.0004	0.0001	0.0008	0.0008	0.0003	0.0005	0.0005	0.0002	0.0013	0.0008	0.0003
Max	0.0013	0.0011	0.0013	0.0004	0.0004	0.0001	0.0008	0.0008	0.0003	0.0005	0.0005	0.0002	0.0013	0.0008	0.0003

The summary statistics shown in Tables 1 to 4 show that the results for the four dermal scenarios (long dermal, short dermal, long short dermal, and hands only) are very similar. This is reflected by the fact that the dermal exposures are dominated by the large measured values on the hands. The results for Tables 1 to 7 also show that the statistics for groups 1aCP and 1aRS are quite similar, especially in view of the fact that they are only based on 3 workers per group, and that there are big differences between 1bCP and 1bRS. The differences between the conventional pour and reduced splash exposures are relatively small within groups 2 and 3. The results show some large differences between groups 1b, 2 and 3, especially between dermal exposures in groups 1b and 2.

To evaluate the differences between the groups, an analysis of variance was used to test for statistically significant differences. The following statistical mixed model fitted to all the exposure data (separately for each exposure route) was used for this test:

Log(normalized exposure) = group + worker + error

For this model, the (fixed effect) group variable is the group category that allocates each exposure measurement to one of the eight groups 1aCP, 1aRS, 1bCP, 1bRS, 2CP, 2RS, 3CP, 3RS. Thus the geometric mean depends upon the container size category (1a, 1b, 2 or 3) and the type of container (conventional or reduced splash). The worker term is a random effect that represents the correlation between multiple measurements on the same worker; each worker has their own random exposure effect that is added to the overall group mean (after taking logarithms). The worker effects are drawn from a normal distribution with mean zero. Each of the 36 measurements also has a random error term drawn from another normal distribution with mean zero. This model was fitted to the data and then used to test for the following differences between the eight groups using a statistical contrast:

- RS=CP for bottles. This tests if the means for groups 1aCP and 1aRS are equal. A non-significant difference supports combining the 1a data from conventional and reduced splash containers.

- RS=CP for other. This tests if the means for groups 1bCP and 1bRS are equal, and the means for groups 2CP and 2RS are equal, and the means for groups 3CP and 3RS are equal. A non-significant difference supports combining the data from conventional and reduced splash containers of the same size, when the receiving container is not a trigger spray bottle. It does not evaluate whether the size groups 1b, 2, and 3 can be combined.

- 1b=2=3 for CP. This tests if the means for groups 1bCP, 2CP, and 3CP are equal. A non-significant difference supports combining the conventional pour data from containers of difference sizes, when the receiving container is not a trigger spray bottle.

- 1b=2=3 for RS. This tests if the means for groups 1bRS, 2RS, and 3RS are equal. A non-significant difference supports combining the reduced splash data from containers of difference sizes, when the receiving container is not a trigger spray bottle.

- bottles=other for CP. This tests if the means for groups 1aCP, 1bCP, 2CP, and 3CP are equal. A non-significant difference supports combining the conventional pour data from containers of difference sizes, and whether or not the receiving container is a trigger spray bottle.

- bottles=other for RS. This tests if the means for groups 1aRS, 1bRS, 2RS, and 3RS are equal. A non-significant difference supports combining the reduced splash data from containers of difference sizes, and whether or not the receiving container is a trigger spray bottle.

The results are shown in Table 8. P-values at or below 0.05 indicate statistically significant differences at the 5 percent significance level. The "RS=CP for bottles" test is not significant for all the exposure routes, which supports combining the group 1a data for CP and RS into a single group. The "1b=2=3 for CP" test is significant for the dermal exposures but not for the inhalation exposures, which fails to support combining the CP data for the different container sizes. The "1b=2=3 for RS" test is significant for the dermal exposures but not for the inhalation exposures, which fails to support combining the RS data for the different container sizes. The "bottles=other for CP" test is significant for all the exposure routes except for the inhalation concentration, which fails to support combining the CP data for the different container sizes and for pouring into trigger spray bottles. The "bottles=other for RS" test is significant for all the exposure routes, which fails to support combining the RS data for the different container sizes and for pouring into trigger spray bottles. Despite these findings, it is not feasible to apply separate unit exposure estimates (and, ultimately, regulatory decisions) for pouring liquids from containers of different sizes, so it was decided that the three groups 1b, 2, and 3 would be combined for the statistical mixed modeling. Under the mixed models, the geometric mean exposure is assumed to be the same for groups 1b, 2 and 3 (although different between conventional pour and reduced splash containers) and any differences between container size groups are treated as being part of the random variability in exposure. Therefore the final mixed models used three groups only:- Bottle: 1a-Pouring into trigger spray bottles; Conventional: 1bCP, 2CP, and 3CP-Pouring from conventional pour containers not into trigger spray bottles; and Reduced Splash: 1bRS, 2RS, and 3RS-Pouring from reduced splash containers not into trigger spray bottles.

Table 8. Statistical tests comparing different groups of source and receiving containers.

Normalized Exposure	**Test**	**P-Value**
Long Dermal mg per pound AI	RS=CP for bottles	0.88
Long Dermal mg per pound AI	RS=CP for other	0.01
Long Dermal mg per pound AI	bottles=other for CP	0.00
Long Dermal mg per pound AI	bottles=other for RS	0.00

Normalized Exposure	Test	P-Value
Long Dermal mg per pound AI	1b=2=3 for CP	0.02
Long Dermal mg per pound AI	1b=2=3 for RS	0.00
Short Dermal mg per pound AI	RS=CP for bottles	0.84
Short Dermal mg per pound AI	RS=CP for other	0.03
Short Dermal mg per pound AI	bottles=other for CP	0.00
Short Dermal mg per pound AI	bottles=other for RS	0.00
Short Dermal mg per pound AI	1b=2=3 for CP	0.01
Short Dermal mg per pound AI	1b=2=3 for RS	0.03
Long Short Dermal mg per pound AI	RS=CP for bottles	0.87
Long Short Dermal mg per pound AI	RS=CP for other	0.01
Long Short Dermal mg per pound AI	bottles=other for CP	0.00
Long Short Dermal mg per pound AI	bottles=other for RS	0.00
Long Short Dermal mg per pound AI	1b=2=3 for CP	0.01
Long Short Dermal mg per pound AI	1b=2=3 for RS	0.00
Hands Only Dermal mg per pound AI	RS=CP for bottles	0.86
Hands Only Dermal mg per pound AI	RS=CP for other	0.01
Hands Only Dermal mg per pound AI	bottles=other for CP	0.00
Hands Only Dermal mg per pound AI	bottles=other for RS	0.00
Hands Only Dermal mg per pound AI	1b=2=3 for CP	0.03
Hands Only Dermal mg per pound AI	1b=2=3 for RS	0.00
Inhalation Concentration mg/m3 per pound AI	RS=CP for bottles	0.74
Inhalation Concentration mg/m3 per pound AI	RS=CP for other	0.03
Inhalation Concentration mg/m3 per pound AI	bottles=other for CP	0.22
Inhalation Concentration mg/m3 per pound AI	bottles=other for RS	0.02
Inhalation Concentration mg/m3 per pound AI	1b=2=3 for CP	0.89
Inhalation Concentration mg/m3 per pound AI	1b=2=3 for RS	0.45
Inhalation Dose mg per pound AI	RS=CP for bottles	0.83
Inhalation Dose mg per pound AI	RS=CP for other	0.10
Inhalation Dose mg per pound AI	bottles=other for CP	0.01

Normalized Exposure	Test	P-Value
Inhalation Dose mg per pound AI	bottles=other for RS	0.00
Inhalation Dose mg per pound AI	1b=2=3 for CP	0.22
Inhalation Dose mg per pound AI	1b=2=3 for RS	0.80
Inhalation 8hr TWA mg/m3 per pound AI	RS=CP for bottles	0.83
Inhalation 8hr TWA mg/m3 per pound AI	RS=CP for other	0.10
Inhalation 8hr TWA mg/m3 per pound AI	bottles=other for CP	0.01
Inhalation 8hr TWA mg/m3 per pound AI	bottles=other for RS	0.00
Inhalation 8hr TWA mg/m3 per pound AI	1b=2=3 for CP	0.22
Inhalation 8hr TWA mg/m3 per pound AI	1b=2=3 for RS	0.80

The statistical analyses use the following three alternative statistical models. Let X be the normalized exposure and X = exp(Y) so that Y = log (X), where log denotes the natural logarithm. LnGM is the log of the geometric mean for a given group. Let Z95 be the 95th percentile of a standard normal distribution, approximately 1.645.

- Empirical simple random sampling model. Code "s." Assumes that all the values of X from a given group g were randomly drawn from an unspecified distribution. Ignores within-worker correlations. Gives empirical estimates such as in Tables 1 to 7 above.
    - Each of the following statistics depends upon the group g and only uses the X and Y values from that group
    - Y = LnGM + Error. Error is independent and identically distributed with mean 0 and a variance that depelognormal nds upon the group g.
    - AMs = Arithmetic mean of X values
    - GMs = Geometric mean of X values = exp(LnGM) (= GMu)
    - GSDs = Geometric standard deviation of X values (= GSDu)
    - P95s = 95th percentile of X values
- Lognormal simple random sampling model. Code "u." Assumes that all the values of X from a given group g were randomly drawn from a log-normal distribution. Ignores within-worker correlations.
    - Each of the following statistics depends upon the group g and only uses the X and Y values from that group
    - Y = LnGM + Error. Error is normally distributed with mean 0, variance Vu, and standard deviation Su = √Vu.
    - AMu = Modeled arithmetic mean of X values = exp(LnGM) exp(½ Vu)
    - GMu = Modeled geometric mean of X values = exp(LnGM)
    - GSDu = Modeled geometric standard deviation of X values = exp(Su)

- P95u = Modeled 95th percentile of X values = exp(LnGM) exp(Z95×Su)

- Lognormal mixed model. Code "m." There are three groups, Bottle, Conventional Pour, and Reduced Splash, as defined above. Each group has a different geometric mean. Assumes that the 18 worker random effects were independently randomly drawn from a normal distribution and that the 36 random error terms were independently drawn from another normal distribution. The error term for each worker and exposure measurement is the sum of the worker effect for that worker and the within-worker random error term.

  - Y = LnGM + Worker + Error. Worker is normally distributed with mean 0, variance Vw, and standard deviation Sw = √Vw. Error is normally distributed with mean 0, variance Vr, and standard deviation Sr = √Vr. Define V = Vw + Vr and S = √V. V is the variance of Y, and S is the standard deviation of Y. LnGM depends upon the group.

  - ICC = Intra-worker correlation coefficient = Vw/V.

  - AMm = Modeled arithmetic mean of X values = exp(LnGM) exp(½ V). Depends upon the group.

  - GMm = Modeled geometric mean of X values = exp(LnGM). Depends upon the group.

  - GSDm = Modeled geometric standard deviation of X values = exp(S)

  - P95m = Modeled 95th percentile of X values = exp(LnGM) exp(Z95×S). Depends upon the group.

For the lognormal mixed model, the ICC value estimates the clustering effect of multiple measurements on the same worker and lies between 0 (no clustering) and 1 (complete clustering and negligible within-cluster variation). An ICC of 0 is when repeated measurements on the same worker are uncorrelated. An ICC of 1 is when all the exposure measurements on the same worker are identical.

Table 9 presents the arithmetic mean and 95th percentile estimates from the lognormal mixed model, together with 95% confidence intervals, for all the exposure routes. These are the values of AMm and P95m. The other summary statistics are presented in more detail below.

Table 9. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure.

Exposure Route	**Clothing**	**Group**	**Arithmetic Mean (95% confidence interval)**	**95th percentile (95% confidence interval)**
Dermal (mg/lb AI)	Long pants and long sleeves	Bottle	298.5 (89.9, 1005.7)	1105.5 (309.4, 3817.5)
		Conventional	10.0 (4,5. 22.8)	36.9 (15.4, 86.7)
		Reduced Splash	3.1 (1.4, 7.4)	11.6 (4.9, 28.1)
	Short pants and short sleeves	Bottle	207.4 (77.3, 568.3)	706.5 (241.3, 2009.2)
		Conventional	9.0 (4,7. 17.6)	30.7 (14.6, 63.2)
		Reduced Splash	4.0 (2.1, 7.9)	13.6 (6.4, 28.7)
	Long pants and short sleeves	Bottle	280.7 (89.5, 892.7)	1020.9 (300.8, 3350.0)
		Conventional	9.9 (4.7, 21.7)	36.0 (15.6, 81.8)

Exposure Route	Clothing	Group	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
		Reduced Splash	3.0 (1.4, 6.8)	11.0 (4.8, 25.7)
	Hands only	Bottle	314.0 (89.8, 1115.2)	1178.7 (315.1, 4245.5)
		Conventional	10.3 (4.5, 24.6)	38.8 (15.7, 93.7)
		Reduced Splash	3.1 (1.3, 7.5)	11.4 (4.6, 28.6)
Inhalation Concentration (mg/m^3/lb AI)		Bottle	0.047 (0.024, 0.093)	0.128 (0.061, 0.264)
		Conventional	0.016 (0.010, 0.024)	0.042 (0.025, 0.071)
		Reduced Splash	0.0049 (0.0032, 0.0076)	0.0132 (0.0079, 0.0223)
Inhalation Dose (mg/lb AI)		Bottle	0.012 (0.006, 0.024)	0.033 (0.016, 0.066)
		Conventional	0.0017 (0.0011, 0.0026)	0.0046 (0.0028, 0.0075)
		Reduced Splash	0.00091 (0.00061, 0.00140)	0.00242 (0.00148, 0.00401)
Inhalation 8-hr TWA (mg/m^3/lb AI)		Bottle	0.0016 (0.0008, 0.0030)	0.0041 (0.0020, 0.0083)
		Conventional	0.00021 (0.00014, 0.00033)	0.00057 (0.00035, 0.00093)
		Reduced Splash	0.00011 (0.00008, 0.00018)	0.00030 (0.00019, 0.00050)

For each exposure route, the above three statistical models were fitted to the observed data and the summary statistics listed above were calculated together with 95% confidence intervals. The 95% confidence intervals in Table 9 were computed using a parametric bootstrap. For these calculations, the parametric bootstrap simulations were all generated from the fitted lognormal mixed model, even for the empirical and simple random sample summary statistics, on the basis that the mixed model is the best choice for modeling the data, even if the summary statistics are developed from a simpler statistical model. For example, in Tables 1 to 7, the empirical arithmetic means are presented, which are the arithmetic means of the group measurements (between 3 and 15 measurements per group). To estimate the uncertainty of those empirical arithmetic means, data are simulated from the lognormal mixed model to calculate the parametric bootstrap confidence intervals. The arithmetic means in Table 9 are estimated using the lognormal mixed model, which is also used to estimate the confidence intervals in Table 9. The unit exposure estimates (from the lognormal mixed model) displayed in Table 9 are recommended over the empirical arithmetic means and 95th percentiles displayed in Tables 1 to 7. (For the original groupings the detailed results in Tables 1 to 7 may be preferable).

The algorithm used was as follows:

Step 1:

Simulate 36 random variables Y, X from the estimated lognormal distribution superimposed upon the observed sampling structure ---;

W = RanNor (Seed) ×Sw (18 values, one for each worker)

Y = W + LnGM + RanNor(Seed)×Sr

X = exp(Y)

where:

LnGM = group intercept of mixed effect log-log regression model

Sw = square root of between worker variance

Sr = square root of within worker variance under mixed-effect model

The allocation of each worker to two groups (one for each measurement) is exactly the same as the observed random design configuration.

Step 2:

For Y:

Calculate GMs = exp(EAM)

Calculate GSDs = exp(Su)

Calculate AMu = GMs×exp(0.5×Su×Su)

Calculate P95u = GMs× exp(Z95×Su)

Fit mixed lognormal model to simulated Y values

Under mixed-effects model:

Calculate GMm = exp(group intercept of mixed-effects model)

Calculate GSDm = exp(square root (total variance V under mixed-effects model))

Calculate ICC = Vw /V

Calculate AMm = exp(group intercept + 0.5×V)

Calculate P95m = exp(group intercept + Z95×S)

where:

EAM = sample arithmetic mean of Y over group = AMu

Su = standard deviation of Y over group

V = total variance under mixed-effects model

S = square root of V

Vw = between worker variance.

For X:

Calculate arithmetic mean for group AMs

Calculate 95th percentile for group P95s

Step 3: Repeat Steps 1 and 2 10,000 times.

Steps 1 to 3 result in 10,000 values each for each of GSDs, GMs, GMm, AMs, AMm, AMu, P95s, P95m, and P95u for each group and 10,000 values each for GSDm and ICC. 95% confidence intervals can be defined for each parameter by the 2.5th and 97.5th percentiles (lower and upper, respectively) of the bootstrap distribution of that corresponding parameter. Note that by definition, GSDs = GSDu and GMs = GMu.

The dermal exposure results in Table 9 based on the lognormal mixed model show that for all three groups the arithmetic mean for long pants and long sleeves is higher than the arithmetic mean for long pants and short sleeves, and that for the Bottle and Conventional groups the arithmetic mean for long pants and short sleeves is higher than the arithmetic mean for short pants and short sleeves. These results would appear to be contrary to the fact that the calculated exposures for short sleeves versus long sleeves are higher due to the outer dosimeter for the lower arm and the calculated exposures for short pants versus long pants are higher due to the outer dosimeter for the lower leg. These results occurred because the estimated arithmetic mean based on the lognormal mixed model is given by the formula GMm×exp(½ V) where GMm is the estimated geometric mean and V is the estimated variance. Even if the estimated geometric mean increases, the estimated variance can decrease producing a net decrease in the estimated arithmetic mean even though the true arithmetic mean must increase. Since all three dermal exposure measures for this liquid pour scenario are dominated by the hands only exposure, the differences in the estimated arithmetic means and between the estimated 95th percentiles for the three dermal exposure measures are small compared to the very wide confidence intervals. For this reason we regard this issue as a statistical "quirk" attributable to large uncertainty in the fitted models for dermal exposure. In the section "Alternative models for dermal exposure" we investigate alternative models and outlier treatments to further understand these statistical "quirks."

Outliers and non-detects

For all the analyses presented in this memorandum, except for Tables 10, 11 and 20 (see below for discussion on Table 20), all the data values were used and values below the LOQ were replaced by one half of the LOQ. For three subjects and MEs (Reduced Splash ME 1 in group 1a, Reduced Splash ME 7 in group 2, and Conventional Pour ME 6 in group 1b), the hand exposure measurements were much higher when normalized by the amount of active ingredient than values for all other subjects in the same group. The liquid pour scenario is one in which unusually large hand exposures can occur through random dripping and spilling events that may be poorly associated with the total amount of active ingredient used. To investigate the impact of this potential outlier, we recomputed the arithmetic mean and 95th percentile estimates (and parametric bootstrap confidence intervals) for Long Dermal exposure after excluding the dermal data for these measurements. As shown in Table 10, the mean is reduced by between 29% and 42% (for Bottle using zero substitution) and the 95th percentile is reduced by between 33% and 45% (for Bottle using zero substitution) for Long Dermal exposure. The outliers have a substantial effect.

Also investigated in Table 10 (for Long Dermal) and in Table 11 (for inhalation concentration) is the impact of the values below the LOQ. All the hand wash in the study were above the LOQ. For the Conventional Pour, 4 of the 18 face and neck measurements, 67 of the 108 outer dosimeter measurements, 107 of the 108 inner dosimeter measurements, and 6 of the 18 OVS measurements were below the LOQ. For the Reduced Splash, 0 of the 18 face and neck measurements, 41 of the 108 outer dosimeter measurements, 105 of the 108 inner dosimeter measurements, and 9 of the 18 OVS measurements were below the LOQ. For the Long Dermal exposure we computed the arithmetic mean and 95th percentiles using the recommended substitution of one half the LOQ for values below the LOQ and compared the estimates using alternative substitutions of the LOQ (the maximum possible exposure estimate) and of zero (the minimum possible exposure estimate. For the inhalation concentration and dose we computed the arithmetic mean and 95th percentiles using the recommended substitution of one half the LOQ for values below the LOQ and compared the estimates using the alternative substitutions of the LOQ (the maximum possible exposure estimate); substitution of zero for inhalation exposure is not useful because the statistical models use the logarithms of the exposure which cannot be calculated when the minimum exposure is zero. We also investigated a statistical imputation scheme described in the following paragraphs.

Note that in some cases replacing non-detect values by zero increased the estimated arithmetic mean and 95th percentile compared to using the default half LOQ method, and replacing non-detect values by the LOQ decreased the estimated arithmetic mean and 95th percentile compared to using the default half LOQ method. This paradoxical finding occurred because using zero instead of half the LOQ increased the estimated variance and using the LOQ instead of half the

LOQ decreased the estimated variance; the arithmetic mean and 95th percentile estimates from the mixed model adjust the geometric mean using the estimated variance of the logarithms.

As a more exact approach for analyzing values below the LOQ, a multiple imputation approach using maximum likelihood methods for censored data was applied, as follows. Each dermal exposure value is known to be between L and U, where L is the value obtained by replacing all values below the LOQ by zero and summing the values for hand wash, face and neck, and the dosimeters, and U is the value obtained by replacing all values below the LOQ by the LOQ and summing the values for hand wash, face and neck, and the dosimeters. The dermal exposure totals data are thus censored and lie between L and U. For inhalation exposure, the values of L and U are equal to the measured value if it is above the LOQ and are given by L equals zero and U equals the LOQ if the value is below the LOQ.

To estimate the unknown values for the dermal exposure, the following mixed model was fitted to the combined censored and uncensored data:

Log (Exposure) = Group + Slope × Log (Pounds of Active Ingredient) + Worker + Error

In this model, the value of Slope is not necessarily 1, Group is a fixed effect value for each of the three groups Bottle, Conventional, and Reduced Splash giving the intercept for each group, Worker is a normally distributed random effect variable with independent, identically distributed values for each worker, and Error is a normally distributed error variable with independent, identically distributed values for each total exposure measurement. Note that this model ignores any information in the data about which of the values were non-detects. This model was fitted using the SAS procedure NLMIXED, using code adapted from the article "Analysis of Lognormally Distributed Exposure Data with Repeated Measures and Values below the Limit of Detection Using SAS" (YAN JIN, MISTY J. HEIN, JAMES A. DEDDENS and CYNTHIA J. HINES, Ann Occup Hyg (2011) 55(1): 97-112, doi:10.1093/annhyg/meq061). For these calculations, the marginal likelihood averaged over the random effects is maximized. The fitted model has values for the following parameters: three Group intercepts, Slope, Variance of Worker, Variance of Error. Separate models were fitted for each clothing and inhalation scenario.

Exposure values were randomly generated from the fitted model by first simulating the eighteen Worker random effects, and then simulating values for the random error using the conditional distribution given that the total exposure for each censored value is between L and U. Uncensored values (where all components were above the LOQ) were not changed. In this manner, all 36 exposure values for a given scenario were simulated. To account for the uncertainty in the simulations, the entire simulation was repeated 5 times for each scenario, producing 5 independent imputation data sets.

For the multiple imputation data, each statistic and confidence bound was averaged over the five imputations to give an overall average statistic and confidence interval. Note that this approach does not fully account for the uncertainty due to the imputation. Instead, the Bayesian methods of Rubin might have been used to account for the variance from the imputation, but those methods use the standard errors of the statistics rather than the confidence intervals, and so would ignore the skewness in the estimated parametric bootstrap confidence intervals.

Table 10. Long Dermal summary statistics calculated with and without the potential outlier data for Reduced Splash ME 1 in group 1a, Reduced Splash ME 7 in group 2, and Conventional Pour ME 6 in group 1b, and using alternative estimated exposures for values below the LOQ.

Group	Data	Method for substituting values below the LOQ	Arithmetic mean (mg / lb AI)	95th percentile (mg / lb AI)
Bottle	All 36 Values	Substitute ½ LOQ	298.5 (89.9, 1005.7)	1105.5 (309.4, 3817.5)
Bottle	All 36 Values	Substitute LOQ	288.3 (90.1, 932.9)	1055.0 (305.7, 3515.3)
Bottle	All 36 Values	Substitute zero	313.9 (89.8, 1114.2)	1177.9 (314.9, 4241.3)
Bottle	All 36 Values	Multiple imputation	298.6 (89.7, 1008.3)	1106.2 (309.3, 3818.5)
Bottle	Exclude outlier data	Substitute ½ LOQ	177.5 (59.9, 550.7)	616.4 (193.9, 1961.3)
Bottle	Exclude outlier data	Substitute LOQ	171.1 (60.8, 520.0)	592.9 (193.7, 1820.6)
Bottle	Exclude outlier data	Substitute zero	183.5 (59.8, 597.7)	651.2 (196.5, 2173.3)
Bottle	Exclude outlier data	Multiple imputation	177.6 (59.4, 553.8)	618.2 (194.0, 1981.6)
Conventional	All 36 Values	Substitute ½ LOQ	10.0 (4.5, 22.8)	36.9 (15.4, 86.7)
Conventional	All 36 Values	Substitute LOQ	9.7 (4.5, 21.5)	35.5 (15.2, 81.5)
Conventional	All 36 Values	Substitute zero	10.4 (4.5, 24.6)	38.8 (15.7, 93.8)
Conventional	All 36 Values	Multiple imputation	10.0 (4.5, 22.9)	37.0 (15.4, 86.9)
Conventional	Exclude outlier data	Substitute ½ LOQ	7.1 (3.5, 14.8)	24.6 (11.1, 54.1)
Conventional	Exclude outlier data	Substitute LOQ	6.9 (3.5, 14.2)	23.6 (10.9, 50.9)

Group	Data	Method for substituting values below the LOQ	Arithmetic mean (mg / lb AI)	95th percentile (mg / lb AI)
Conventional	Exclude outlier data	Substitute zero	7.3 (3.5, 16.0)	25.9 (11.4, 59.6)
Conventional	Exclude outlier data	Multiple imputation	71. (3.5, 14.8)	24.8 (11.2, 55.1)
Reduced Splash	All 36 Values	Substitute ½ LOQ	3.1 (1.4, 7.4)	11.6 (4.9, 28.1)
Reduced Splash	All 36 Values	Substitute LOQ	3.2 (1.5, 7.3)	11.8 (5.0, 27.7)
Reduced Splash	All 36 Values	Substitute zero	3.1 (1.3, 7.5)	11.5 (4.7, 28.8)
Reduced Splash	All 36 Values	Multiple imputation	3.1 (1.4, 7.3)	11.6 (4.8, 28.0)
Reduced Splash	Exclude outlier data	Substitute ½ LOQ	2.0 (1.0, 4.1)	6.9 (3.1, 15.0)
Reduced Splash	Exclude outlier data	Substitute LOQ	2.1 (1.1, 4.1)	7.0 (3.2, 14.8)
Reduced Splash	Exclude outlier data	Substitute zero	1.9 (0.9, 4.1)	6.8 (3.0, 15.3)
Reduced Splash	Exclude outlier data	Multiple imputation	2.0 (1.0, 4.1)	6.9 (3.1, 15.1)

Table 11. Inhalation concentration summary statistics calculated using alternative estimated exposures for values below the LOQ.

Group	Data	Method for substituting values below the LOQ	Arithmetic mean (mg / m^3/lb AI)	95th percentile (mg / m^3/ lb AI)
Bottle	All 36	Substitute ½	0.047 (0.024, 0.093)	0.128 (0.061, 0.264)

Group	Data	Method for substituting values below the LOQ	Arithmetic mean (mg / m^3/lb AI)	95th percentile (mg / m^3/ lb AI)
	Values	LOQ		
Bottle	All 36 Values	Substitute LOQ	0.086 (0.049, 0.150)	0.206 (0.111, 0.377)
Bottle	All 36 Values	Multiple imputation	0.001 (0.001, 0.002)	0.003 (0.001, 0.007)
Conventional	All 36 Values	Substitute ½ LOQ	0.016 (0.010, 0.024)	0.042 (0.025, 0.071)
Conventional	All 36 Values	Substitute LOQ	0.016 (0.011. 0.023)	0.039 (0.025, 0.060)
Conventional	All 36 Values	Multiple imputation	0.017 (0.011, 0.029)	0.051 (0.028, 0.090)
Reduced Splash	All 36 Values	Substitute ½ LOQ	0.0049 (0.0032, 0.0076)	0.0132 (0.0079, 0.0223)
Reduced Splash	All 36 Values	Substitute LOQ	0.0058 (0.0041, 0.0084)	0.0141 (0.0092, 0.0217)
Reduced Splash	All 36 Values	Multiple imputation	0.0049 (0.0030, 0.0081)	0.0143 (0.0081, 0.0257)

The results in Tables 10 demonstrate that all the alternative approaches for treating values below the LOQ have a very small effect on Long Dermal exposure (the change in the estimates is less than 7%). The results were similar for Short Dermal and Long Short Dermal exposure.

The results in Table 11 demonstrate very large impacts of the alternative approaches for treating values below the LOQ on the inhalation concentration, because of the large percentage of OVS values below the LOQ: For the Bottle group, using the LOQ substitution instead of the half LOQ substitution increases the arithmetic mean and 95th percentile by up to 81%, and using the multiple imputation instead of the half LOQ substitution decreases the arithmetic mean and 95th percentile by up to 98%. For the Conventional and Reduced Splash groups, using the LOQ substitution instead of the half LOQ substitution changes the arithmetic mean and 95th percentile by up to 8%, and using the multiple imputation instead of the half LOQ substitution increases the arithmetic mean and 95th percentile by up to 20%. The inhalation exposure results were similar for the inhalation dose and the inhalation 8-hour time weighted average concentration; results not shown.

Fold relative accuracy

Fold relative accuracy (*fRA*) is a measure that can be used to determine how well a statistic can describe its population parameter. Let us assume θ is a parameter and T is the sample statistic of θ (i.e., an estimate of θ). If the 2.5th and 97.5th percentiles of the sampling distribution of T can be denoted by $T_{2.5}$ and $T_{97.5}$, respectively, then the 95th percentile of sample fold relative accuracy can be theoretically calculated using the following formula provided in the AHETF Governing Document (AHETF, 2007, pg. 136 and AHETF, 2011, pg. 120):

$$fRA_{95} = \text{Max}\ (T_{97.5} / \theta, \theta / T_{2.5})$$

The actual value of θ is unknown. Thus, fRA_{95} was calculated by substituting θ with T. If the fRA_{95} of a statistic were equal to 3, then it would be correct to say: "At least 95% of the time the sample statistic will be accurate to within 3-fold of the population value". According to the AHETF Governing Document, the statistical design of the exposure monitoring study should be adequate to produce a fRA_{95} less than or equal to 3. Thus the confidence intervals calculated in the above algorithm can be used to estimate the fold relative accuracy and compare the observed fRA with the study design benchmark of 3. If the observed fold relative accuracy is greater than 3, this means that the experiment did not meet the benchmark, which would be due to differences between the distributions of the CMA data used to design the study and the experimental data collected in the study. If the fold relative accuracy benchmark is not met, then it might be desirable to collect more data for this scenario in order to meet the benchmark. Fold relative accuracy was not computed for the ICC since the estimated ICC is 0 in many cases.

In previously reported statistical analyses, following HSRB recommendations, confidence intervals were estimated using both a parametric bootstrap approach and a non-parametric bootstrap approach. For this scenario, non-parametric confidence intervals were not developed because of the difficulty in accounting for both the worker and group effects in a fully non-parametric framework.

Detailed summary statistics with parametric confidence intervals and fold relative accuracy

Tables 12 to 18 present the estimates, parametric confidence intervals and fold relative accuracy values for all the summary statistics for the four dermal and twelve inhalation exposure routes, respectively.

Table 12. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long dermal exposure (mg/lb AI).

	Bottle				Conventional				Reduced Splash			
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.2	1.7	8.7	4.0	4.0	2.3	6.4	1.7	4.3	2.4	6.4	1.8
GSDm	3.9	2.8	5.4	1.4	3.9	2.8	5.4	1.4	3.9	2.8	5.4	1.4
ICC	0.3	0.0	0.7		0.3	0.0	0.7		0.3	0.0	0.7	
GMs	116.2	39.5	376.4	3.2	4.1	2.0	8.0	2.0	1.2	0.6	2.5	2.0
GMm	120.0	39.1	370.3	3.1	4.0	2.0	7.9	2.0	1.3	0.6	2.5	2.0
AMs	155.3	63.4	1007.6	6.5	8.4	3.8	24.3	2.9	3.7	1.2	7.6	3.2
AMu	158.1	70.1	1755.5	11.1	10.9	4.1	28.1	2.6	3.6	1.3	8.9	2.8

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
AMm	298.5	89.9	1005.7	3.4	10.0	4.5	22.8	2.3	3.1	1.4	7.4	2.3
P95s	459.5	132.4	4287.3	9.3	35.2	11.5	210.6	6.0	31.4	3.6	65.5	8.7
P95u	422.3	183.6	6158.5	14.6	40.9	12.8	106.7	3.2	13.7	4.0	33.8	3.5
P95m	1105.5	309.4	3817.5	3.6	36.9	15.4	86.7	2.4	11.6	4.9	28.1	2.4

Table 13. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized short dermal exposure (mg/lb AI).

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	2.2	1.6	6.2	2.8	3.7	2.1	4.8	1.8	3.0	2.1	4.7	1.6
GSDm	3.1	2.3	4.2	1.3	3.1	2.3	4.2	1.3	3.1	2.3	4.2	1.3
ICC	0.4	0.0	0.7		0.4	0.0	0.7		0.4	0.0	0.7	
GMs	118.6	41.7	288.4	2.8	4.6	2.7	8.4	1.8	2.0	1.2	3.7	1.8
GMm	108.1	42.2	279.0	2.6	4.7	2.7	8.3	1.8	2.1	1.2	3.7	1.8
AMs	157.8	60.0	583.7	3.7	9.1	4.2	18.4	2.2	4.2	1.9	8.1	2.3
AMu	160.7	64.3	828.4	5.2	10.7	4.5	20.0	2.4	3.7	1.9	8.8	2.4
AMm	207.4	77.3	568.3	2.7	9.0	4.7	17.6	2.0	4.0	2.1	7.9	2.0
P95s	464.6	114.9	2175.6	4.7	40.0	11.5	130.2	3.5	32.2	5.1	59.7	6.3
P95u	427.9	151.8	3060.5	7.2	39.0	12.5	75.6	3.1	12.1	5.5	33.2	2.7
P95m	706.5	241.3	2009.2	2.9	30.7	14.6	63.2	2.1	13.6	6.4	28.7	2.1

Table 14. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long short dermal exposure (mg/lb AI).

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	2.2	1.7	7.9	3.6	3.6	2.3	5.9	1.6	4.2	2.3	5.9	1.8
GSDm	3.6	2.6	5.0	1.4	3.6	2.6	5.0	1.4	3.6	2.6	5.0	1.4
ICC	0.3	0.0	0.7		0.3	0.0	0.7		0.3	0.0	0.7	
GMs	116.7	42.0	364.5	3.1	4.4	2.2	8.3	2.0	1.3	0.7	2.5	1.9
GMm	121.6	41.3	357.2	2.9	4.3	2.2	8.3	1.9	1.3	0.7	2.5	1.9
AMs	155.8	65.1	896.8	5.8	8.5	4.0	23.1	2.7	3.8	1.2	7.0	3.1
AMu	158.5	71.4	1477.6	9.3	10.1	4.3	26.1	2.6	3.7	1.3	8.0	2.8
AMm	280.7	89.5	892.7	3.2	9.9	4.7	21.7	2.2	3.0	1.4	6.8	2.2
P95s	461.2	133.5	3704.9	8.0	35.2	11.8	190.7	5.4	31.5	3.6	57.8	8.8
P95u	423.1	181.4	5285.8	12.5	36.6	13.0	99.5	2.8	13.8	3.9	30.6	3.5
P95m	1020.9	300.8	3350.0	3.4	36.0	15.6	81.8	2.3	11.0	4.8	25.7	2.3

Table 15. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized hands only exposure (mg/lb AI).

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	2.2	1.8	9.4	4.2	4.2	2.4	6.8	1.7	4.6	2.4	6.8	1.9
GSDm	4.1	2.9	5.7	1.4	4.1	2.9	5.7	1.4	4.1	2.9	5.7	1.4
ICC	0.2	0.0	0.6		0.2	0.0	0.6		0.2	0.0	0.6	
GMs	113.6	37.3	385.3	3.4	4.0	1.9	8.0	2.1	1.1	0.6	2.3	2.0
GMm	118.0	37.0	379.2	3.2	3.9	1.9	7.9	2.0	1.1	0.6	2.3	2.0
AMs	153.1	61.4	1111.4	7.3	8.3	3.8	26.1	3.2	3.6	1.1	7.7	3.4
AMu	156.3	68.8	2027.0	13.0	11.1	4.1	31.0	2.8	3.6	1.2	9.2	3.1
AMm	314.0	89.8	1115.2	3.6	10.3	4.5	24.6	2.4	3.1	1.3	7.5	2.4
P95s	456.9	131.8	4862.3	10.6	35.0	11.6	235.2	6.7	31.3	3.4	68.1	9.2
P95u	422.5	182.1	7036.8	16.7	42.1	12.9	116.7	3.3	14.0	3.8	34.7	3.7

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
P95m	1178.7	315.2	4245.5	3.7	38.8	15.7	93.7	2.5	11.4	4.6	28.6	2.5

Table 16. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation concentration (mg/m^3/lb AI).

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.1858	1.3981	3.6254	3.1	2.7484	1.6565	2.9691	1.7	2.0072	1.6592	2.9904	1.5
GSDm	2.2311	1.8484	2.7008	1.2	2.2311	1.8484	2.7008	1.2	2.2311	1.8484	2.7008	1.2
ICC	0.0000	0.0000	0.4762		0.0000	0.0000	0.4762		0.0000	0.0000	0.4762	
GMs	0.0343	0.0180	0.0651	1.9	0.0113	0.0076	0.0171	1.5	0.0035	0.0024	0.0053	1.5
GMm	0.0343	0.0178	0.0655	1.9	0.0113	0.0076	0.0171	1.5	0.0035	0.0024	0.0053	1.5
AMs	0.0347	0.0220	0.0929	2.7	0.0170	0.0097	0.0245	1.8	0.0044	0.0030	0.0076	1.7
AMu	0.0348	0.0229	0.1045	3.0	0.0189	0.0099	0.0253	1.9	0.0045	0.0031	0.0079	1.8
AMm	0.0473	0.0240	0.0930	2.0	0.0156	0.0102	0.0243	1.6	0.0049	0.0032	0.0076	1.6
P95s	0.0423	0.0377	0.2912	6.9	0.0571	0.0211	0.1184	2.7	0.0107	0.0065	0.0373	3.5
P95u	0.0453	0.0453	0.3503	7.7	0.0598	0.0225	0.0785	2.7	0.0111	0.0070	0.0249	2.2
P95m	0.1283	0.0613	0.2640	2.1	0.0424	0.0253	0.0705	1.7	0.0132	0.0079	0.0223	1.7

Table 17. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation dose (mg/lb AI).

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.1045	1.3829	3.4757	3.1	2.6982	1.6294	2.8651	1.7	1.9286	1.6319	2.8850	1.5
GSDm	2.1732	1.8116	2.6143	1.2	2.1732	1.8116	2.6143	1.2	2.1732	1.8116	2.6143	1.2
ICC	0.0000	0.0000	0.4762		0.0000	0.0000	0.4762		0.0000	0.0000	0.4762	

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GMs	0.0092	0.0049	0.0172	1.9	0.0013	0.0009	0.0019	1.5	0.0007	0.0005	0.0010	1.5
GMm	0.0092	0.0049	0.0173	1.9	0.0013	0.0009	0.0019	1.5	0.0007	0.0005	0.0010	1.5
AMs	0.0093	0.0060	0.0238	2.6	0.0019	0.0011	0.0026	1.8	0.0008	0.0006	0.0014	1.7
AMu	0.0093	0.0062	0.0266	2.9	0.0021	0.0011	0.0027	1.9	0.0008	0.0006	0.0014	1.7
AMm	0.0125	0.0065	0.0239	1.9	0.0017	0.0011	0.0026	1.5	0.0009	0.0006	0.0014	1.5
P95s	0.0107	0.0101	0.0730	6.8	0.0067	0.0023	0.0123	2.9	0.0020	0.0012	0.0066	3.3
P95u	0.0109	0.0121	0.0873	8.0	0.0065	0.0025	0.0083	2.6	0.0020	0.0013	0.0045	2.2
P95m	0.0330	0.0162	0.0664	2.0	0.0046	0.0028	0.0075	1.7	0.0024	0.0015	0.0040	1.7

Table 18. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation 8-hour time-weighted average (mg/m^3/lb AI).

	Bottle				Conventional				Reduced Splash			
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.10454	1.38288	3.47565	3.1	2.69819	1.62939	2.86515	1.7	1.92864	1.63191	2.88502	1.5
GSDm	2.17321	1.81159	2.61432	1.2	2.17321	1.81159	2.61432	1.2	2.17321	1.81159	2.61432	1.2
ICC	0.00000	0.00000	0.47616		0.00000	0.00000	0.47616		0.00000	0.00000	0.47616	
GMs	0.00115	0.00062	0.00214	1.9	0.00016	0.00011	0.00024	1.5	0.00008	0.00006	0.00013	1.5
GMm	0.00115	0.00061	0.00216	1.9	0.00016	0.00011	0.00024	1.5	0.00008	0.00006	0.00013	1.5
AMs	0.00116	0.00075	0.00298	2.6	0.00024	0.00014	0.00033	1.8	0.00010	0.00007	0.00018	1.7
AMu	0.00116	0.00078	0.00333	2.9	0.00026	0.00014	0.00034	1.9	0.00010	0.00007	0.00018	1.7
AMm	0.00156	0.00081	0.00299	1.9	0.00021	0.00014	0.00033	1.5	0.00011	0.00008	0.00017	1.5
P95s	0.00134	0.00126	0.00913	6.8	0.00084	0.00029	0.00154	2.9	0.00025	0.00015	0.00083	3.3
P95u	0.00136	0.00151	0.01092	8.0	0.00081	0.00031	0.00103	2.6	0.00025	0.00016	0.00056	2.2
P95m	0.00413	0.00202	0.00830	2.0	0.00057	0.00035	0.00093	1.7	0.00030	0.00018	0.00050	1.7

Tables 12 to 18 show that the ICC estimated value is between 0.2 and 0.4 for the dermal exposure routes showing that there is some variation between workers and some correlation between measurements on the same worker. The ICC values were zero for all the inhalation exposure measures showing no variation between workers. For the Bottle group, most of the dermal exposure measures did not meet the study benchmark design value of 3 for the fold relative accuracy. For the empirical and lognormal simple random sampling model, this is partially explained by the fact that the bootstrap confidence intervals were based on a very different statistical model that assumed equal covariance parameters for all three groups, but several of the mixed model parameters also did not meet the study benchmark design value of 3. A plausible explanation is that the Bottle data was only based on 6 exposure measurements (although the mixed model was fitted to all 36 measurements). For the inhalation exposures in the Bottle group, the study benchmark design of 3 for the fold relative accuracy was met for the summary statistics that used the mixed model. For dermal exposures in the Conventional and Reduced Splash groups, the study benchmark design of 3 for the fold relative accuracy was met for the summary statistics that used the mixed model but was not met for several of the AMs, P95s, and P95u statistics. For inhalation exposures in the Conventional and Reduced Splash groups, the study benchmark design of 3 for the fold relative accuracy was met for all cases except for the empirical 95^{th} percentile for the Reduced Splash group.

Quantile plots

Quantile-quantile plots of the normalized exposure values were used to evaluate whether the data were lognormally distributed, as implied by the assumed statistical mixed models. In each case the quantile-quantile plot compared the observed quantiles of the 36 measured values with the corresponding quantiles of a normal or lognormal distribution. Since the mixed model assumes that the mean exposure can depend upon the group, the corresponding group mean normalized exposure was subtracted from the normalized exposure when creating the normal distribution plots, and the corresponding group mean logarithm of the normalized exposure was subtracted from the logarithm of the normalized exposure when creating the lognormal distribution plots. In this manner the quantile-quantile plots combined all 36 measurements. A perfect fit would imply that the plotted values lie in a straight line. The quantile-quantile plots are presented in Figures 1 to 14. They clearly show that the lognormal distribution is a better fit than a normal distribution, and that the lognormal distribution fits reasonably well for all of the exposure routes.

Figure 1

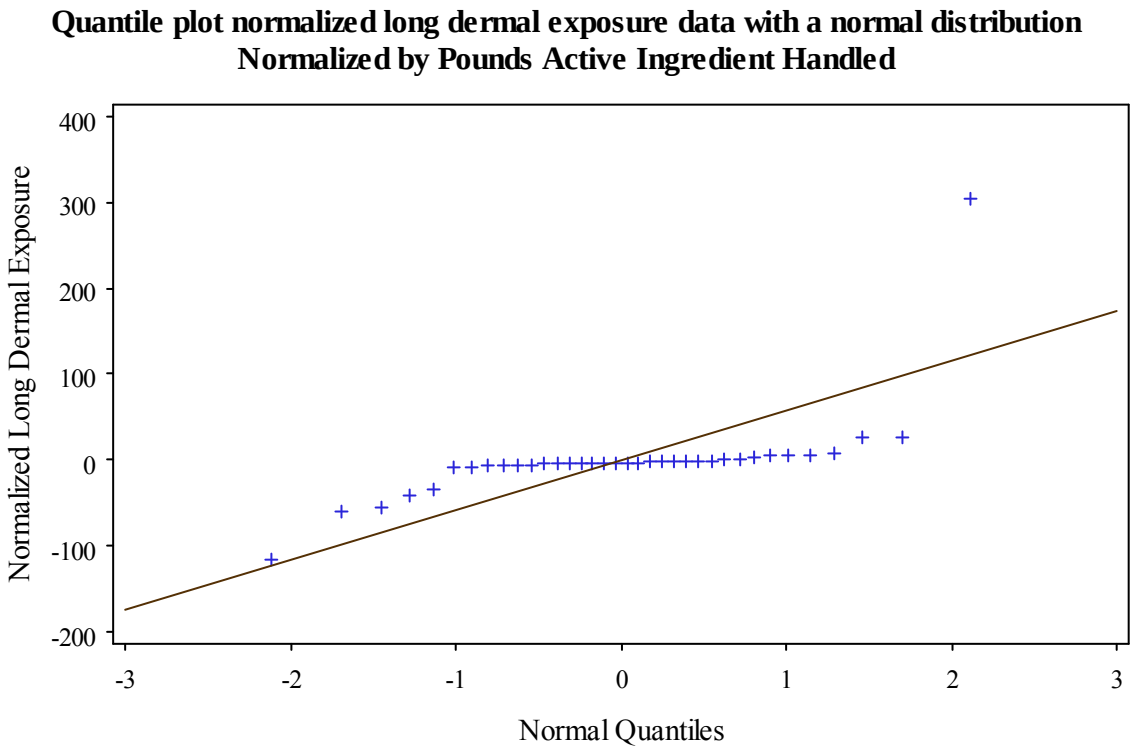

Quantile plot normalized long dermal exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized Long Dermal Exposure
400
300
200
100
0
-100
-200
-3
-2
-1
0
1
2
3
Normal Quantiles

Figure 2

Quantile plot normalized long dermal exposure data with a lognormal distribution Normalized by Pounds Active Ingredient Handled

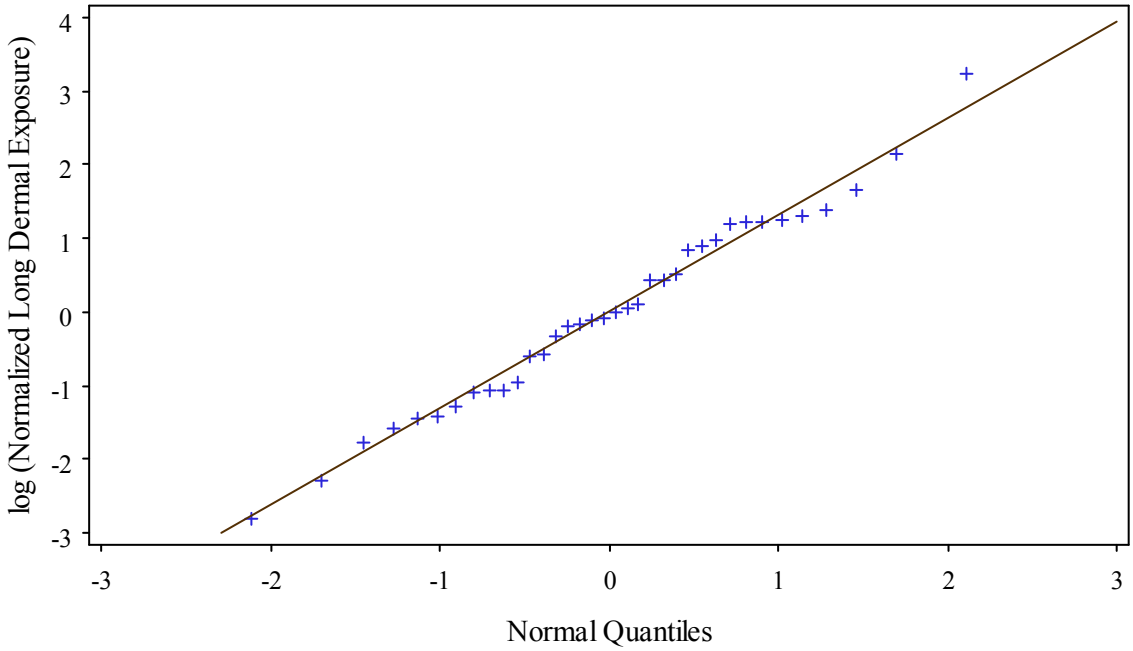


Figure 3

Quantile plot normalized short dermal exposure data with a normal distribution Normalized by Pounds Active Ingredient Handled

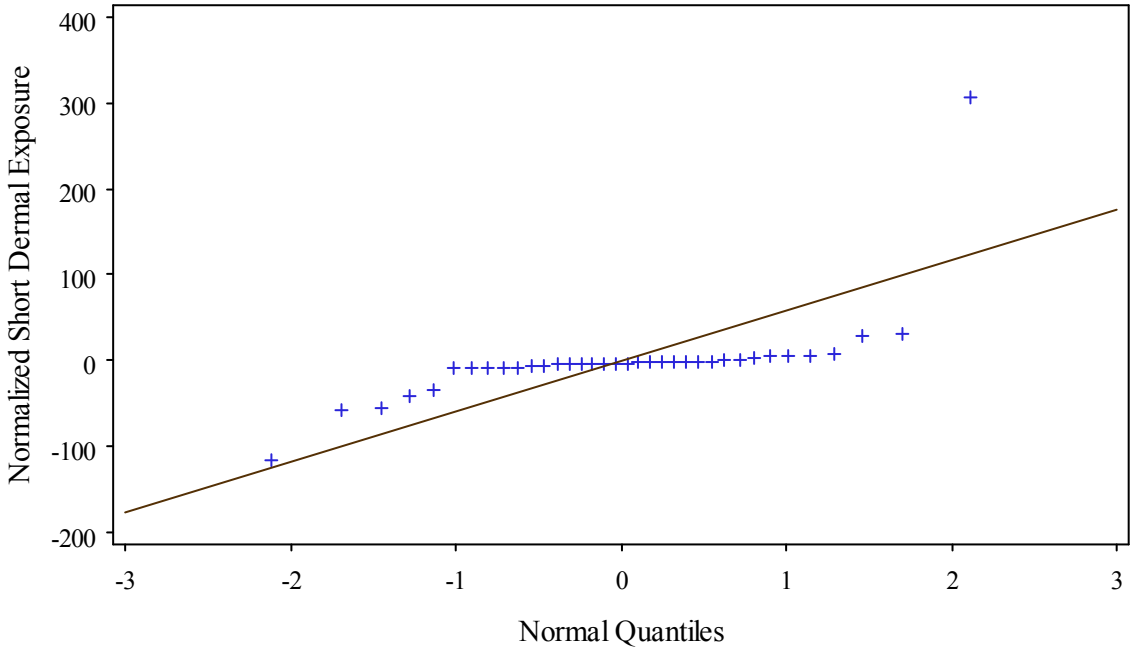


Figure 4

Quantile plot normalized short dermal exposure data with a lognormal distribution Normalized by Pounds Active Ingredient Handled

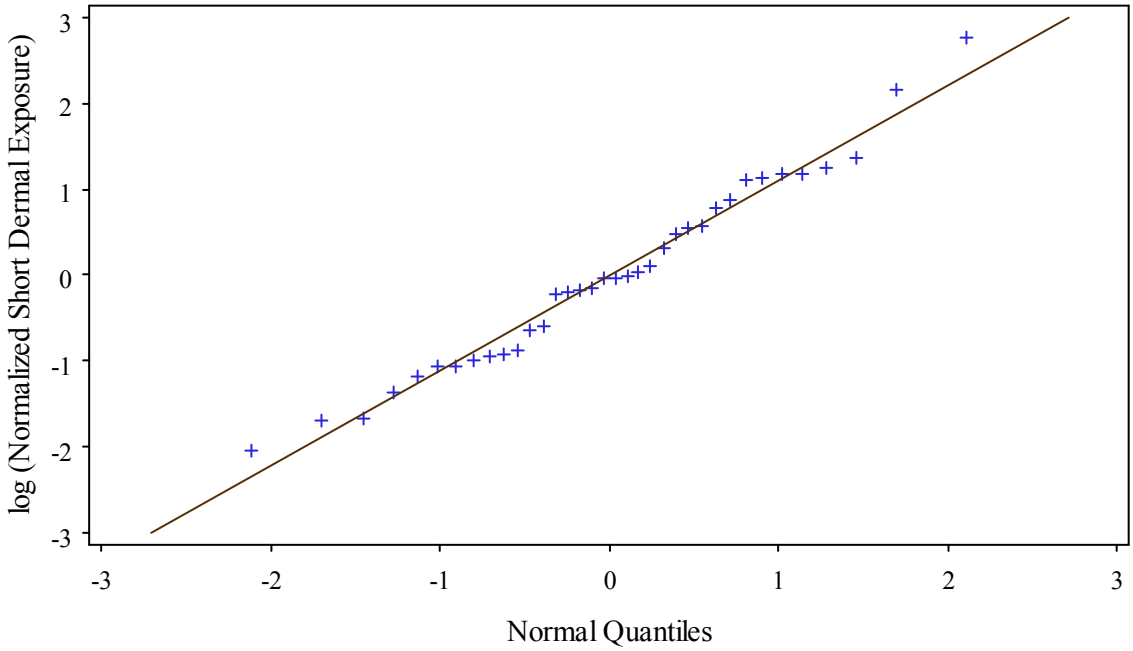


Figure 5

Quantile plot normalized long short dermal exposure data with a normal distribution Normalized by Pounds Active Ingredient Handled

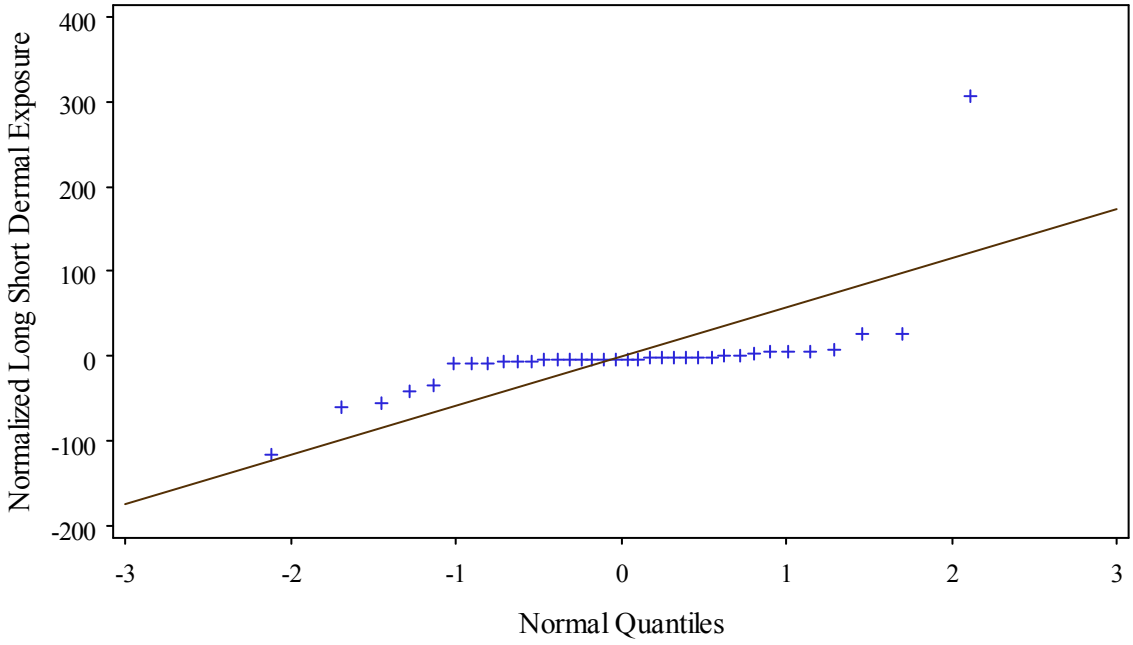


Figure 6

Quantile plot normalized long short dermal exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled

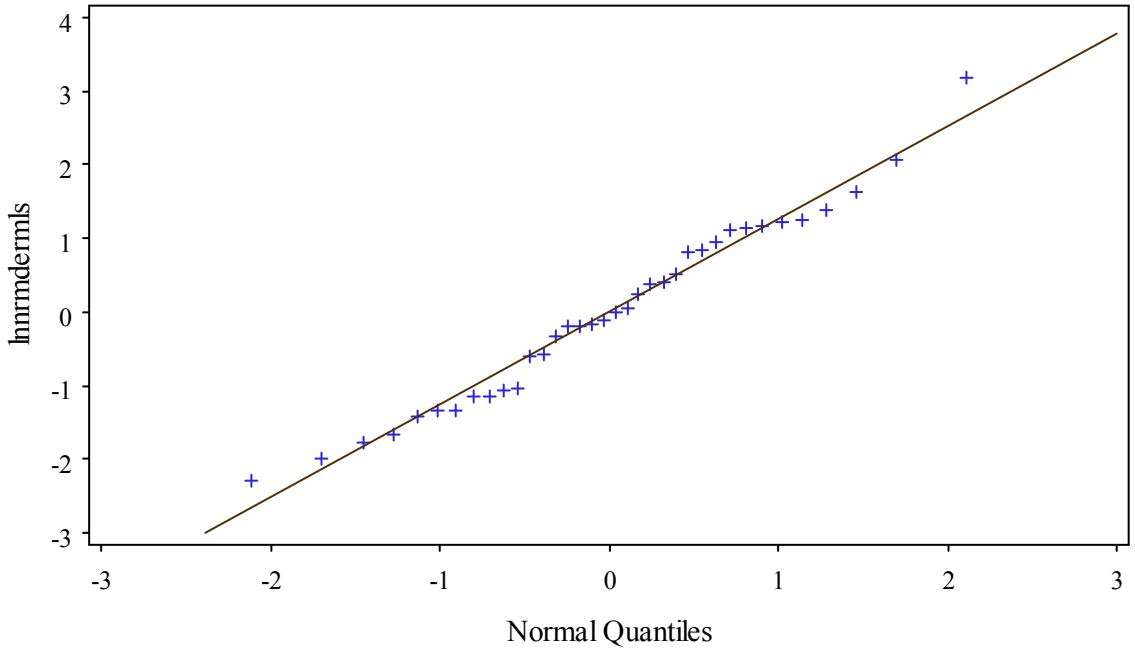


Figure 7

Quantile plot normalized hands only exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled

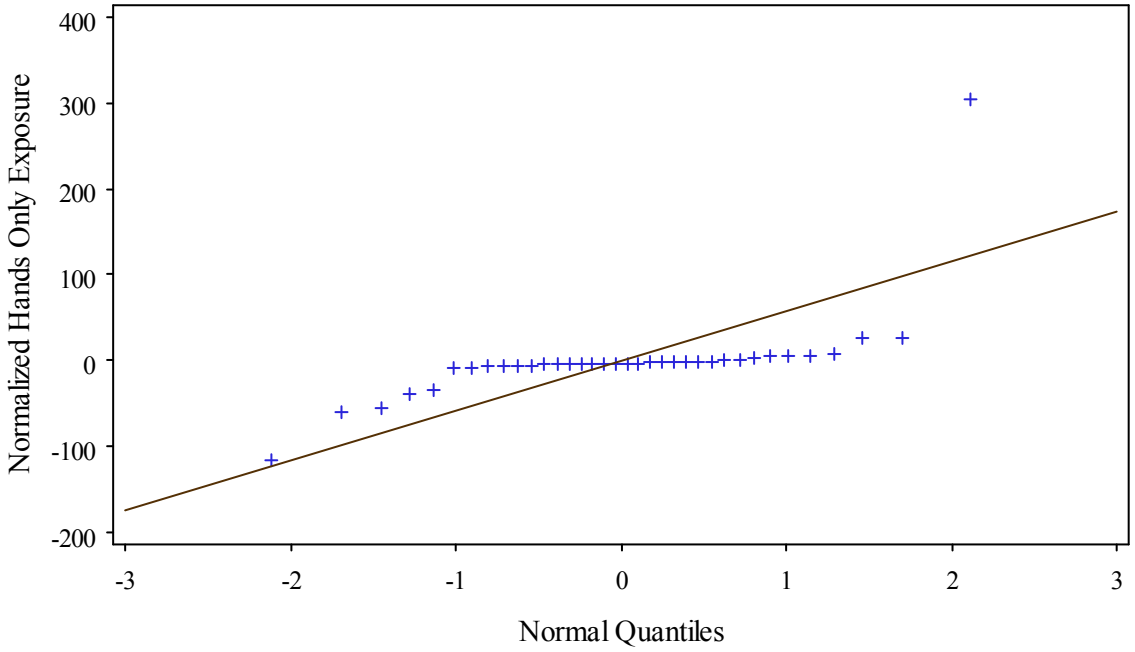


Figure 8

Quantile plot normalized hands only exposure data with a lognormal distribution Normalized by Pounds Active Ingredient Handled

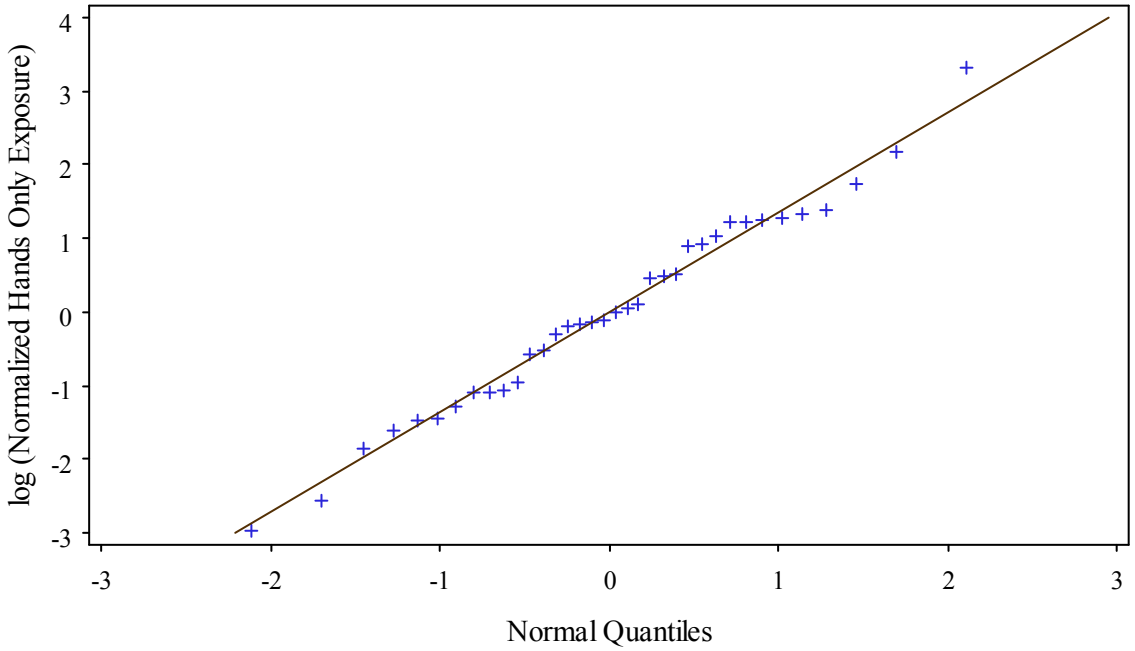


Figure 9

Quantile plot normalized inhalation conc exposure data with a normal distribution Normalized by Pounds Active Ingredient Handled

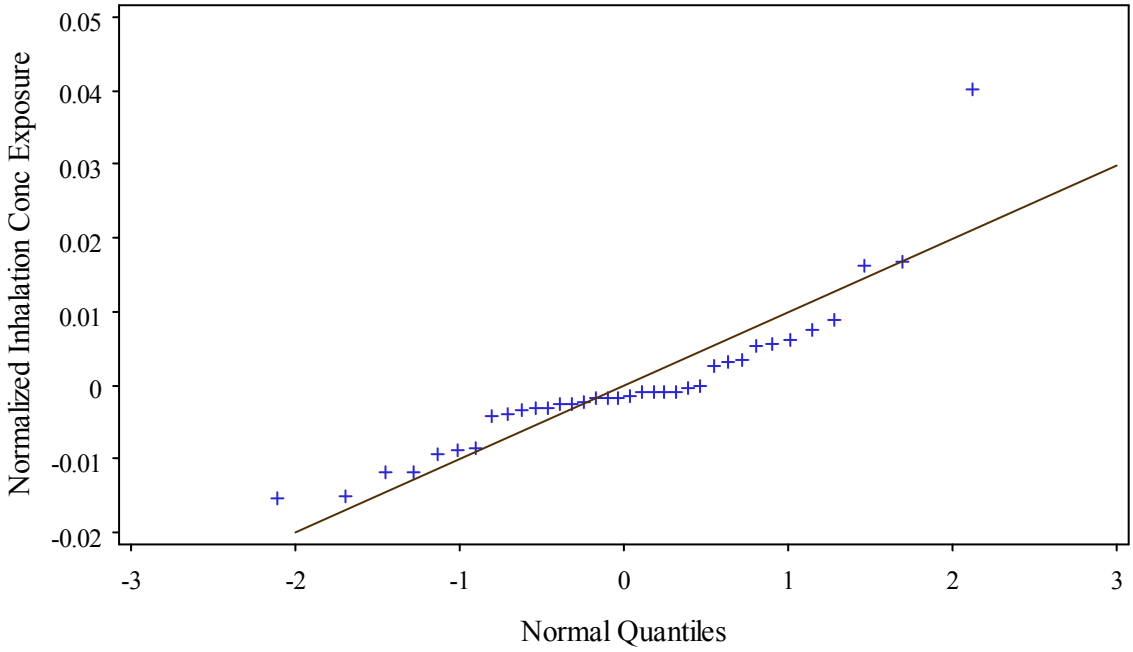


Figure 10

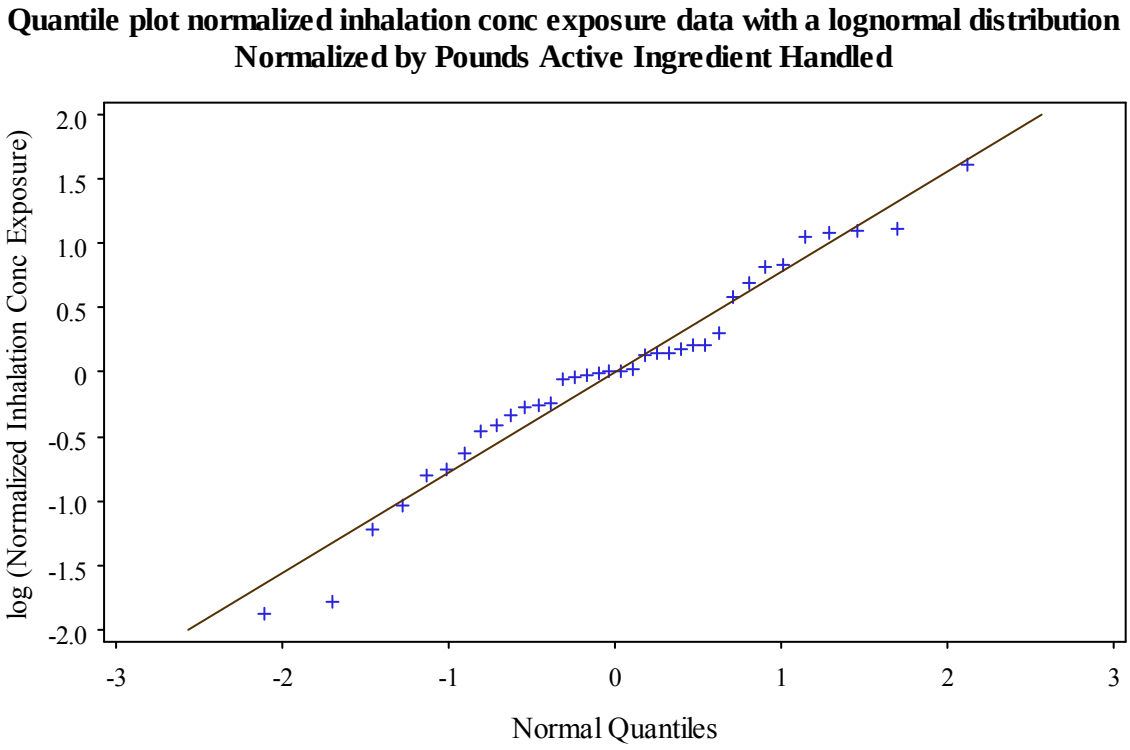

Quantile plot normalized inhalation conc exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Inhalation Conc Exposure)
2.0
1.5
1.0
0.5
0
-0.5
-1.0
-1.5
-2.0
-3
-2
-1
0
1
2
3
Normal Quantiles

Figure 11

Quantile plot normalized inhalation dose exposure data with a normal distribution Normalized by Pounds Active Ingredient Handled

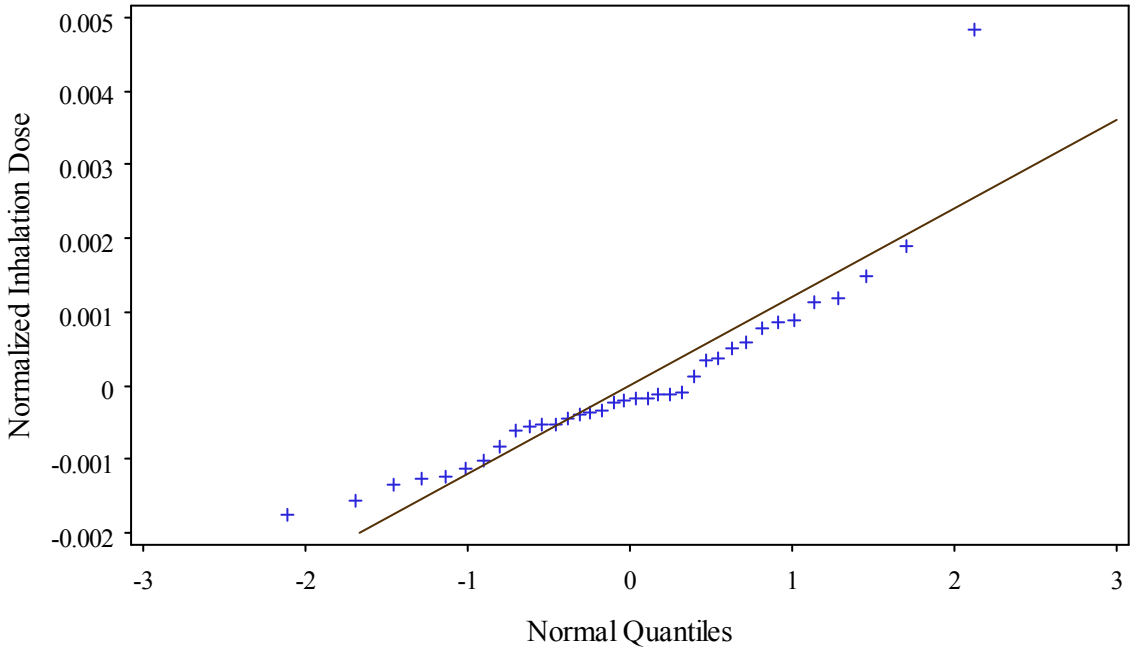


Figure 12

Quantile plot normalized inhalation dose exposure data with a lognormal distribution Normalized by Pounds Active Ingredient Handled

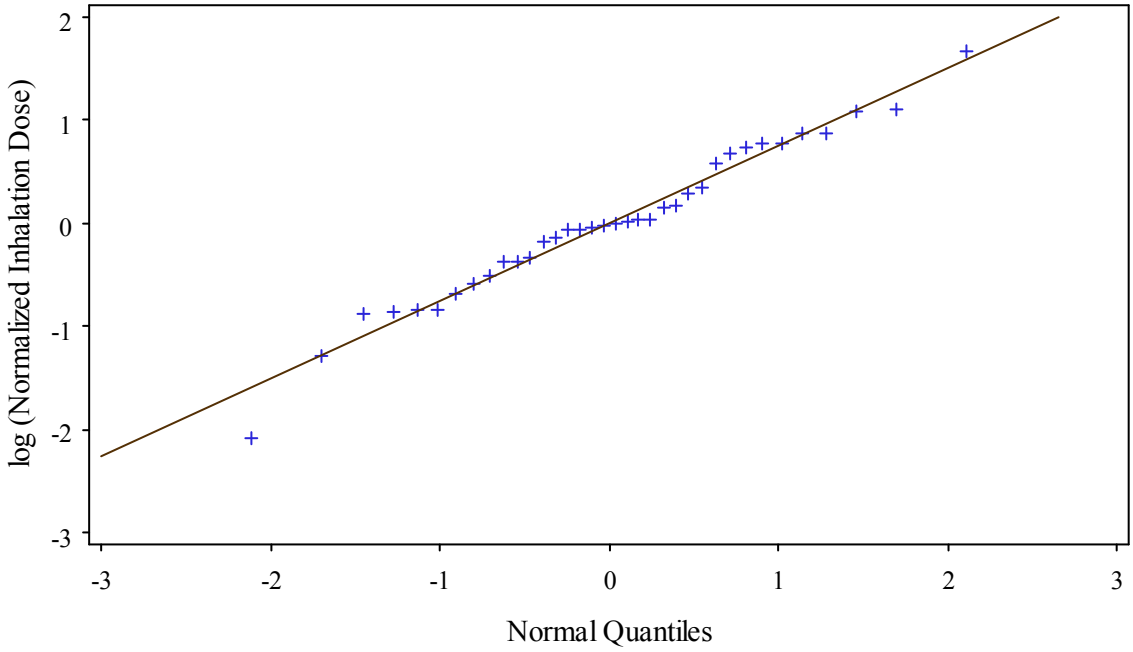


Figure 13

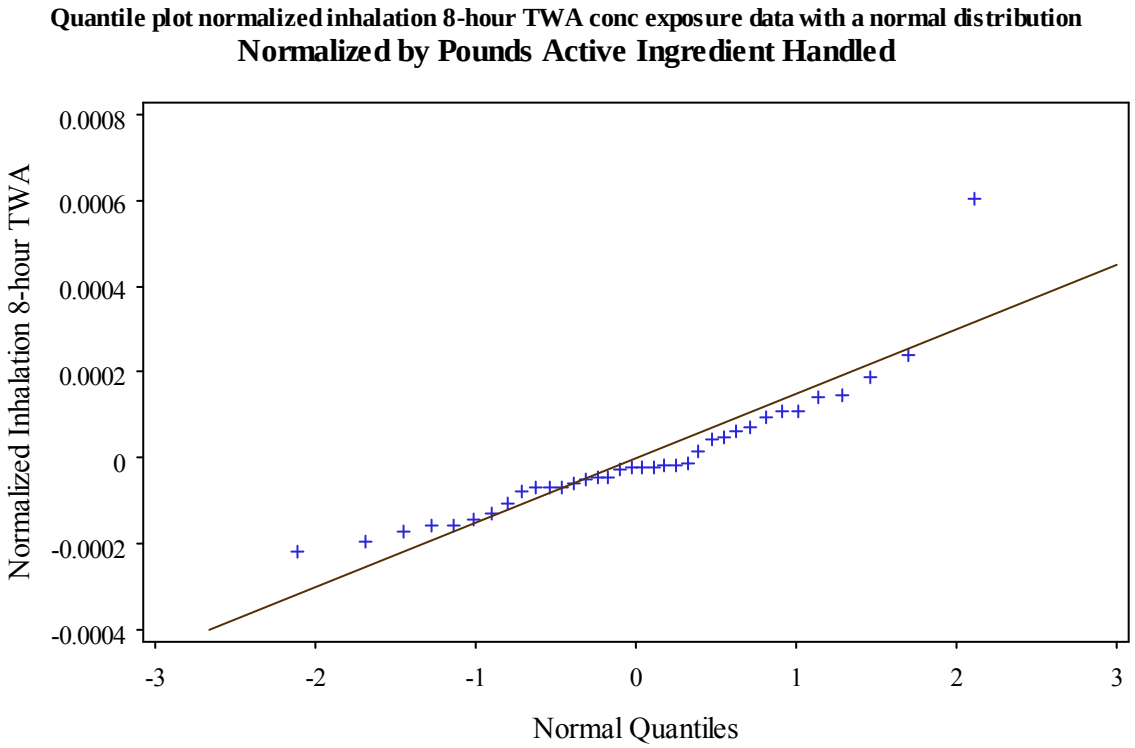
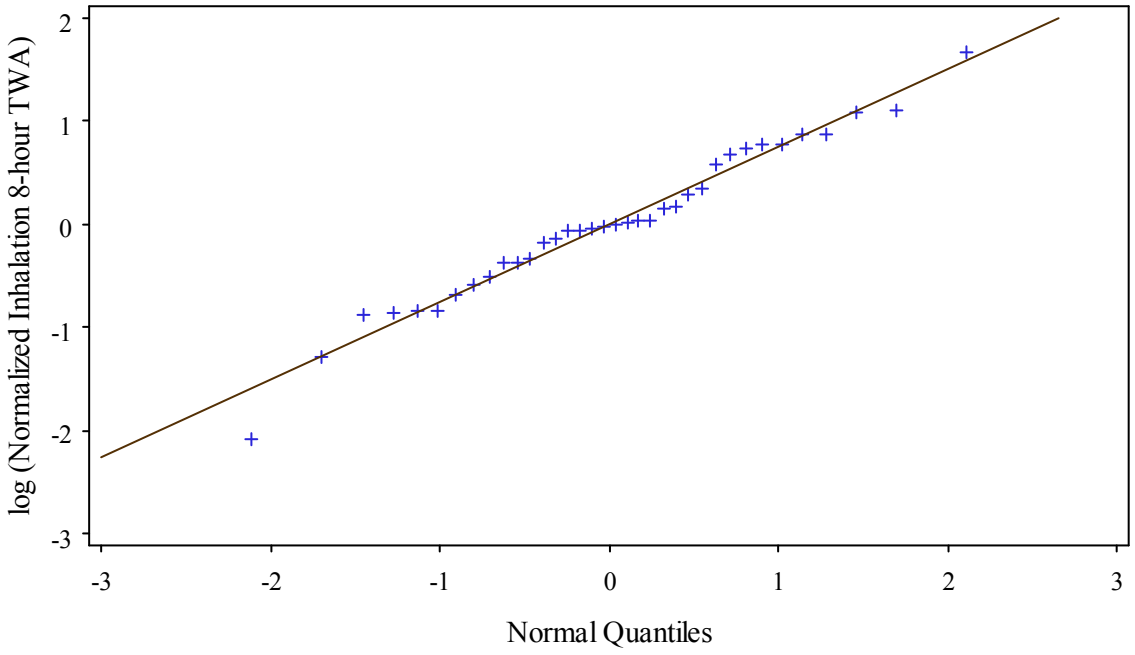


Figure 14



Log-log-linearity analyses and estimated log-log slopes

The following analyses evaluate whether the logarithm of exposure is linear in the logarithm of the amount of active ingredient handled (AI) with a slope of 1. We now refer to these analyses as the log-log-linearity analyses. In the Governing Documents and in our statistical memoranda analyzing previous AEATF studies we have referred to these analyses as a "proportionality" analysis, but this has caused some confusion because the statistical models do not assume that the exposure is directly proportional to the AI but instead assume that the logarithm of the exposure is linear in the logarithm of AI with a slope of 1, which is a related finding but a very different model, as explained here. We have therefore changed the terminology from "proportionality" to "log-log-linearity."

The use of the normalized or unit exposure is based on the assumption that the exposure is proportional to the normalizing variable pounds of active ingredient handled. Exact proportionality is defined as

Exposure = K × Pounds of Active Ingredient,

where K is the proportionality constant. Exact proportionality implies that

Normalized Exposure = Exposure / Pounds of Active Ingredient = K,

so that if the pounds of active ingredient is doubled, then the exposure is exactly doubled, which is not a reasonable assumption due to the variability of exposure for any given amount of active ingredient. Instead we allow for random multiplicative error terms, which do not depend on the amount of active ingredient, so that

Exposure = K × Pounds of Active Ingredient × Multiplicative Errors, or

Normalized Exposure = K × Multiplicative Errors.

Since the above quantile plots support the assumption that the normalized exposure is log-normally distributed, rather than being normally distributed, we can take natural logarithms of both sides to get a log-log-linear model of the form

Log (Exposure) = Intercept + 1 × Log (Pounds of Active Ingredient) + Error Terms.

The additive Error Terms are assumed to be normally distributed with a mean of zero. Thus proportionality of exposure to the pounds of active ingredient is statistically modeled by assuming a Slope equal to 1 in the more general log-log linear model:

Log (Exposure) = Intercept + Slope × Log (Pounds of Active Ingredient) + Error Terms.

Using this general model, taking exponentials of both sides gives

$\text{Exposure} = e^{\text{Intercept}} \times (\text{Pounds of Active Ingredient})^{\text{Slope}} \times e^{\text{Error Terms}}$, so that

$\text{Arithmetic Mean Exposure} = C \times (\text{Pounds of Active Ingredient})^{\text{Slope}}$, where

$C = \text{Arithmetic Mean } \{e^{\text{Intercept}} \times e^{\text{Error Terms}}\}$.

Therefore, the arithmetic mean exposure will be proportional to the pounds of active ingredient if and only if the Slope in the log-log linear model equals 1. Note that the proportionality constant is C, which is very different to the estimated value of Slope. Also note that for this scenario in the mixed model we assume that the intercept, but not the slope, depends upon which group the source and receiving container belongs to.

Possible alternative models include the same formulation with a Slope of zero, implying that the exposure does not depend upon the amount of active ingredient handled, even though the amount of active ingredient handled varied between the subjects as part of the study design. Other possible models include the same model with a slope not equal to zero or one, the quadratic models discussed below, or models with more complicated relationships between the exposure and the experimental conditions. To evaluate whether the slope is zero, one, or other possible values, we fitted the above statistical model and computed confidence intervals for the slope.

To analyze the log-log-linearity, we also considered an additional hypothetical clothing scenario with no clothing at all. The dermal exposure for the No clothing scenario was calculated by summing all the inner and outer dermal exposure measurements:

All Dermal. This case represents the dermal exposure for a subject wearing no clothes. The exposure is the sum of the mass from hand wash, face and neck, and the six inner and six outer dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

We can use these statistical models to calculate confidence intervals for the slope. The calculation of the confidence intervals depends upon the value of the denominator degrees of freedom for the mixed models used. A review of the alternative methods for calculating the denominator degrees of freedom for fixed effects in a mixed model using the SAS MIXED procedure is given in an article by Schaalje et al[1]. Based on that article, the following Table 19 summarizes the five available methods:

Table 19. SAS Methods for Computing the Fixed Effects Denominator Degrees of Freedom in PROC MIXED.

DDF Method	**SAS Abbreviation**	**Comments**
Residual	residual	Uses residual degrees of freedom. Ignores covariance structure as defined by the RANDOM and REPEATED statements. This method is not recommended.
Containment	contain	Default method when RANDOM statements are present. Accounts for the minimum contribution of the random effects that syntactically contain the fixed effects of interest.
Between-Within	bw	Default method when REPEATED statements are present and RANDOM statements are not present. Only exact when the data are balanced and the design is a repeated measures design with compound symmetry, and where the levels of the within-subjects effects are not replicated within any of the subjects. Otherwise the method

[1] Schaalje, G. B., J. B. McBride, G. W. Fellingham. "Approximations to Distributions of Test Statistics in Complex Mixed Linear Models Using SAS® Proc MIXED" *Proceedings of the Twenty Sixth Annual SAS Users Group International Conference*. April 2001. Long Beach, CA. ISBN 1-58025-864-6. SAS Institute, Cary, NC 27513.

DDF Method	SAS Abbreviation	Comments
		is at best approximate and can be unpredictable.
Satterthwaite / Fai-Cornelius	satterth	Designed to approximate the denominator degrees of freedom for split-plot designs with complicated covariance structures and/or unbalanced data sets.
Kenwood-Rogers	kr	Designed to approximate the denominator degrees of freedom for designs with complicated covariance structures and/or unbalanced data sets. Results from simulations suggest better performance than the Satterthwaite method. If a covariance parameter has zero variance then this method ignores that covariance.

To interpret this table for this study, note that the RANDOM statement was used to define the worker effect. If the ICC equals zero, then there is no worker clustering and the worker variance equals zero. The REPEATED statement was used to define the repeated measures model. A balanced data set is one where each treatment combination is applied to the same number of subjects. For this study, this implies that there are the same number of workers in every group, and each worker has the same number of measured exposure values.

The study data were not balanced using the mixed model groups Bottle, Conventional, and Reduced Splash, since those groups had 6, 15, and 15 measurements, respectively. Based on this summary, the recommended method is the Kenwood-Rogers method for the mixed models and for the repeated measures model (detailed below). The confidence intervals for the regression coefficients presented in this memorandum follow these recommendations. Note that this issue does not impact the calculated confidence intervals for the summary statistics in Tables 12 to 18, since they were based on a bootstrap method.

Table 20 shows the 95% confidence intervals for the slope calculated from the above lognormal mixed model. Also shown is the width of the confidence interval for the slope. A confidence interval that includes one but not zero supports the assumptions of the normalized exposure models. A confidence interval that includes zero but not one suggests that the exposure does not depend on the amount of active ingredient handled. A confidence interval that includes both zero and one suggests that either the basic statistical model is incorrect or there are not enough data to statistically infer whether the slope is zero or one. The Repeated Measures statistical model (bottom two rows) is described and discussed below. Note that, because the inhalation dose measured on the OVS tube is mathematically an exact multiple of the corresponding inhalation TWA measured on the OVS tube, the estimated slopes and confidence intervals are exactly the same. As discussed above, there were three MEs where the measured hands only exposure was unusually high compared to other measurements in the same subgroup (1a, 1b, 2, 3 with CP or with RS) and so the slope estimates for dermal exposures were computed with and without these potential outliers.

Table 20. 95 percent confidence intervals for the slope of log exposure versus log pounds active ingredient handled. with and without the potential outlier dermal exposure data for Reduced Splash ME 1 in group 1a, Reduced Splash ME 7 in group 2, and Conventional Pour ME 6 in group 1b.

Exposure Route	Clothing	Data	Estimate	Lower	Upper	Confidence Interval Width
Dermal (mg)	Long pants and long sleeves	All 36 Values	-0.28	-1.06	0.49	1.5
		Exclude outlier data	-0.14	-0.84	0.56	1.4
	Short pants and short sleeves	All 36 Values	-0.04	-0.68	0.60	1.3
		Exclude outlier data	0.14	-0.50	0.78	1.3
	Long pants and short sleeves	All 36 Values	-0.26	-0.99	0.48	1.5
		Exclude outlier data	-0.13	-0.78	0.52	1.3
	Hands Only	All 36 Values	-0.31	-1.12	0.50	1.6
		Exclude outlier data	-0.17	-0.91	0.56	1.5
	None	All 36 Values	-0.05	-0.69	0.59	1.3
		Exclude outlier data	0.16	-0.50	0.82	1.3
Inhalation Concentration (mg/m^3)		All 36 Values	1.21	0.71	1.72	1.0
Inhalation Dose (mg)		All 36 Values	0.92	0.43	1.42	1.0
Inhalation 8-hour TWA (mg/m^3)		All 36 Values	0.92	0.43	1.42	1.0
Dermal (mg) Repeated Measures Model	Any	All 36 Values	0.04	-0.61	0.68	1.3
		Exclude outlier data	0.14	-0.42	0.71	0.7

For all of the dermal exposure cases, the confidence interval for the slope includes 0 but not 1. Thus, for these cases, the assumption of independence was not rejected and the assumption of log-log-linearity with slope 1 was rejected. The

estimate slopes are small but sometimes negative, ranging from -0.31 to 0.16. The slopes are higher when the potential outliers are excluded. The negative slope estimates are not expected since one would usually assume that the exposure will tend to increase if the amount of active ingredient increases. This may indicate some issues with the assumed statistical model, particularly the assumption that the geometric mean is the same for the three subgroups 1bCP, 2CP and 3CP that are combined into the Conventional group and is the same for the three subgroups 1bRS, 2RS, 3RS that are combined into the Reduced Splash group. As discussed above, this assumption was needed so that the same unit exposure estimates could be applied for source containers of all sizes not pouring into trigger spray bottles.

In the section "Alternative models for dermal exposure" we investigate alternative models and outlier treatments to further understand these negative slopes and in particular to investigate models where the slope is different for the three groups Bottle, Conventional, and Reduced Splash.

For all the inhalation exposure cases, the confidence interval for the slope includes 1 but not 0. Thus, for these cases, the assumption of independence was rejected and the assumption of log-log-linearity with a slope of 1 was not rejected and is therefore supported. The slope value for the inhalation concentration is above 1. As discussed below, when the slope is greater than one, the predicted means from the normalized exposure model will underestimate the predicted means from the mixed model with an estimated slope (of the log exposure against the log amount of active ingredient) when the amount of active ingredient is high. However, this underestimation will be small since the slope is only slightly above 1 for the inhalation concentrations, except if the amount of active ingredient handled is extremely high.

The results in Table 20 show that the actual confidence interval widths were mostly less than 1.4 and were at most 1.6 (for hands only). In previous statistical analyses of the AEATF studies, an expected confidence interval width of at most 1.4 was needed so that the statistical power of detecting log-log-linearity would be at least 80%. For this study the statistical design was very different and that power calculation does not apply. Nevertheless, the observed confidence intervals widths in this study are comparable to those found for the mop, wipe, and aerosol studies.

The lognormal mixed model regression results are shown in Figures 15 to 22. The scatter plots show the data points in each of the three groups, Bottle, Conventional, and Reduced Splash. The fitted regression lines are shown for each group. The slopes of the regression lines are the same for all three groups (an assumption of the statistical model), but the intercepts are different.

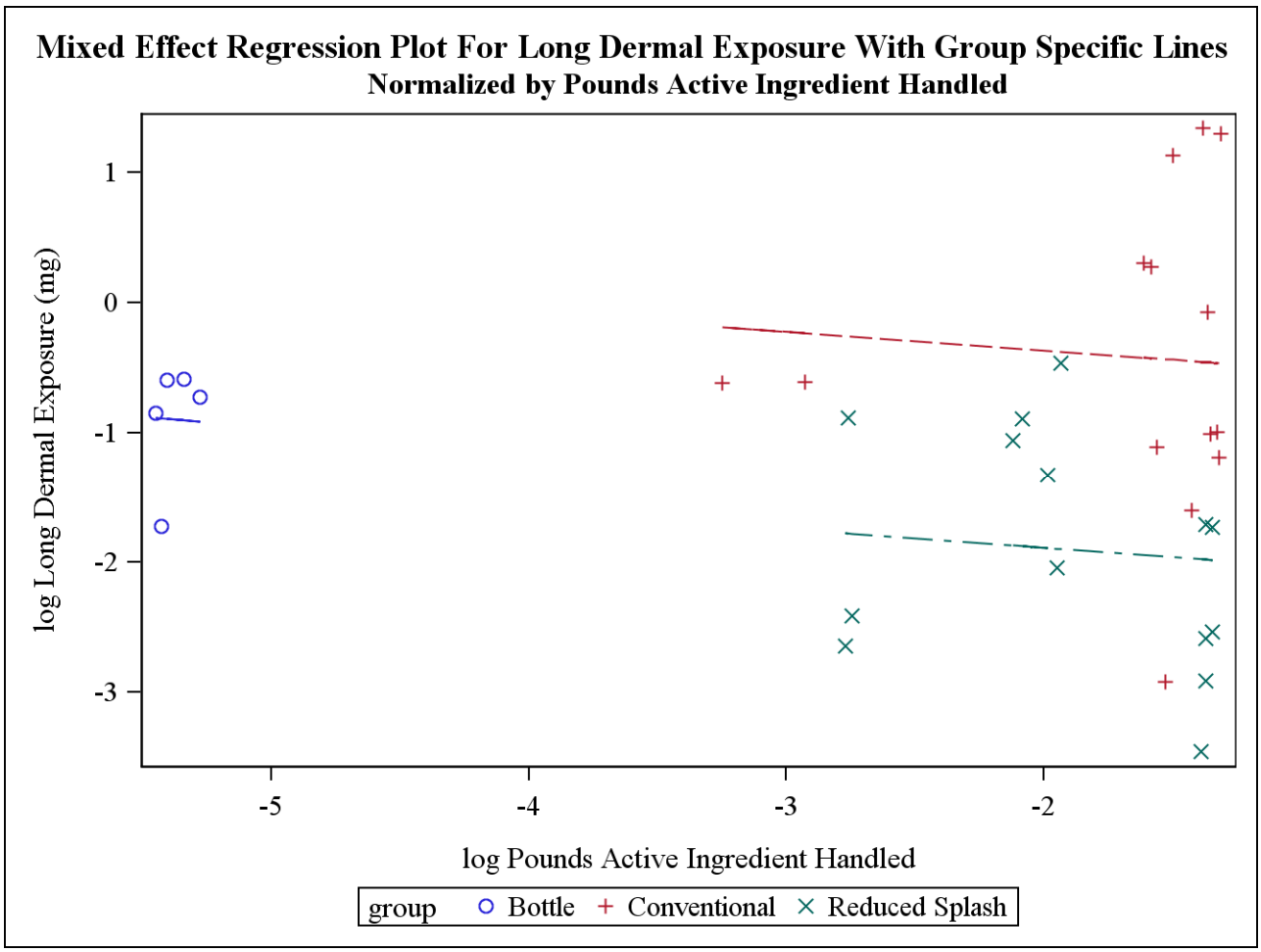

Mixed Effect Regression Plot For Long Dermal Exposure With Group Specific Lines
Normalized by Pounds Active Ingredient Handled
log Long Dermal Exposure (mg)
1
0
-1
-2
-3
-5
-4
-3
-2
log Pounds Active Ingredient Handled
group
Bottle
Conventional
Reduced Splash

Figure 15

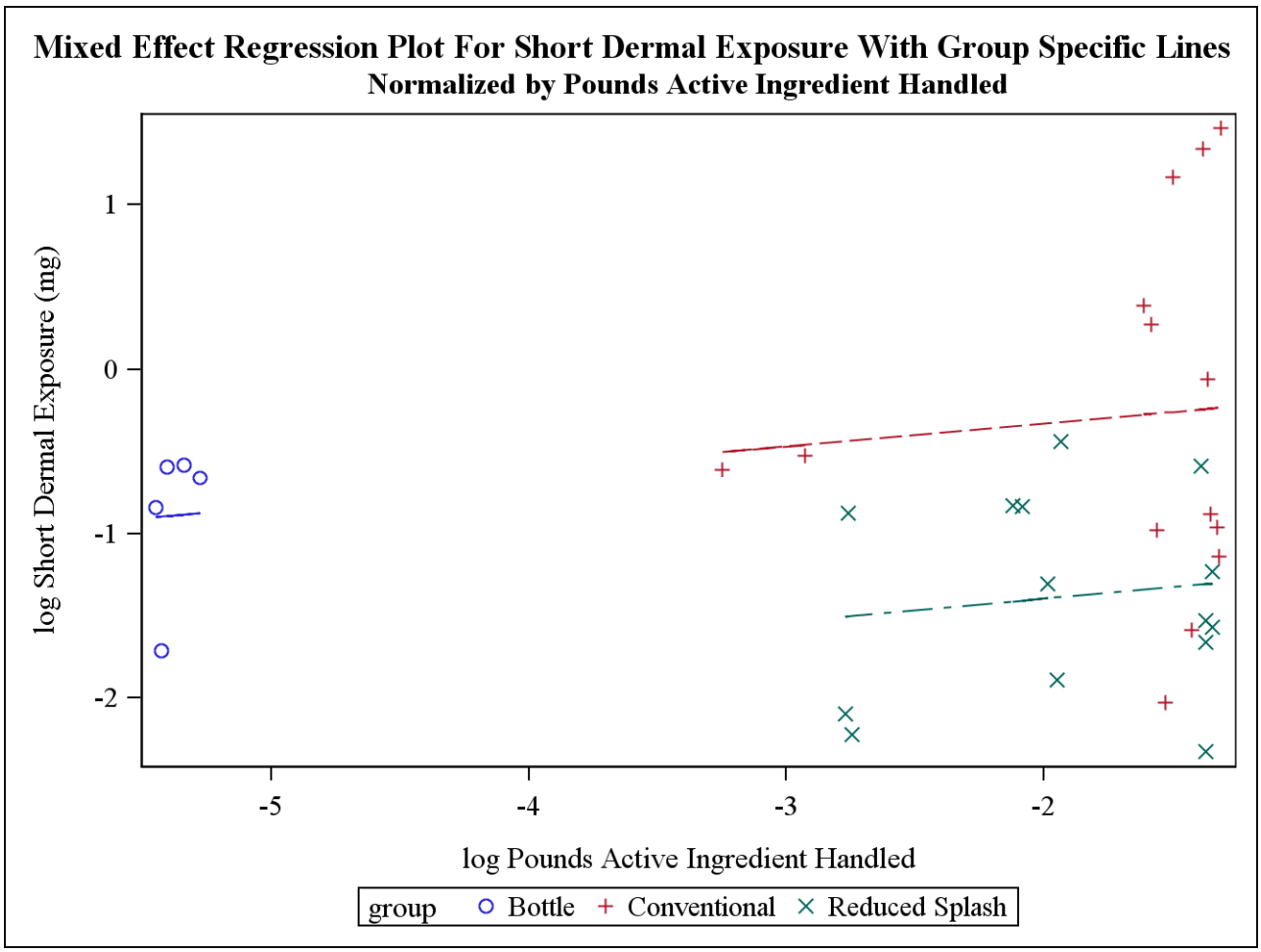

Mixed Effect Regression Plot For Short Dermal Exposure With Group Specific Lines
Normalized by Pounds Active Ingredient Handled
log Short Dermal Exposure (mg)
1
0
-1
-2
-5
-4
-3
-2
log Pounds Active Ingredient Handled
group
Bottle
Conventional
Reduced Splash

Figure 16

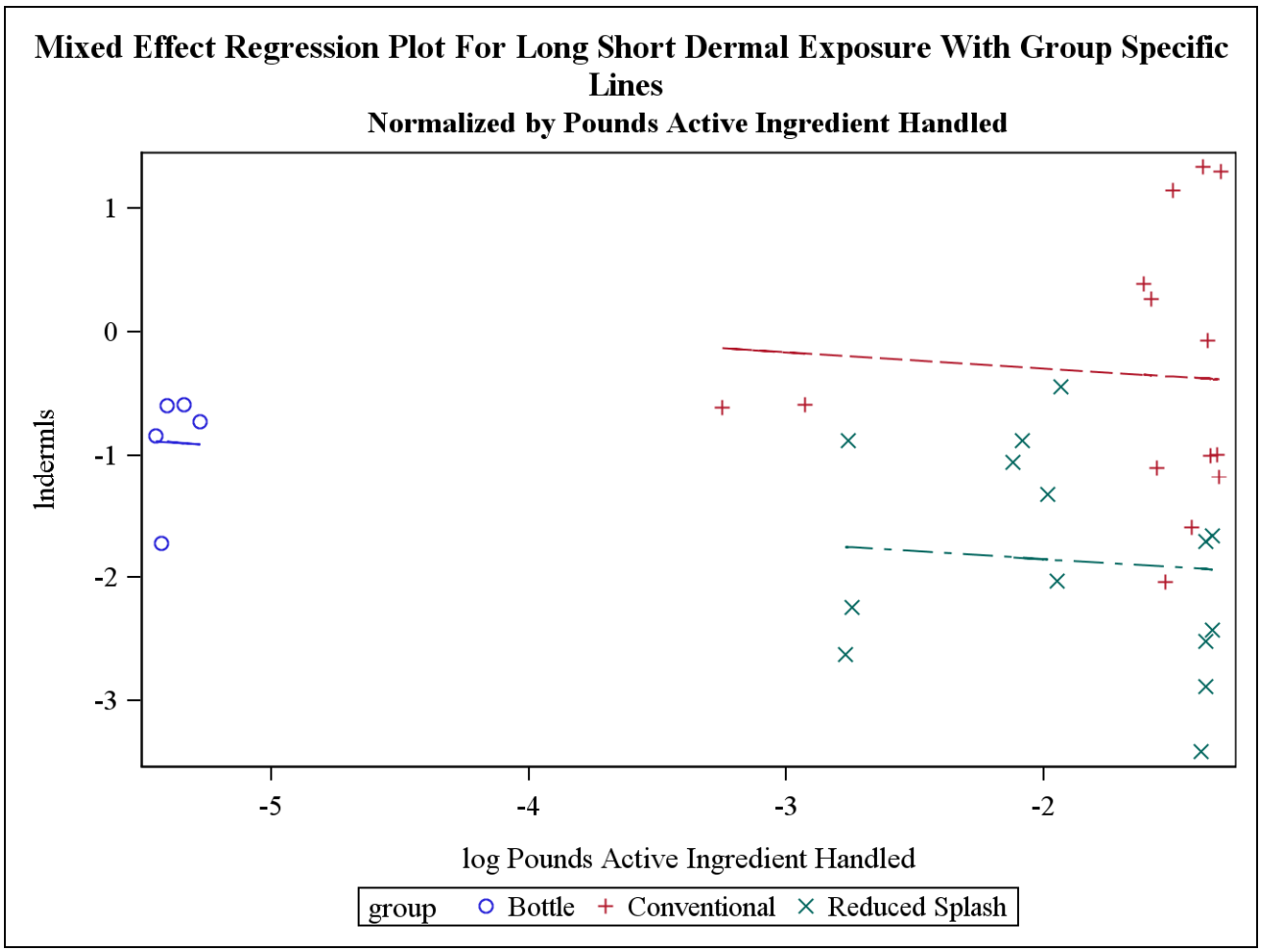

Mixed Effect Regression Plot For Long Short Dermal Exposure With Group Specific Lines
Normalized by Pounds Active Ingredient Handled
Indermls
1
0
-1
-2
-3
-5
-4
-3
-2
log Pounds Active Ingredient Handled
group
Bottle
Conventional
Reduced Splash

Figure 17

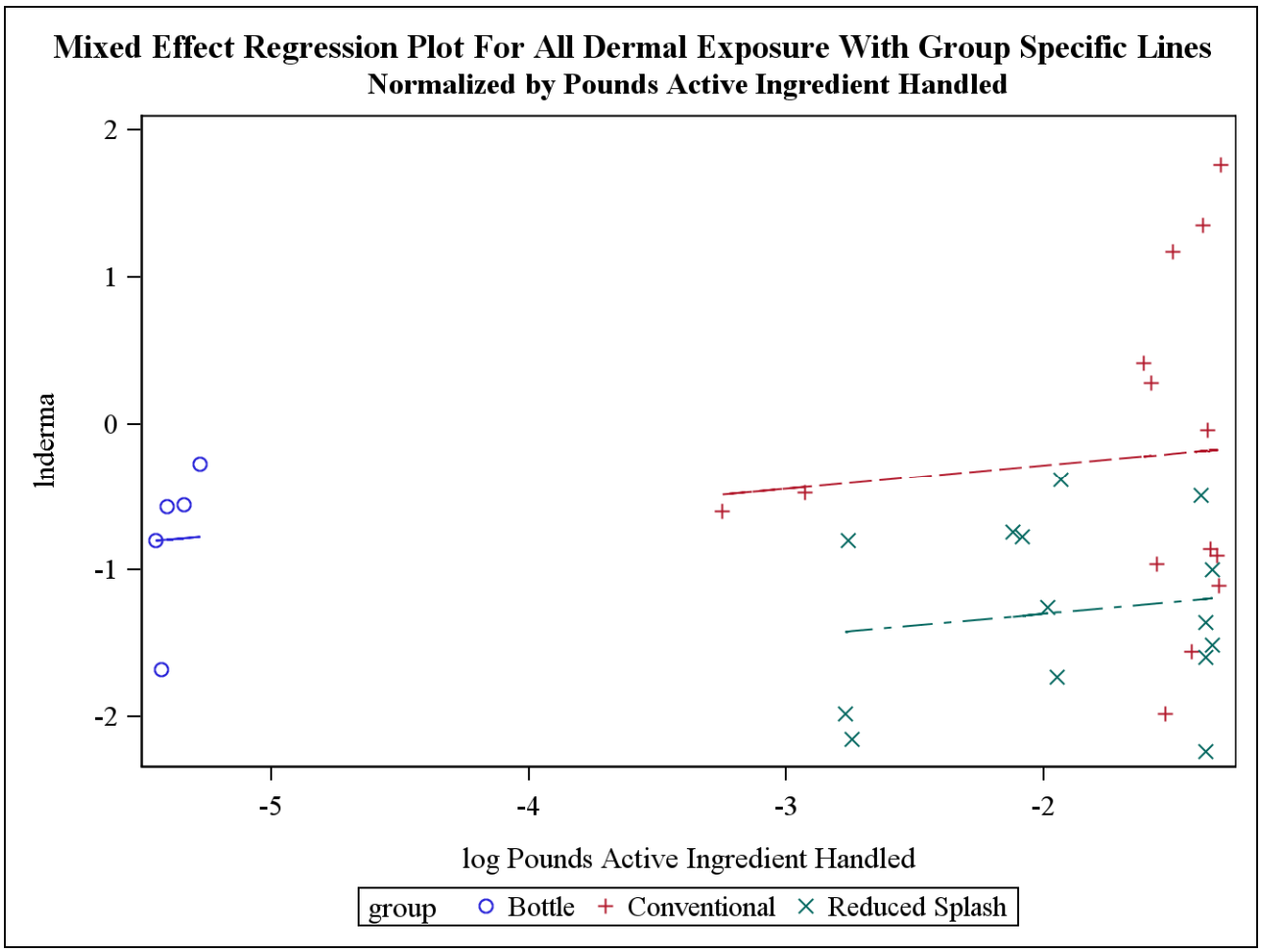

Mixed Effect Regression Plot For All Dermal Exposure With Group Specific Lines
Normalized by Pounds Active Ingredient Handled
lnderma
2
1
0
-1
-2
-5
-4
-3
-2
log Pounds Active Ingredient Handled
group
Bottle
Conventional
Reduced Splash

Figure 18

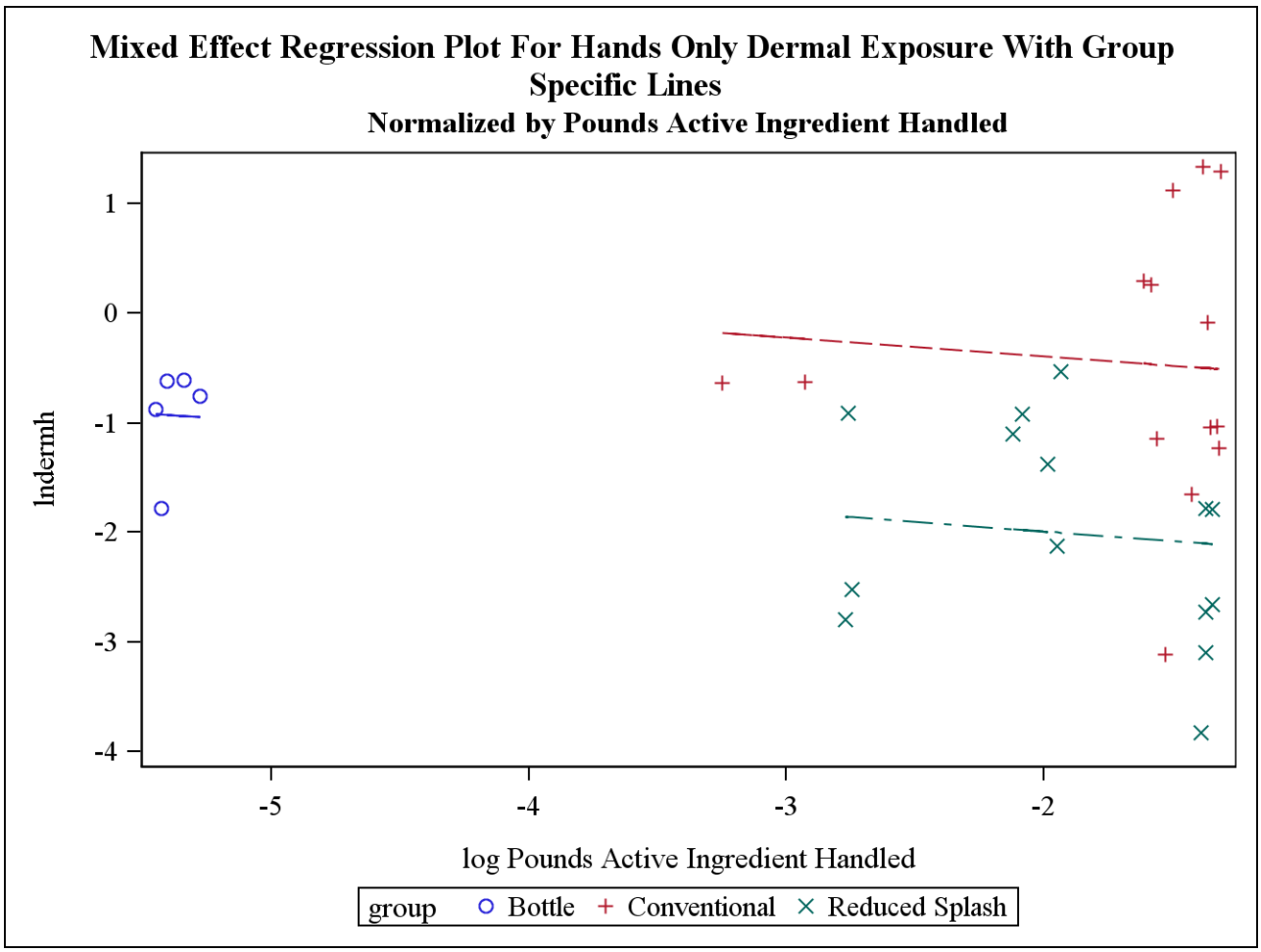

Mixed Effect Regression Plot For Hands Only Dermal Exposure With Group Specific Lines
Normalized by Pounds Active Ingredient Handled
lndermh
1
0
-1
-2
-3
-4
-5
-4
-3
-2
log Pounds Active Ingredient Handled
group
Bottle
Conventional
Reduced Splash

Figure 19

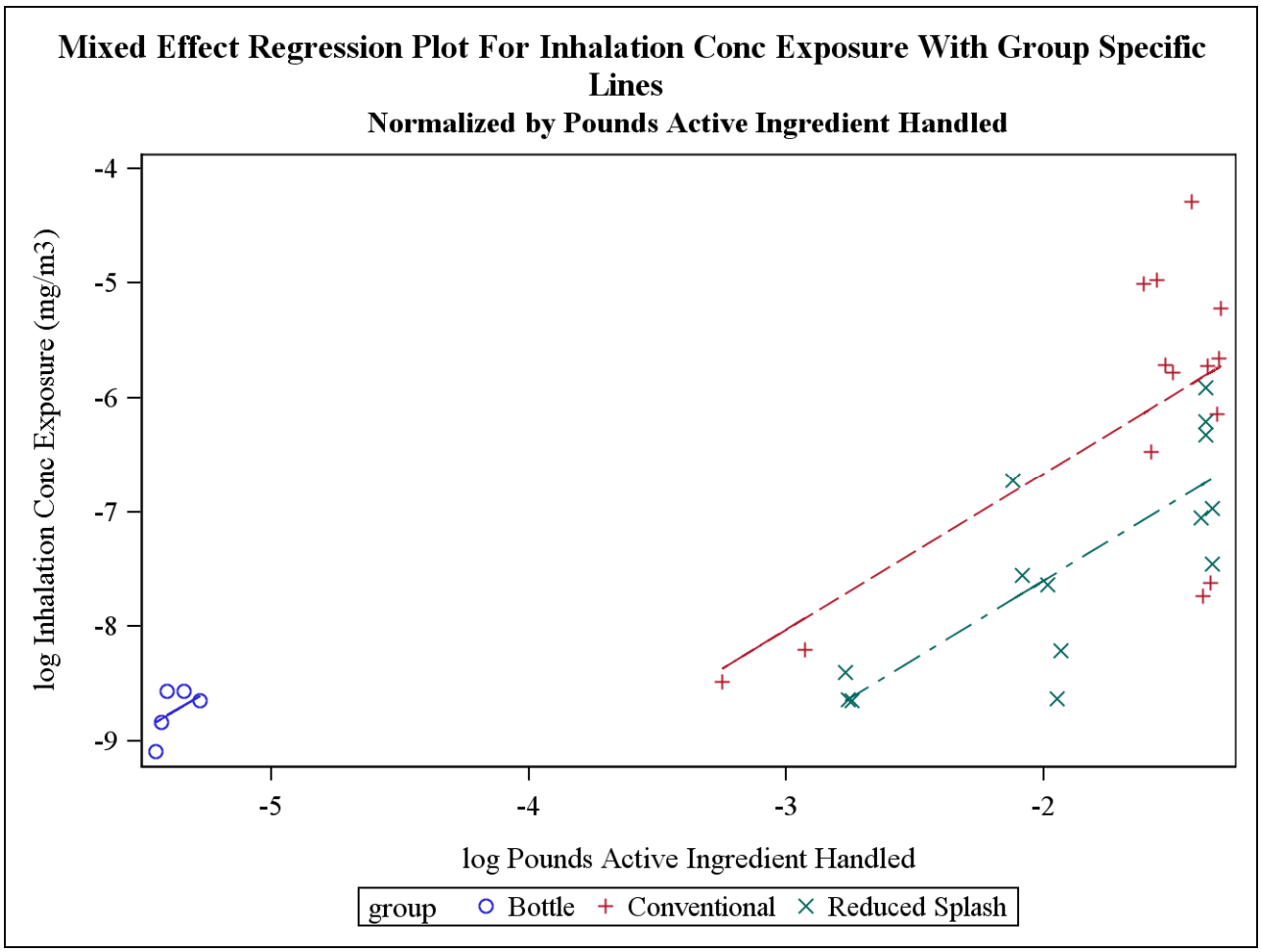

Mixed Effect Regression Plot For Inhalation Conc Exposure With Group Specific Lines
Normalized by Pounds Active Ingredient Handled
log Inhalation Conc Exposure (mg/m3)
-4
-5
-6
-7
-8
-9
-5
-4
-3
-2
log Pounds Active Ingredient Handled
group
Bottle
Conventional
Reduced Splash

Figure 20

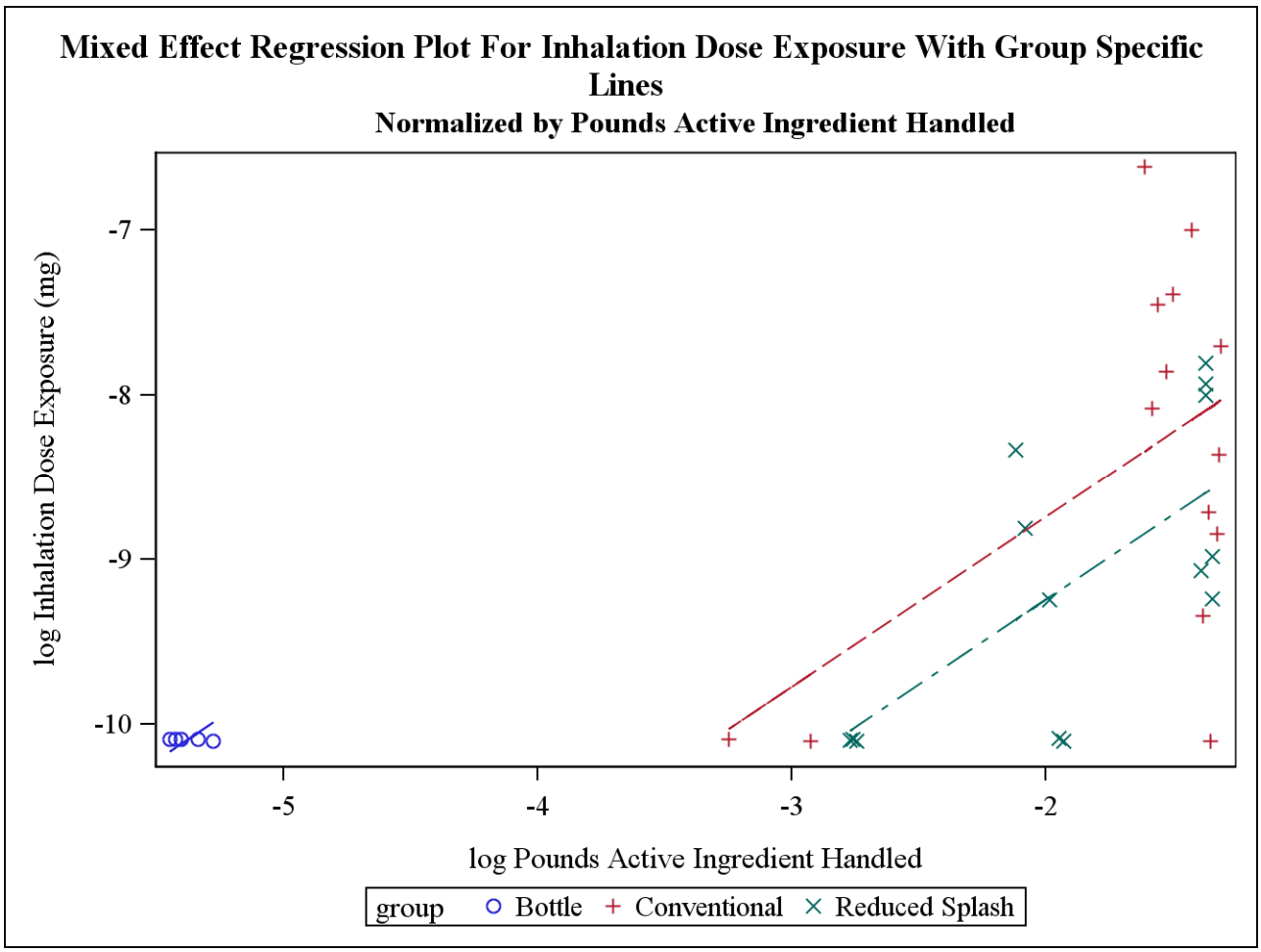

Mixed Effect Regression Plot For Inhalation Dose Exposure With Group Specific Lines
Normalized by Pounds Active Ingredient Handled
log Inhalation Dose Exposure (mg)
-7
-8
-9
-10
-5
-4
-3
-2
log Pounds Active Ingredient Handled
group
Bottle
Conventional
Reduced Splash

Figure 21

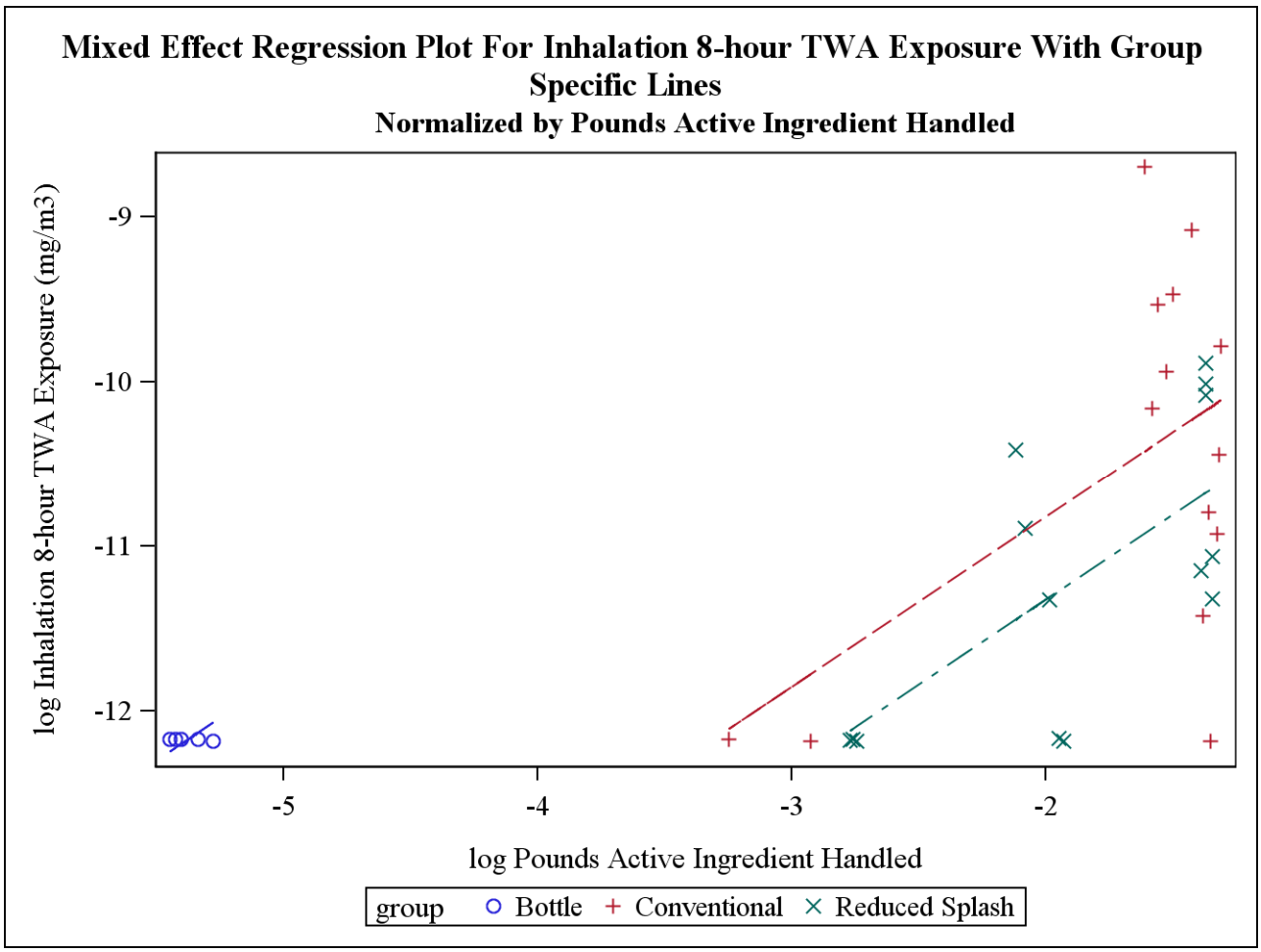

Mixed Effect Regression Plot For Inhalation 8-hour TWA Exposure With Group Specific Lines
Normalized by Pounds Active Ingredient Handled
log Inhalation 8-hour TWA Exposure (mg/m3)
-9
-10
-11
-12
-5
-4
-3
-2
log Pounds Active Ingredient Handled
group
Bottle
Conventional
Reduced Splash

Figure 22

Repeated measures model

The above analyses of the log-log-linearity for dermal exposure show similar small slopes. To investigate this issue further, the following more complicated statistical model was fitted to the data of all three dermal exposures (excluding the unrealistic hands only and no clothing case) for all 18 subjects and both Conventional and Reduced Splash containers. The model was of the form:

> Log (dermal exposure) = LnGM (clothing type and group) + Slope × Log (Pounds of Active Ingredient) + Worker + Error

In this model, the intercept depends upon the clothing type and group, so there are six intercepts. The slope is the same for all three clothing types and both groups. The Worker term accounts for possible within-worker correlations between their two MEs (i.e. the Conventional Pour and Reduced Splash experiments). Finally, to account for the expected correlations between different dermal exposure measurements on the same worker during the same ME, the three error terms (one per clothing type) for each worker are assumed to be correlated (with an unspecified covariance matrix), but errors for different workers are assumed to be independent. Thus in SAS terminology, the Worker effect is a RANDOM effect and the Error is a REPEATED effect where the subject is the combination of the worker and the ME. Thus each worker is treated as two subjects, for their two MEs. We will call this model the "Repeated Measures" model. The confidence interval for the slope using this statistical model are shown in the bottom two rows of Table 20. Since the confidence interval includes zero and does not include one, the log-log-linearity for dermal exposure has not been shown using this statistical model, but the positive slope estimate suggests that the exposure tends to increase as the AI increases.

Quadratic models

The log-log-linearity test was based on a linear model for log exposure versus log pounds active ingredient handled. The HSRB suggested that a quadratic model should also be considered.

There are two quadratic models that could be considered. Since the original linear model is of the form

> Log (Exposure) = Intercept + Slope × Log (Pounds of Active Ingredient) + Error Terms,

where the intercept depends upon the group but the slope is the same for all three groups, the main quadratic model is of the form

> Log (Exposure) =
>
> Intercept + Slope × Log (Pounds of Active Ingredient) +
> Quad × $\{\text{Log (Pounds of Active Ingredient)}\}^2$ + Error Terms.

The intercept depends upon the group, but the Slope and Quad parameters are the same for all three groups. Note that the quadratic term is the square of the logarithm of the pounds of active ingredient rather than the logarithm of the square; the latter approach produces an ill-defined model with two multiples of the logarithm of the pounds of active ingredient.

Another approach might be to consider a quadratic model for exposure:

> Exposure =
>
> Intercept + Slope × (Pounds of Active Ingredient) +
> Quad × $(\text{Pounds of Active Ingredient})^2$ + Error Terms.

We do not recommend this second approach for these data since the exposures are known to be non-negative and the quantile plots indicate that the exposure data are better modeled using a log-normal distribution than using a normal distribution. Furthermore, unless the intercept is zero, this model predicts a nonzero exposure when the pounds of active ingredient is zero, and so a more realistic (though possibly poorer-fitting) model of this form would have a zero intercept for every group. For other exposure data a log-log-linearity test could be carried out by fitting the zero intercept model

$$\text{Exposure} = \text{Slope} \times (\text{Pounds of Active Ingredient}) + \text{Quad} \times (\text{Pounds of Active Ingredient})^2 + \text{Error Terms}$$

and testing if Quad equals zero.

The parsimony principle suggests that the appropriate statistical procedure for this study is to first fit the quadratic regression model for the logarithm of the exposure

$$\text{Log (Exposure)} = \text{Intercept} + \text{Slope} \times \text{Log (Pounds of Active Ingredient)} + \text{Quad} \times \{\text{Log (Pounds of Active Ingredient)}\}^2 + \text{Error Terms.}$$

If the coefficient Quad is statistically significant at the 5% level, which is equivalent to requiring that the 95% confidence interval does not include zero, than the quadratic model is supported. Otherwise the linear model should be used.

Table 21 presents the fitted quadratic models from the study for the mixed models of seven exposure measurements (Long Dermal, Short Dermal, Long Short Dermal, Hands Only, and for Inhalation Concentration, Dose and 8-Hour TWA) and for the Repeated Measures model for Dermal exposures. For the Repeated Measures model, the model has different intercepts (but the same Slope and Quad coefficients) for the six combinations of group and clothing type. In view of the earlier discussion about denominator degrees of freedom, the confidence intervals are calculated using the Kenwood-Rogers method. The group-specific intercepts are not shown.

Table 21. Quadratic mixed models with 95% confidence intervals for the log exposure versus log pounds active ingredient handled.

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Long Dermal	Slope	-3.78	25.64	-9.10	1.54	3.19	0.35	10.64
Long Dermal	Quad	-0.81	26.37	-2.03	0.41	3.19	0.35	2.44
Short Dermal	Slope	-1.07	24.69	-5.52	3.37	2.74	0.42	8.89
Short Dermal	Quad	-0.24	25.42	-1.26	0.78	2.74	0.42	2.05
Long	Slope	-3.75	25.57	-8.76	1.26	2.99	0.35	10.02

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Short Dermal								
Long Short Dermal	Quad	-0.81	26.29	-1.96	0.34	2.99	0.35	2.30
Hands Only	Slope	-4.08	25.80	-9.66	1.49	3.35	0.34	11.15
Hands Only	Quad	-0.88	26.53	-2.15	0.40	3.35	0.34	2.56
Inhalation Conc	Slope	0.96	31.00	-2.91	4.82	2.27	0.00	7.74
Inhalation Conc	Quad	-0.06	31.00	-0.94	0.82	2.27	0.00	1.77
Inhalation Dose	Slope	0.25	31.00	-3.52	4.02	2.22	0.00	7.54
Inhalation Dose	Quad	-0.15	31.00	-1.02	0.71	2.22	0.00	1.72
Inhalation TWA	Slope	0.25	31.00	-3.52	4.02	2.22	0.00	7.54
Inhalation TWA	Quad	-0.15	31.00	-1.02	0.71	2.22	0.00	1.72
Dermal Repeated Measures	Slope	-0.96	25.10	-5.53	3.61	NA	NA	-1.91
Dermal Repeated Measures	Quad	-0.23	25.84	-1.28	0.82	NA	NA	-0.45

Since the 95% confidence intervals for Quad include zero in every case, the quadratic coefficient is not statistically significant and the quadratic models are not supported.

Threshold Analyses

As described above, the following two mixed models were fitted to the dermal and inhalation exposure data.

Linear mixed model:

Log (Exposure) = Intercept1 + Slope × Log (Pounds of Active Ingredient) + Worker + Error

Normalized exposure mixed model:

Log (Exposure) = Intercept2 + Log (Pounds of Active Ingredient) + Worker + Error,

which is mathematically the same as

Log (Exposure/Pounds of Active Ingredient) = Intercept2 + Worker + Error

The intercepts for these two models are denoted as Intercept1 and Intercept2 since their estimated values will in general be different. Intercept1 and Intercept2 both depend upon the group and so each has different values for Bottle, Conventional, and Reduced Splash exposures.

Worker is a normally distributed random effect variable with independent, identically distributed values for each worker, and Error is a normally distributed error variable with independent, identically distributed values for each total exposure measurement. If the linear mixed model has a slope of 1, then the model is mathematically the same as the normalized exposure mixed model.

These two statistical models can be compared by calculating the threshold value of the pounds of active ingredient at which both models predict the same mean exposure. The threshold values are computed as follows.

Suppose first that the linear mixed model for log Exposure is correct. Then, as shown above, the predicted arithmetic mean exposure for a given amount of active ingredient is given by the equation

Predicted arithmetic mean exposure from linear mixed model =

$$C1 \times (\text{Pounds of Active Ingredient})^{\text{Slope}}, \quad (1)$$

where C1 is given by

C1 = Arithmetic Mean $\{e^{\text{Intercept1}} \times e^{\text{Error Terms}}\}$ for the linear mixed model, so that

$$C1 = \exp(\text{Intercept1}) \times \exp(\tfrac{1}{2} V1),$$

where V1 is the total variance for the linear mixed model, calculated as the sum of the worker variance and the error variance. C1 and Intercept1 depends upon the group but V1 is the same for every group. The predicted arithmetic mean exposure is the expected value of the exposure for a given amount of active ingredient and thus estimates the average (arithmetic mean) exposure for a large number of scenarios that are all using the same amount of active ingredient.

Suppose instead that the normalized exposure mixed model for log Exposure is correct. Then the predicted arithmetic mean exposure is given by the equation

Predicted arithmetic mean exposure from normalized exposure mixed model =

$C2 \times (\text{Pounds of Active Ingredient})^{1}$, (2)

where C2 is given by

C2 = Arithmetic Mean $\{e^{\text{Intercept2}} \times e^{\text{Error Terms}}\}$ for the normalized exposure mixed model, so that

$C2 = \exp(\text{Intercept2}) \times \exp(\frac{1}{2} V2)$,

where V2 is the total variance for the normalized exposure mixed model, calculated as the sum of the worker variance and the error variance. C2 and Intercept2 depends upon the group but V2 is the same for every group.

We now have two estimates of the predicted arithmetic mean exposure for a given amount of active ingredient, equations (1) and (2). The graphs in Figures 22 to 43 below compare the predicted arithmetic means for each clothing configuration (Long Dermal, Short Dermal, Long Short Dermal, Hands Only) and for the three inhalation exposure metrics. There are three plots for each exposure measure corresponding to the three groups, because the threshold value depends upon the group. Exposure is plotted against the pounds of active ingredient. To make it easier to see the effects of source container sizes, the data points in groups 1, 2, and 3 are labeled by their group number. The green curve gives the predictions for the linear mixed model in equation (1). The purple line gives the predictions for the normalized exposure mixed model in equation (2). The two estimates (1) and (2) are equal if the pounds of active ingredient equals the Threshold value:

$\text{Threshold} = \{C2/C1\}^{1/(\text{Slope} - 1)}$

The Threshold values are tabulated in Table 22 below.

Suppose that the estimated slope is less than 1. This is true for all the exposure measures studied here except for the inhalation concentration. The predicted arithmetic mean exposure from the normalized exposure mixed model will be greater than the predicted arithmetic mean exposure from the linear mixed model for amounts of active ingredient above the threshold (right hand side of the graph). The predicted arithmetic mean exposure from the normalized exposure mixed model will be less than the predicted mean exposure from the linear mixed model for amounts of active ingredient below the threshold (left hand side of the graph). What this means is that if we assume log-log-linearity and use the normalized exposure mixed model, then we will tend to over-predict the exposure unless the amount of active ingredient is below the threshold. (If the amount of active ingredient is below the threshold, then it will be low enough that the exposure will not usually be of concern).

For the inhalation concentration, the estimated slope was greater than one. In these cases the inequalities are reversed: The predicted arithmetic mean exposure from the normalized exposure mixed model will be greater than the predicted arithmetic mean exposure from the linear mixed model for amounts of active ingredient below the threshold (left hand side of the graph). The predicted arithmetic mean exposure from the normalized exposure mixed model will be less than the predicted arithmetic mean exposure from the linear mixed model for amounts of active ingredient above the threshold (right hand side of the graph). Although these cases show a tendency for exposure estimates from the normalized exposure mixed model to under-predict exposure, the estimated slope is not very much greater than 1 for the inhalation concentration, and then it is clearly seen from the graphs that the two curves are numerically extremely close so that the under-prediction is very small at levels of active ingredient similar to those used in this study.

Table 22. Threshold values for the amount of active ingredient.

Exposure Route	**Clothing**	**Slope**	**Threshold Level (lb active ingredient) for Bottle**	**Threshold Level (lb active ingredient) for Conventional**	**Threshold Level (lb active ingredient) for Reduced Splash**

Exposure Route	Clothing	Slope	Threshold Level (lb active ingredient) for Bottle	Threshold Level (lb active ingredient) for Conventional	Threshold Level (lb active ingredient) for Reduced Splash
Dermal (mg)	Long pants and long sleeves	-0.28	1.14	1.43	0.38
	Short pants and short sleeves	-0.04	0.83	1.34	0.50
	Long pants and short sleeves	-0.26	1.07	1.42	0.37
	Hands only	-0.31	1.19	1.48	0.37
Inhalation Concentration (mg/m^3)		1.21	0.00025*	0.00271*	0.00073*
Inhalation Dose (mg)		0.92	0.000062	0.00033	0.00015
Inhalation 8-hour TWA (mg/m^3)		0.92	0.0000078	0.000041	0.000019

*For this case, slope > 1 and so the normalized exposure mixed model under-predicts exposure for pounds of active ingredient above the threshold.

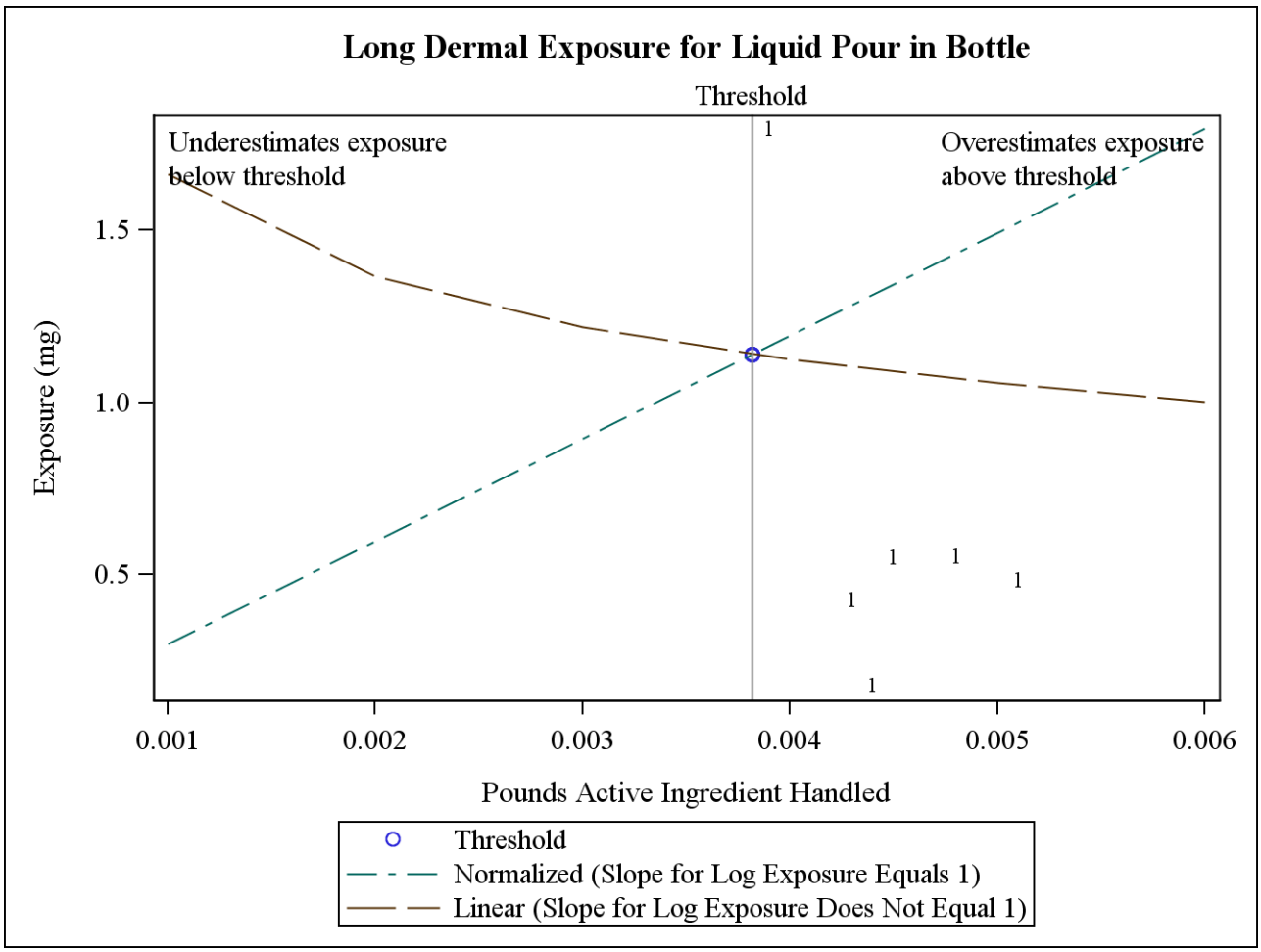

Long Dermal Exposure for Liquid Pour in Bottle
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
1
1
1
1
1
1
1.5
1.0
0.5
Exposure (mg)
0.001
0.002
0.003
0.004
0.005
0.006
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 23

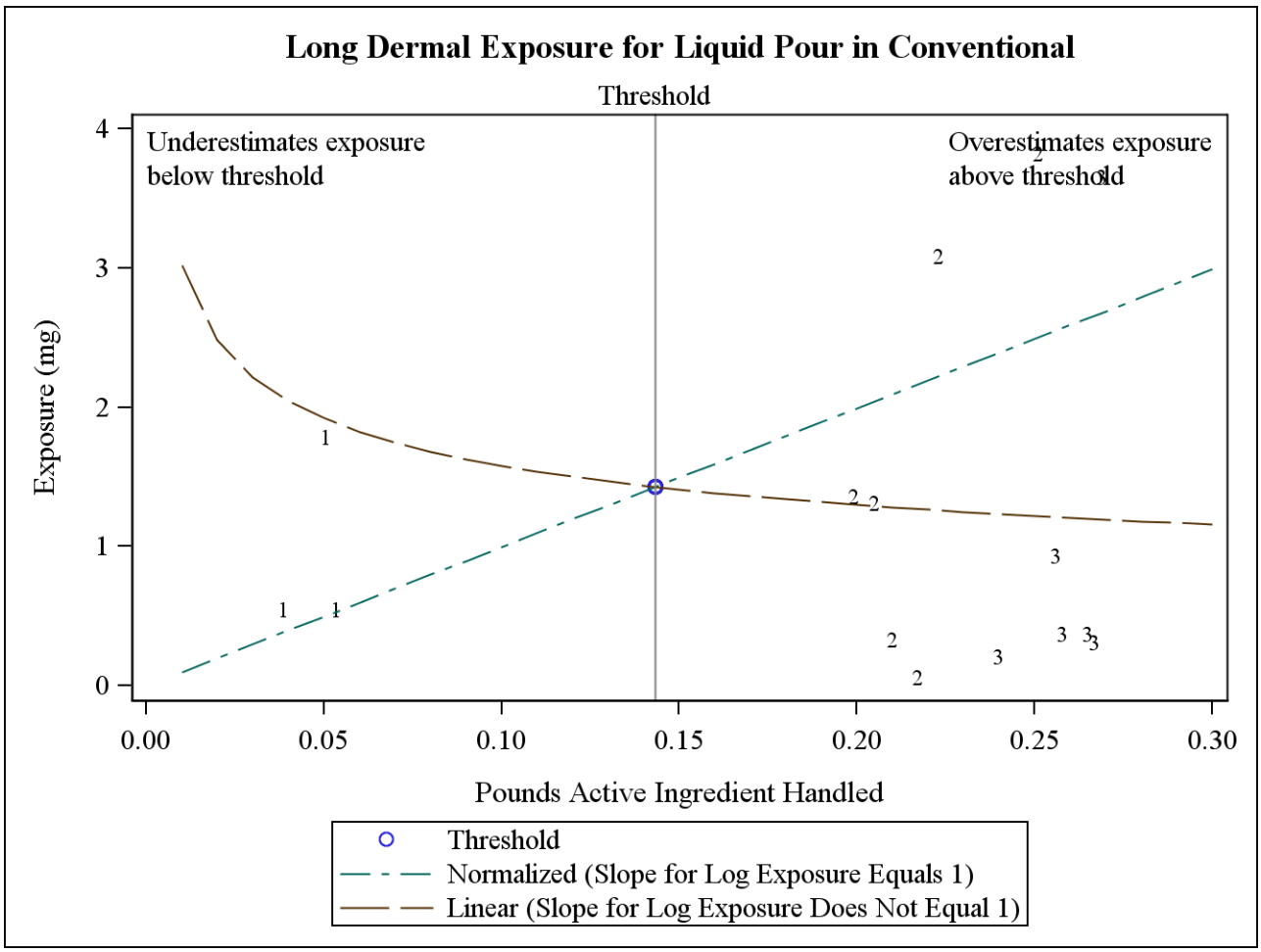

Long Dermal Exposure for Liquid Pour in Conventional
Threshold
Underestimates exposure
below threshold
Overestimates exposure
above threshold
Exposure (mg)
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 24

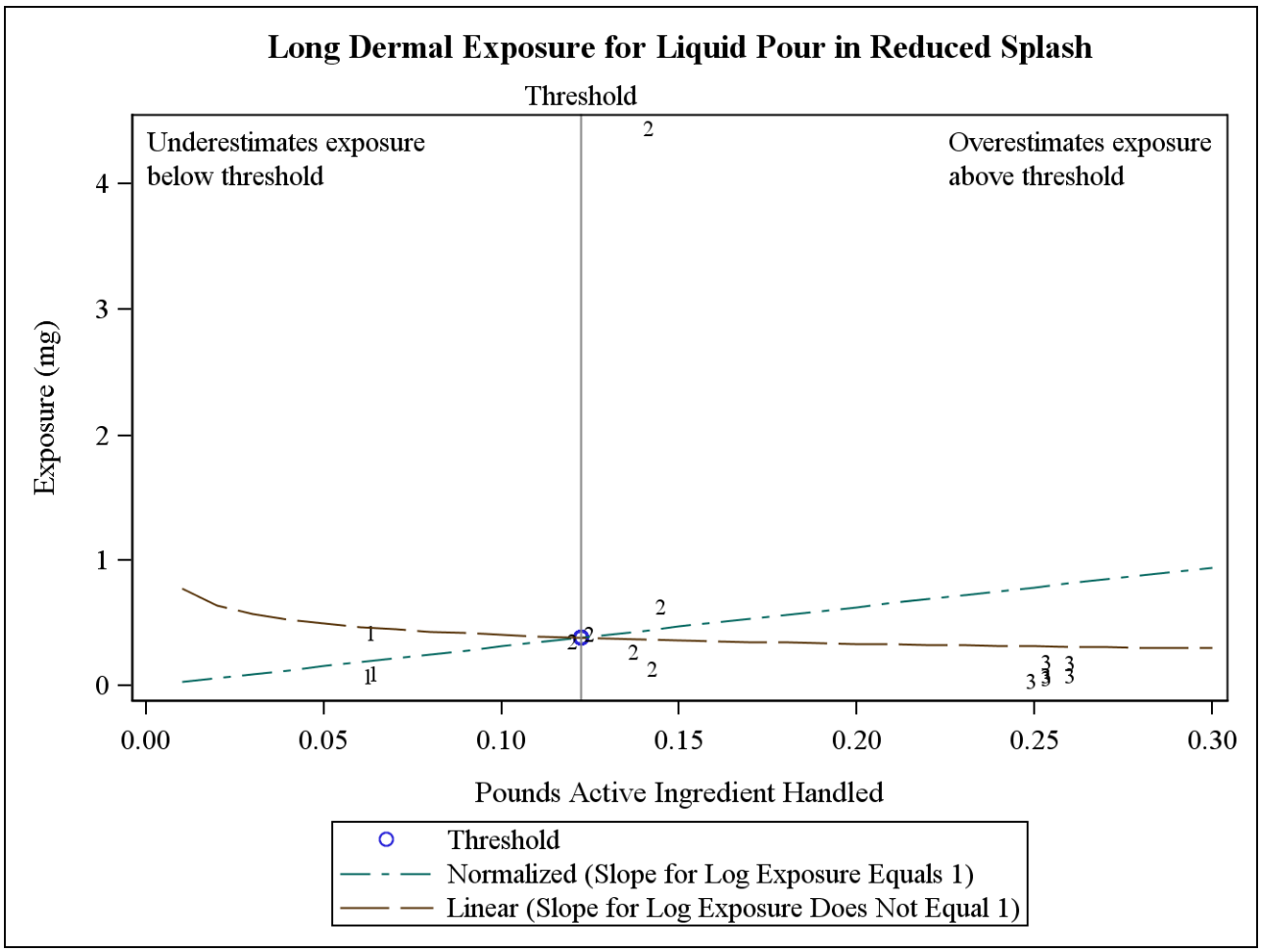

Long Dermal Exposure for Liquid Pour in Reduced Splash
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 25

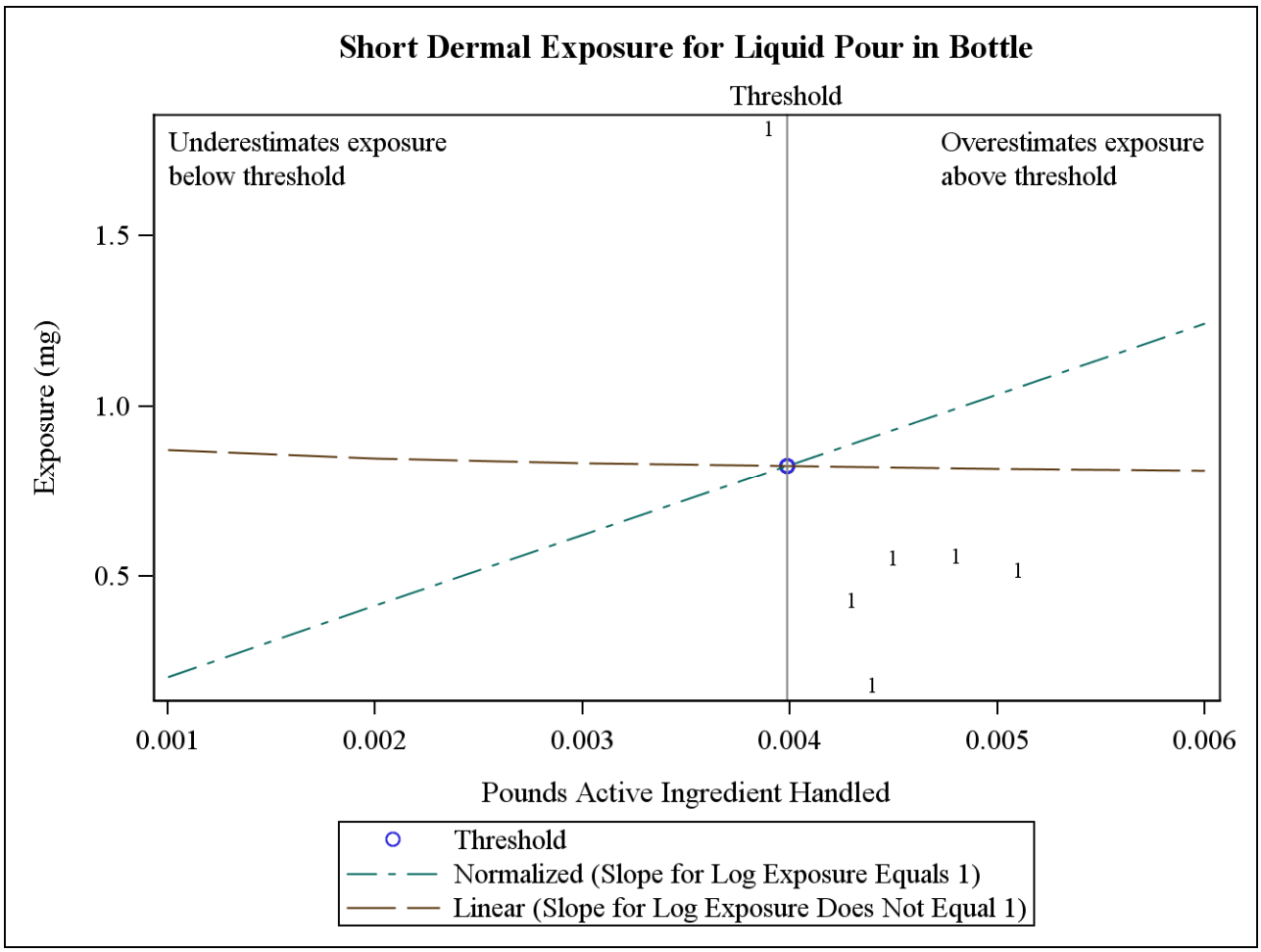

Short Dermal Exposure for Liquid Pour in Bottle
Threshold
Underestimates exposure
below threshold
Overestimates exposure
above threshold
1
1
1
1
1
1
1.5
1.0
0.5
Exposure (mg)
0.001
0.002
0.003
0.004
0.005
0.006
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 26

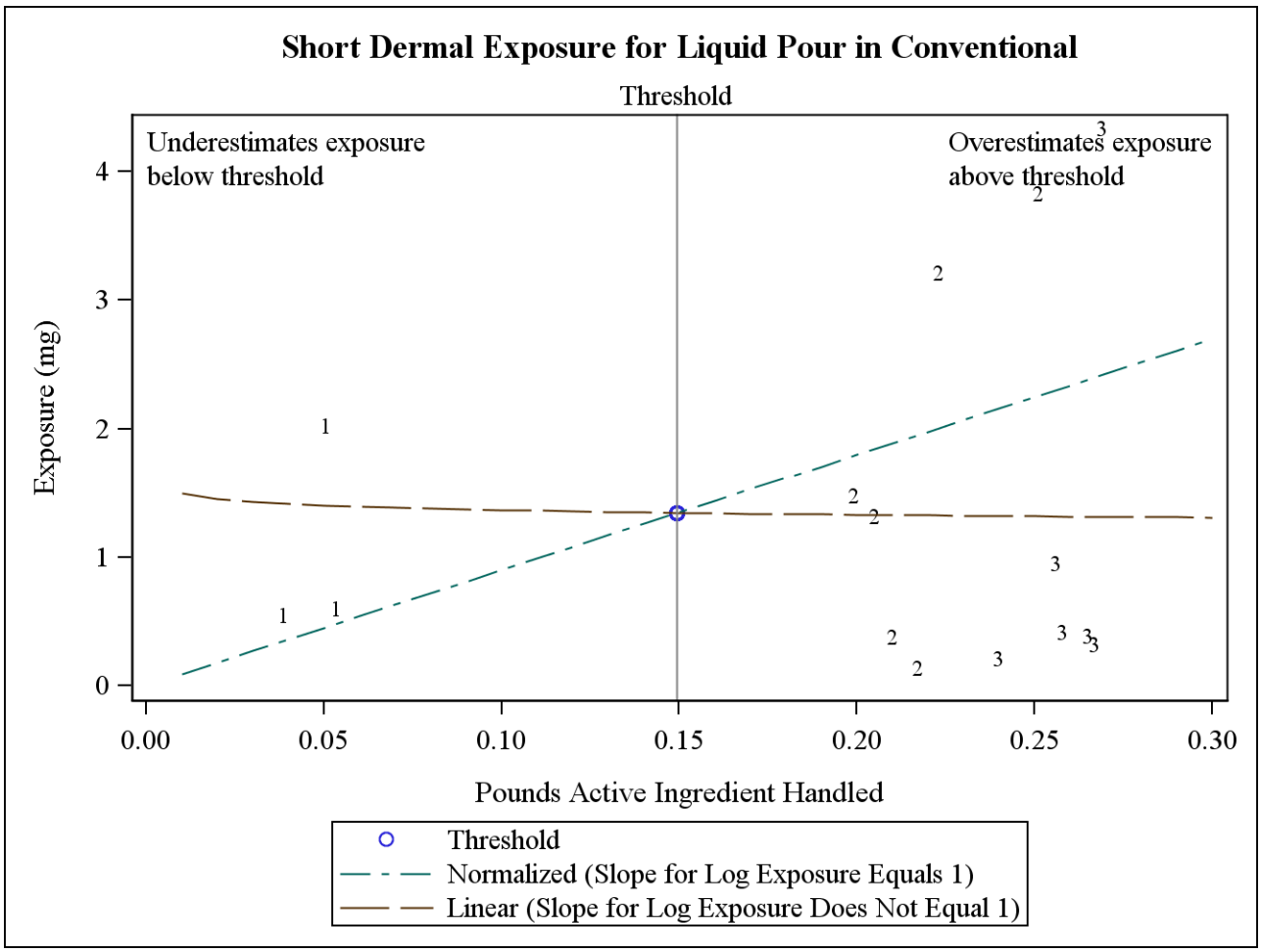

Short Dermal Exposure for Liquid Pour in Conventional
Threshold
Underestimates exposure
below threshold
Overestimates exposure
above threshold
Exposure (mg)
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 27

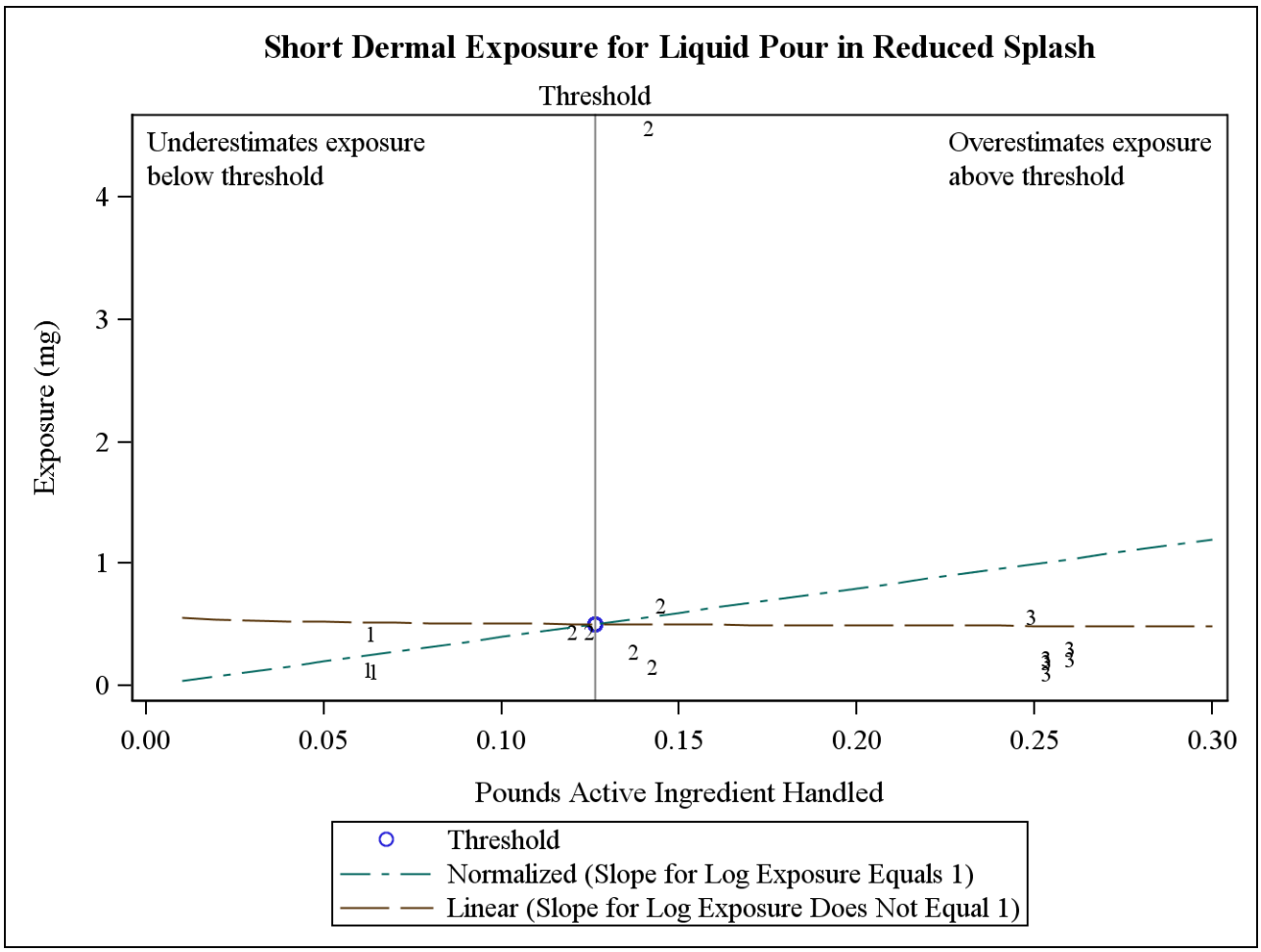

Short Dermal Exposure for Liquid Pour in Reduced Splash
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 28

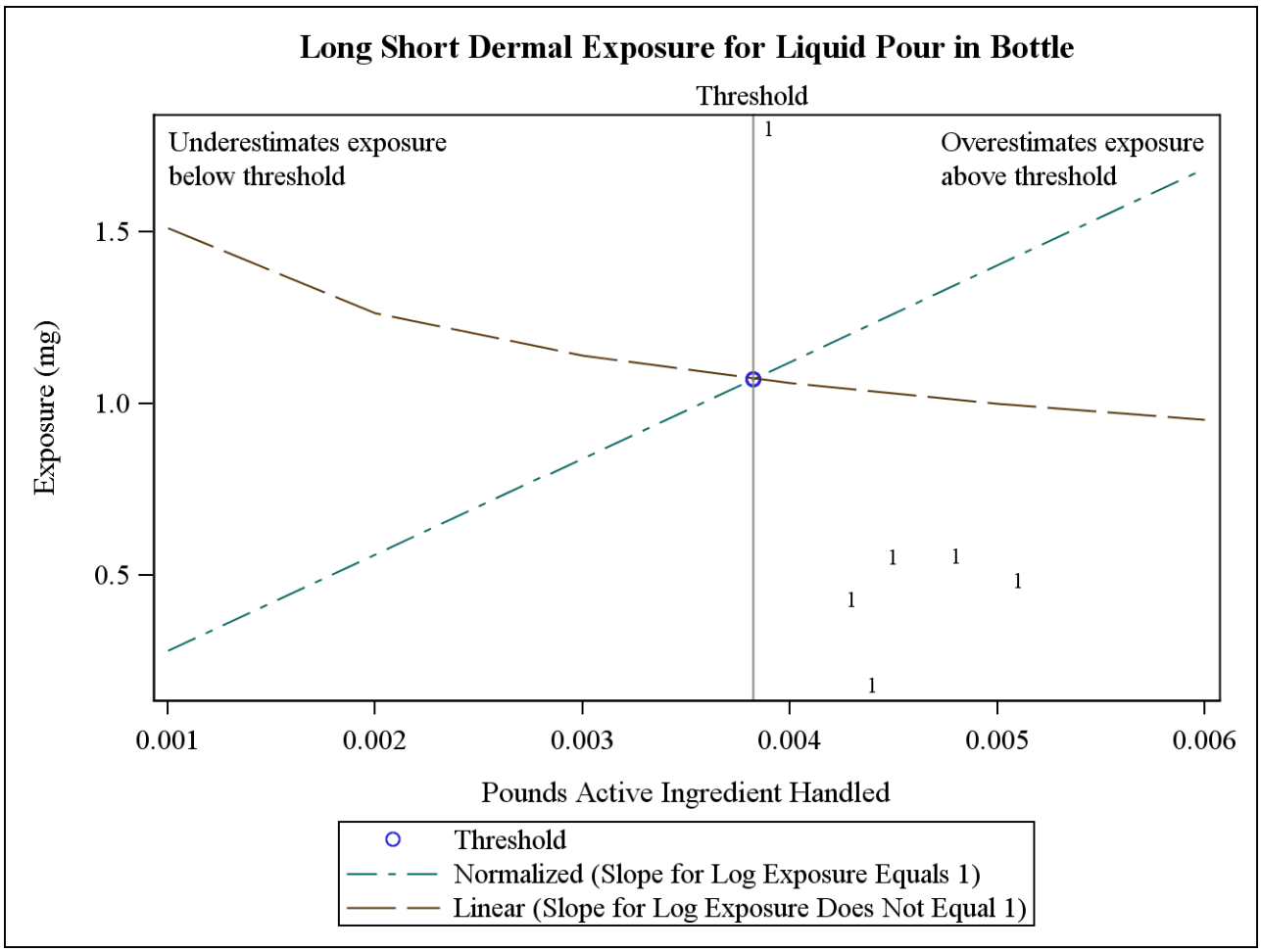

Long Short Dermal Exposure for Liquid Pour in Bottle
Threshold
Underestimates exposure
below threshold
Overestimates exposure
above threshold
1
1
1
1
1
1
1.5
1.0
0.5
Exposure (mg)
0.001
0.002
0.003
0.004
0.005
0.006
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 29

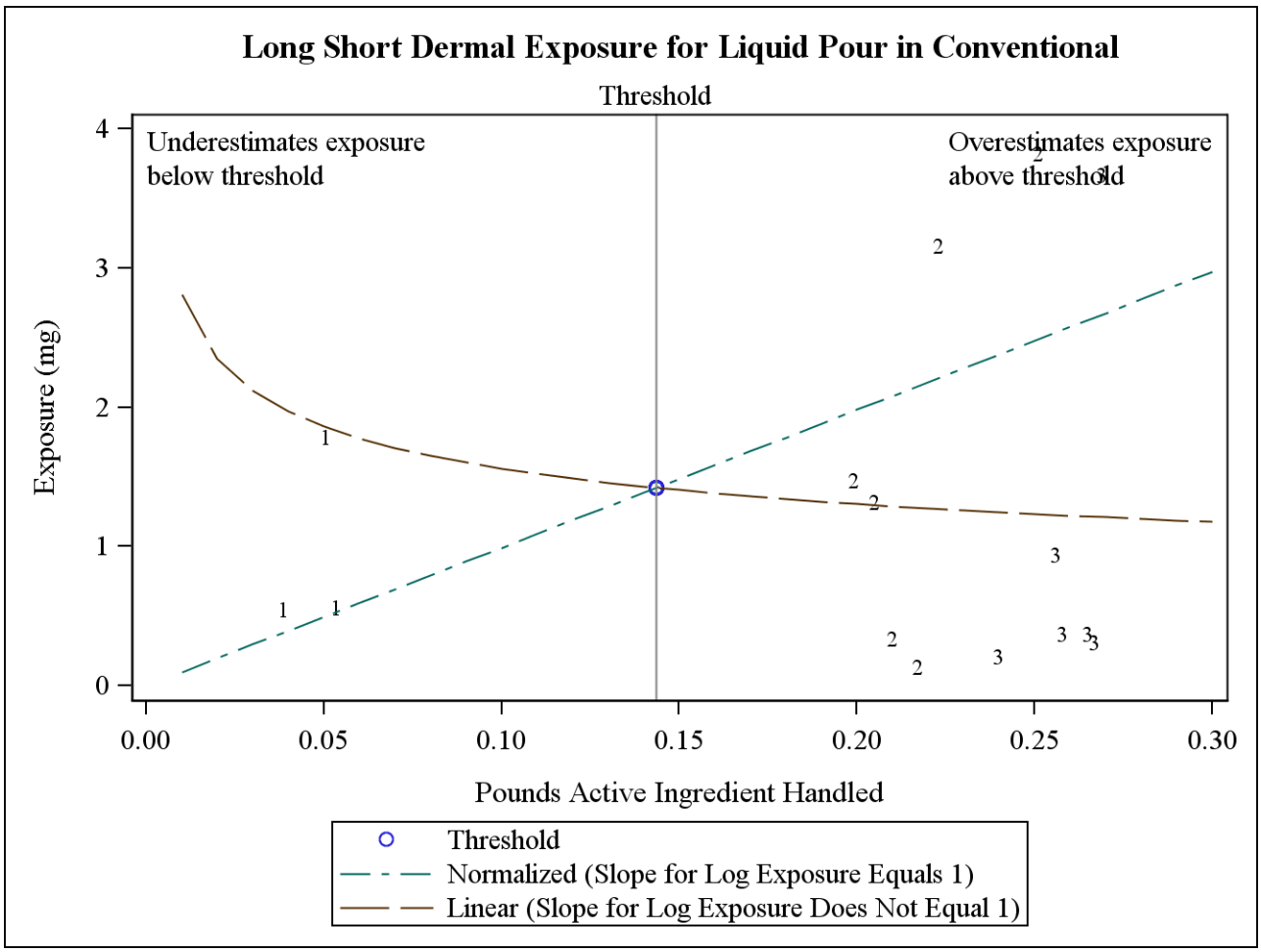

Long Short Dermal Exposure for Liquid Pour in Conventional
Threshold
Underestimates exposure
below threshold
Overestimates exposure
above threshold
Exposure (mg)
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 30

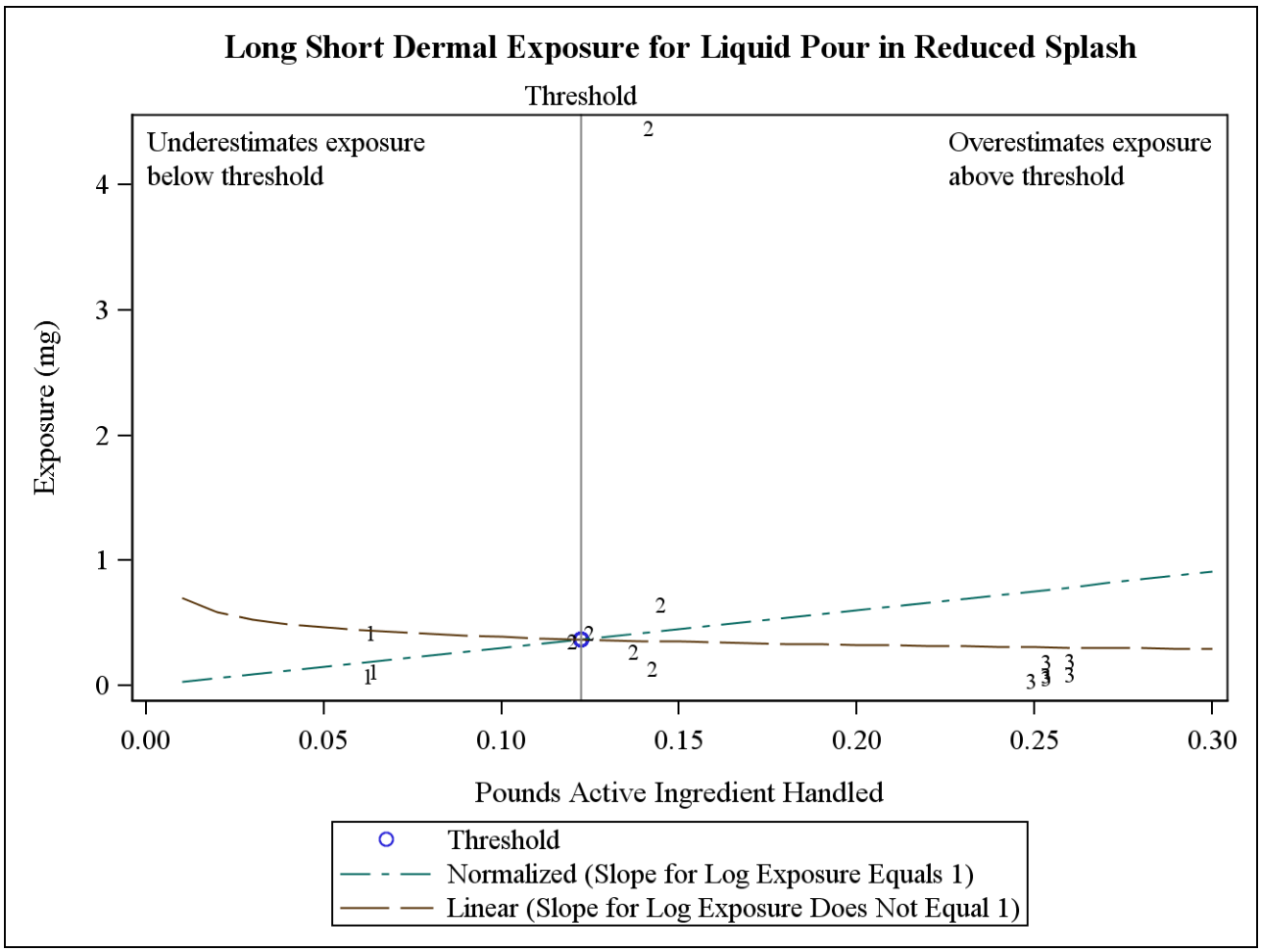

Long Short Dermal Exposure for Liquid Pour in Reduced Splash
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 31

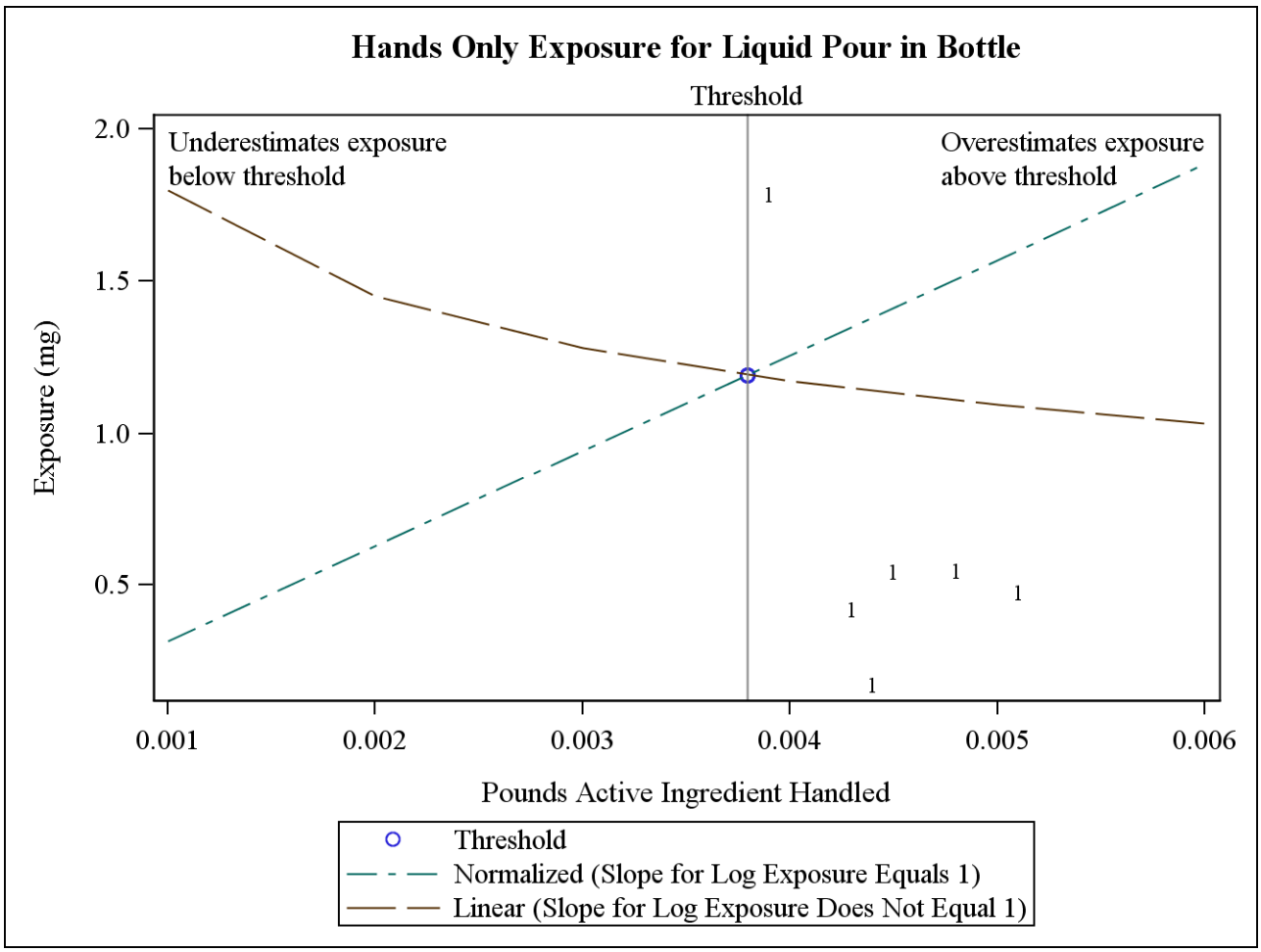

Hands Only Exposure for Liquid Pour in Bottle
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
2.0
1.5
1.0
0.5
0.001
0.002
0.003
0.004
0.005
0.006
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 32

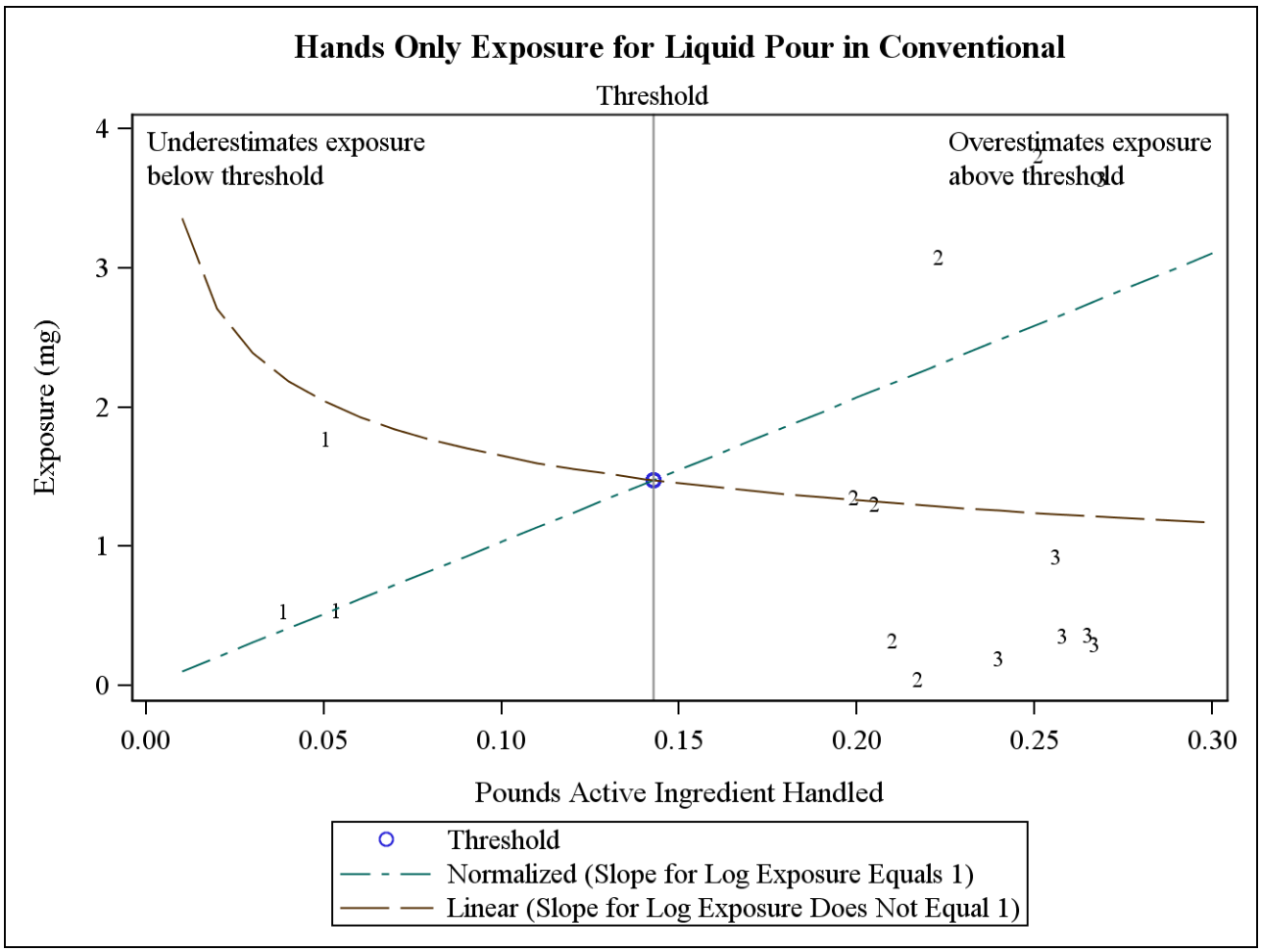

Hands Only Exposure for Liquid Pour in Conventional
Threshold
Underestimates exposure
below threshold
Overestimates exposure
above threshold
Exposure (mg)
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 33

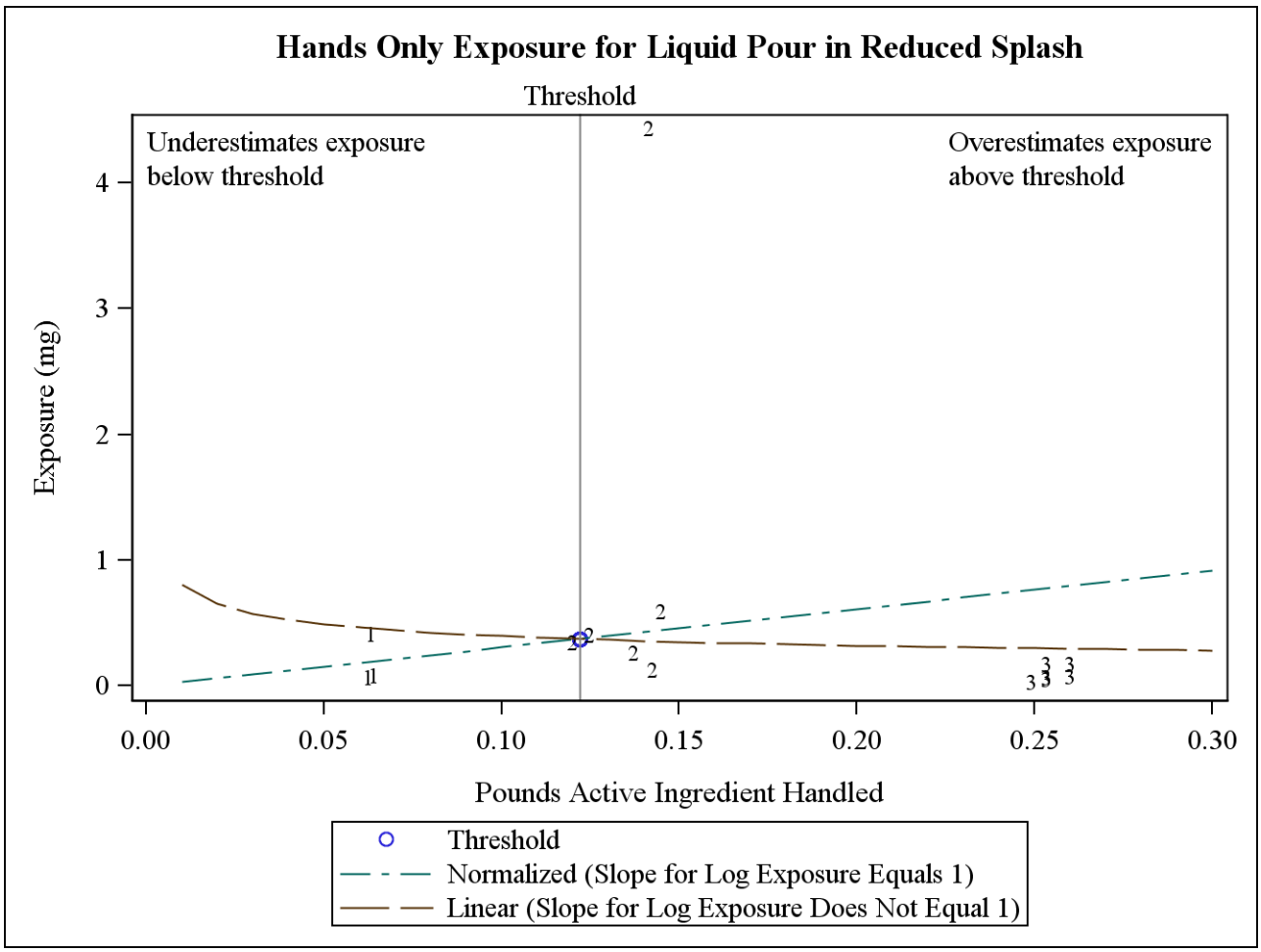

Hands Only Exposure for Liquid Pour in Reduced Splash
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0
1
2
3
4
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 34

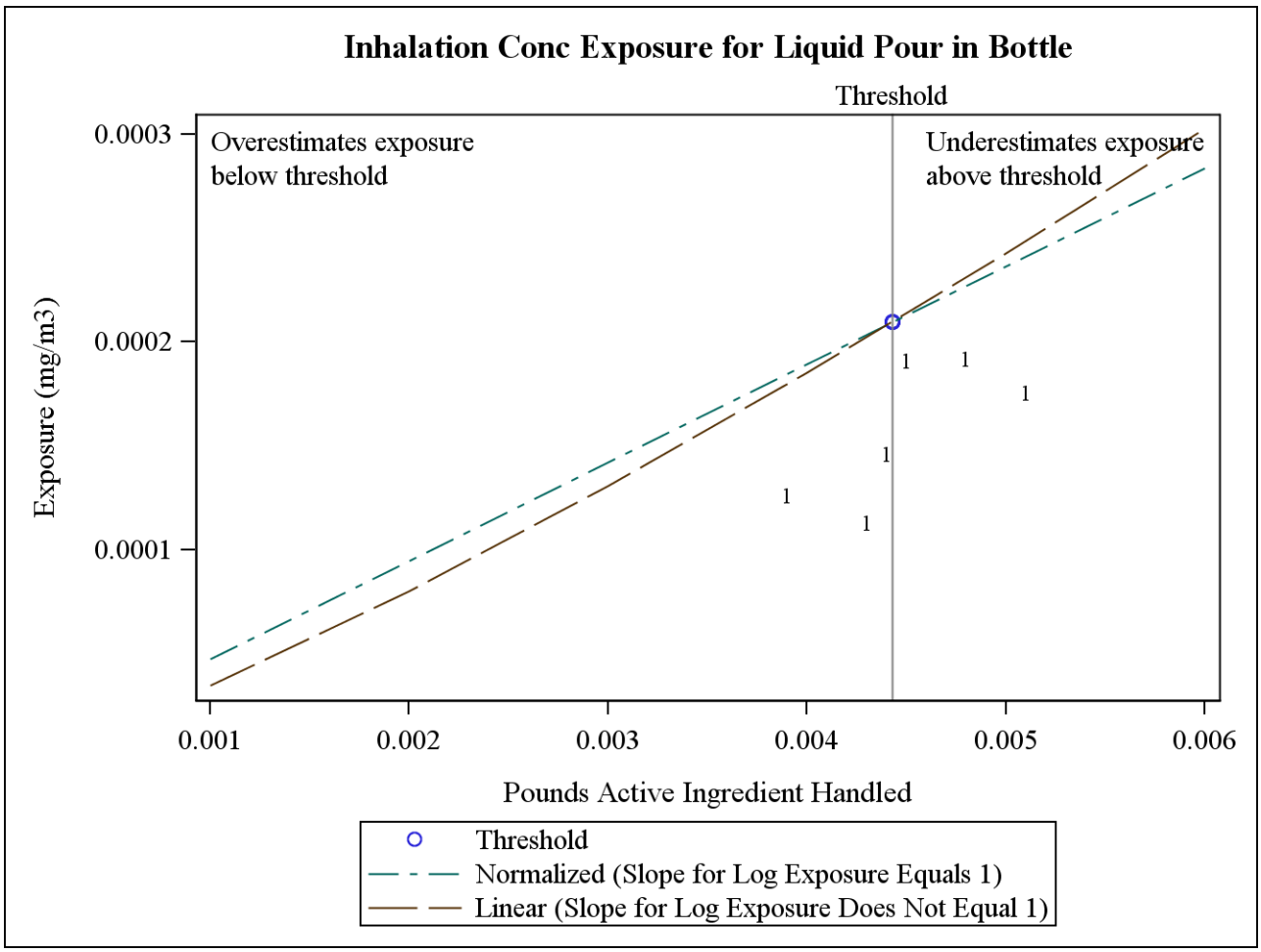

Inhalation Conc Exposure for Liquid Pour in Bottle
Threshold
Overestimates exposure below threshold
Underestimates exposure above threshold
0.0003
0.0002
0.0001
Exposure (mg/m3)
0.001
0.002
0.003
0.004
0.005
0.006
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 35

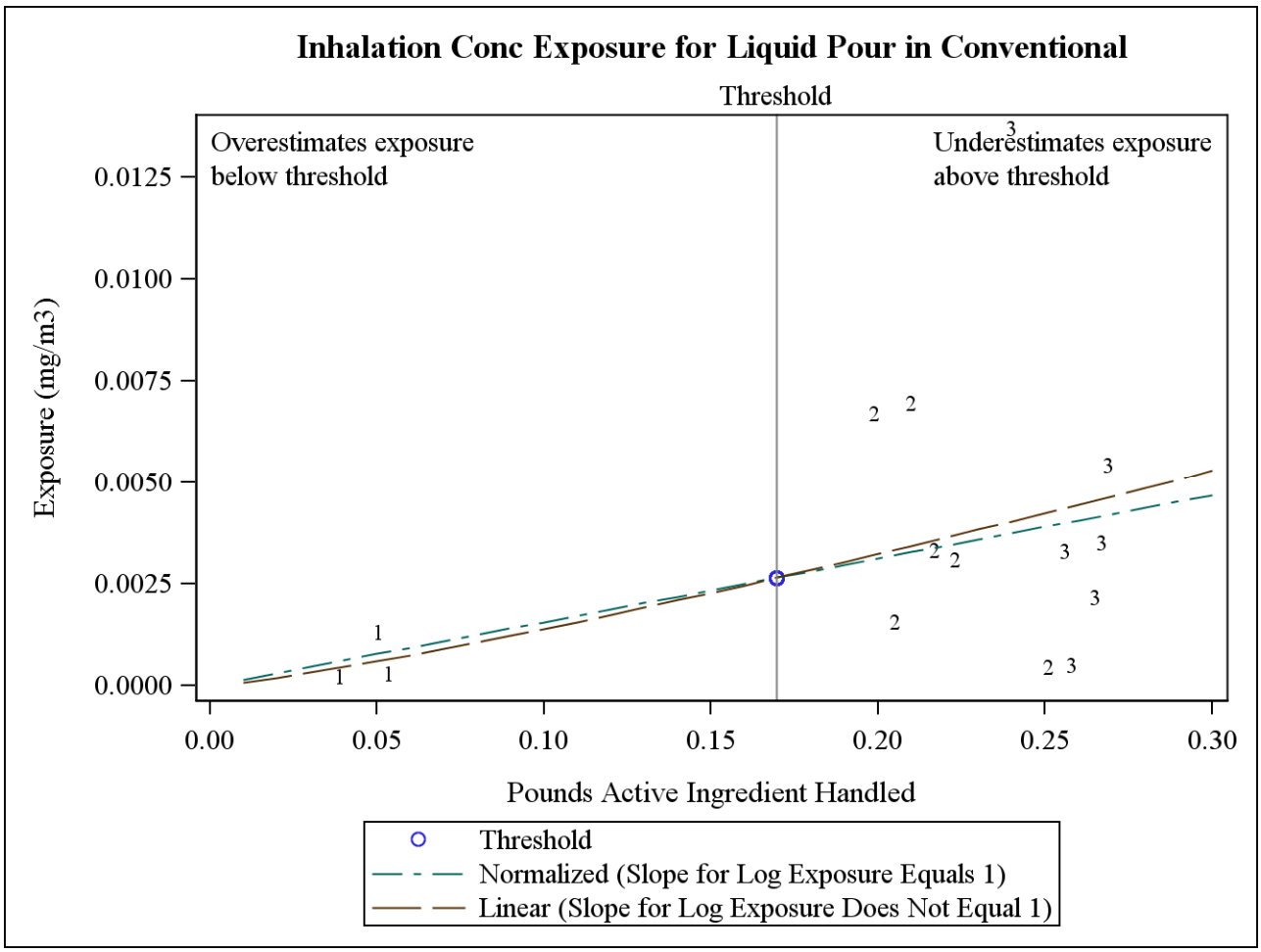

Inhalation Conc Exposure for Liquid Pour in Conventional
Threshold
Overestimates exposure
below threshold
Underestimates exposure
above threshold
Exposure (mg/m3)
0.0125
0.0100
0.0075
0.0050
0.0025
0.0000
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 36

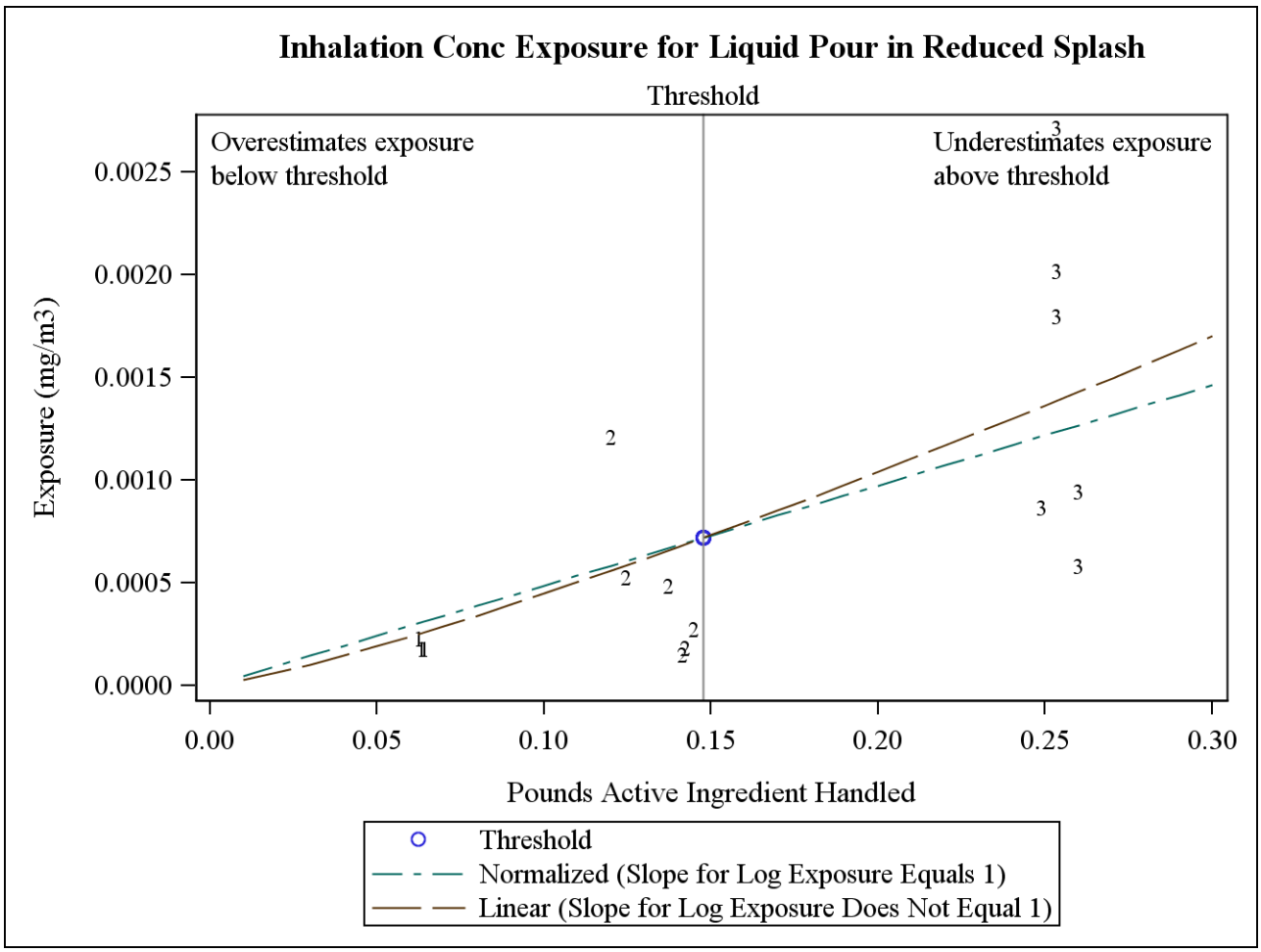

Inhalation Conc Exposure for Liquid Pour in Reduced Splash
Threshold
Overestimates exposure below threshold
Underestimates exposure above threshold
Exposure (mg/m3)
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 37

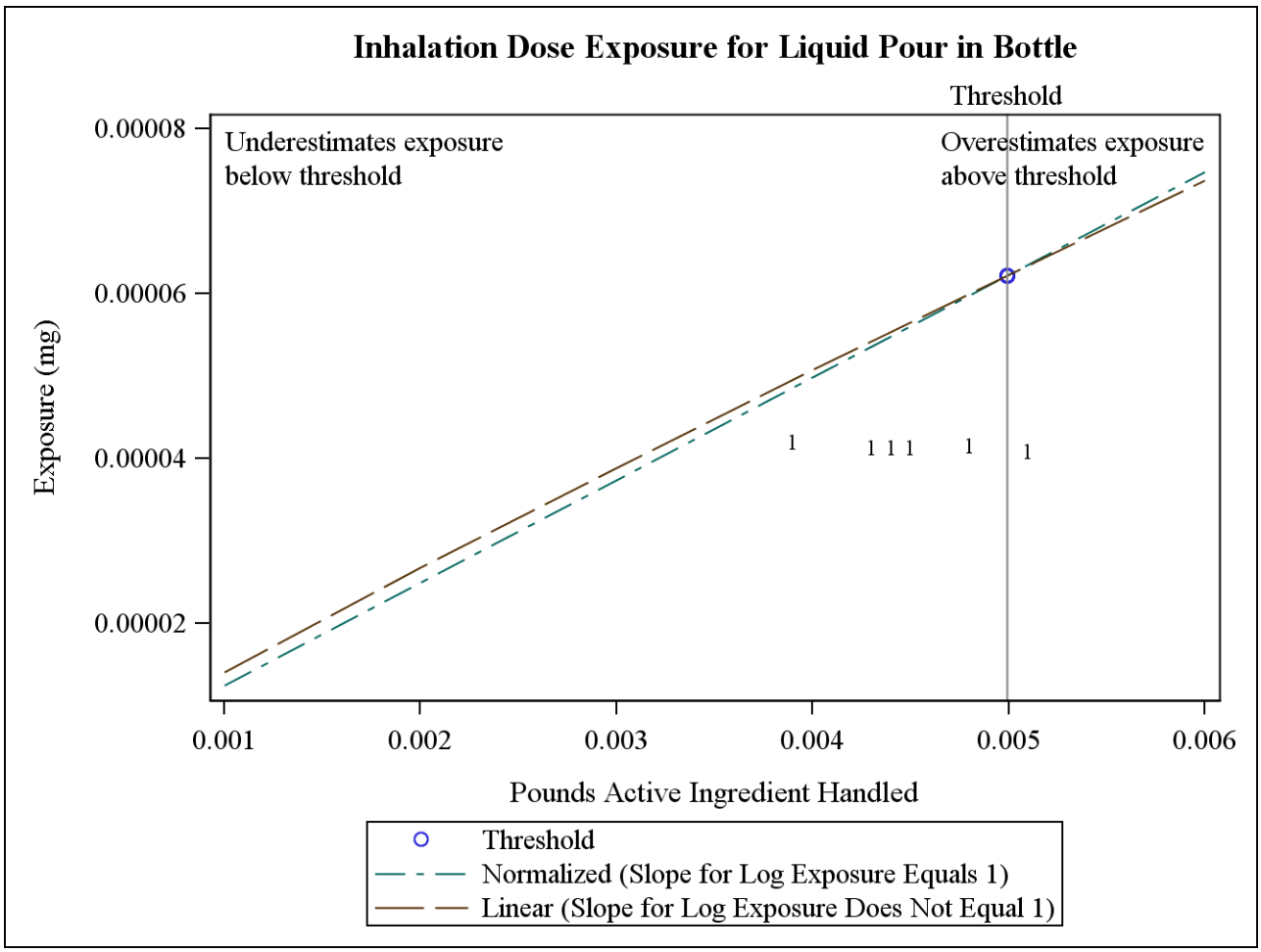

Inhalation Dose Exposure for Liquid Pour in Bottle
Threshold
Underestimates exposure
below threshold
Overestimates exposure
above threshold
0.00008
0.00006
0.00004
0.00002
Exposure (mg)
1
1 1 1
1
1
0.001
0.002
0.003
0.004
0.005
0.006
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 38

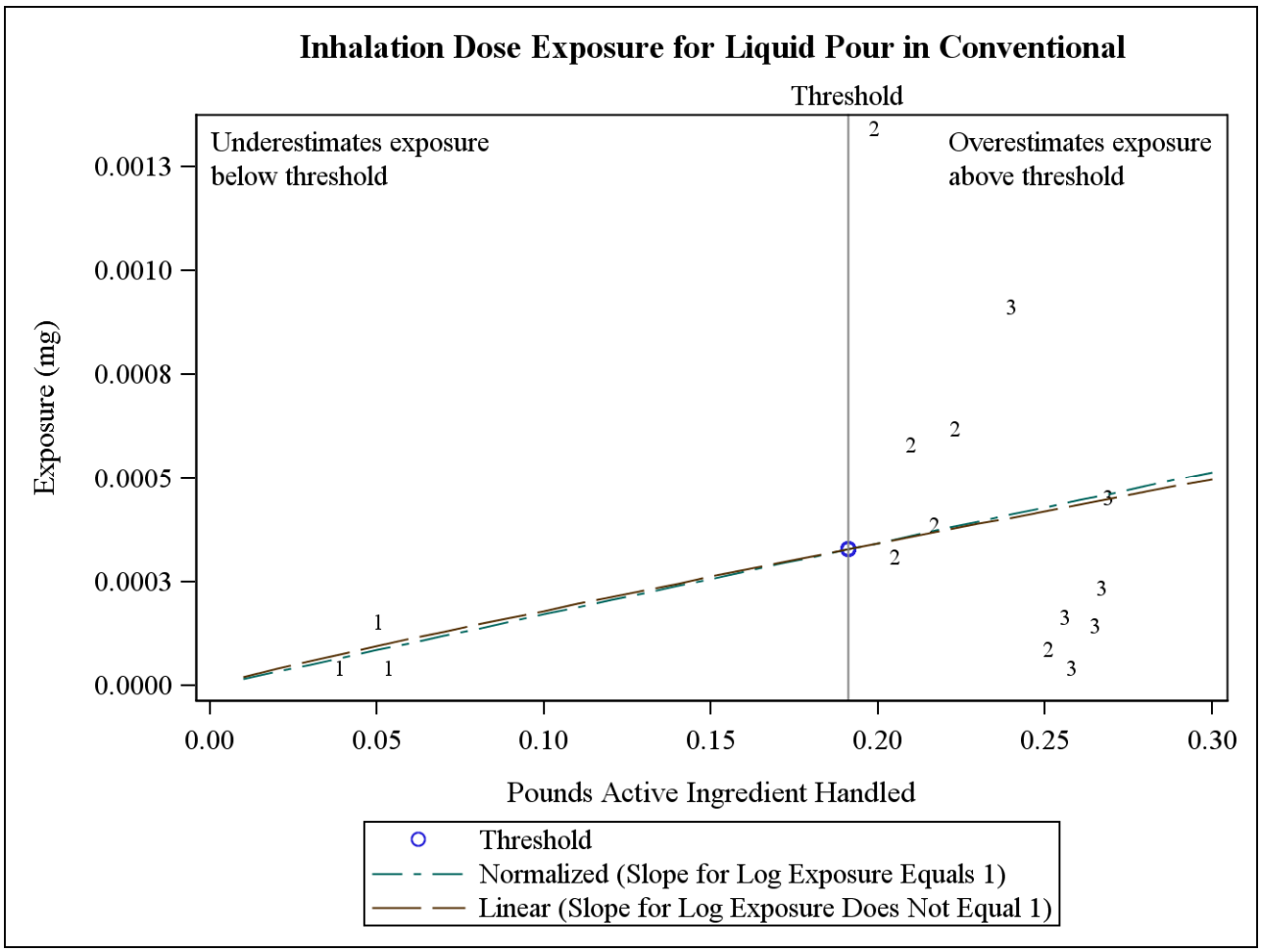

Inhalation Dose Exposure for Liquid Pour in Conventional
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0.0013
0.0010
0.0008
0.0005
0.0003
0.0000
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 39

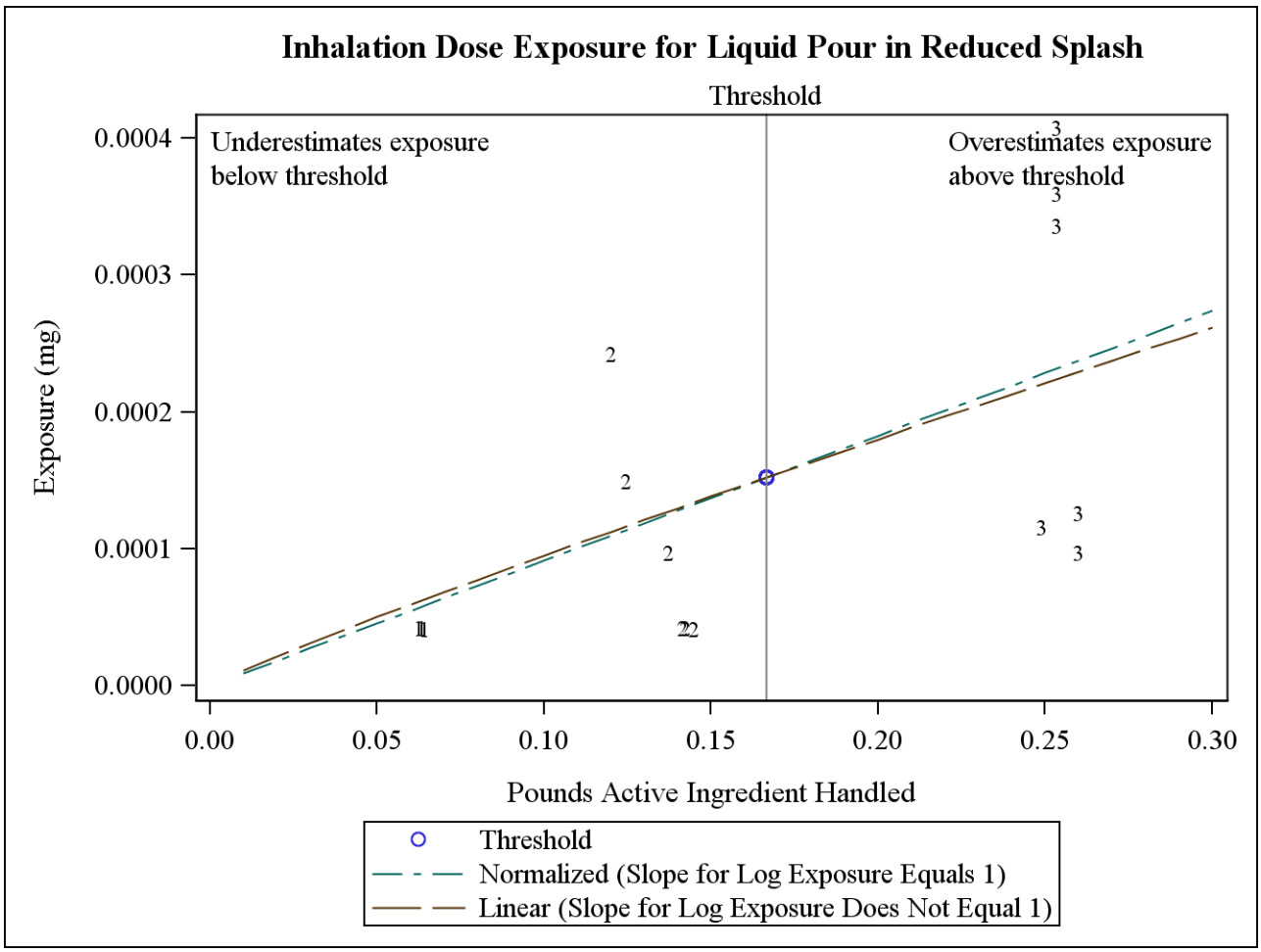

Inhalation Dose Exposure for Liquid Pour in Reduced Splash
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg)
0.0004
0.0003
0.0002
0.0001
0.0000
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 40

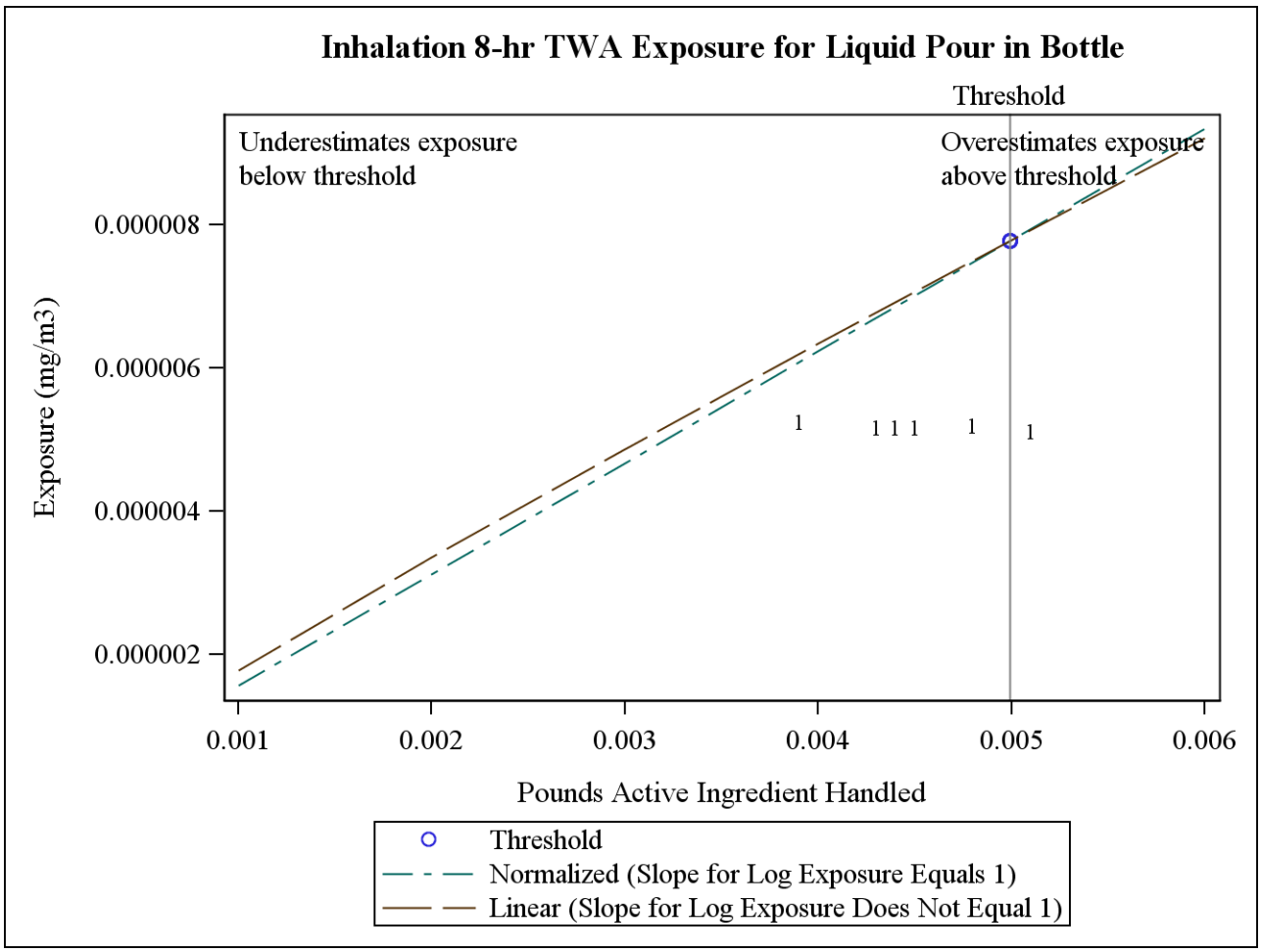

Inhalation 8-hr TWA Exposure for Liquid Pour in Bottle
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
0.000008
0.000006
0.000004
0.000002
Exposure (mg/m3)
1
1 1 1
1
1
0.001
0.002
0.003
0.004
0.005
0.006
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 41

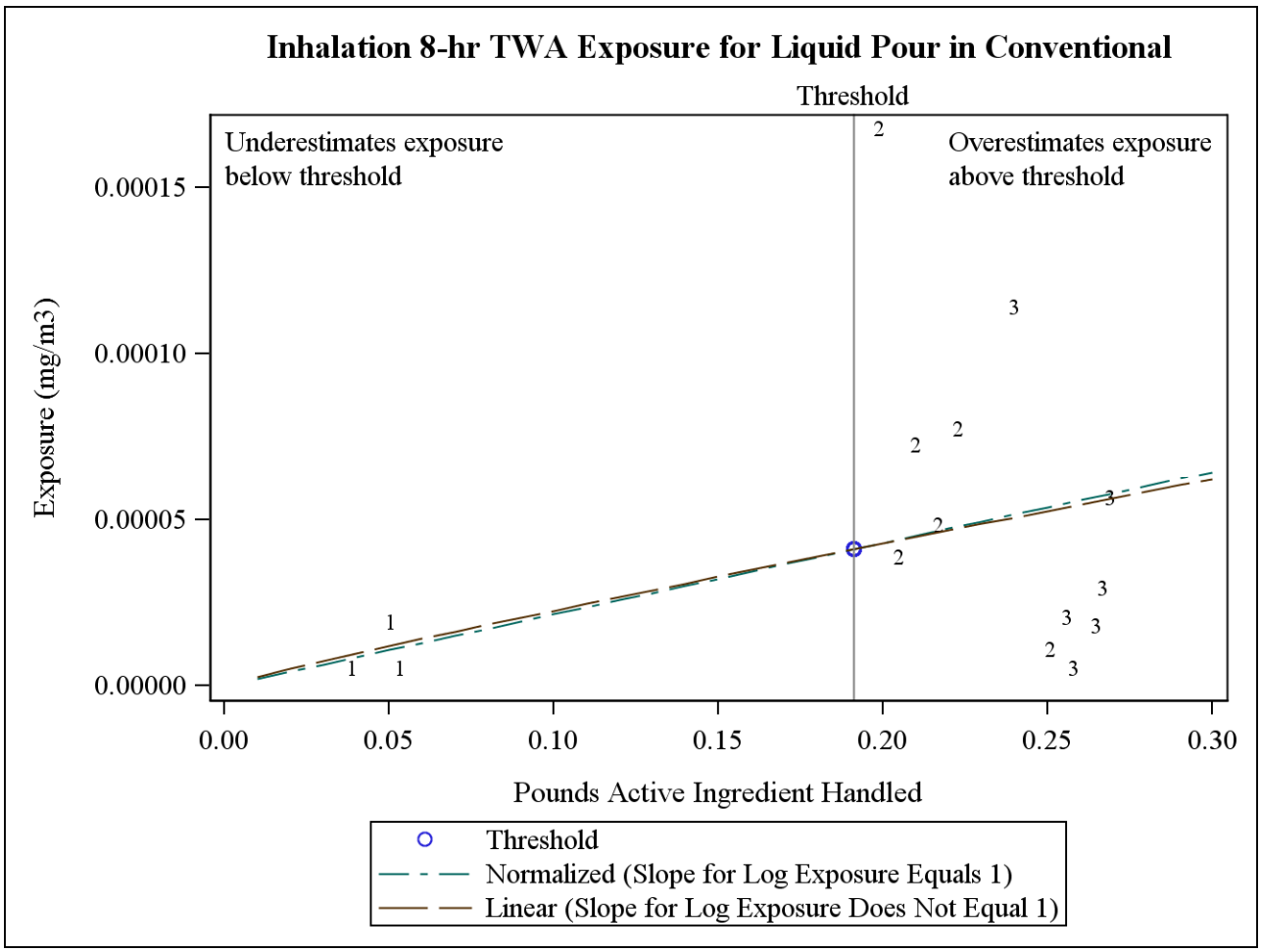

Inhalation 8-hr TWA Exposure for Liquid Pour in Conventional
Threshold
Underestimates exposure below threshold
Overestimates exposure above threshold
Exposure (mg/m3)
0.00015
0.00010
0.00005
0.00000
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Pounds Active Ingredient Handled
Threshold
Normalized (Slope for Log Exposure Equals 1)
Linear (Slope for Log Exposure Does Not Equal 1)

Figure 42

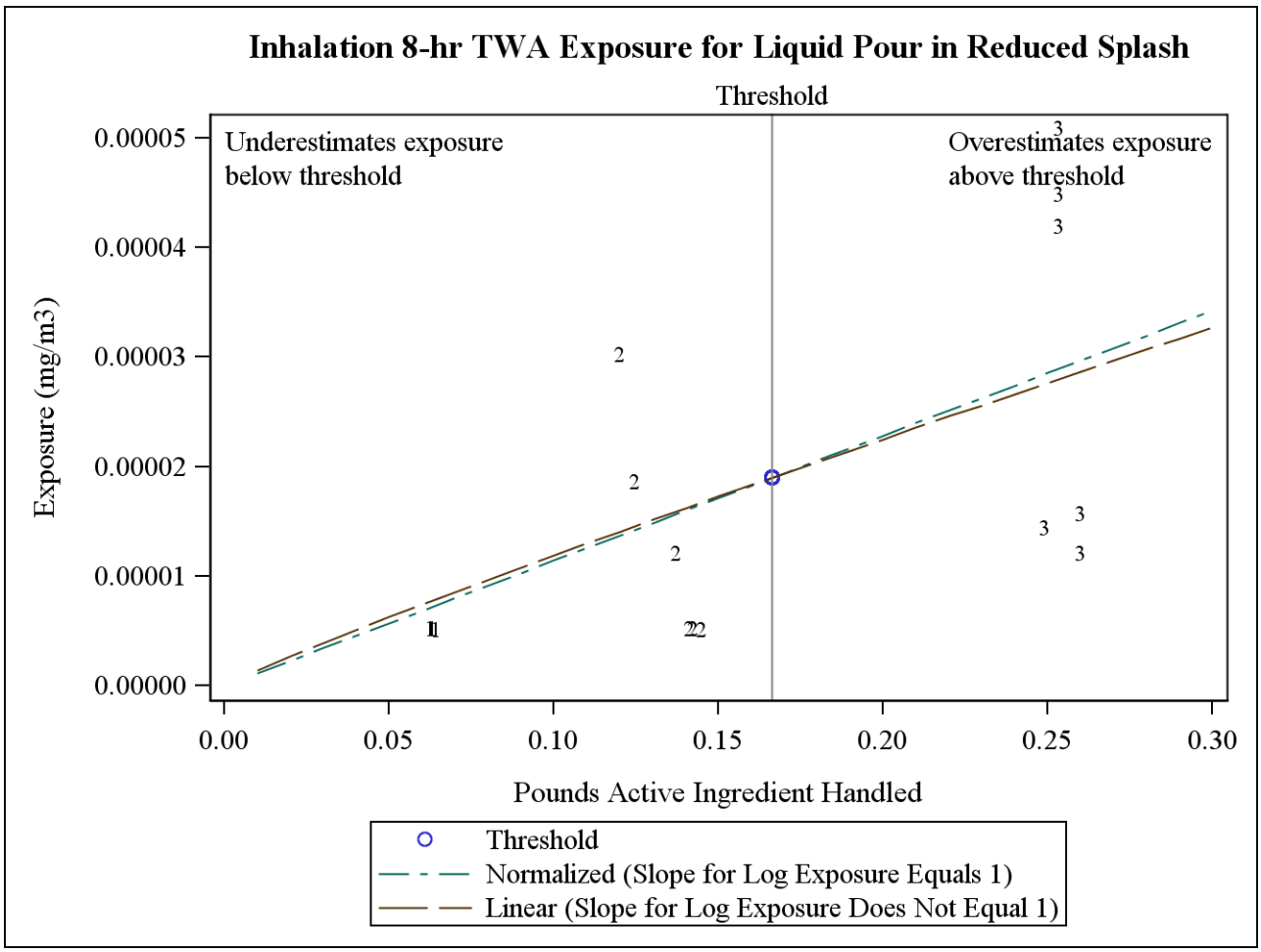


Figure 43

Alternative models for dermal exposure

As discussed above, the dermal exposure estimates show some unexpected patterns, with estimated arithmetic means that are higher for Long Dermal than for Long Short Dermal or higher for Long Short Dermal than for Short Dermal, and with some negative slopes or slopes very close to zero. Although the true arithmetic means must increase between Long Dermal, Long Short Dermal and Short Dermal (since the outer dosimeter values for the lower arm and lower leg are added), the estimated arithmetic means from the fitted models do not necessary increase. A negative slope is unexpected since that implies that the exposure decreases if the amount of active ingredient increases, which also seems counter-intuitive. To further investigate these findings we re-fitted the three original models after excluding some outlier values and also investigated alternative models for the slopes of the log-log-linear models.

Three alternative sets of outliers were considered:

- No outliers
- Three outliers. These potential outliers are for Reduced Splash ME 1 in group 1a, Reduced Splash ME 7 in group 2, and Conventional Pour ME 6 in group 1b. These are three cases where the hands only exposure normalized by the amount of active ingredient is unusually high compared to other MEs in the same group.
- Four outliers. These potential outliers are for Reduced Splash ME 1 in group 1a, Reduced Splash ME 7 in group 2, Conventional Pour ME 6 in group 1b, and Conventional Pour ME 10 in group 2. The first three are cases

where the hands only exposure normalized by the amount of active ingredient is unusually high compared to other MEs in the same group. The last case is where the hands only exposure is extremely low compared to the other hands only measurements in group 2 but the outer dosimeter for the lower arm is higher than the hands only measurement.

Table 23 shows the arithmetic and geometric means of the unit exposure for each clothing scenario and group calculated using the empirical, log-normal simple random sampling, and mixed models after excluding these sets of outliers. For each group and data set, the arithmetic and geometric means from the empirical model (AMs and GMs) increase between Long Dermal, Long Short Dermal, and Short Dermal. For the lognormal model, the arithmetic mean AMu is estimated as GMs×exp(GSDs) where GSDs is the empirical geometric standard deviation. Although the GMs increases between Long Dermal, Long Short Dermal, and Short Dermal, the GSDs and hence the arithmetic mean GMu can decrease. The estimated arithmetic means from the lognormal model increase as expected between Long Dermal, Long Short Dermal, and Short Dermal when the four outliers are excluded. For the mixed model it is possible that neither the arithmetic mean AMm nor the geometric mean GMm increase as expected. The estimated geometric means from the lognormal model increase as expected when the three or four outliers are excluded, but the estimated arithmetic means did not consistently increase as expected.

This statistical finding can be regarded as a statistical "quirk" of the fitted statistical models since the differences between the three dermal unit exposure arithmetic and geometric mean estimates are small when compared to their uncertainty (as illustrated in the wide parametric bootstrap confidence intervals displayed in Tables 9, 12, 13, and 14 above). The dermal exposure for this liquid pour scenario is dominated by the hands only exposure, but the outer dosimeter values for the lower arm and lower leg vary considerably.

Table 23. Dermal unit exposure (mg/lb AI) arithmetic means and geometric means using alternative statistical models and removing zero, three, or four outliers.

Clothing	**Data**	**Group**	**Arithmetic Mean**			**Geometric Mean**	
			Empirical	**Lognormal**	**Mixed**	**Empirical**	**Mixed**
			AMs	**AMu**	**AMm**	**GMs**	**GMm**
Long Dermal	No outliers	Bottle	155.2511	158.0606	298.4676	116.1970	119.9586
Long Short Dermal	No outliers	Bottle	155.8029	158.5404	280.7180	116.6646	121.5849
Short Dermal	No outliers	Bottle	157.7836	160.7434	207.3503	118.5562	108.1348
Long Dermal	No outliers	Conventional	8.3529	10.9082	9.9637	4.1123	4.0046
Long Short Dermal	No outliers	Conventional	8.4623	10.0848	9.9085	4.4159	4.2916
Short Dermal	No outliers	Conventional	9.0506	10.7192	9.0011	4.6348	4.6941
Long Dermal	No outliers	Reduced Splash	3.7373	3.6006	3.1400	1.2447	1.2620
Long Short Dermal	No outliers	Reduced Splash	3.7864	3.6543	3.0301	1.2967	1.3124
Short Dermal	No outliers	Reduced Splash	4.2148	3.6551	3.9898	2.0312	2.0807
Long Dermal	Remove 3 outliers	Bottle	94.4075	97.6548	177.5334	88.2638	88.5023

Clothing	Data	Group	Arithmetic Mean			Geometric Mean	
			Empirical	Lognormal	Mixed	Empirical	Mixed
			AMs	AMu	AMm	GMs	GMm
Long Short Dermal	Remove 3 outliers	Bottle	94.7334	97.9490	166.1035	88.6254	89.0304
Short Dermal	Remove 3 outliers	Bottle	96.4299	99.7846	142.2019	90.2199	89.7684
Long Dermal	Remove 3 outliers	Conventional	6.4343	8.3406	7.0752	3.5275	3.5271
Long Short Dermal	Remove 3 outliers	Conventional	6.5494	7.7556	7.1010	3.8070	3.8061
Short Dermal	Remove 3 outliers	Conventional	6.8408	8.0949	6.3627	3.9736	4.0166
Long Dermal	Remove 3 outliers	Reduced Splash	1.7623	2.0198	1.9827	0.9884	0.9884
Long Short Dermal	Remove 3 outliers	Reduced Splash	1.8084	2.0722	1.9260	1.0325	1.0323
Short Dermal	Remove 3 outliers	Reduced Splash	2.2127	2.2907	2.6401	1.6672	1.6666
Long Dermal	Remove 4 outliers	Bottle	94.4075	97.6548	159.0276	88.2638	88.2638
Long Short Dermal	Remove 4 outliers	Bottle	94.7334	97.9490	158.5748	88.6254	88.6254
Short Dermal	Remove 4 outliers	Bottle	96.4299	99.7846	135.8073	90.2199	90.1188
Long Dermal	Remove 4 outliers	Conventional	6.9103	8.0051	7.7983	4.3282	4.3282
Long Short Dermal	Remove 4 outliers	Conventional	7.0070	8.1406	7.8506	4.3876	4.3876
Short Dermal	Remove 4 outliers	Conventional	7.3203	8.4728	6.9460	4.5907	4.6092
Long Dermal	Remove 4 outliers	Reduced Splash	1.7623	2.0198	1.7809	0.9884	0.9884
Long Short Dermal	Remove 4 outliers	Reduced Splash	1.8084	2.0722	1.8475	1.0325	1.0325
Short Dermal	Remove 4 outliers	Reduced Splash	2.2127	2.2907	2.5096	1.6672	1.6653

The mixed log-log-linear model used to estimate the slopes was of the form:

Log (Exposure) = Group Intercept + Slope1 × Log (Pounds of Active Ingredient) + Worker1 + Error1 (1)

Worker1 is a normally distributed random effect variable with independent, identically distributed values for each worker, and Error1 is a normally distributed error variable with independent, identically distributed values for each total exposure measurement. The group intercept varies with the group. The slope, denoted here as Slope1, and the Worker1 variance, and Error1 variance are each assumed to be the same for each group.

Since the mixed model produced negative and small slope estimates for the dermal exposures, we investigated the following alternative models:

Log (Exposure) = Group Intercept + Group Slope2 × Log (Pounds of Active Ingredient) + Worker2 + Error2 (2)

Worker2 is a normally distributed random effect variable with independent, identically distributed values for each worker, and Error2 is a normally distributed error variable with independent, identically distributed values for each total exposure measurement. The group intercept and group slope Slope2 each vary with the group. The slope, denoted here as Slope2, and the Worker2 variance, and Error2 variance are each assumed to be the same for each group.

Log (Exposure) = Group Intercept + Group Slope3 × Log (Pounds of Active Ingredient) + Error3 (3)

Error3 is a normally distributed error variable with independent, identically distributed values for each total exposure measurement. The group intercept, group slope Slope3, and Error3 variance each vary with the group.

The difference between models 2 and 3 is that in model 2 the variances of worker and error are assumed to be the same across all there groups, but in model 3 there is no worker error and the error variances can be different for the different groups. Model 3 is exactly the same as assuming that for each group we have the simple linear regression model:

Log (Exposure) = Intercept + Slope × Log (Pounds of Active Ingredient) + Error

Table 24 shows the estimated slopes and 95% confidence intervals for these three models for each clothing scenario and group after excluding each of the three sets of outliers. If no outliers are removed, then all the estimated slopes are negative except for a small positive slope for model 3, Short Dermal, in the Reduced Splash group. Compared to model 1, the group-specific slopes in models 2 and 3 have wider confidence intervals and are much more negative for the Bottle group and are more negative for Reduced Splash (except for model 3, Short Dermal). After excluding three or four outliers, the slopes are still negative for model 1, but the slopes become positive and very large (about 3) with very wide confidence intervals for Bottle and become small (about 0.2) for Conventional. After removing three or four outliers, the slopes in models 2 and 3 are about -0.5 and significantly lower than 1 for Reduced Splash Long Dermal and Long Short Dermal.

For the Bottle and Conventional groups, after decreasing the amount of data (by removing outliers) and increasing the number of parameters (by allowing the slope to vary with the group), the confidence intervals for the slope become wide enough that neither the log-log-linearity with slope 1 assumption nor the independence assumption can be rejected. For Reduced Splash, the log-log-linearity with slope 1 assumption is rejected and the independence assumption is not rejected in all cases. The finding that these data support independence of exposure and the amount of active ingredient for dermal exposure is likely to be due to the fact that for this scenario, the bulk of the dermal exposure occurs due to accidental splashes and spills on the hands.

Table 24. Dermal exposure (mg) versus pounds of active ingredient estimated log-log-linear slopes using alternative statistical models and removing zero, three, or four outliers.

Clothing	**Data**	**Group**	**Slope1**			**Slope2**			**Slope3**		
			Estimate	**Lower**	**Upper**	**Estimate**	**Lower**	**Upper**	**Estimate**	**Lower**	**Upper**
Long Dermal	No outliers	Bottle	-0.28	-1.06	0.49	-2.05	-14.03	9.92	-3.49	-13.47	6.50
Long Short Dermal	No outliers	Bottle	-0.26	-0.99	0.48	-2.04	-13.35	9.28	-3.49	-13.45	6.47
Short Dermal	No outliers	Bottle	-0.04	-0.68	0.60	-3.35	-13.14	6.44	-3.31	-13.37	6.76
Long Dermal	No outliers	Conventional	-0.28	-1.06	0.49	-0.09	-1.06	0.89	-0.07	-1.12	0.98
Long Short Dermal	No outliers	Conventional	-0.26	-0.99	0.48	-0.05	-0.97	0.87	-0.04	-0.99	0.91

Clothing	Data	Group	Slope1			Slope2			Slope3		
			Estimate	Lower	Upper	Estimate	Lower	Upper	Estimate	Lower	Upper
Short Dermal	No outliers	Conventional	-0.04	-0.68	0.60	-0.07	-0.87	0.73	-0.04	-1.00	0.91
Long Dermal	No outliers	Reduced Splash	-0.28	-1.06	0.49	-0.61	-1.84	0.63	-0.57	-1.90	0.76
Long Short Dermal	No outliers	Reduced Splash	-0.26	-0.99	0.48	-0.60	-1.77	0.57	-0.57	-1.88	0.74
Short Dermal	No outliers	Reduced Splash	-0.04	-0.68	0.60	-0.03	-1.04	0.97	0.04	-1.03	1.11
Long Dermal	Remove 3 outliers	Bottle	-0.14	-0.84	0.56	2.97	-12.27	18.20	2.97	-8.32	14.25
Long Short Dermal	Remove 3 outliers	Bottle	-0.13	-0.78	0.52	2.95	-11.15	17.05	2.95	-8.28	14.18
Short Dermal	Remove 3 outliers	Bottle	0.14	-0.50	0.78	2.96	-11.02	16.94	3.28	-7.79	14.35
Long Dermal	Remove 3 outliers	Conventional	-0.14	-0.84	0.56	0.16	-0.81	1.12	0.16	-1.09	1.40
Long Short Dermal	Remove 3 outliers	Conventional	-0.13	-0.78	0.52	0.18	-0.71	1.08	0.18	-0.93	1.30
Short Dermal	Remove 3 outliers	Conventional	0.14	-0.50	0.78	0.19	-0.70	1.07	0.19	-0.93	1.31
Long Dermal	Remove 3 outliers	Reduced Splash	-0.14	-0.84	0.56	-0.52	-1.58	0.54	-0.52	-1.48	0.43
Long Short Dermal	Remove 3 outliers	Reduced Splash	-0.13	-0.78	0.52	-0.52	-1.50	0.46	-0.52	-1.45	0.41
Short Dermal	Remove 3 outliers	Reduced Splash	0.14	-0.50	0.78	0.08	-0.89	1.05	0.08	-0.61	0.78
Long Dermal	Remove 4 outliers	Bottle	-0.10	-0.73	0.53	2.97	-10.59	16.52	2.97	-8.32	14.25
Long Short Dermal	Remove 4 outliers	Bottle	-0.10	-0.72	0.52	2.95	-10.48	16.38	2.95	-8.28	14.18
Short Dermal	Remove 4 outliers	Bottle	0.18	-0.42	0.78	3.28	-8.85	15.41	3.28	-7.79	14.35
Long Dermal	Remove 4 outliers	Conventional	-0.10	-0.73	0.53	0.24	-0.62	1.10	0.24	-0.81	1.29
Long Short Dermal	Remove 4 outliers	Conventional	-0.10	-0.72	0.52	0.24	-0.61	1.09	0.24	-0.81	1.29
Short Dermal	Remove 4 outliers	Conventional	0.18	-0.42	0.78	0.25	-0.52	1.02	0.25	-0.80	1.30
Long Dermal	Remove 4 outliers	Reduced Splash	-0.10	-0.73	0.53	-0.52	-1.47	0.42	-0.52	-1.48	0.43
Long Short Dermal	Remove 4 outliers	Reduced Splash	-0.10	-0.72	0.52	-0.52	-1.46	0.41	-0.52	-1.45	0.41
Short Dermal	Remove 4 outliers	Reduced Splash	0.18	-0.42	0.78	0.08	-0.76	0.93	0.08	-0.61	0.78