MEMORANDUM

To:	Timothy Leighton, EPA; Kathryn Korthauer, EPA
From:	Jonathan Cohen, ICF
Date:	September 11, 2021
Re:	Statistical Review of the AEATF II Immersion Dip Soak Study

1. Introduction and Summary

In May 2021, AEATF II submitted the final report for their study AEA12 "A Study for Measurement of Potential Dermal and Inhalation Exposure During Antimicrobial Applications Involving Immersion, Dip, and Soak." ICF was asked by EPA to analyze the immersion dip soak study data to investigate the relationship between dermal and inhalation exposures and the pesticide product usage when professionals conduct manual immersion/dipping/soaking (IDS) of articles, equipment, and/or utensils into solutions containing an antimicrobial and the immersion/dip/soak of a rag or sponge into a bucket containing an antimicrobial to sanitize hard surfaces. This was a scripted occupational monitoring study conducted at simulated work sites containing a variety of equipment, surfaces, and articles that were immersed.

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 report for the main study describes the experimental study methodology and the measurements in detail. Briefly, the study was carried out as three IDS scenarios that each represented a different immersion, dip, soak activity. As summarized in the main study report, the three scenarios were:

- Bucket: Bucket & rag/sponge (dipping a rag or sponge into a diluted sanitizing solution in a bucket or pail, wringing out the rag/sponge, and wiping hard surfaces): professional workers, short-sleeved shirts and long pants, no gloves worn. This study was carried out at 3 locations in the Orlando, Florida area using 18 volunteer subjects working in the food service and janitorial / cleaning industries. The 18 subjects were randomly assigned into three groups of 6 subjects (MEs) where the target total quat concentrations were 1,760, 880, and 440 ppm, respectively. Within each group of 6 subjects, half the subjects were randomly assigned to a target sampling duration of 20 minutes and the other half were assigned to a target sampling duration of 60 minutes.

- Sink: 3-compartment sink in the food service industry (manual washing, rinsing, and sanitizing of cookware/bakeware in commercial 3-compartment sinks): professional workers, short-sleeved shirts and long pants, no gloves worn. This study was carried out at three locations in the Orlando, Florida area using 18 volunteer subjects working in the food service and janitorial / cleaning industries. The 18 subjects were randomly assigned into three groups of 6 subjects (MEs) where the target total quat concentrations were 1,000, 600, and 100 ppm, respectively. Within each group of 6 subjects, half the subjects were randomly assigned to a target sampling duration of 60 minutes and the other half were assigned to a target sampling duration of 120 minutes.

- COP: Clean-Out-of-Place (COP) tank in the food processing industry (using a stainless-steel COP tank to clean and sanitize industrial equipment parts): professional workers, long-sleeved shirts and long pants, chemical-resistant gloves worn. This study was carried out at a single location in the Madison, Wisconsin area using 18 volunteer subjects with occupational experience in the food processing and dairy industries. The 18 subjects were randomly assigned into three groups of 6 subjects (MEs) where the target total quat concentrations were 1,000, 600, and 100 ppm, respectively. Within each group of 6 subjects, half the subjects were randomly assigned to do one cleaning cycle (duration about 60 minutes) and the other half were assigned to do two cleaning cycles (duration about 120 minutes).

In this memorandum, for each scenario, the main analyses use data from all 18 MEs in the three total quat concentration groups. For some analyses, we also present separate analyses for the 6 MEs in each total quat concentration group; detailed results by groups are available upon request.

The statistical analyses presented in this memorandum only use the exposure measurements, the quat concentrations, and the sampling durations. To make the analyses simpler and less voluminous, the statistical analyses did not take into account possible site effects for the Bucket and Sink scenarios, which might suggest the use of a mixed model with random site effects. For dermal exposure, the statistical analyses used the measured C14-ADBAC exposures. For inhalation exposure, the statistical analyses used the measured DDAC exposures, since all of the C14-ADBAC inhalation exposure data from the Bucket and Sink scenario, as well as a third of the C14-ADBAC inhalation exposure data from the COP scenario, was below the level of detection.

We considered three alternative approaches for normalizing the exposures, the unnormalized exposure (corresponding to a normalizing factor of 1), the exposure divided by the pesticide concentration (C14-ADBAC for dermal and DDAC for inhalation), and the exposure divided by the product of the pesticide concentration and the sampling duration (C14-ADBAC times the duration for dermal and DDAC times the duration for inhalation). The study report used the unnormalized exposure values. In the main memorandum we present the results for the exposure normalized by the product of the pesticide concentration and the sampling duration. Reasons for this choice include the desire to account for the sample duration, the desire to use a reasonable surrogate for the undefined amount of active ingredient used, and also the fact that the statistical models generally fitted better using this normalizing factor. In the Supplement we present the results for the unnormalized exposure and for the exposure normalized by the pesticide concentration.

Each subject was given inner and outer dosimeters. Gloves were worn for the COP scenario only. Hats were not worn. Each subject also wore eye protection. Each subject was given a low-volume, personal air-sampling pump attached to an OVS sampling tube with glass filter and XAD2 sorbent placed in the subject's breathing zone. For the Bucket and Sink scenarios, the subjects wore short sleeved inner and outer dosimeters, and the outer and inner dosimeters were each sectioned into five sections: upper arm, lower leg, upper leg, front torso and rear torso. For the Bucket and Sink scenarios, a forearm wipe was used to measure exposure to the lower arm. For the COP scenarios, the subjects wore

long sleeved inner and outer dosimeters, and the outer and inner dosimeters were each sectioned into six sections: lower arm, upper arm, lower leg, upper leg, front torso and rear torso. In the analytical laboratory, the concentrations of C14-ADBAC were measured on each inner and outer dosimeter section, hand wash, face and neck wipe, and forearm wipe (for the COP scenario only) and the concentrations of C14-ADBAC and DDAC were measured on the OVS tubes. Since the C14-ADBAC concentrations in the OVS tubes were mainly below the detection limit, the analyses reported in this memorandum only use the DDAC concentrations in the OVS tubes.

The average percentage recovery of field fortification samples from the set of field fortification samples was calculated. Adjustments for field fortification recovery were not made for this study because the average percentage recovery was above 100% for the field fortification set. The residues from the hand wash and the forearm and face and neck wipes were corrected for removal efficiency using a 90% removal efficiency correction factor for the hand wash residues and a 89% removal efficiency correction factor for the forearm and face and neck wipes. In addition, the face and neck residues were corrected for the surface area covered by the protective eyewear, by applying a factor of 1.1.

These analyses used the corrected measurements. Excel spreadsheets containing the data in the report were supplied by the Study Director and used for these analyses. Some of the numerical results may differ a little from those in the study report because of rounding conventions; these analyses did not round any intermediate calculations.

The dermal exposure data were used to develop exposure measurements for the following dermal exposure routes:

- **Long Dermal**. This case represents the dermal exposure to a person wearing long pants and a long-sleeved shirt. For the Bucket and Sink scenarios, this is the sum of the C14-ADBAC mass from the five inner dosimeters, hand wash, and the face/neck wipes. For the COP scenario, this is the sum of the C14-ADBAC mass from the six inner dosimeters, hand wash, and the face/neck wipes.
- **Short Dermal**. This case represents the dermal exposure to a person wearing short pants and a short-sleeved shirt. For the Bucket and Sink scenarios, this is the sum of the C14-ADBAC mass from the five inner dosimeters, hand wash, the face/neck wipes, the forearm wipes, and the lower leg outer dosimeter. For the COP scenario, this is the sum of the C14-ADBAC mass from the six inner dosimeters, hand wash, the face/neck wipes, the lower leg outer dosimeter, and the lower arm outer dosimeter.
- **Long Short Dermal**. This case represents the dermal exposure to a person wearing long pants and a short-sleeved shirt. For the Bucket and Sink scenarios, this is the sum of the C14-ADBAC mass from the five inner dosimeters, hand wash, the face/neck wipes, and the forearm wipes. For the COP scenario, this is the sum of the C14-ADBAC mass from the six inner dosimeters, hand wash, the face/neck wipes, and the lower arm outer dosimeter.
- **Hands Only**. This case represents the dermal exposure to the hands only and is the C14-ADBAC mass from hand wash.

Total inhalable Inhalation exposure was measured by the OVS sampler using the total DDAC residue from the air sampling tube glass fiber filters. The exposure concentration (mg/m^3) was calculated by dividing the corrected residue mass by the volume of air drawn.

The following inhalation exposure metrics are analyzed in this memorandum:

- **Inhalation Concentration (mg/m^3).** DDAC concentration measured by the OVS Sampler.
- **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) Inhalation Concentration (mg/m^3).** Average inhalation concentration over eight hours that includes this period of IDS activity. Inhalation Concentration (mg/m^3) × Air Sampling Duration (hr) / 8 (hr).

Some of the measured residue values were below the level of quantitation (LOQ), and some were also below the level of detection (LOD). Such values are called "non-detects." In the study report, all values below the LOQ or below the LOD were replaced by LOQ/2. In this memorandum we use the LOQ/2 substitution for the primary analyses but also evaluate alternative censored statistical models that take into account the fact that the true value is between 0 and the LOQ. (Since the impact is small, to simplify the analysis, we did not treat values < LOQ and values < LOD differently). All the values for hand and forearm exposures were above the LOQ but there were several other cases with values below the corresponding LOQ.

In this memorandum we present the analysis of the unit or normalized exposure defined as the dermal or inhalation exposure divided by a normalizing factor. As noted above, in the main body of this memorandum, the normalizing factor chosen is the product of the concentration and the sample duration. In the Supplement, we evaluate using the concentration as a normalizing factor and also using a normalizing factor of 1 (corresponding to no normalizing factor). Estimates of the arithmetic and geometric means and standard deviation as well as the 95th percentile are computed using the empirical data as well as a lognormal simple random sampling model. For simplicity we decided not to evaluate lognormal mixed models although it is possible that there may be a random site effect for the Bucket and Sink scenarios that each had three locations. Each group is assumed to be a simple random sample of subjects. The empirical model calculates statistics for all the unit exposure measurements assuming the data are statistically independent. The lognormal simple random sampling model calculates statistics for all the unit exposure measurements, assuming the unit exposure measurements are statistically independent with a lognormal distribution.

For each scenario, we used analysis of variance to compare the geometric means of the unit exposures for the three target total quat concentration groups. We assumed that the unit exposures for the 18 MEs are log-normally distributed with different geometric means for each group and possibly different geometric standard deviations. For the Bucket scenario, these analyses showed that there were no statistically significant differences (at the 5% significance level) between the three concentration groups. For the Sink scenario, these analyses showed that there were no statistically significant differences (at the 5% significance level) for dermal exposures between the three concentration groups, but there were statistically significant differences for inhalation exposures. For the COP scenario, these analyses showed that there were statistically significant differences (at the 5% significance level) between the three concentration groups for Long Dermal, Hands Only, and the inhalation exposures. Group-specific results are not reported for all the analyses to limit the size of the memorandum, but are available upon request.

For each summary statistic we present confidence intervals. We also compute the fold relative accuracies of the summary statistics and compare them with the (primary) study design benchmark of 3-fold accuracy. For the Bucket scenario, this primary benchmark was met for all the various arithmetic mean and 95th percentile estimates (for all MEs combined), with the exception of the empirical 95th percentile for the inhalation concentration, dose, and time-weighted average concentration. For the Sink scenario, the primary benchmark was met in every case, with the exception of the parametric bootstrap empirical 95th percentile for the inhalation concentration, dose, and time-weighted average concentration. For the COP scenario, the primary benchmark was met in every case, with the exception of the parametric bootstrap empirical 95th percentile for all exposure routes, the non-parametric bootstrap empirical 95th percentile for the inhalation exposures, and the non-parametric bootstrap lognormal empirical 95th percentile for the inhalation exposures.

To evaluate the statistical models, we present quantile-quantile plots of the data to determine whether the normalized exposure should be treated as being normally or lognormally distributed. The results support the lognormal model over the normal model.

For the concentration times duration and concentration normalizing factors, 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 normalizing factor, where the slope equals 1. To test this "log-log-linearity with a slope of 1" assumption, the lognormal simple random sampling 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 normalizing factor. We applied this test to each exposure metric using the lognormal simple random sampling model. We also present quantile-quantile plots of the residuals from the lognormal simple random sampling model with a slope term to evaluate the fitted models.

For the Bucket scenario, using the concentration times duration normalizing factor, the slopes for the different exposure routes ranged from 0.28 to 0.75, the confidence intervals for the slope exclude 0 except for the inhalation concentration, and in all but one case the confidence intervals include 1. Thus the assumption of independence was rejected in every case except for the inhalation concentration, and the assumption of log-linearity with slope 1 was supported in every case except for the inhalation concentration.

For the Sink scenario, using the concentration times duration normalizing factor, the slopes for dermal exposures ranged from 0.91 to 0.94, the confidence intervals include 1 but not 0. For inhalation exposures, the slopes are all negative and the confidence intervals include 0 but not 1. Thus for dermal exposure the assumption of independence was rejected and the assumption of log-log-linearity with slope 1 was supported. However for inhalation exposure the assumption of independence was supported and the assumption of log-log-linearity with slope 1 was rejected. The negative slopes for inhalation exposure seem to be counterintuitive.

For the COP scenario, using the concentration times duration normalizing factor, the slopes ranged from -0.1 to 0.5, showing a weak linear relationship. Except for Short Dermal, the confidence intervals include 0 but not 1, suggesting that the exposure does not depend on the normalizing factor based on the linear model. For Short Dermal the slope is 0.45, and the confidence interval excludes both 0 and 1 showing that the exposure increases with the normalizing factor, but the model does not support the use of unit exposures.

A secondary objective is for meeting 80% power for detecting log-log-linearity with a slope of 1. This objective is approximately met if the widths of the confidence intervals for the slope based on the lognormal model are at most 1.4. For all three scenarios, using the concentration times duration normalizing factor, the results show that the observed widths were all less than 1.4. Therefore, the secondary objective of meeting 80% power for detecting proportionality was met.

We also evaluated quadratic regression models where the logarithm of the exposure is regressed against the logarithm of the normalizing factor and the square of the logarithm of the normalizing factor. For all three scenarios, for all exposure modes, the quadratic coefficient was not statistically significant, so the linear model was preferred over the quadratic model.

Finally, we evaluated and compared several alternative statistical model formulations. In addition to the above linear and quadratic models for the logarithm of exposure we considered log-log-logistic and three-parameter logistic models

for exposure, and a gamma model for exposure. We used the Akaike Information Criterion to compare the goodness-of-fit, penalizing potentially over-parametrized models with more parameters. For the Bucket scenario using the concentration times duration normalizing factor, the linear model performed best for all of the exposure routes. For the Sink scenario using the concentration times duration normalizing factor, the linear model performed best for all the dermal exposure routes except for Hands Only, as well as for the inhalation concentration, but the gamma model performed best for Hands Only, inhalation dose and the inhalation time-weighted average concentration. For the COP scenario using the concentration times duration normalizing factor, the linear model performed best for Hands Only and the inhalation exposure routes, but the gamma model performed best for Long Dermal, Short Dermal, and Long Short Dermal.

For each scenario we use the following labeling scheme for the tables and figures. Each Table or Figure is labeled as Table XYn or Figure XYn. The letter X indicates the normalizing factor which is either A for normalizing by concentration times duration, B for normalizing by concentration, or C for normalizing by 1. For the concentration times duration normalizing factor, normalizing factor A is in the main text and normalizing factors B and C are in the Supplement. The letter Y denotes the scenario, which is either B for Bucket, C for COP, or S for Sink. The number n denotes the table or figure number for normalizing factor X and scenario Y. The same sequence of analyses applies for each combination of normalizing factor and scenario. In this manner the first two letters of each Figure or Table identify the normalizing factor and the scenario.

2. Bucket Scenario

Summary Statistics of Exposure per Concentration Times Duration

Tables AB1 to AB7 summarize the normalized exposure data (per concentration times duration) with the summary statistics from the 18 (all concentrations), or 6 (specific concentrations) measurements for each concentration group, and each dermal and inhalation exposure route. These analyses assume that the exposure measurements within each subset come from some unspecified distribution for that subset.

Table AB1. Summary statistics for normalized long dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
Arithmetic Mean	1.598E-03	2.087E-03	1.537E-03	1.171E-03
Arithmetic Standard Deviation	1.129E-03	1.743E-03	6.511E-04	5.979E-04
Geometric Mean	1.344E-03	1.598E-03	1.448E-03	1.050E-03
Geometric Standard Deviation	1.794E+00	2.239E+00	1.428E+00	1.679E+00
Min	4.900E-04	4.902E-04	1.010E-03	4.900E-04
5%	4.900E-04	4.902E-04	1.010E-03	4.900E-04
10%	4.902E-04	4.902E-04	1.010E-03	4.900E-04
25%	1.010E-03	1.147E-03	1.197E-03	7.626E-04
50%	1.264E-03	1.517E-03	1.333E-03	1.117E-03

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
75%	1.794E-03	2.480E-03	1.535E-03	1.335E-03
90%	2.812E-03	5.373E-03	2.812E-03	2.203E-03
95%	5.373E-03	5.373E-03	2.812E-03	2.203E-03
Max	5.373E-03	5.373E-03	2.812E-03	2.203E-03

Table AB2. Summary statistics for normalized short dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
Arithmetic Mean	1.610E-03	2.098E-03	1.550E-03	1.183E-03
Arithmetic Standard Deviation	1.131E-03	1.743E-03	6.622E-04	5.988E-04
Geometric Mean	1.357E-03	1.611E-03	1.459E-03	1.062E-03
Geometric Standard Deviation	1.788E+00	2.227E+00	1.433E+00	1.672E+00
Min	4.982E-04	4.982E-04	1.014E-03	5.025E-04
5%	4.982E-04	4.982E-04	1.014E-03	5.025E-04
10%	5.025E-04	4.982E-04	1.014E-03	5.025E-04
25%	1.014E-03	1.167E-03	1.202E-03	7.658E-04
50%	1.285E-03	1.527E-03	1.336E-03	1.137E-03
75%	1.808E-03	2.484E-03	1.566E-03	1.344E-03
90%	2.844E-03	5.386E-03	2.844E-03	2.210E-03
95%	5.386E-03	5.386E-03	2.844E-03	2.210E-03
Max	5.386E-03	5.386E-03	2.844E-03	2.210E-03

Table AB3. Summary statistics for normalized long short dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
Arithmetic Mean	1.605E-03	2.094E-03	1.543E-03	1.179E-03
Arithmetic Standard Deviation	1.128E-03	1.742E-03	6.514E-04	5.974E-04
Geometric Mean	1.353E-03	1.607E-03	1.455E-03	1.059E-03
Geometric Standard Deviation	1.788E+00	2.229E+00	1.428E+00	1.671E+00
Min	4.959E-04	4.959E-04	1.012E-03	5.017E-04
5%	4.959E-04	4.959E-04	1.012E-03	5.017E-04

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
10%	5.017E-04	4.959E-04	1.012E-03	5.017E-04
25%	1.012E-03	1.164E-03	1.201E-03	7.638E-04
50%	1.276E-03	1.521E-03	1.335E-03	1.128E-03
75%	1.799E-03	2.481E-03	1.563E-03	1.343E-03
90%	2.814E-03	5.379E-03	2.814E-03	2.206E-03
95%	5.379E-03	5.379E-03	2.814E-03	2.206E-03
Max	5.379E-03	5.379E-03	2.814E-03	2.206E-03

Table AB4. Summary statistics for normalized hands only dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
Arithmetic Mean	1.596E-03	2.083E-03	1.535E-03	1.169E-03
Arithmetic Standard Deviation	1.128E-03	1.744E-03	6.495E-04	5.976E-04
Geometric Mean	1.342E-03	1.593E-03	1.447E-03	1.048E-03
Geometric Standard Deviation	1.794E+00	2.242E+00	1.427E+00	1.679E+00
Min	4.889E-04	4.889E-04	1.009E-03	4.895E-04
5%	4.889E-04	4.889E-04	1.009E-03	4.895E-04
10%	4.895E-04	4.889E-04	1.009E-03	4.895E-04
25%	1.009E-03	1.136E-03	1.196E-03	7.621E-04
50%	1.261E-03	1.512E-03	1.332E-03	1.114E-03
75%	1.790E-03	2.479E-03	1.532E-03	1.333E-03
90%	2.807E-03	5.369E-03	2.807E-03	2.202E-03
95%	5.369E-03	5.369E-03	2.807E-03	2.202E-03
Max	5.369E-03	5.369E-03	2.807E-03	2.202E-03

Table AB5. Summary statistics for normalized inhalation concentration exposure (mg/m^3/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
Arithmetic Mean	8.250E-08	6.642E-08	1.410E-07	4.009E-08
Arithmetic Standard Deviation	1.613E-07	6.197E-08	2.769E-07	3.716E-08
Geometric Mean	3.865E-08	4.536E-08	4.510E-08	2.822E-08

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
Geometric Standard Deviation	2.986E+00	2.759E+00	4.074E+00	2.564E+00
Min	7.276E-09	9.346E-09	1.401E-08	7.276E-09
5%	7.276E-09	9.346E-09	1.401E-08	7.276E-09
10%	9.346E-09	9.346E-09	1.401E-08	7.276E-09
25%	1.920E-08	2.633E-08	2.033E-08	1.753E-08
50%	3.819E-08	5.337E-08	3.236E-08	2.997E-08
75%	6.787E-08	7.337E-08	4.105E-08	4.612E-08
90%	1.827E-07	1.827E-07	7.058E-07	1.097E-07
95%	7.058E-07	1.827E-07	7.058E-07	1.097E-07
Max	7.058E-07	1.827E-07	7.058E-07	1.097E-07

Table AB6. Summary statistics for normalized inhalation dose exposure (mg/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
Arithmetic Mean	3.663E-08	3.108E-08	5.798E-08	2.083E-08
Arithmetic Standard Deviation	5.718E-08	1.737E-08	9.854E-08	1.483E-08
Geometric Mean	2.280E-08	2.690E-08	2.682E-08	1.643E-08
Geometric Standard Deviation	2.358E+00	1.861E+00	3.150E+00	2.179E+00
Min	6.399E-09	9.346E-09	1.312E-08	6.399E-09
5%	6.399E-09	9.346E-09	1.312E-08	6.399E-09
10%	7.397E-09	9.346E-09	1.312E-08	6.399E-09
25%	1.368E-08	2.488E-08	1.368E-08	7.397E-09
50%	2.261E-08	2.623E-08	1.729E-08	1.660E-08
75%	3.656E-08	3.887E-08	2.767E-08	3.656E-08
90%	6.091E-08	6.091E-08	2.588E-07	4.143E-08
95%	2.588E-07	6.091E-08	2.588E-07	4.143E-08
Max	2.588E-07	6.091E-08	2.588E-07	4.143E-08

Table AB7. Summary statistics for normalized inhalation time-weighted average concentration exposure (mg/m^3/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 440 ppm	Target Quat: 880 ppm	Target Quat: 1760 ppm
Arithmetic Mean	4.578E-09	3.885E-09	7.247E-09	2.604E-09
Arithmetic Standard Deviation	7.147E-09	2.172E-09	1.232E-08	1.854E-09
Geometric Mean	2.850E-09	3.362E-09	3.353E-09	2.053E-09
Geometric Standard Deviation	2.358E+00	1.861E+00	3.150E+00	2.179E+00
Min	7.998E-10	1.168E-09	1.641E-09	7.998E-10
5%	7.998E-10	1.168E-09	1.641E-09	7.998E-10
10%	9.246E-10	1.168E-09	1.641E-09	7.998E-10
25%	1.710E-09	3.111E-09	1.710E-09	9.246E-10
50%	2.826E-09	3.278E-09	2.161E-09	2.075E-09
75%	4.570E-09	4.859E-09	3.458E-09	4.570E-09
90%	7.614E-09	7.614E-09	3.235E-08	5.179E-09
95%	3.235E-08	7.614E-09	3.235E-08	5.179E-09
Max	3.235E-08	7.614E-09	3.235E-08	5.179E-09

The results show the high proportions of the normalized dermal exposure from hands only. For All and for each concentration group, based on the arithmetic means, the overall percentages of normalized exposure from hands only are about 99% of the Long Dermal, Short Dermal, and Long Short Dermal. Similarly, for the unnormalized dermal exposure, the arithmetic mean hands only exposure is 99% of the arithmetic mean total dermal exposure (defined as the sum of the residues from hand wash, forearm wipe, face/neck wipe, and the inner dosimeters).

Compare Concentration Groups

The results in Tables AB1 to AB7 show some differences between the normalized exposure statistics for the three concentration groups “Target Quat: 440 ppm,” “Target Quat: 880 ppm,” and “Target Quat: 1760 ppm.” To compare these groups, an analysis of variance was performed to test whether the geometric means were statistically significantly different at the 5% significance level. Because later analyses in this memorandum confirm that log-normal distributions provide a better fit to the data than normal distributions, this analysis used the logarithms of the normalized exposure and tested whether the population means of the logarithms of the normalized exposure are the same across the two or three groups. This is equivalent to testing whether the geometric means of the normalized exposure are the same across the groups. The one way analysis of variance (ANOVA) test assumes that the geometric standard deviations of the normalized exposure are the same across the groups, which is the same as assuming that the variances of the logarithms of the normalized exposure are the same across the groups. The Welch’s ANOVA test avoids this equal variance assumption.

The p-values for these ANOVA tests are shown in Table AB8. These analyses show that there were no statistically significant differences (at the 5% significance level) between the three concentration groups for any of the exposure modes.

Table AB8. P-values for testing differences in geometric means for different concentration groups

Exposure Route	ANOVA	Welch's ANOVA
Long Dermal	0.454	0.444
Short Dermal	0.458	0.449
Long Short Dermal	0.456	0.447
Hands Only	0.457	0.445
Inhalation Conc	0.715	0.680
Inhalation Dose	0.547	0.498
Inhalation 8-hr TWA	0.547	0.498

Statistical Models

The statistical analyses of the normalized exposure use the following two 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. 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 were randomly drawn from an unspecified distribution. Gives empirical estimates such as in Tables AB1 to AB7 above.
  - Y = LnGM + Error. Error is independent and identically distributed with mean 0 and the same variance for every measurement.
  - 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 were randomly drawn from a lognormal distribution.
  - 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)

Table AB9 presents the arithmetic mean and 95th percentile estimates from the lognormal simple random sampling model, together with 95% confidence intervals, for each of the exposure routes, for all concentration groups combined. These are the values of AMu and P95u. The other summary statistics are presented in more detail below.

Table AB9. Arithmetic mean and 95th percentile estimates from lognormal simple random sampling model for normalized exposure for All

Exposure Route	Clothing	Arithmetic Mean (95% Confidence Interval)	95th Percentile (95% Confidence Interval)
Dermal (mg/(ppm ADBAC × mins))	Long Dermal	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Short Dermal	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Long Short Dermal	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Hands Only	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
Inhalation Concentration ((mg/m^3)/ (ppm DDAC × mins))		7.03×10^{-8} (3.79×10^{-8}, 1.38×10^{-7})	2.34×10^{-7} (1.06×10^{-7}, 5.11×10^{-7})
Inhalation Dose (mg/ (ppm DDAC × mins))		3.29×10^{-8} (2.09×10^{-8}, 5.37×10^{-8})	9.35×10^{-8} (5.02×10^{-8}, 1.73×10^{-7})
Inhalation 8-hr TWA ((mg/m^3)/ ppm DDAC × mins))		4.12×10^{-9} (2.62×10^{-9}, 6.71×10^{-9})	1.17×10^{-8} (6.28×10^{-9}, 2.16×10^{-8})

For each exposure route, the two 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 AB9 were computed using a parametric bootstrap. For these calculations, the parametric bootstrap simulations were all generated from the fitted lognormal simple random sampling model, even for the empirical summary statistics, on the basis that the lognormal simple random sampling 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 AB1 to AB7, the empirical arithmetic means are presented, which are the arithmetic means of the 18 measurements for the "All" group, and the 6 measurements in each of the three concentration groups "Target Quat: 440 ppm," "Target Quat: 880 ppm," and "Target Quat: 1760 ppm." To estimate the uncertainty of those empirical arithmetic means, data are simulated from the lognormal simple random sampling model to calculate the parametric bootstrap confidence intervals. The arithmetic means in Table AB9 are estimated using the lognormal simple random sampling model, which is also used to estimate the confidence intervals in Table AB9. The unit exposure estimates (from the lognormal simple random sampling model) displayed in Table AB9 are recommended over the empirical arithmetic means and 95th percentiles displayed in the Tables AB1 to AB7 for the All group.

The algorithm used was as follows:

Step 1:
Assume that there are N subjects in a data subset. (N = 18 for the "All" group).
Simulate N random variables Y, X from the estimated lognormal distribution superimposed upon the observed sampling structure ---;

Y = LnGM + RanNor(Seed)×Sr

X = exp(Y)

where:

LnGM = natural logarithm of fitted geometric mean

Sr = natural logarithm of fitted geometric standard deviation

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)

where:

EAM = sample arithmetic mean of Y = AMu

Su = standard deviation of Y

For X:

Calculate arithmetic mean AMs

Calculate 95th percentile 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, AMs, AMu, P95s, and P95u. 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.

Non-detects

For all the analyses presented in this memorandum except for Table AB10 and AB18, measurements below the LOQ or LOD were replaced by the mid-value, the midpoint of the lowest and highest possible value for that measurement. In Tables AB10 and AB18 we investigated the impact on the summary statistics of the censored values.

For each exposure metric, we used the approach in the last paragraph to compute the arithmetic mean and 95th percentiles using the recommended substitution of the midpoint value for values below the LOQ and compared those results to estimates using the alternative substitutions of the minimum and maximum for that non-detect value. For the dermal exposure modes, the exposure values are sums of the measured values for the relevant dosimeter, face, head and neck, forearm, and hand wash components, so the minimum exposure is the sum of all the minimum component values and the maximum exposure is the sum of all the maximum component values. We also investigated a censored maximum likelihood statistical method described in the following paragraph.

The lognormal simple random sampling model assumes that the exposure values are independent and identically lognormally distributed. For uncensored values with a mass m, the mass is between a lower bound of m and an upper bound of m. For censored mass values, the mass value is known to be between a lower bound and an upper bound. The SAS procedure LIFEREG was used to fit the lognormal model to the combined censored and uncensored data using the maximum likelihood method. The procedure produces estimates of the geometric mean and geometric standard deviation for the fitted lognormal distribution.

To calculate confidence intervals for the arithmetic means and 95th percentiles, a parametric bootstrap method was used. This is exactly the same bootstrap method that was used for the original case where the non-detects were replaced by the midpoint value. 10,000 values of the unit exposure were simulated from the fitted lognormal distribution, and for each simulation, the geometric mean and geometric standard deviation were calculated and used

to calculate the arithmetic mean (AMu) and 95th percentile (P95u) of the corresponding lognormal distribution. The simulated unit exposures are all uncensored numerical values even though the corresponding residues can be lower than the LOQs. The confidence intervals for the AMu and P95u range from the 2.5th percentile to the 97.5th percentile.

Results for all the exposure metrics are presented in Table AB10. The results are compared for the default substitution of the midpoint value ("mid value") the alternative substitutions of the maximum value ("max value") and minimum value ("min value"), and estimates calculated using the maximum likelihood method for censored data, referred to as "Censored data MLE." Note that in several cases the rounded values shown in the table do not show noticeable differences between the alternative methods. Also note that in some cases there are differences between the confidence intervals in Table AB9 and the confidence intervals for "substitute mid value" in Table AB10 due to random variations between the bootstrap simulations.

Table AB10. Exposure summary statistics calculated using alternative estimated exposures for values below the LOQ

Exposure Route	Method for Substituting Values Below the LOQ	Arithmetic Mean	95th Percentile
Long Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Substitute max value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Substitute min value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Censored data MLE	0.0016 (0.0012, 0.0021)	0.0034 (0.0023, 0.0051)
Short Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Substitute max value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0054)
	Substitute min value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0054)
	Censored data MLE	0.0016 (0.0012, 0.0021)	0.0034 (0.0023, 0.0051)
Long Short Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Substitute max value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Substitute min value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Censored data MLE	0.0016 (0.0012, 0.0021)	0.0034 (0.0023, 0.0051)
Hands Only (mg/(ppm ADBAC × mins))	Substitute mid value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Substitute max value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Substitute min value	0.0016 (0.0012, 0.0022)	0.0035 (0.0023, 0.0053)
	Censored data MLE	0.0016 (0.0012, 0.0021)	0.0034 (0.0023, 0.0051)
Inhalation Concentration ((mg/m^3)/ (ppm DDAC × mins))	Substitute mid value	7.03×10^{-8} (3.79×10^{-8}, 1.38×10^{-7})	2.34×10^{-7} (1.05×10^{-7}, 5.11×10^{-7})
	Substitute max value	9.04×10^{-8} (4.76×10^{-8}, 1.81×10^{-7})	3.03×10^{-7} (1.35×10^{-7}, 6.73×10^{-7})

Exposure Route	Method for Substituting Values Below the LOQ	Arithmetic Mean	95th Percentile
	Substitute min value	9.02×10^{-8} (4.27×10^{-8}, 2.06×10^{-7})	3.22×10^{-7} (1.30×10^{-7}, 7.85×10^{-7})
	Censored data MLE	6.32×10^{-8} (3.13×10^{-8}, 1.36×10^{-7})	2.20×10^{-7} (9.26×10^{-7}, 5.17×10^{-7})
Inhalation Dose (mg/ (ppm DDAC × mins))	Substitute mid value	3.29×10^{-8} (2.08×10^{-8}, 5.37×10^{-8})	9.35×10^{-8} (5.01×10^{-8}, 1.73×10^{-7})
	Substitute max value	3.88×10^{-8} (2.58×10^{-8}, 5.96×10^{-8})	1.03×10^{-7} (5.85×10^{-8}, 1.80×10^{-7})
	Substitute min value	4.36×10^{-8} (2.70×10^{-8}, 7.28×10^{-8})	1.27×10^{-7} (6.64×10^{-8}, 2.41×10^{-7})
	Censored data MLE	3.26×10^{-8} (1.99×10^{-8}, 5.49×10^{-8})	9.58×10^{-8} (4.96×10^{-8}, 1.83×10^{-7})
Inhalation 8-hr TWA ((mg/m^3)/ ppm DDAC × mins))	Substitute mid value	4.12×10^{-9} (2.60×10^{-9}, 6.71×10^{-9})	1.17×10^{-8} (6.26×10^{-9}, 2.16×10^{-8})
	Substitute max value	4.85×10^{-9} (3.23×10^{-9}, 7.45×10^{-9})	1.29×10^{-8} (7.32×10^{-9}, 2.24×10^{-8})
	Substitute min value	5.46×10^{-9} (3.37×10^{-9}, 9.10×10^{-9})	1.59×10^{-8} (8.30×10^{-9}, 3.01×10^{-8})
	Censored data MLE	4.07×10^{-9} (2.49×10^{-9}, 6.86×10^{-9})	1.20×10^{-8} (6.20×10^{-9}, 2.29×10^{-8})

The results in Table AB10 for dermal exposure show very small impacts of the alternative substitution approaches for treating values below the LOQ on the unit exposure arithmetic mean and 95th percentile. This is mainly because the dermal exposure is dominated by the hand exposures which were all above the LOQ. For inhalation exposure, the results show large impacts of the max and min value substitution methods compared to substituting the mid value, but the results for the censored data MLE are very similar to the results for substituting the mid value.

Fold Relative Accuracy

Fold relative accuracy (fRA_{95}) 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). In this memorandum we will use a more accurate calculation of the fold relative accuracy than the method used for the statistical analyses of several previous studies. The new method can be proven to produce lower values for the fold relative accuracy compared to the previous calculations, although the differences are in most cases quite small. By definition, if T and θ are known, the fold relative accuracy of T is the maximum of T/θ and θ/T. The fold relative accuracy measure is defined as the 95th percentile of the fold relative accuracy of T where the unknown value of θ is replaced by its estimated value E. Define FRA as the maximum of T/E and E/T. The fold relative accuracy measure (fRA_{95}) is calculated using a parametric or nonparametric bootstrap with N bootstrap replicates by simulating N values for FRA and then finding the 95th percentile of FRA. We used N = 10000 bootstrap replicates for these analysis. If the fRA_{95} of a statistic were equal to 3, and θ was known, then it would be correct to say: "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_{95} 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 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. The fRA_{95} is also referred to as the K-factor.

Following HSRB recommendations, confidence intervals and fold relative accuracy measures were estimated using both a parametric bootstrap approach, as described above, and the following non-parametric bootstrap approach. The non-parametric bootstrap method should be more robust since it does not assume that the fitted parametric model is the correct one. For the non-parametric bootstrap, exactly the same algorithm was used except that Step 1 above was replaced by the following:

Step 1:
Simulate N random variables Y, X by resampling at random with replacement from the original data:

The original exposure data are X(1), X(2), …, X(N), where N is the number of subjects in the data set.
Sample N values at random with replacement from the exposure values X(1), X(2), …, X(N). This gives the N simulated random variables X.
Y = log(X).

Detailed Summary Statistics with Confidence Intervals and Fold Relative Accuracy

Tables AB11 to AB17 present the estimates, parametric and non-parametric confidence intervals and fold relative accuracy values for all the summary statistics for the All group. All these analyses use non-detects substituted by the mid-value.

Table AB11. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.7939	1.4769	2.1875	1.22	1.4132	2.1467	1.24
GMs	0.0013	0.0010	0.0018	1.31	0.0010	0.0018	1.30
AMs	0.0016	0.0012	0.0021	1.34	0.0012	0.0022	1.37
AMu	0.0016	0.0012	0.0022	1.34	0.0012	0.0022	1.37
P95s	0.0054	0.0023	0.0077	2.21	0.0022	0.0054	2.17
P95u	0.0035	0.0023	0.0053	1.52	0.0021	0.0055	1.62

Table AB12. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.7882	1.4737	2.1780	1.22	1.4119	2.1361	1.24
GMs	0.0014	0.0010	0.0018	1.31	0.0011	0.0018	1.30
AMs	0.0016	0.0012	0.0021	1.34	0.0012	0.0022	1.36
AMu	0.0016	0.0012	0.0022	1.34	0.0012	0.0022	1.36

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
P95s	0.0054	0.0023	0.0077	2.21	0.0022	0.0054	2.17
P95u	0.0035	0.0023	0.0053	1.52	0.0021	0.0055	1.61

Table AB13. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.7876	1.4734	2.1772	1.22	1.4108	2.1358	1.24
GMs	0.0014	0.0010	0.0018	1.31	0.0010	0.0018	1.30
AMs	0.0016	0.0012	0.0021	1.34	0.0012	0.0022	1.37
AMu	0.0016	0.0012	0.0022	1.34	0.0012	0.0022	1.36
P95s	0.0054	0.0023	0.0077	2.21	0.0022	0.0054	2.17
P95u	0.0035	0.0023	0.0053	1.52	0.0021	0.0055	1.61

Table AB14. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.7945	1.4772	2.1884	1.22	1.4134	2.1474	1.24
GMs	0.0013	0.0010	0.0018	1.31	0.0010	0.0018	1.30
AMs	0.0016	0.0012	0.0021	1.34	0.0012	0.0022	1.37
AMu	0.0016	0.0012	0.0022	1.34	0.0012	0.0022	1.37
P95s	0.0054	0.0023	0.0077	2.22	0.0022	0.0054	2.17
P95u	0.0035	0.0023	0.0053	1.52	0.0021	0.0055	1.62

Table AB15. 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 exposure ((mg/m^3)/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.986E+00	2.075E+00	4.327E+00	1.44	1.854E+00	4.329E+00	1.55
GMs	3.865E-08	2.351E-08	6.499E-08	1.66	2.451E-08	6.407E-08	1.62
AMs	8.250E-08	3.616E-08	1.344E-07	2.11	3.193E-08	1.626E-07	2.39

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
AMu	7.029E-08	3.791E-08	1.384E-07	1.91	3.235E-08	1.620E-07	2.22
P95s	7.058E-07	1.048E-07	1.012E-06	6.00	7.337E-08	7.058E-07	6.43
P95u	2.336E-07	1.058E-07	5.108E-07	2.20	7.870E-08	6.083E-07	2.83

Table AB16. 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 exposure (mg/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.358E+00	1.772E+00	3.155E+00	1.33	1.614E+00	3.251E+00	1.44
GMs	2.280E-08	1.544E-08	3.427E-08	1.49	1.579E-08	3.419E-08	1.47
AMs	3.663E-08	2.040E-08	5.267E-08	1.70	1.889E-08	6.530E-08	1.90
AMu	3.294E-08	2.094E-08	5.365E-08	1.60	1.905E-08	6.129E-08	1.80
P95s	2.588E-07	4.986E-08	2.953E-07	4.74	3.887E-08	2.588E-07	6.25
P95u	9.348E-08	5.022E-08	1.727E-07	1.85	4.032E-08	2.068E-07	2.28

Table AB17. 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 time-weighted average concentration exposure ((mg/m^3)/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.358E+00	1.772E+00	3.155E+00	1.33	1.614E+00	3.251E+00	1.44
GMs	2.850E-09	1.930E-09	4.284E-09	1.49	1.973E-09	4.274E-09	1.47
AMs	4.578E-09	2.550E-09	6.583E-09	1.70	2.361E-09	8.162E-09	1.90
AMu	4.117E-09	2.617E-09	6.707E-09	1.60	2.381E-09	7.661E-09	1.80
P95s	3.235E-08	6.233E-09	3.691E-08	4.74	4.859E-09	3.235E-08	6.25
P95u	1.168E-08	6.278E-09	2.158E-08	1.85	5.040E-09	2.586E-08	2.28

Tables AB11 to AB17 show that the study benchmark design value of 3 for the fold relative accuracy was met in every case, with the exception of the empirical 95th percentile for the inhalation concentration, dose, and time-weighted average concentration.

Empirical 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 lognormal models. These plots were intended to help determine whether the data supported using untransformed normalized exposure values or log-transformed values or neither. The plots are not intended to evaluate the fitted regression models for the un-normalized exposure to be described below, for which the residual quantile plots were developed.

In each case the quantile-quantile plot compared the observed quantiles of the measured values with the corresponding quantiles of a normal or lognormal distribution. A perfect fit would imply that the plotted values lie in a straight line. The quantile-quantile plots for all exposure routes are presented in Figures AB1 to AB14. In all cases the plots seem to show a better fit for the lognormal distributions, supporting the use of the log-transformed exposure values over the untransformed values.

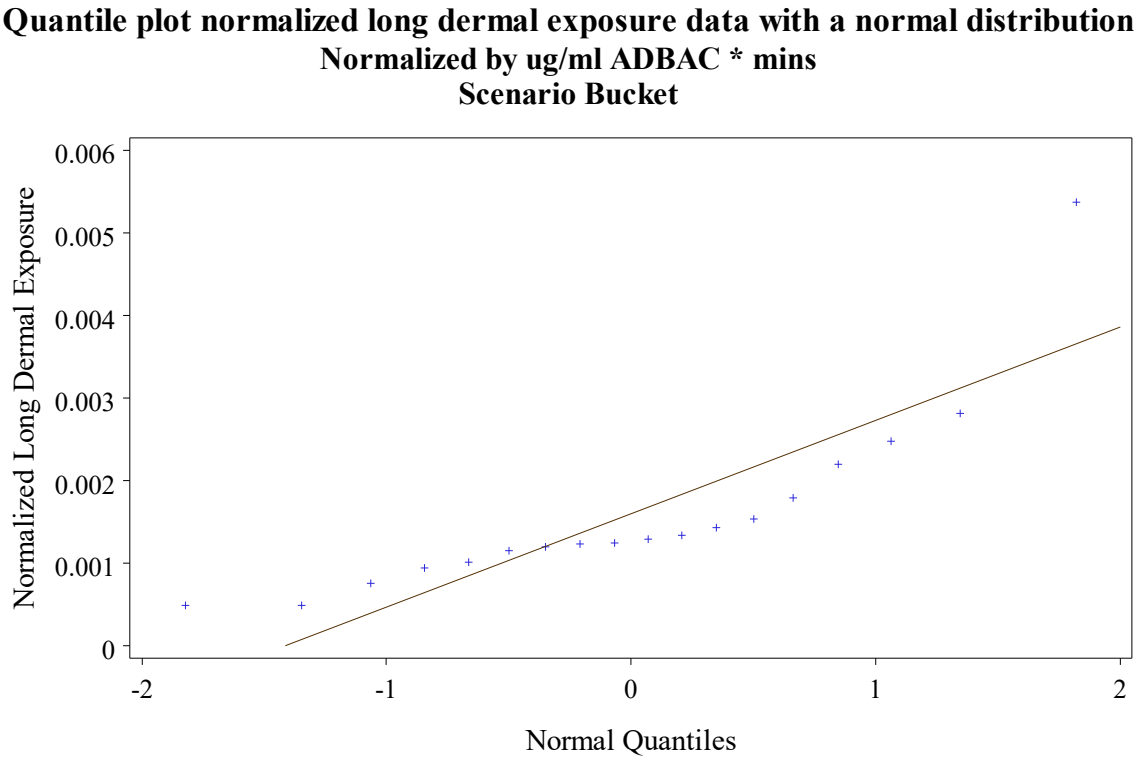

Figure AB1. Empirical quantile plot for Long Dermal, with a normal distribution

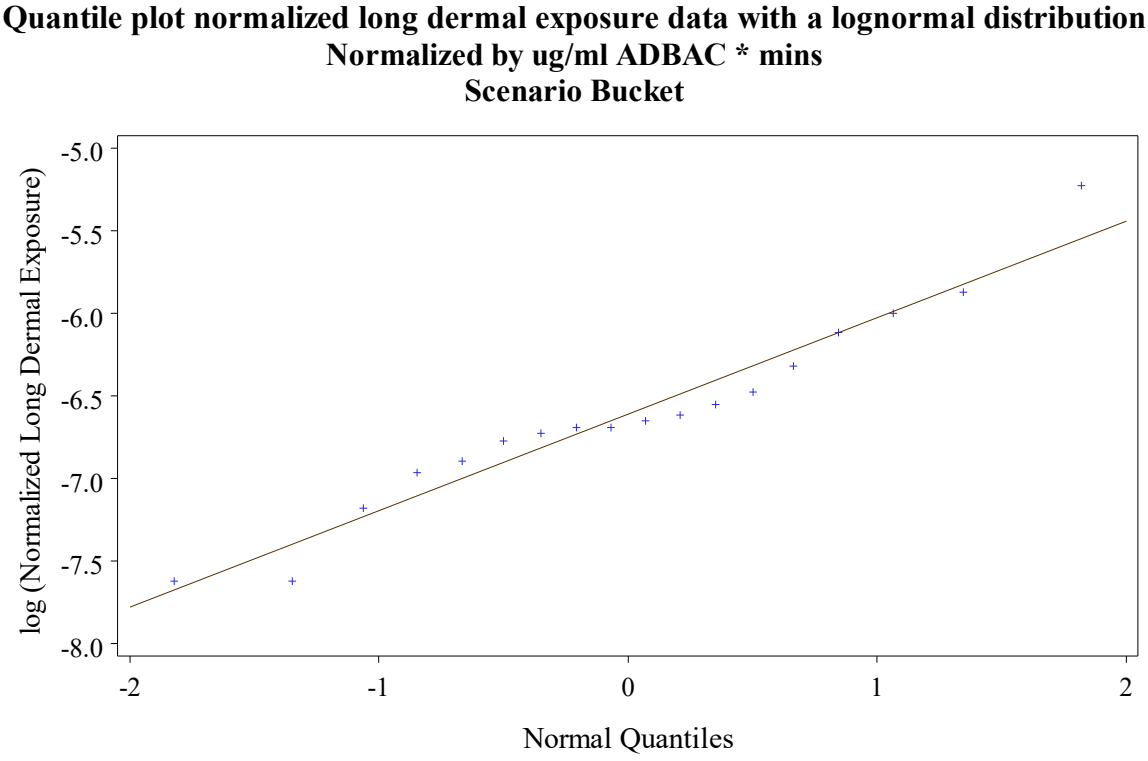

Figure AB2. Empirical quantile plot for Long Dermal, with a lognormal distribution

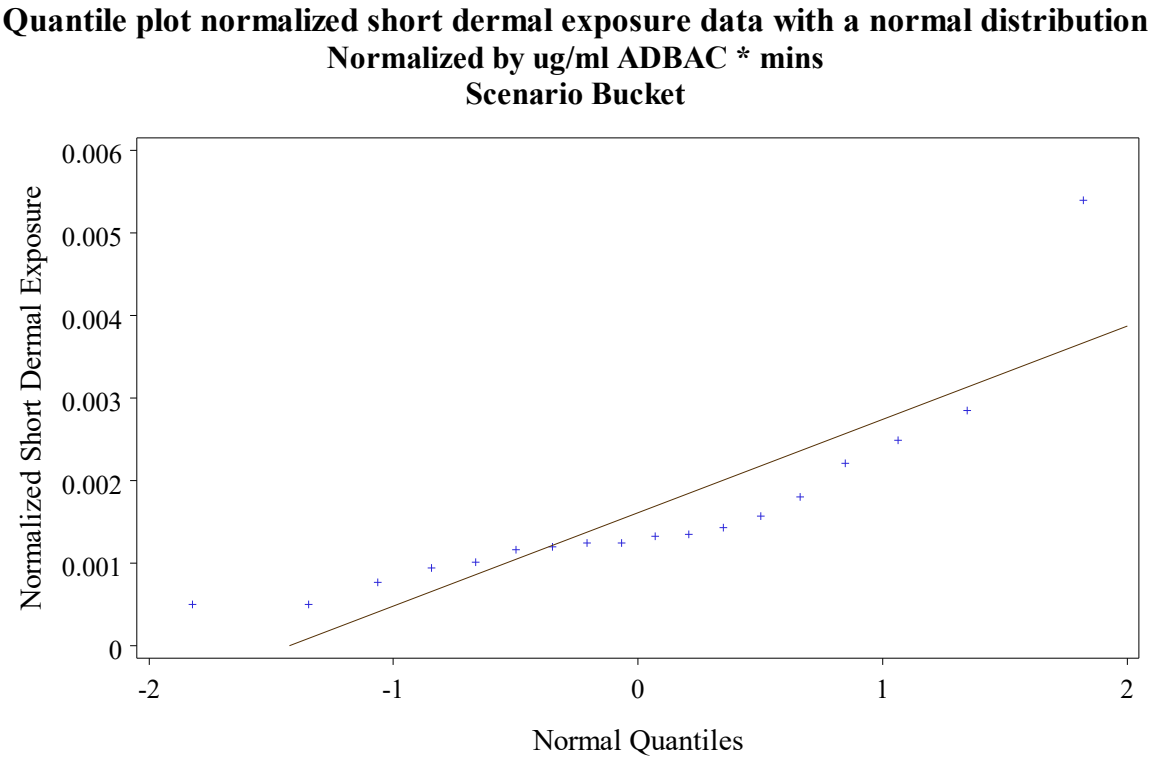

Figure AB3. Empirical quantile plot for Short Dermal, with a normal distribution

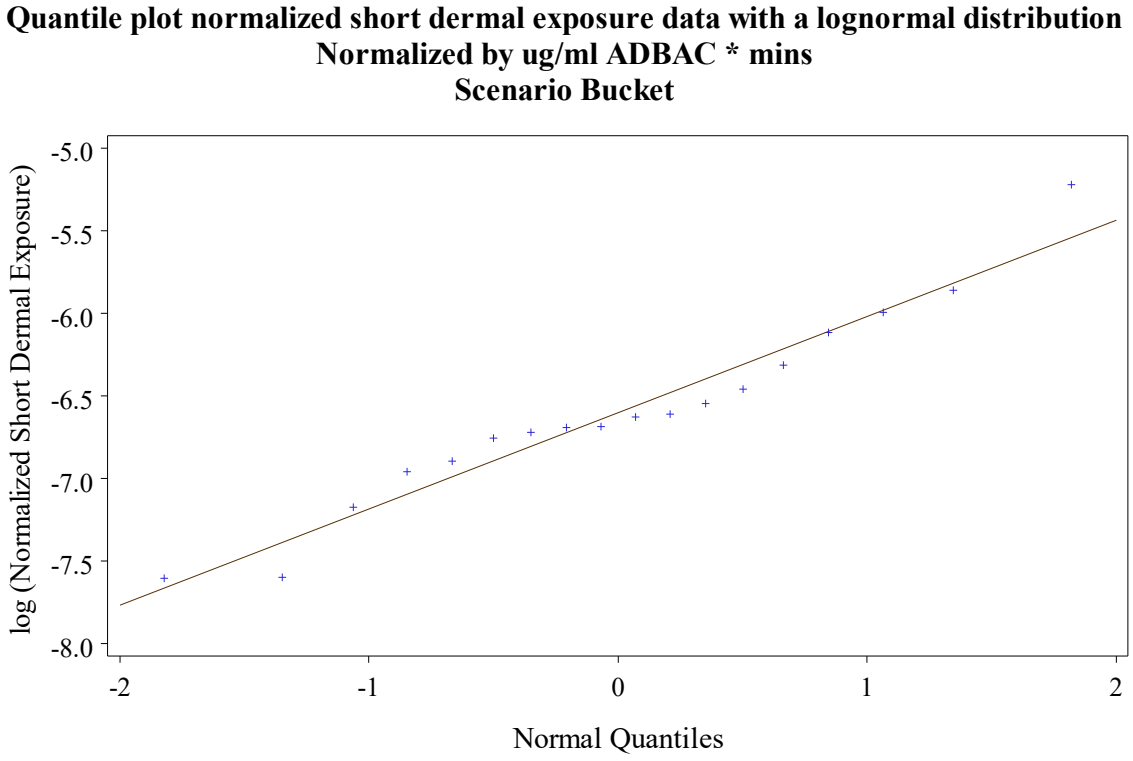

Figure AB4. Empirical quantile plot for Short Dermal, with a lognormal distribution

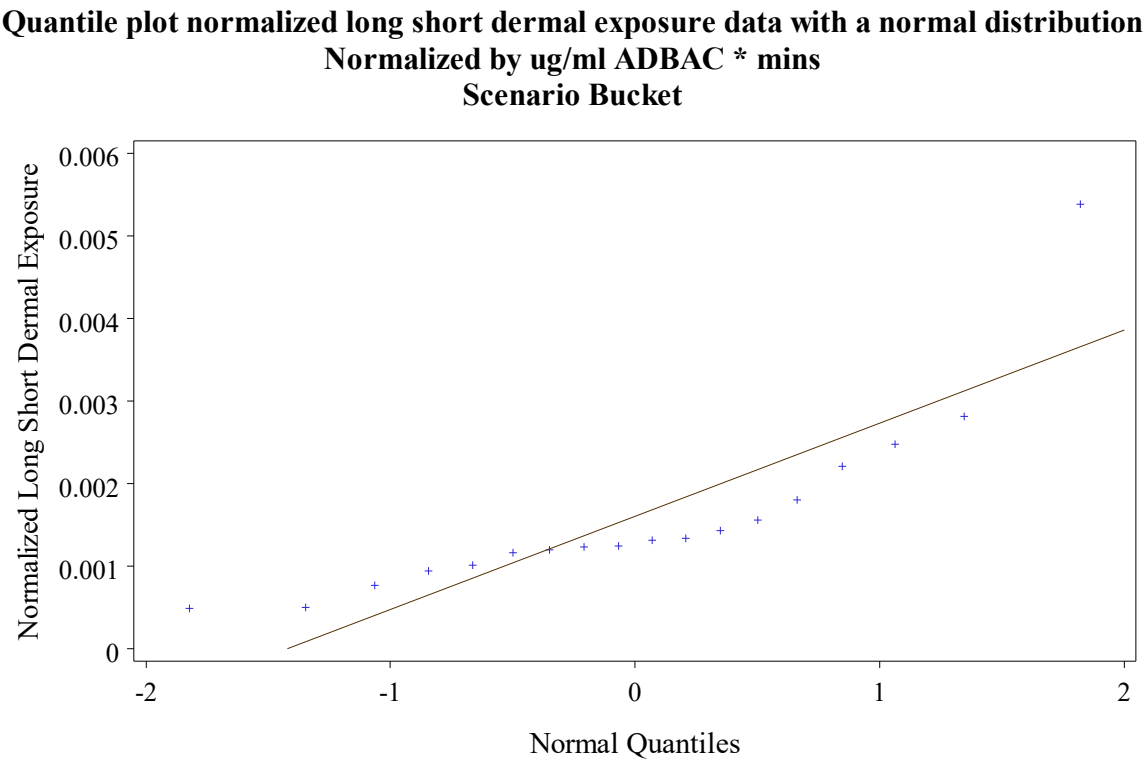

Figure AB5. Empirical quantile plot for Long Short Dermal, with a normal distribution

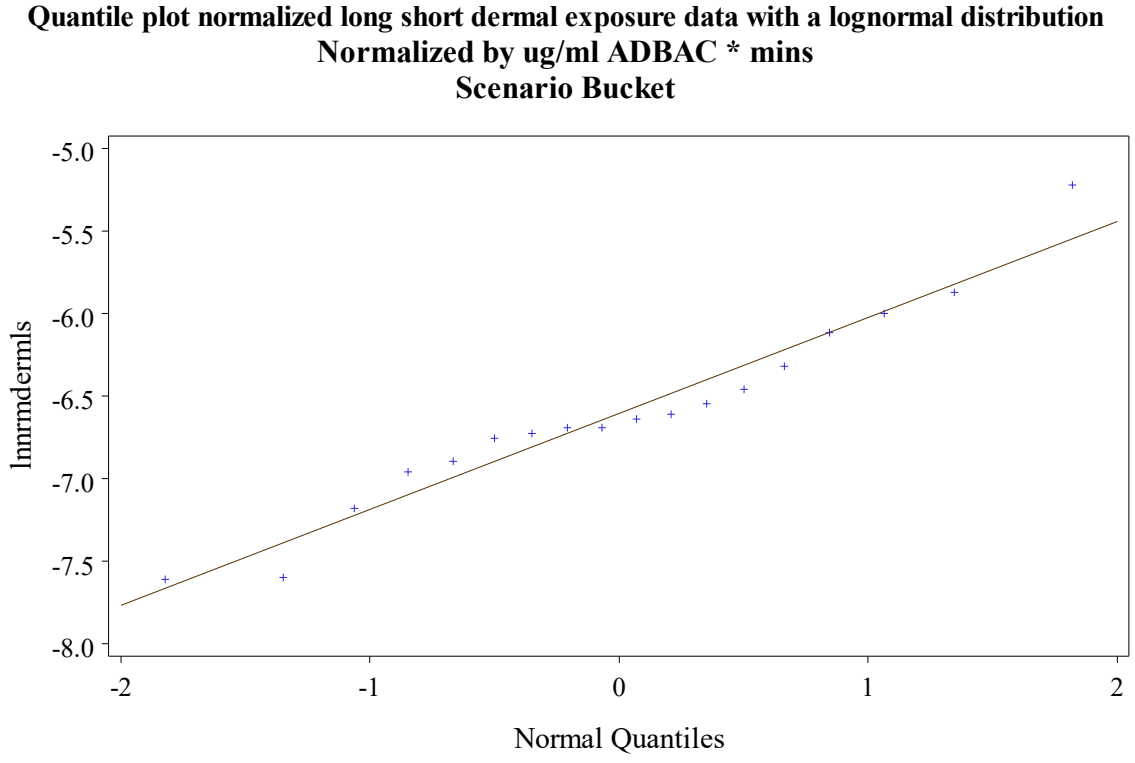

Figure AB6. Empirical quantile plot for Long Short Dermal, with a lognormal distribution

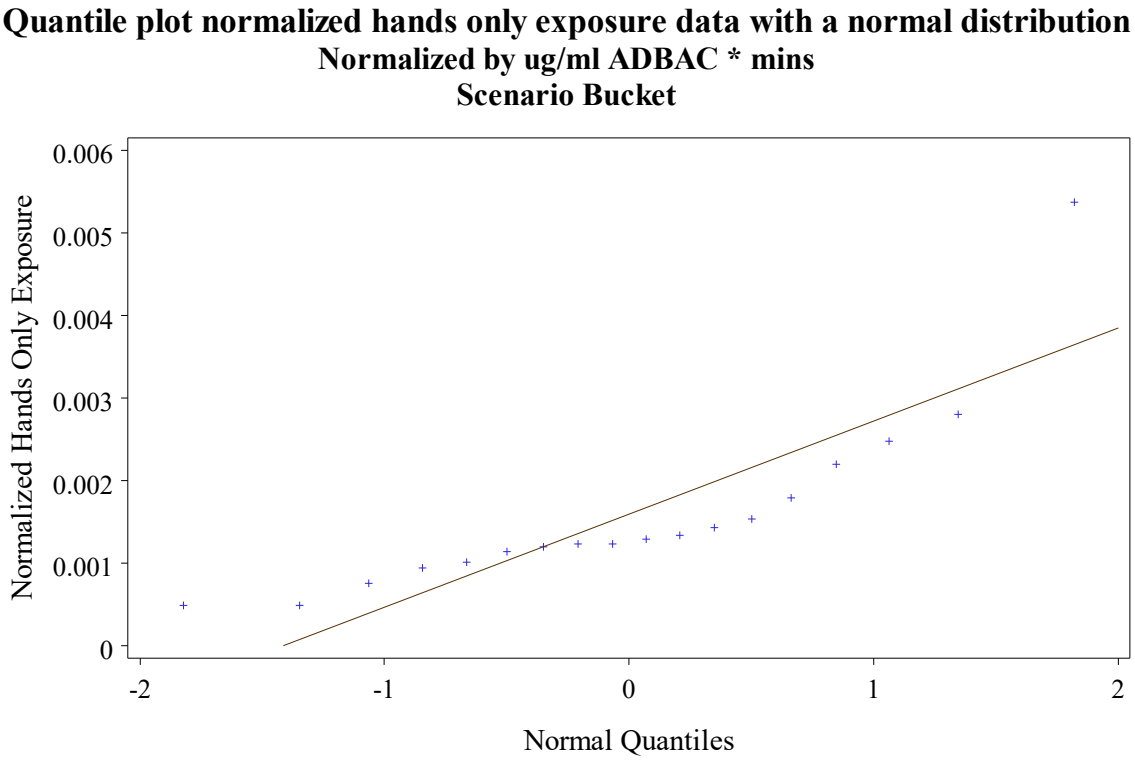

Figure AB7. Empirical quantile plot for Hands Only, with a normal distribution

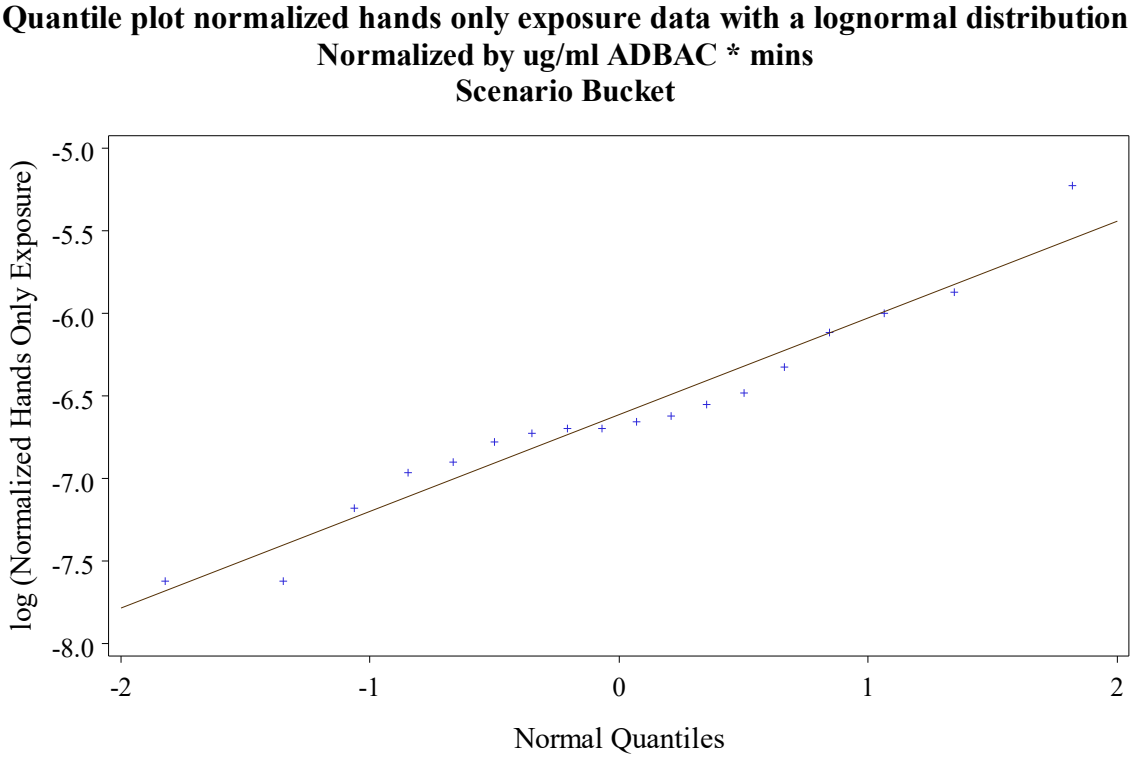

Figure AB8. Empirical quantile plot for Hands Only, with a lognormal distribution

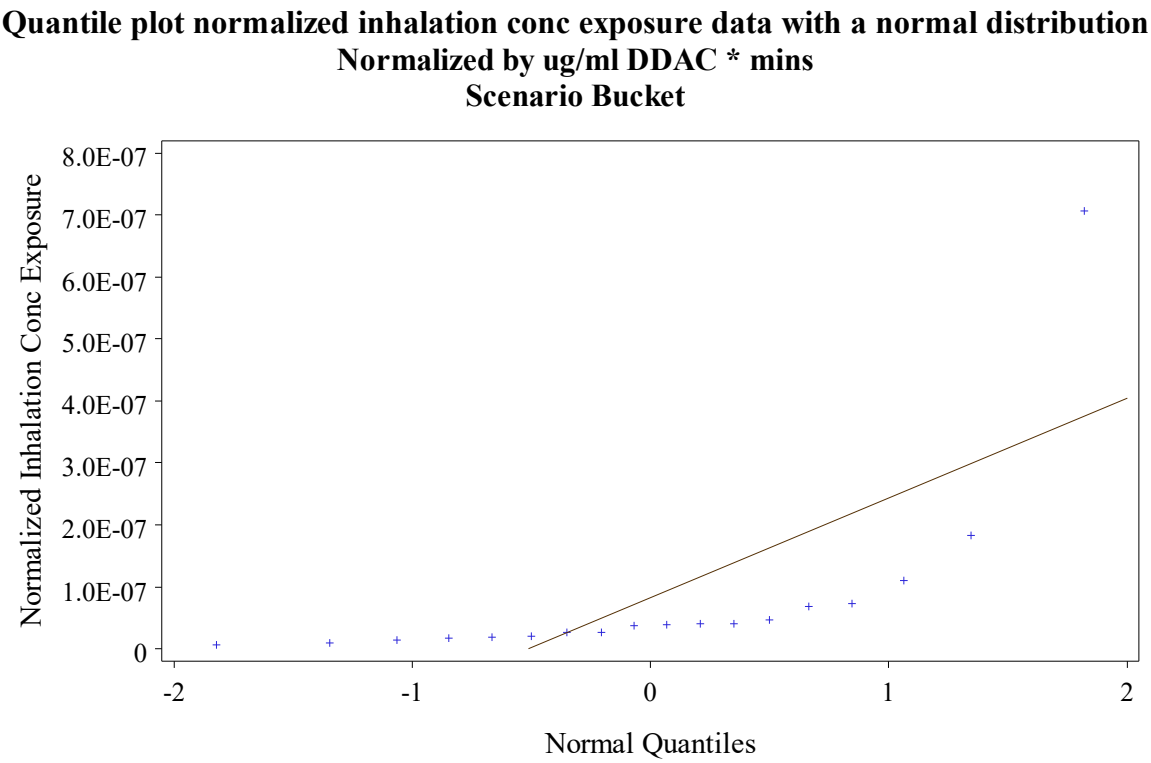

Figure AB9. Empirical quantile plot for Inhalation Concentration, with a normal distribution

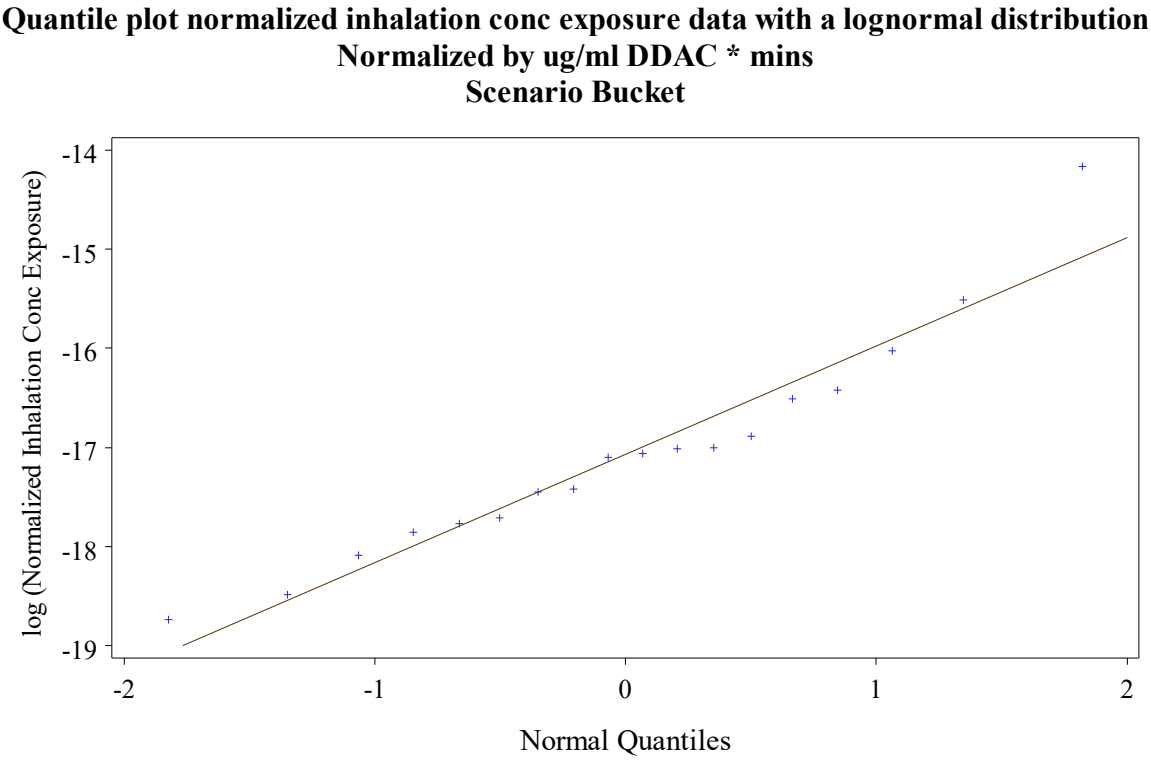

Figure AB10. Empirical quantile plot for Inhalation Concentration, with a lognormal distribution

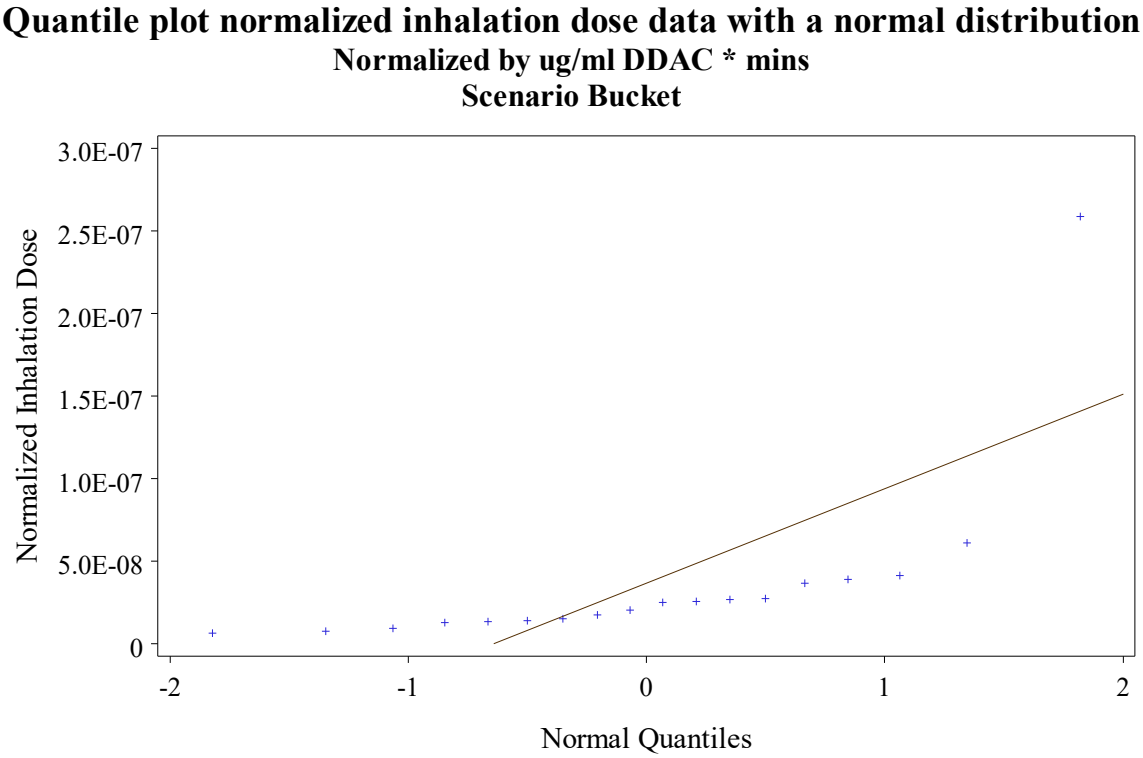

Figure AB11. Empirical quantile plot for Inhalation Dose, with a normal distribution

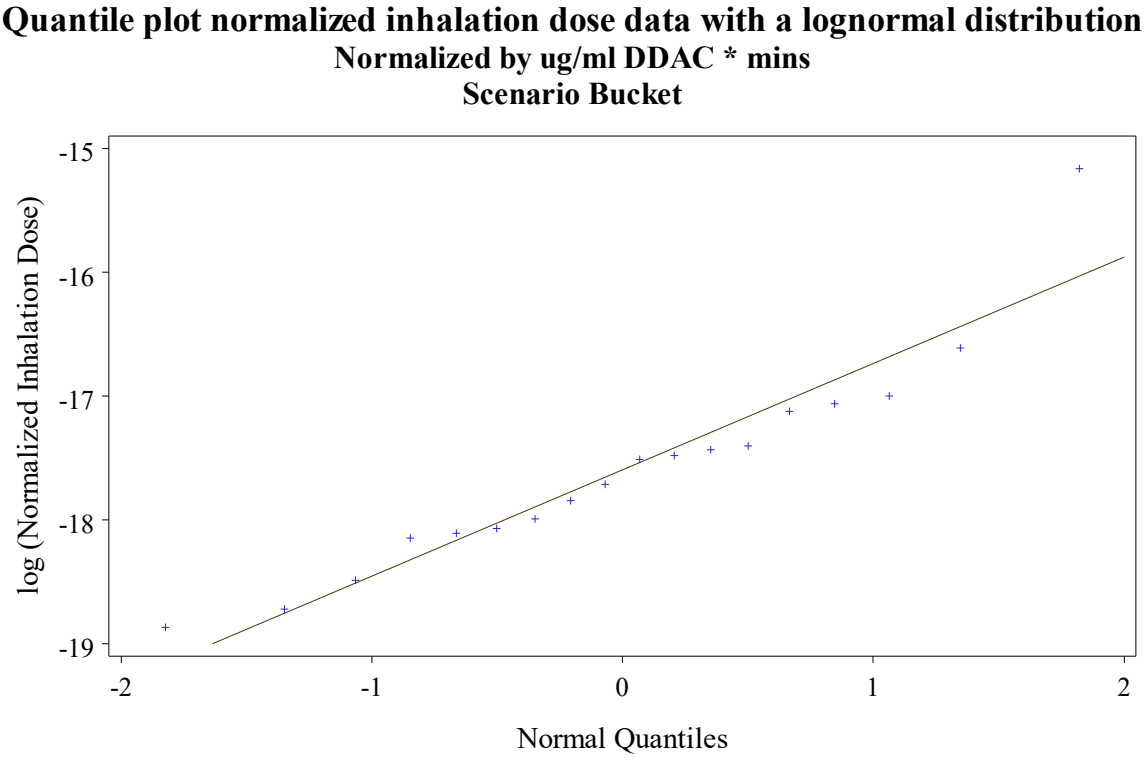

Figure AB12. Empirical quantile plot for Inhalation Dose, with a lognormal distribution

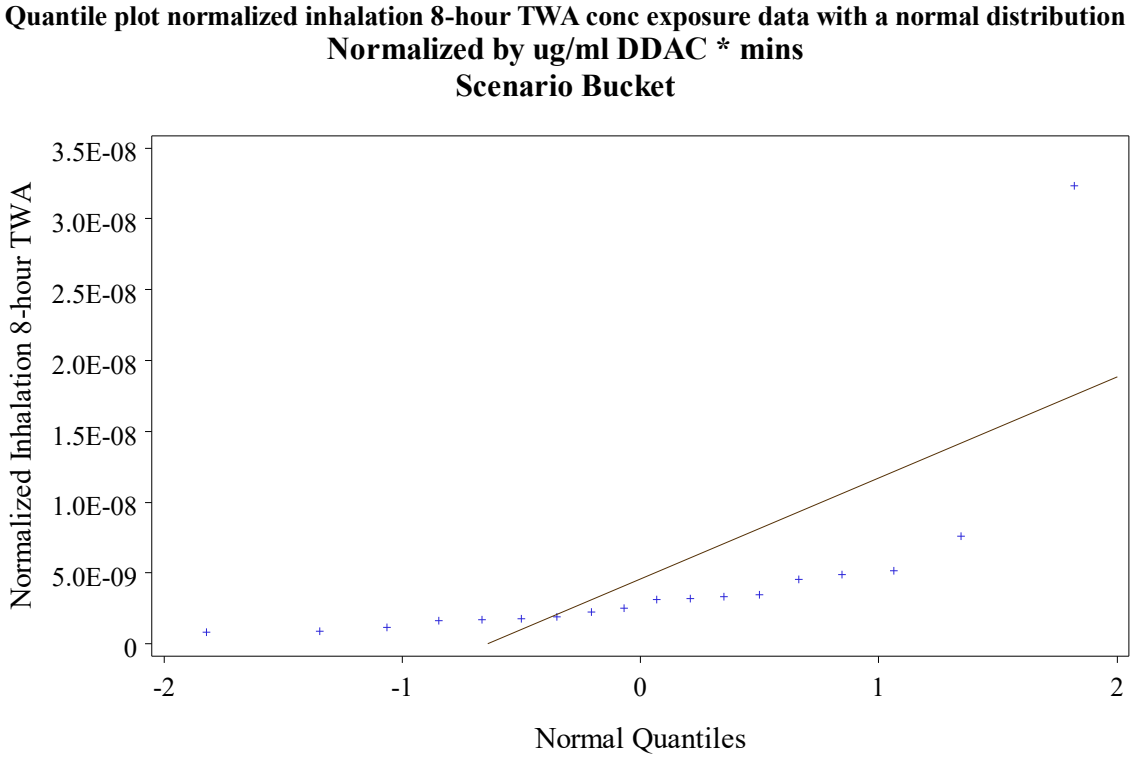

Figure AB13. Empirical quantile plot for Inhalation Time-weighted Average Conc, with a normal distribution

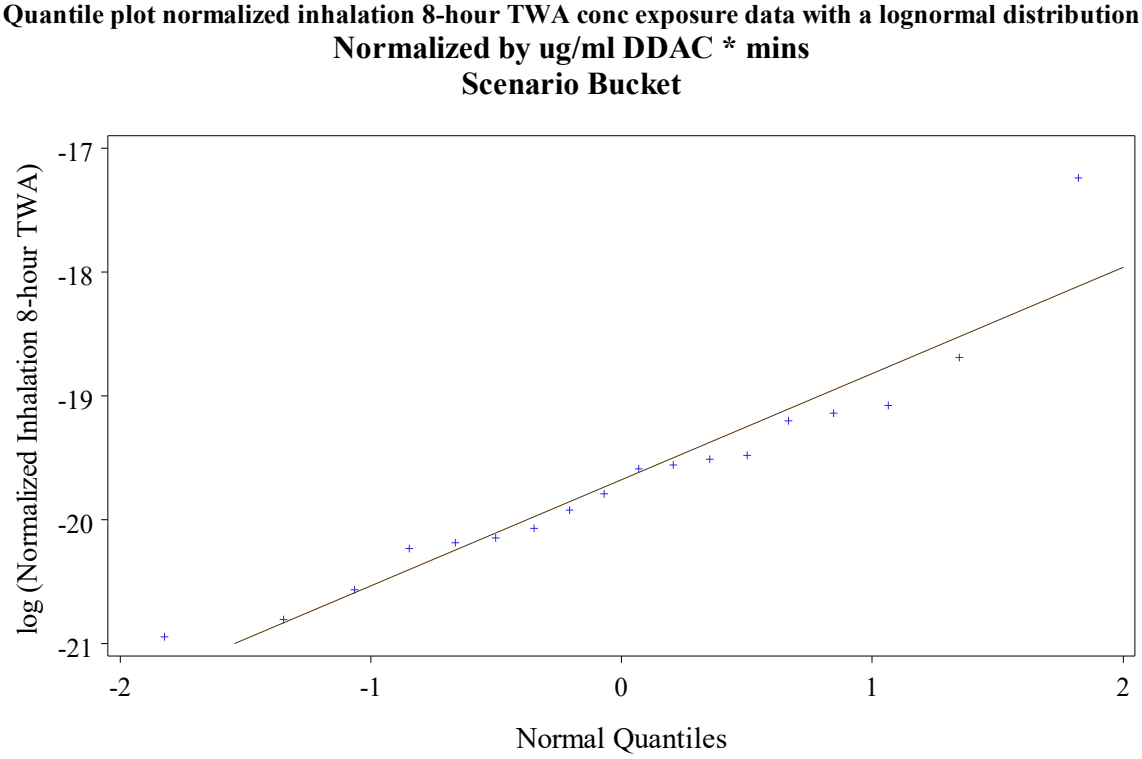

Figure AB14. Empirical quantile plot for Inhalation Time-weighted Average Conc, with a lognormal distribution

Log-log-Linearity Analyses and Estimated Log-log Slopes

The use of the normalized or unit exposure is based on the assumption that the exposure is proportional to the normalizing factor. The normalizing factor is either A) the concentration times the duration, B) the concentration, or C) one. The regression analyses described in this section do not apply to the case C where the normalizing factor equals one. Exact proportionality is defined as

Exposure = K × Normalizing Factor,

where K is the proportionality constant. Exact proportionality implies that

Normalized Exposure = Exposure / Normalizing Factor = K,

so that if the normalizing factor is doubled, then the exposure is exactly doubled, which is not a reasonable assumption due to the variability of exposure for any given value of the normalizing factor. Instead of exact proportionality we allow for random multiplicative error terms, which do not depend on the value of the normalizing factor so that

Exposure = K × Normalizing Factor × Multiplicative Errors, or

Normalized Exposure = K × Multiplicative Errors.

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

Log (Exposure) = Intercept + 1 × Log (Normalizing Factor) + Error Terms.

The statistical analyses of log-log-linearity, previously referred to as proportionality, is based on the following more general log-log-linear statistical model:

Linear Model

Log (Exposure) = Intercept + Slope × Log (Normalizing Factor) + Random Error.

The Random Error terms are assumed to be normally distributed with a mean of zero and a variance of Varerror. The error terms are also assumed to be independent of the Normalizing Factor, which is the explanatory variable in this regression model. The values of Intercept, Slope, and Varerror are parameters of the fitted model. This linear model is for the Exposure rather than the Normalized Exposure (Exposure / Normalizing Factor).

Using this model, taking exponentials of both sides gives

Exposure = $e^{\text{Intercept}} \times (\text{Normalizing Factor})^{\text{Slope}} \times e^{\text{Random Error}}$, so that

E{Exposure | Normalizing Factor} = Expected Exposure Given the Normalizing Factor

= C × $(\text{Normalizing Factor})^{\text{Slope}}$, where

C = Expected Value $\{e^{\text{Intercept}} \times e^{\text{Random Error}}\} = e^{\text{Intercept}} \times e^{\text{Varerror}/2}$

The value of E{Exposure | Normalizing Factor} is the arithmetic mean of the distribution of exposures for a future set of randomly selected consumers or workers that have the same value of the normalizing factor, i.e., for case A the product of the pesticide concentration and duration is the same, and for case B the pesticide concentration is the same. The parameters Intercept and Varerror are unknown, but are estimated by fitting the linear model to the data.

Therefore, the expected exposure given the value of the Normalizing Factor will be proportional to the value of the Normalizing Factor if and only if the Slope in the linear model equals 1. Note that the proportionality constant is C, which is very different to the estimated value of Slope.

Lognormal Model

If the value of Slope in the linear model is 1, then

Log (Exposure) = Intercept + 1 × Log (Normalizing Factor) + Random Error,

so that

Log (Normalized Exposure) = Log(Exposure / Normalizing Factor)

= Intercept + Random Error,

This statistical model is exactly the same as the lognormal simple random sampling model that was defined above.

The same calculations that we used for the linear model give

E{Exposure | Normalizing Factor} = Expected Exposure Given the Normalizing Factor

= C* × (Normalizing Factor), whre

C* = Expected Value $\{e^{Intercept^* \times Random\ Error}\} = e^{Intercept^*} \times e^{Varerror^*/2}$

These parameters are shown with asterisks to emphasize that they will in general be different from the ones for the model with a slope parameter not necessarily equal to 1.

Test for log-log-linearity with slope 1

Proportionality, or log-log-linearity with slope 1, of exposure to the Normalizing Factor is statistically modeled by assuming a Slope equal to 1 in the linear model.

Possible alternative models include the same formulation with a slope of zero, implying that the exposure does not depend upon the value of the normalizing factor, even though the normalizing factor 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 and test whether the slope is zero, one, or other possible values, we fitted the above linear model and computed confidence intervals for the slope.

Table AB18 shows the 95% confidence intervals for the slope calculated from the above linear model. A confidence interval that includes one but not zero supports the use of unit exposures. A confidence interval that includes zero but

not one suggests that the exposure does not depend on the normalizing factor. 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. This table also shows the widths of the confidence intervals used to evaluate the second benchmark for post-hoc power discussed in the next sub-section. The table also shows the values of the threshold concentration × duration (case A) or threshold concentration (case B) and the corresponding estimated exposure, to be described and discussed In the Supplement. Threshold values were not computed for the censored data models.

There were several non-detects reported in the data for both dermal and inhalation exposure. The rows marked "Substitute mid value" calculate the slope estimates after replacing each non-detect residue by the midpoint of the lowest and highest possible value for that residue. The rows marked "Censored data MLE" calculate the slope estimates for the linear model using a censored maximum likelihood statistical method and the lower and upper bounds for each non-detect. This procedure was implemented using the LIFEREG SAS procedure.

Table AB18. 95 percent confidence intervals for the slope of log exposure versus the log of the normalizing factor.

Exposure Route	Treatment of Non-detects	Estimate	Lower	Upper	Width	Threshold	Exposure
Long Dermal (mg)	Substitute mid value	0.711	0.346	1.077	0.731	5714	9.11
	Censored data MLE	0.711	0.393	1.030	0.637		
Short Dermal (mg)	Substitute mid value	0.713	0.349	1.076	0.727	5715	9.18
	Censored data MLE	0.713	0.396	1.030	0.634		
Long Short Dermal (mg)	Substitute mid value	0.711	0.348	1.074	0.726	5711	9.14
	Censored data MLE	0.711	0.395	1.027	0.633		
Hands Only (mg)	Substitute mid value	0.712	0.346	1.078	0.732	5717	9.10
	Censored data MLE	0.712	0.393	1.031	0.638		
Inhalation Concentration (mg/m^3)	Substitute mid value	0.282	–0.293	0.858	1.151	5494	0.00039
	Censored data MLE	0.377	–0.254	1.007	1.261		
Inhalation Dose (mg)	Substitute mid value	0.712	0.193	1.231	1.038	6636	0.00022
	Censored data MLE	0.750	0.214	1.286	1.072		
Inhalation Time-Weighted Average Concentration (mg/m^3)	Substitute mid value	0.712	0.193	1.231	1.038	6636	0.000027
	Censored data MLE	0.750	0.214	1.286	1.072		

Table AB18 gives the slopes for all the exposure routes.

The slopes range from 0.28 to 0.75, the confidence intervals for the slope exclude 0 except for the inhalation concentration, and in all but one case include 1. Thus the assumption of independence was rejected except for the inhalation concentration and the assumption of log-log-linearity with slope 1 was supported except for the inhalation concentration.

Suppose that the study had a (post-hoc) power of at least 80% for detecting "proportionality" (i.e., log-log-linearity with a slope of 1) under the null hypothesis of independence (slope = 0). It follows that the confidence intervals have an approximate width of 1.4 or less. The results in Table AB18 show that observed widths are all below 1.4. The maximum width was about 1.3. Therefore, based on the confidence intervals, the secondary objective of meeting the 80% power for detecting proportionality was met.

Quantile plots for residuals

To evaluate the fitted linear regression models we created quantile-quantile[1] plots of the studentized residuals for each fitted model. The residual is the observed value of log exposure minus the predicted value. The studentized residual is the residual divided by its standard error. For these analyses we used the internally studentized residual where the estimated standard error is calculated using all the data. An alternative approach that is sometimes preferred when checking for outliers in small samples is to use the externally studentized residual where the estimated standard error is calculated after excluding the data point. If the plotted points lie close to the straight line then the model assumptions for the linear model are supported. Furthermore, a standard rule of thumb identifies statistical outliers as cases where the studentized residual is above +3 or below −3 (a stricter criterion of ±2 is sometimes used, and more complex statistical outlier tests taking into account the sample size are also available). These quantile-quantile plots are for the Linear Model. Quantile-quantile plots for the Lognormal Model were presented in the even-numbered Figures AB1 to AB14 above, since in that case both the predicted values and the standard errors are the same for every ME. The quantile-quantile plots of the studentized residuals for all exposure routes are shown below in Figures AB15 to AB21.

[1] These quantile plots compare the distribution of the studentized residuals to a standard normal distribution. Some authors prefer a more exact approach where the distribution of the studentized residuals is compared to a t distribution. That method is not easily available using current SAS software.

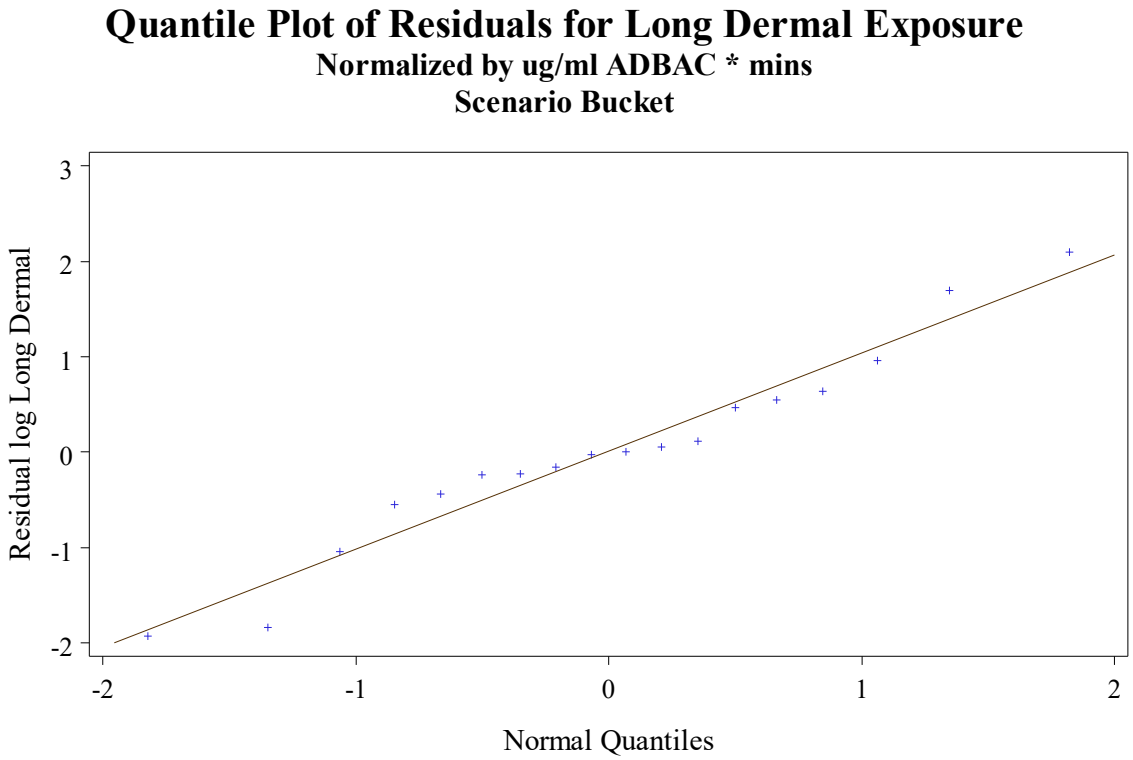

Figure AB15. Quantile plot of residuals from linear model for Long Dermal

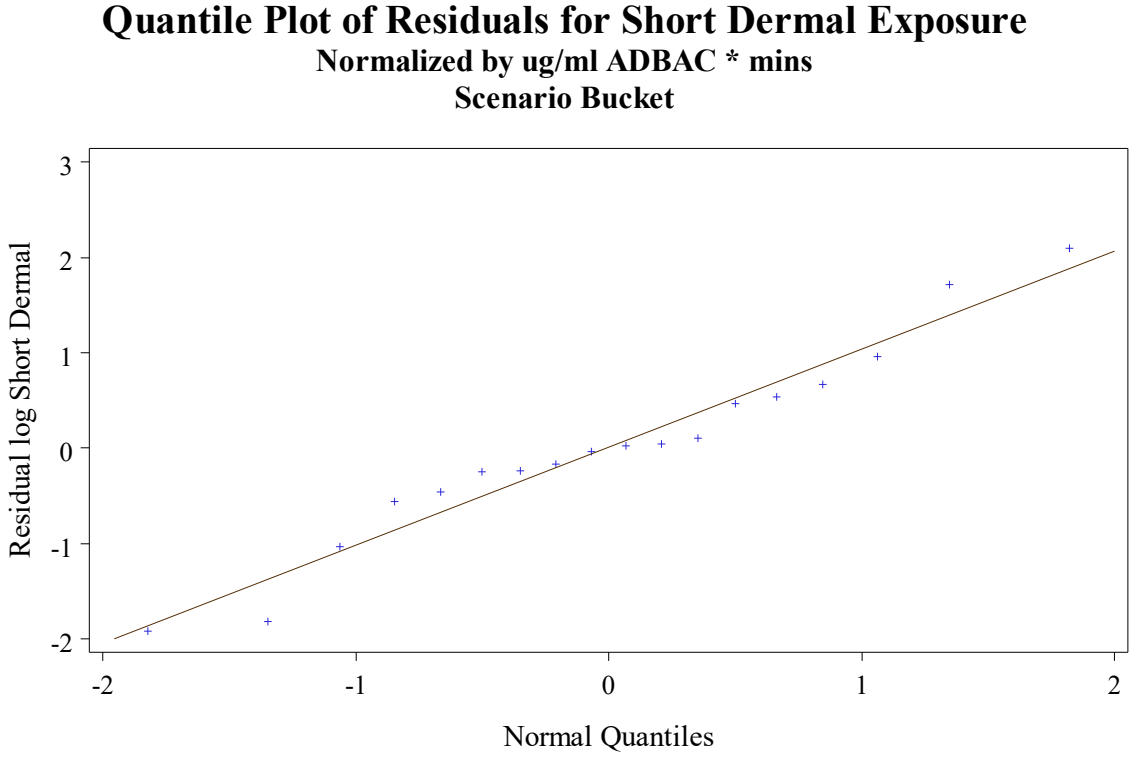

Figure AB16. Quantile plot of residuals from linear model for Short Dermal

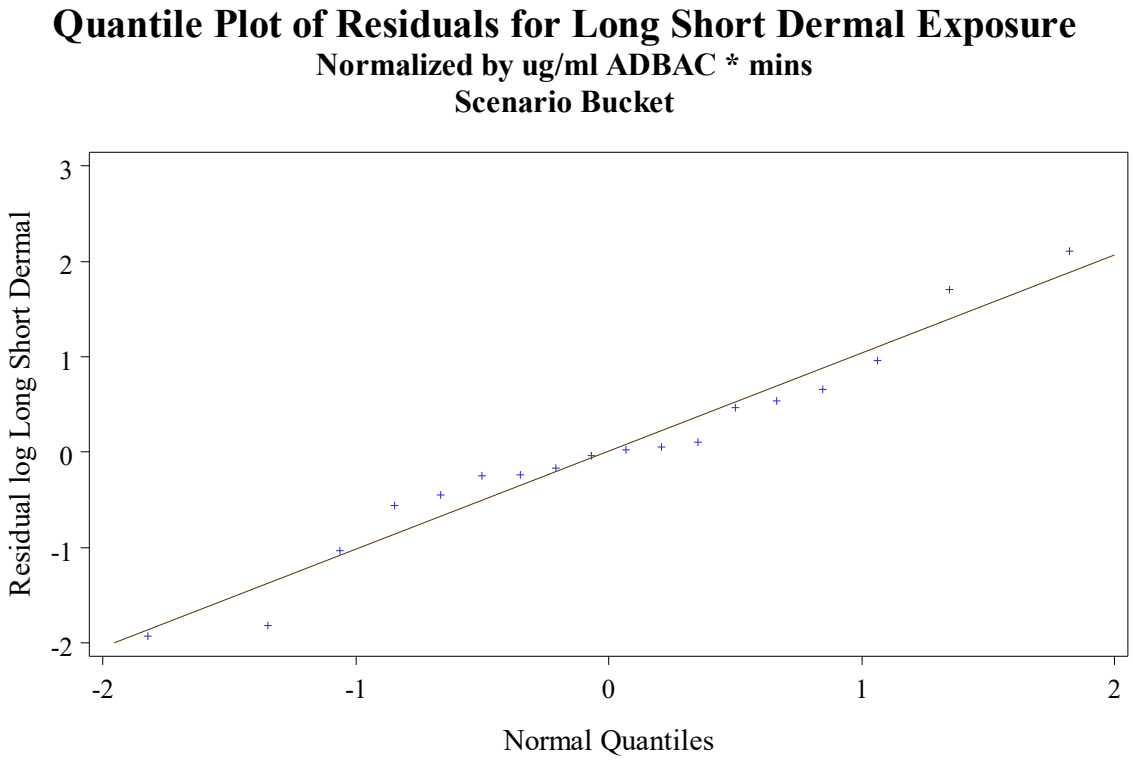

Figure AB17. Quantile plot of residuals from linear model for Long Short Dermal

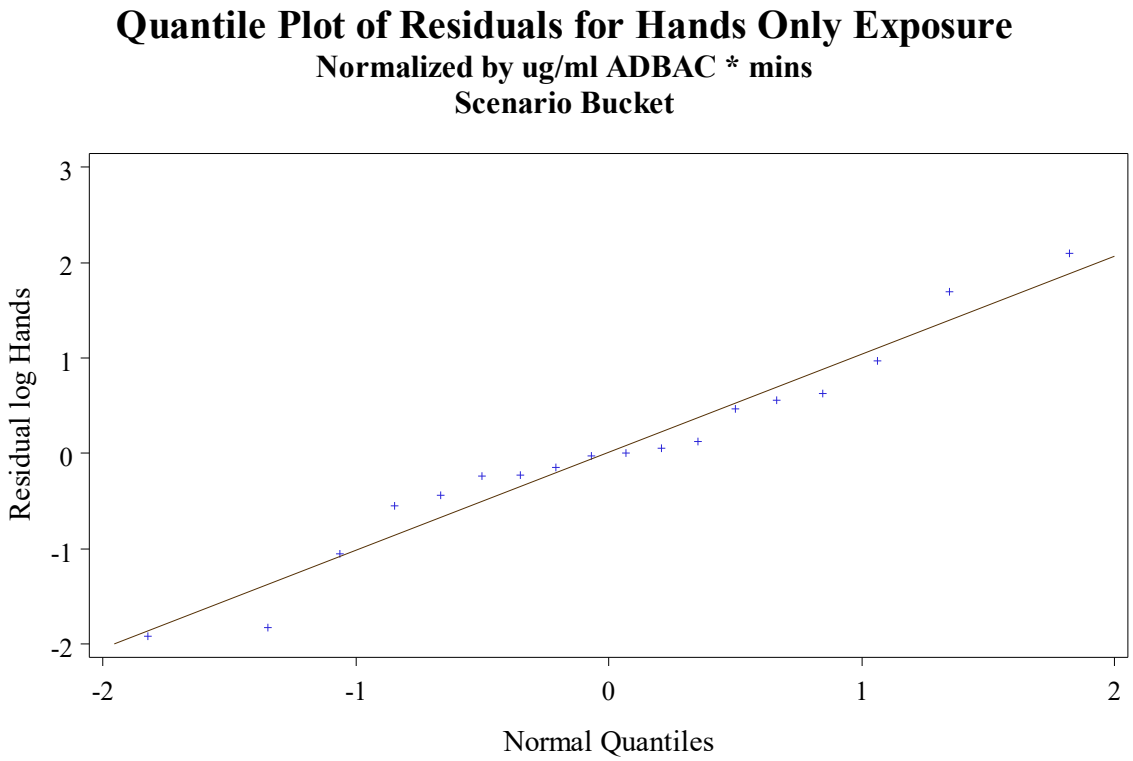

Figure AB18. Quantile plot of residuals from linear model for Hands Only

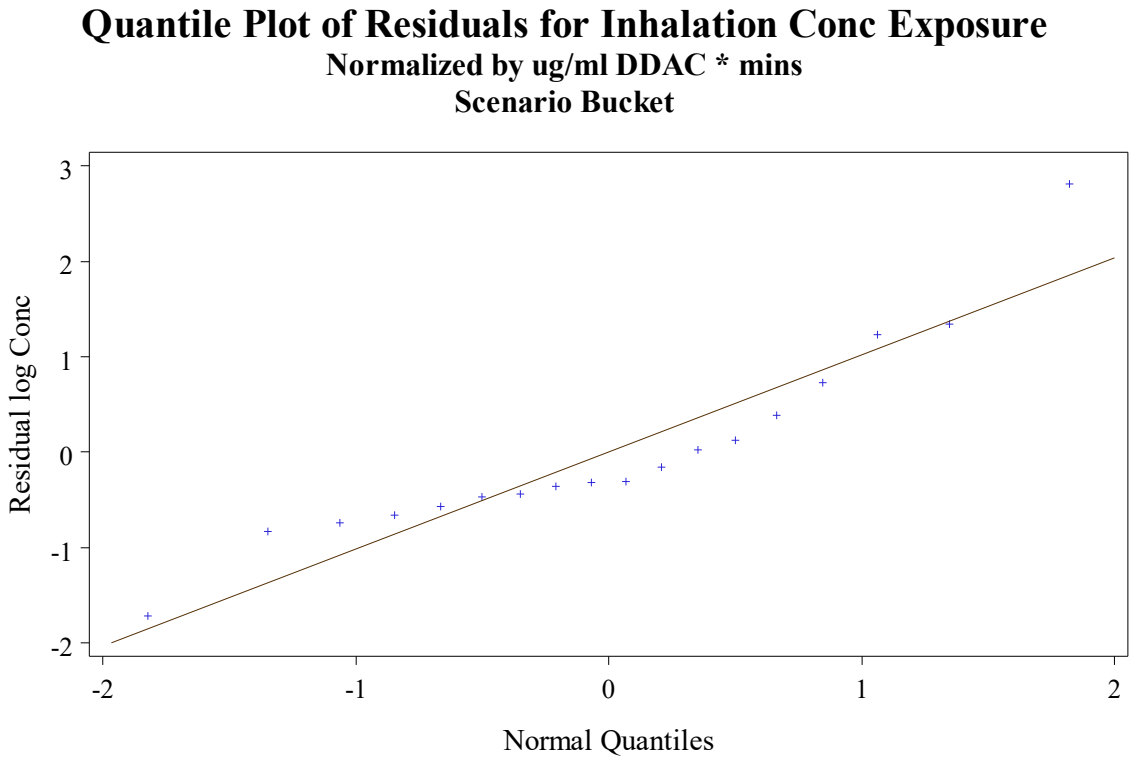

Figure AB19. Quantile plot of residuals from linear model for Inhalation Concentration

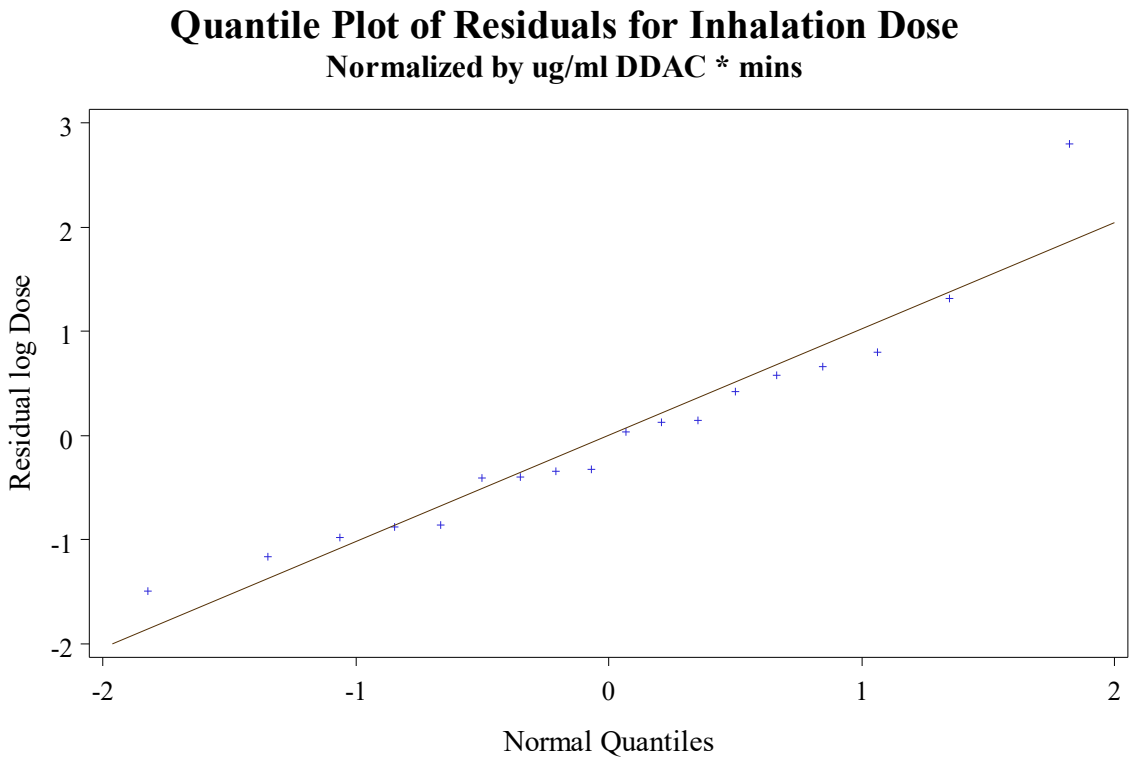

Figure AB20. Quantile plot of residuals from linear model for Inhalation Dose

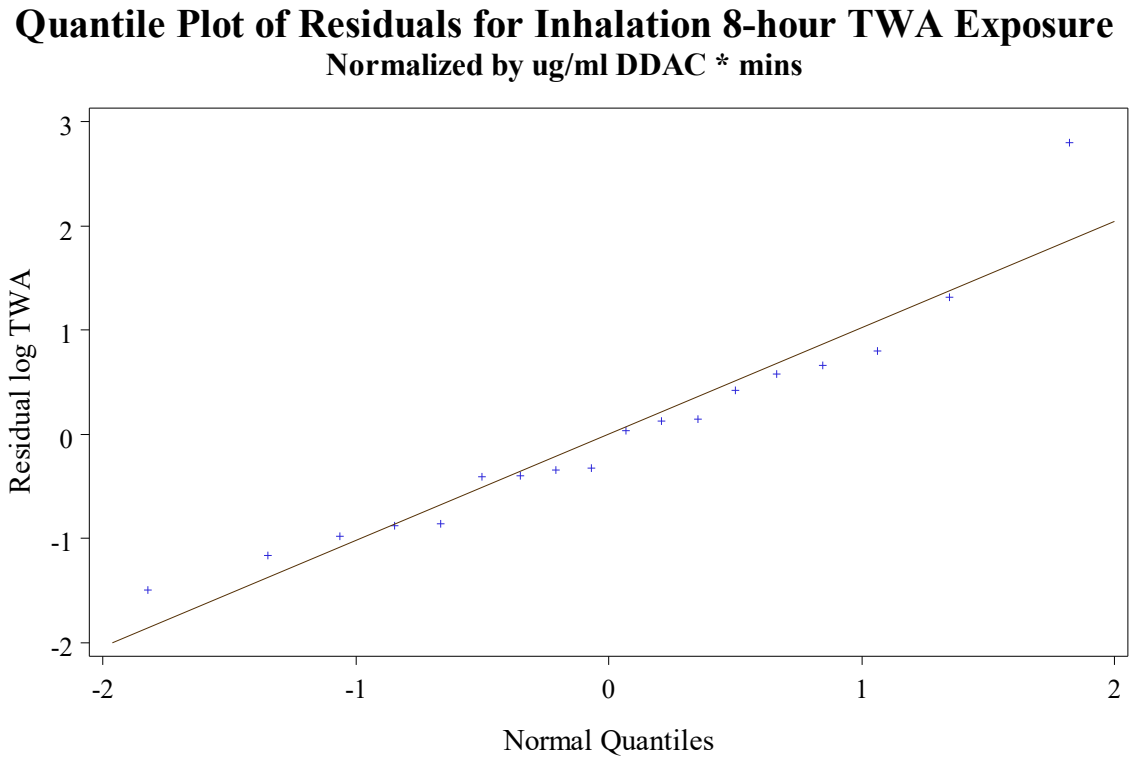

Figure AB21. Quantile plot of residuals from linear model for Inhalation Tine-Weighted Average Concentration

The quantile-quantile plots of the studentized residuals are reasonably close to the straight line. None of the studentized residuals exceeded the standard outlier cutoff of ±3.

Regression plots

The lognormal linear regression results for all the exposure routes are shown below using the mid value substitution method for non-detect values. The data points are labeled to show the targeted durations.

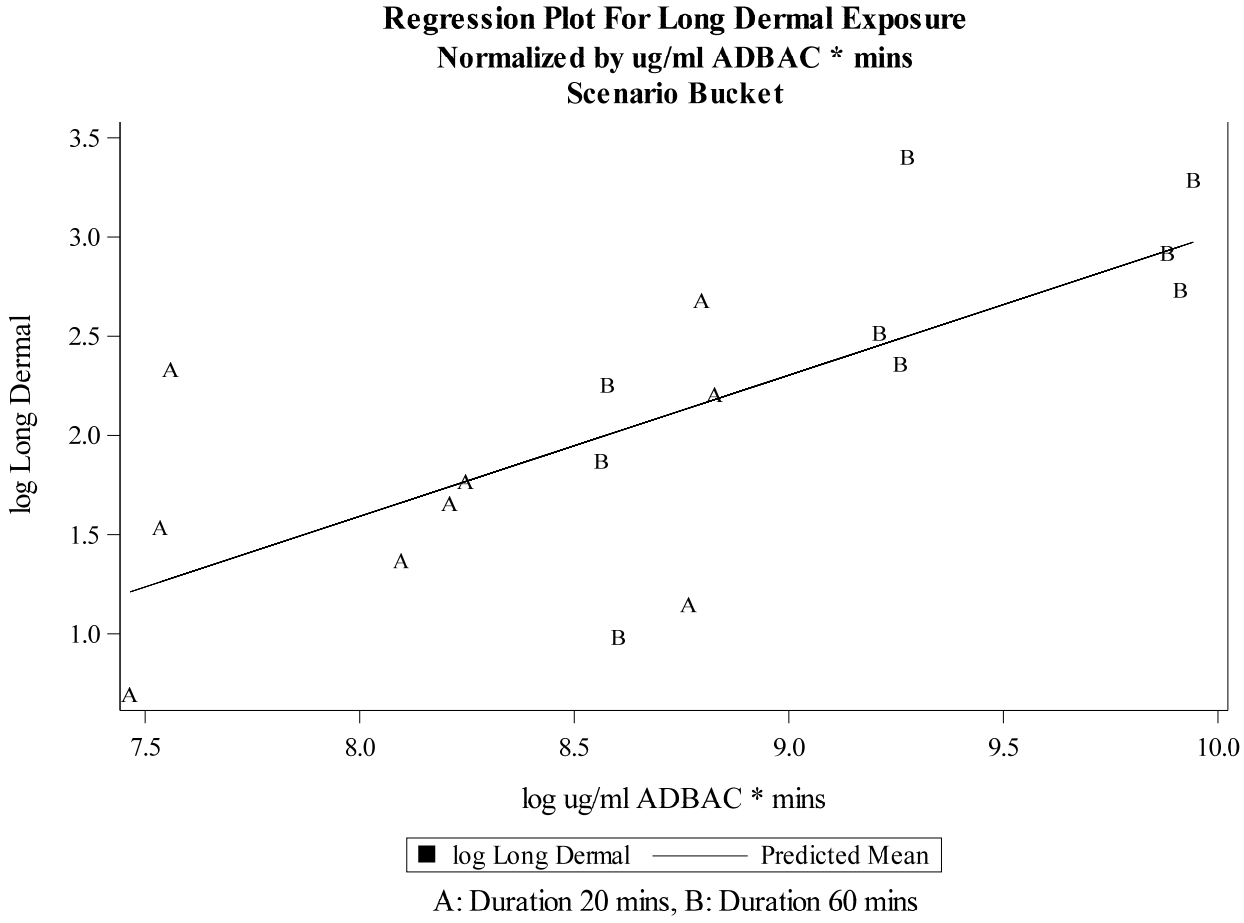

Figure AB22. Regression plot for Long Dermal Exposure (mg)

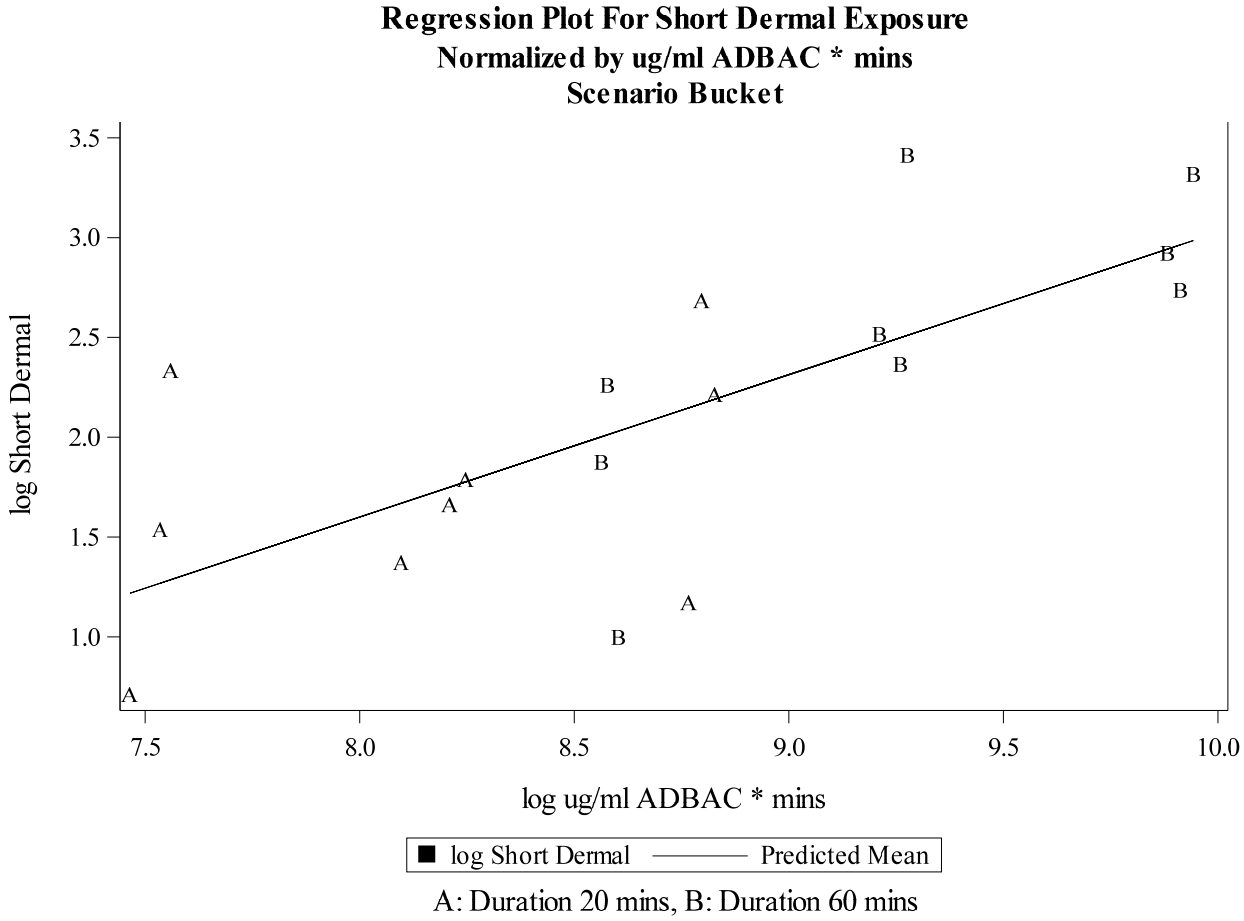

Figure AB23. Regression plot for Short Dermal Exposure (mg)

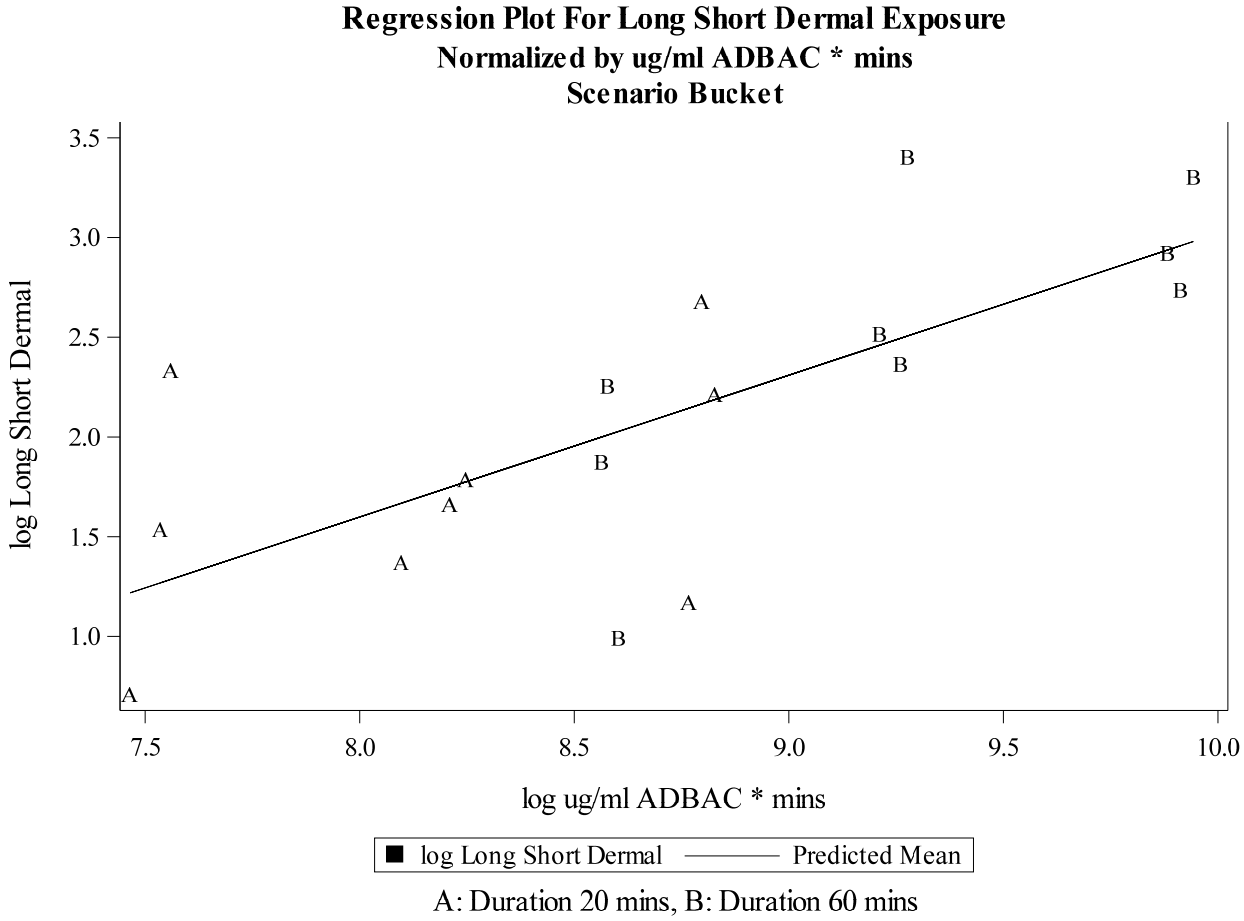

Figure AB24. Regression plot for Long Short Dermal Exposure (mg)

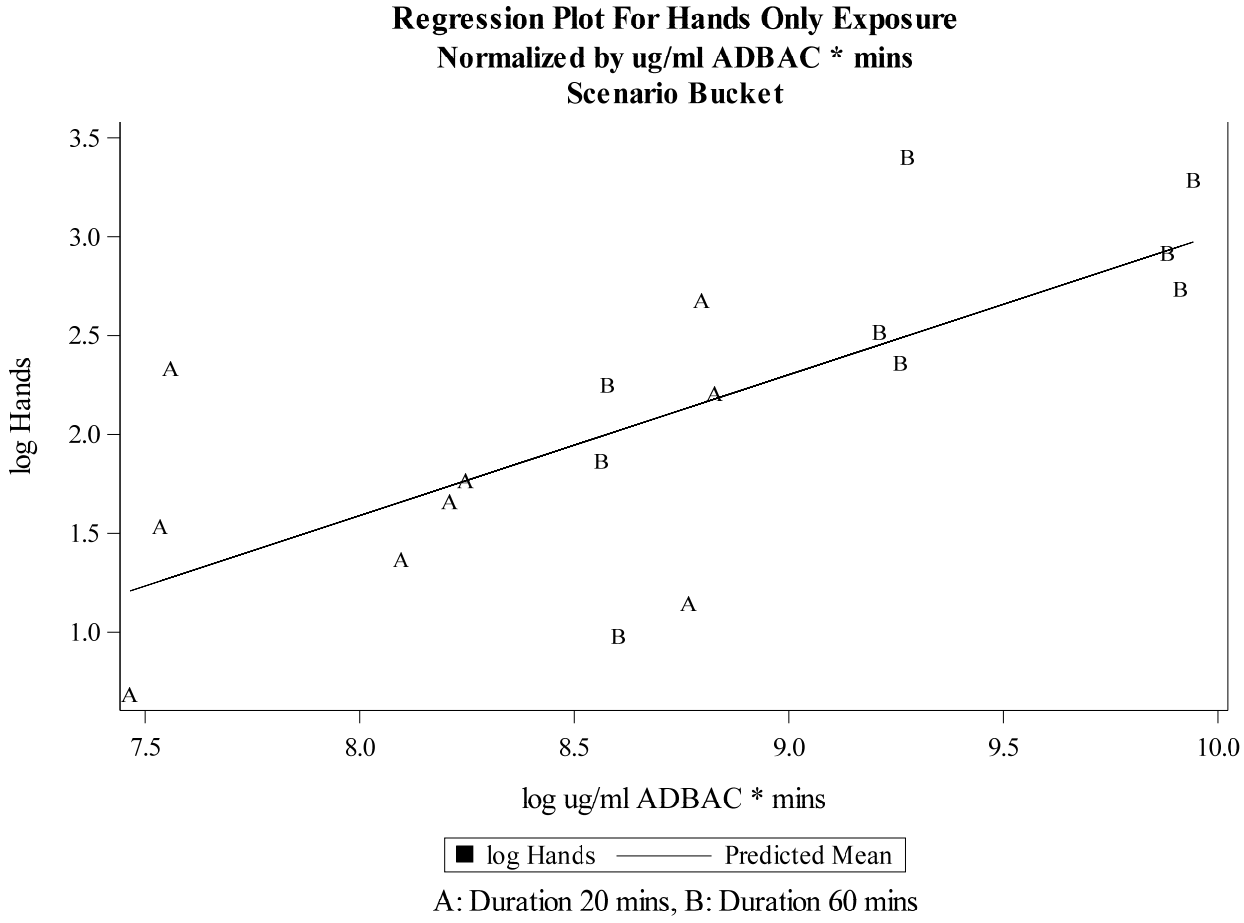

Figure AB25. Regression plot for Hands Only Exposure (mg)

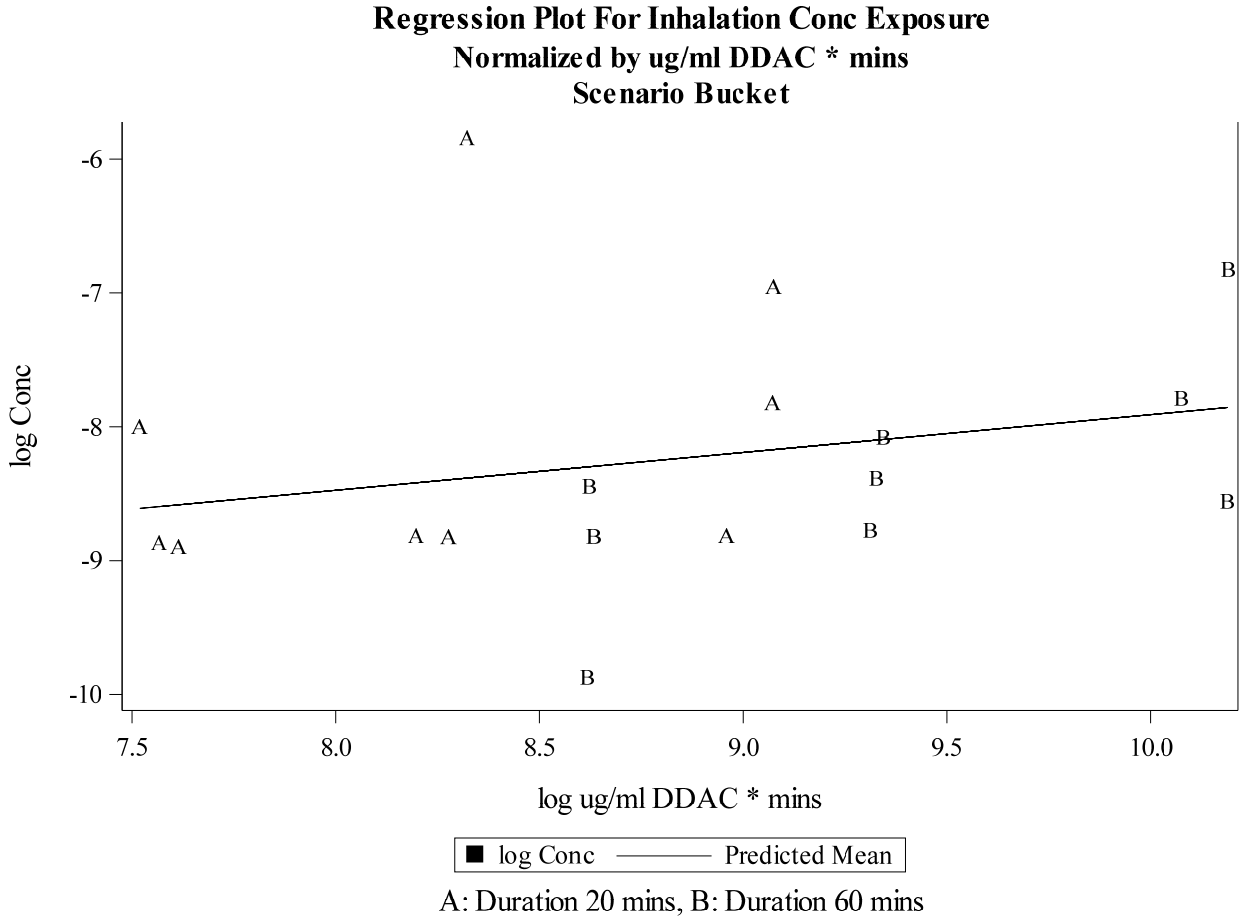

Figure AB26. Regression plot for Inhalation Concentration Exposure (mg/m^3)

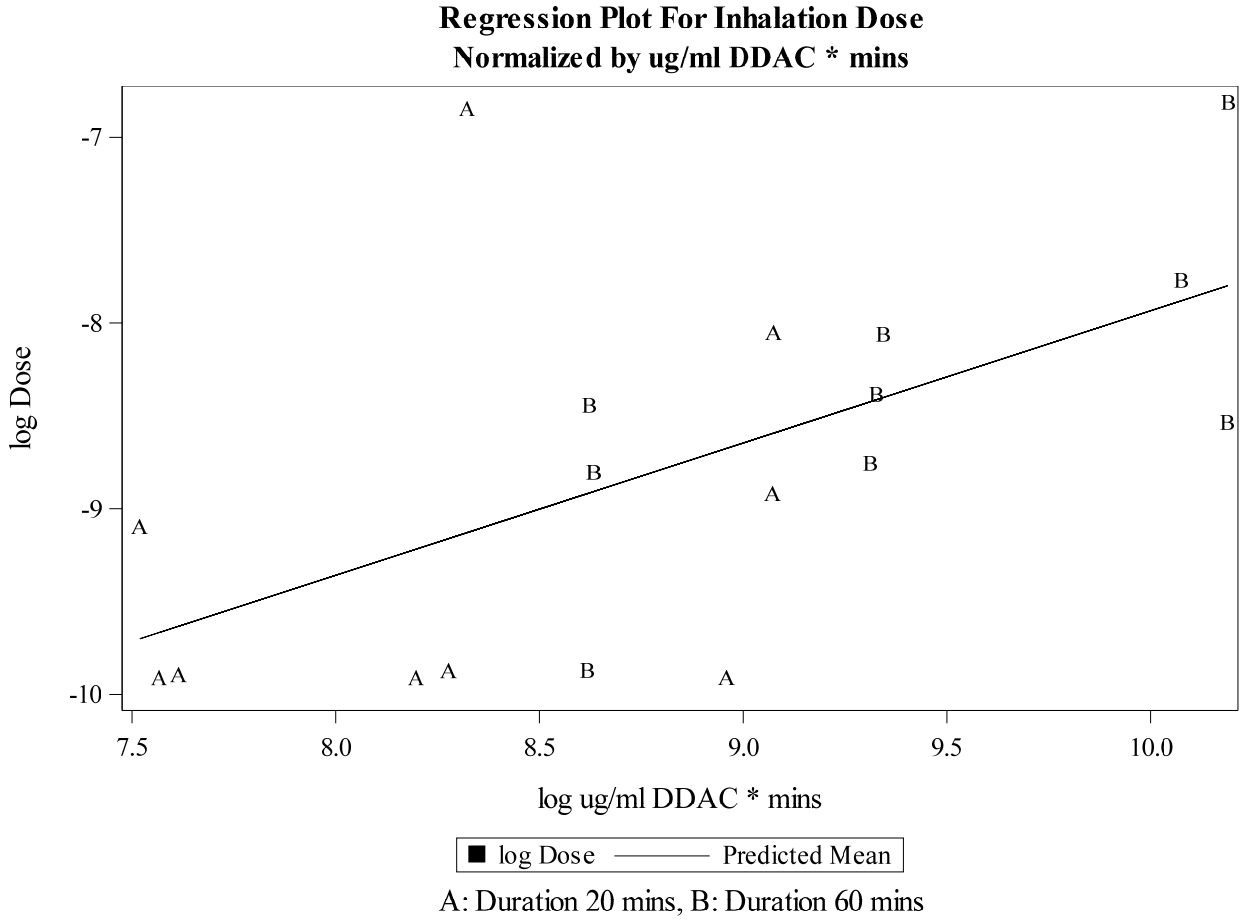

Figure AB27. Regression plot for Inhalation Dose (mg)

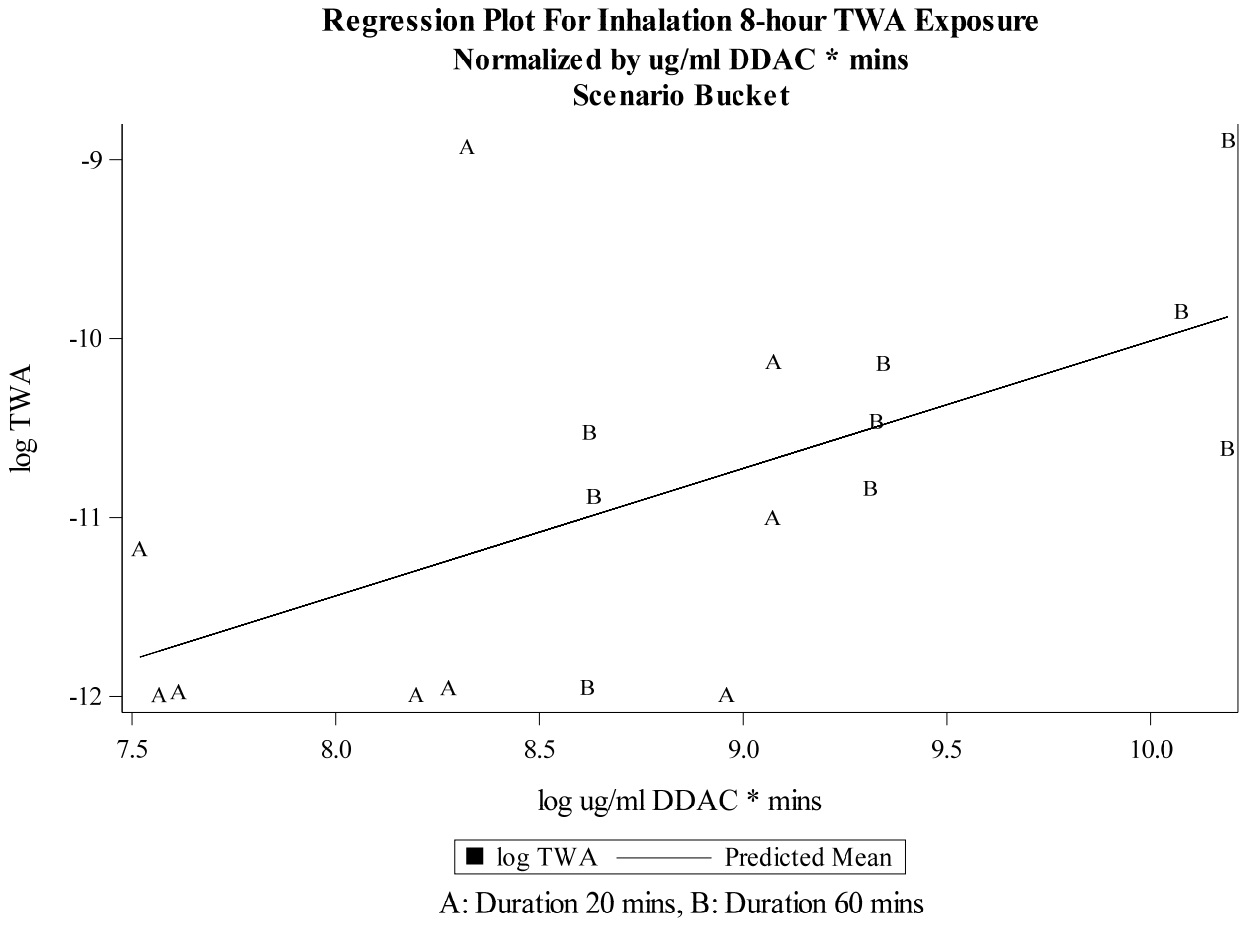

Figure AB28. Regression plot for Inhalation Time-Weighted Average Exposure (mg/m^3)

Quadratic models

The log-log-linearity test was based on a linear model for log exposure versus log (Normalizing Factor). The HSRB has 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 (Normalizing Factor) + Error Terms,

the main quadratic model is of the form

Log (Exposure) = Intercept + Slope × Log (Normalizing Factor) + Quad × {Log (Normalizing Factor)}^{2}

+ Error Terms.

Note that the quadratic term is the square of the logarithm of the Normalizing Factor rather than the logarithm of the square; the latter approach produces an ill-defined model with two multiples of the logarithm of the Normalizing Factor).

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

$$\text{Exposure} = \text{Intercept} + \text{Slope} \times (\text{Normalizing Factor}) + \text{Quad} \times (\text{Normalizing Factor})^2 + \text{Error Terms}.$$

We do not recommend this second approach for these data since the exposures are known to be non-negative and the quantile plots showed that the exposure data are better modeled using a log-normal distribution than using a normal distribution.

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

$$\text{Log (Exposure)} = \text{Intercept} + \text{Slope} \times \text{Log (Normalizing Factor)} + \text{Quad} \times \{\text{Log (Normalizing Factor)}\}^2 + \text{Error Terms}.$$

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, then the quadratic model is supported. Otherwise the linear model should be used.

Table AB19 presents the quadratic coefficient Quad from the fitted quadratic regression models for all the exposure routes using All data. Coefficients for the Intercept and Slope are shown under model 2 in Tables AB20 to AB26 below.

Table AB19. Quadratic coefficients with 95% confidence intervals for quadratic regression models for the log exposure versus log (Normalizing Factor)

Exposure Route	Estimate	Lower Bound	Upper Bound
Long Dermal	0.18	−0.28	0.64
Short Dermal	0.18	−0.27	0.63
Long Short Dermal	0.18	−0.27	0.63
Hands Only	0.18	−0.28	0.64
Inhalation Concentration	0.12	−0.56	0.79
Inhalation Dose	0.11	−0.50	0.71
Inhalation Time-weighted Average	0.11	−0.50	0.71

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

Alternative Statistical Approaches

In this section we present and compare some alternative statistical approaches to the linear and quadratic models.

For estimating the 95th percentile of the normalized or unit exposure, our preferred approach is to fit a lognormal statistical model. HSRB has previously recommended consideration of a quantile regression approach, which would provide confidence intervals for the 95th percentile assuming a simple random sample from an unspecified distribution. This is exactly the same as the above calculations of the confidence intervals for P95s calculated using the non-parametric bootstrap approach. The quantile regression approach could also be applied to the exposure to estimate the 95th percentile of the exposure as a linear or non-linear function of the amount of active ingredient. We chose not to apply the latter approach due to its complexity and because it would not be consistent with the modeling approaches used for estimating the arithmetic mean.

For estimating the dependence of exposure on the amount of active ingredient, our main model was the linear model described above, where the mean log(exposure) is a linear function of the log(Normalizing Factor). All logarithms in this memorandum are natural logarithms. For convenience let NF denote the Normalizing Factor (which is the concentration times the duration in the main text).

This model is described by the equation:

Model 1: Log(Exposure) = μ + β log(NF) + Error

We also considered a quadratic model, although we found above that the quadratic term was not significant for the main analyses. This model is described by the equation:

Model 2: Log(Exposure) = μ + β log(NF) + γ {log(NF)}^{2} + Error

The HSRB has previously suggested including non-linear functions of the log-log-logistic or logistic forms:

Model 3. Log-log-logistic: Exposure = $\delta + \frac{\alpha-\delta}{1+\gamma\, exp\{\beta\, log(NF)\}}$ + Error.

Model 4. 3-parameter logistic: Exposure = $\frac{C}{1+exp\{\alpha+\beta\times NF\}}$ + Error.

Since there is no background exposure in most of these scenarios, we will assume δ = 0 for the log-log-logistic model. A major problem with using the log-log-logistic model is that the mean exposure is bounded above, which is possibly unrealistic.

For each of the above models, the errors are assumed to be normally distributed.

Another HRSB suggestion was to fit a gamma model instead of a log-normal model. We chose to assume a log link, so that the exposure has a gamma distribution with a mean exp(μ + β log(NF) and variance = (mean)^2/ϕ. This is model 5.

The fitted model parameters and confidence intervals are presented in Tables AB20 to AB26 below. Note that the nonlinear models 4 and 5 were fitted using SAS's iterative procedure NLIN and it is possible that better estimates of the parameters could have been obtained using different starting points for the estimated parameters. Furthermore, in several cases the iterative methods failed to converge or some of the confidence bounds were not calculated and in those cases the model was not tabulated. For the dermal exposure log-log logistic model the estimated coefficients were extremely large, which also might suggest a poorly fitting model. In rare cases a model might converge for the inhalation dose but not for the inhalation time-weighted average, or vice versa, which is theoretically impossible (since

the exposure values differ by a factor of 8), but this can happen due to computer overflow issues. For the same reason, for these two models, the calculated AIC values described in the next sub-section below might not be identical.

Model Parameters

Table AB20. Alternative fitted statistical models for Long Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-4.099	-7.294	-0.903
	β	0.711	0.346	1.077
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	9.515	-25.072	44.102
	β	-2.435	-10.402	5.532
	γ	0.180	-0.276	0.637
3. Log-log logistic regression of exposure on NF	**α**	32.637	-37.660	102.934
	γ	152064.085	-2285665.982	2589794.153
	β	-1.267	-3.438	0.904
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-3.475	-6.045	-0.906
	β	0.655	0.361	0.949
	ϕ	3.862	2.063	7.232

Table AB21. Alternative fitted statistical models for Short Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-4.102	-7.279	-0.924
	β	0.713	0.349	1.076

Model	Parameter	Estimate	Lower Bound	Upper Bound
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	9.547	-24.831	43.926
	β	-2.442	-10.361	5.478
	γ	0.181	-0.273	0.635
3. Log-log logistic regression of exposure on NF	**α**	33.558	-41.547	108.664
	γ	146650.344	-2201382.226	2494682.914
	β	-1.259	-3.438	0.919
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-3.497	-6.056	-0.939
	β	0.659	0.366	0.951
	ϕ	3.891	2.078	7.286

Table AB22. Alternative fitted statistical models for Long Short Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-4.089	-7.261	-0.917
	β	0.711	0.348	1.074
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	9.502	-24.823	43.827
	β	-2.430	-10.337	5.477
	γ	0.180	-0.273	0.633
3. Log-log logistic regression of exposure on NF	**α**	33.569	-42.585	109.724
	γ	132862.574	-1964807.347	2230532.495
	β	-1.247	-3.405	0.910

Model	Parameter	Estimate	Lower Bound	Upper Bound
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-3.479	-6.033	-0.925
	β	0.656	0.364	0.948
	ϕ	3.908	2.087	7.320

Table AB23. Alternative fitted statistical models for Hands Only Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-4.108	-7.307	-0.909
	β	0.712	0.346	1.078
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	9.449	-25.186	44.083
	β	-2.421	-10.399	5.557
	γ	0.180	-0.277	0.637
3. Log-log logistic regression of exposure on NF	**α**	32.522	-37.126	102.171
	γ	154597.984	-2325999.037	2635195.005
	β	-1.269	-3.440	0.902
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-3.478	-6.050	-0.906
	β	0.655	0.361	0.950
	ϕ	3.854	2.059	7.216

Table AB24. Alternative fitted statistical models for Inhalation Concentration (mg/m^3)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-10.734	-15.838	-5.630
	β	0.282	-0.293	0.858
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-1.626	-54.321	51.069
	β	-1.791	-13.743	10.160
	γ	0.117	-0.557	0.791
3. Log-log logistic regression of exposure on NF	**α**			
	γ			
	β			
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-8.482	-13.545	-3.420
	β	0.088	-0.483	0.659
	ϕ	1.070	0.600	1.908

Table AB25. Alternative fitted statistical models for Inhalation Dose (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-15.055	-19.658	-10.452
	β	0.712	0.193	1.231

Model	Parameter	Estimate	Lower Bound	Upper Bound
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-6.715	-54.230	40.800
	β	-1.187	-11.964	9.590
	γ	0.107	-0.500	0.715
3. Log-log logistic regression of exposure on NF	**α**			
	γ			
	β			
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-13.327	-17.720	-8.935
	β	0.564	0.068	1.059
	ϕ	1.345	0.746	2.425

Table AB26. Alternative fitted statistical models for Inhalation Time Weighted Average Concentration (mg/m^3)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-17.135	-21.738	-12.532
	β	0.712	0.193	1.231
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-8.794	-56.310	38.721
	β	-1.187	-11.964	9.590
	γ	0.107	-0.500	0.715
3. Log-log logistic regression of exposure on NF	**α**			
	γ			

Model	Parameter	Estimate	Lower Bound	Upper Bound
	β			
4. 3-parameter logistic regression of exposure on NF	α			
	c			
	β			
5. Gamma model for exposure	μ	-15.407	-19.799	-11.014
	β	0.564	0.068	1.059
	ϕ	1.345	0.746	2.425

Model Comparisons

One way to compare the fit of the 7 models presented above is to use the Akaike Information Criterion (AIC), which takes minus twice the log-likelihood and then makes an adjustment or penalty for the number of parameters in the model. To properly apply this approach to the seven models it was first necessary to re-express all of them using the same dependent variable, ln(exposure), since models 1 and 2 were specified using ln(exposure) but models 3 to 5 were specified using exposure. The following two tables compare the AIC values for the various Dermal and Inhalation exposure measures. The smaller values of the AIC suggest a better-fitting model. AIC values for models that failed to converge are not shown.

Table AB27. Akaike Information Criteria values for alternative models for Dermal Exposure

Model	Long Dermal	Short Dermal	Long Short Dermal	Hands Only
1. Linear regression of Ln(exposure) on Ln(NF)	33.8	33.6	33.5	33.9
2. Quadratic regression of Ln(exposure) on Ln(NF)	35.0	34.8	34.7	35.0
3. Log-log logistic regression of exposure on NF	43.0	43.2	42.9	43.0
4. 3-parameter logistic regression of exposure on NF				

Model	Long Dermal	Short Dermal	Long Short Dermal	Hands Only
5. Gamma model for exposure	34.3	34.2	34.1	34.3

Table AB28. Akaike Information Criteria values for alternative models for Inhalation Exposure

Model	Inhalation Concentration	Inhalation Dose	Inhalation Time-Weighted Average Concentration
1. Linear regression of Ln(exposure) on Ln(NF)	52.8	49.0	49.0
2. Quadratic regression of Ln(exposure) on Ln(NF)	54.6	50.9	50.9
3. Log-log logistic regression of exposure on NF			
4. 3-parameter logistic regression of exposure on NF			
5. Gamma model for exposure	61.2	56.1	56.1

Based on the AIC, the best-fitting models are the linear model for every exposure route.

3. Sink Scenario

This entire section contains the same sets of tables and figures as Section 2. Bucket Scenario but the data and results are for the Sink scenario instead of the Bucket scenario and the Table and Figure numbers start with AS instead of AB. The methods and formats are exactly the same for the Bucket and Sink scenarios and so the details of the methods

descriptions are not repeated. One exception is that for the Sink scenario the three concentration groups are: “Target Quat: 100 ppm,” “Target Quat: 600 ppm,” and “Target Quat: 1000 ppm.”

Summary Statistics of Exposure per Concentration Times Duration

Tables AS1 to AS7 summarize the normalized exposure data (per concentration times duration) with the summary statistics from the 18 (all concentrations), or 6 (specific concentrations) measurements for each concentration group, and each dermal and inhalation exposure route. These analyses assume that the exposure measurements within each subset come from some unspecified distribution for that subset.

Table AS1. Summary statistics for normalized long dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	5.826E-04	5.600E-04	6.516E-04	5.361E-04
Arithmetic Standard Deviation	2.784E-04	2.206E-04	4.129E-04	1.882E-04
Geometric Mean	5.246E-04	5.233E-04	5.504E-04	5.013E-04
Geometric Standard Deviation	1.613E+00	1.508E+00	1.909E+00	1.539E+00
Min	2.119E-04	2.884E-04	2.119E-04	2.320E-04
5%	2.119E-04	2.884E-04	2.119E-04	2.320E-04
10%	2.320E-04	2.884E-04	2.119E-04	2.320E-04
25%	4.118E-04	3.710E-04	4.232E-04	4.118E-04
50%	5.496E-04	5.785E-04	4.996E-04	5.814E-04
75%	6.846E-04	6.262E-04	9.333E-04	6.846E-04
90%	9.333E-04	9.171E-04	1.342E-03	7.253E-04
95%	1.342E-03	9.171E-04	1.342E-03	7.253E-04
Max	1.342E-03	9.171E-04	1.342E-03	7.253E-04

Table AS2. Summary statistics for normalized short dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	6.217E-04	6.031E-04	6.894E-04	5.726E-04
Arithmetic Standard Deviation	2.897E-04	2.226E-04	4.349E-04	1.946E-04
Geometric Mean	5.641E-04	5.703E-04	5.867E-04	5.365E-04
Geometric Standard Deviation	1.581E+00	1.443E+00	1.869E+00	1.535E+00
Min	2.391E-04	3.599E-04	2.391E-04	2.435E-04

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
5%	2.391E-04	3.599E-04	2.391E-04	2.435E-04
10%	2.435E-04	3.599E-04	2.391E-04	2.435E-04
25%	4.332E-04	3.970E-04	4.332E-04	4.570E-04
50%	5.779E-04	6.146E-04	5.370E-04	6.262E-04
75%	7.209E-04	6.552E-04	9.514E-04	7.209E-04
90%	9.771E-04	9.771E-04	1.439E-03	7.619E-04
95%	1.439E-03	9.771E-04	1.439E-03	7.619E-04
Max	1.439E-03	9.771E-04	1.439E-03	7.619E-04

Table AS3. Summary statistics for normalized long short dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	6.137E-04	5.864E-04	6.858E-04	5.691E-04
Arithmetic Standard Deviation	2.927E-04	2.313E-04	4.360E-04	1.951E-04
Geometric Mean	5.541E-04	5.488E-04	5.824E-04	5.322E-04
Geometric Standard Deviation	1.601E+00	1.497E+00	1.877E+00	1.545E+00
Min	2.367E-04	3.081E-04	2.367E-04	2.382E-04
5%	2.367E-04	3.081E-04	2.367E-04	2.382E-04
10%	2.382E-04	3.081E-04	2.367E-04	2.382E-04
25%	4.283E-04	3.950E-04	4.283E-04	4.534E-04
50%	5.709E-04	6.002E-04	5.315E-04	6.236E-04
75%	7.196E-04	6.455E-04	9.500E-04	7.196E-04
90%	9.694E-04	9.694E-04	1.437E-03	7.561E-04
95%	1.437E-03	9.694E-04	1.437E-03	7.561E-04
Max	1.437E-03	9.694E-04	1.437E-03	7.561E-04

Table AS4. Summary statistics for normalized hands only dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	5.632E-04	5.218E-04	6.337E-04	5.341E-04
Arithmetic Standard Deviation	2.899E-04	2.396E-04	4.284E-04	1.889E-04

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Geometric Mean	4.947E-04	4.726E-04	5.137E-04	4.987E-04
Geometric Standard Deviation	1.724E+00	1.665E+00	2.104E+00	1.547E+00
Min	1.575E-04	2.025E-04	1.575E-04	2.279E-04
5%	1.575E-04	2.025E-04	1.575E-04	2.279E-04
10%	2.025E-04	2.025E-04	1.575E-04	2.279E-04
25%	4.066E-04	3.705E-04	4.066E-04	4.105E-04
50%	5.288E-04	5.128E-04	4.833E-04	5.805E-04
75%	6.803E-04	6.221E-04	9.328E-04	6.803E-04
90%	9.328E-04	9.100E-04	1.339E-03	7.249E-04
95%	1.339E-03	9.100E-04	1.339E-03	7.249E-04
Max	1.339E-03	9.100E-04	1.339E-03	7.249E-04

Table AS5. Summary statistics for normalized inhalation concentration exposure (mg/m^3/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	4.198E-08	1.049E-07	1.475E-08	6.342E-09
Arithmetic Standard Deviation	5.951E-08	6.569E-08	2.346E-08	4.164E-09
Geometric Mean	1.513E-08	9.202E-08	7.027E-09	5.354E-09
Geometric Standard Deviation	4.668E+00	1.699E+00	3.391E+00	1.863E+00
Min	1.503E-09	5.486E-08	1.503E-09	2.830E-09
5%	1.503E-09	5.486E-08	1.503E-09	2.830E-09
10%	2.830E-09	5.486E-08	1.503E-09	2.830E-09
25%	4.452E-09	5.886E-08	4.529E-09	3.405E-09
50%	9.893E-09	8.235E-08	5.768E-09	4.247E-09
75%	6.242E-08	1.205E-07	8.520E-09	1.127E-08
90%	1.205E-07	2.302E-07	6.242E-08	1.206E-08
95%	2.302E-07	2.302E-07	6.242E-08	1.206E-08
Max	2.302E-07	2.302E-07	6.242E-08	1.206E-08

Table AS6. Summary statistics for normalized inhalation dose exposure (mg/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	5.506E-08	1.393E-07	1.752E-08	8.363E-09
Arithmetic Standard Deviation	6.872E-08	5.170E-08	2.352E-08	3.364E-09
Geometric Mean	2.167E-08	1.323E-07	9.992E-09	7.697E-09
Geometric Standard Deviation	4.388E+00	1.410E+00	2.941E+00	1.604E+00
Min	3.006E-09	8.707E-08	3.006E-09	3.519E-09
5%	3.006E-09	8.707E-08	3.006E-09	3.519E-09
10%	3.519E-09	8.707E-08	3.006E-09	3.519E-09
25%	5.878E-09	1.097E-07	5.658E-09	5.659E-09
50%	1.186E-08	1.206E-07	7.468E-09	8.638E-09
75%	1.097E-07	1.675E-07	1.704E-08	1.127E-08
90%	1.675E-07	2.302E-07	6.450E-08	1.246E-08
95%	2.302E-07	2.302E-07	6.450E-08	1.246E-08
Max	2.302E-07	2.302E-07	6.450E-08	1.246E-08

Table AS7. Summary statistics for normalized inhalation time-weighted average concentration exposure (mg/m^3/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	6.882E-09	1.741E-08	2.190E-09	1.045E-09
Arithmetic Standard Deviation	8.590E-09	6.462E-09	2.940E-09	4.205E-10
Geometric Mean	2.709E-09	1.653E-08	1.249E-09	9.621E-10
Geometric Standard Deviation	4.388E+00	1.410E+00	2.941E+00	1.604E+00
Min	3.758E-10	1.088E-08	3.758E-10	4.399E-10
5%	3.758E-10	1.088E-08	3.758E-10	4.399E-10
10%	4.399E-10	1.088E-08	3.758E-10	4.399E-10
25%	7.347E-10	1.371E-08	7.073E-10	7.074E-10
50%	1.483E-09	1.508E-08	9.335E-10	1.080E-09
75%	1.371E-08	2.094E-08	2.130E-09	1.408E-09
90%	2.094E-08	2.877E-08	8.063E-09	1.557E-09
95%	2.877E-08	2.877E-08	8.063E-09	1.557E-09

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Max	2.877E-08	2.877E-08	8.063E-09	1.557E-09

The results show the high proportions of the normalized dermal exposure from hands only. For All and for each concentration group, based on the arithmetic means, the overall percentages of the normalized exposure from hands only are between 93 and 100% of the Long Dermal, between 87 and 93% of the Short Dermal, and between 89 and 94% of the Long Short Dermal. Similarly, for the unnormalized dermal exposure, the arithmetic mean hands only exposure is 92% of the arithmetic mean total dermal exposure (defined as the sum of the residues from hand wash, forearm wipe, face/neck wipe, and the inner dosimeters).

Compare Concentration Groups

The results in Tables AS1 to AS7 show some differences between the normalized exposure statistics for the three concentration groups "Target Quat: 100 ppm," "Target Quat: 600 ppm," and "Target Quat: 1000 ppm." To compare these groups, an analysis of variance was performed to test whether the geometric means were statistically significantly different at the 5% significance level.

The p-values for these ANOVA tests are shown in Table AS8. These analyses show that there were no statistically significant differences (at the 5% significance level) between the three concentration groups for the dermal exposure modes, but very significant differences for the inhalation modes.

Table AS8. P-values for testing differences in geometric means for different concentration groups

Exposure Route	ANOVA	Welch's ANOVA
Long Dermal	0.950	0.958
Short Dermal	0.948	0.951
Long Short Dermal	0.951	0.962
Hands Only	0.968	0.971
Inhalation Conc	0.000	0.000
Inhalation Dose	0.000	0.000
Inhalation 8-hr TWA	0.000	0.000

Statistical Models

Table AS9 presents the arithmetic mean and 95th percentile estimates from the lognormal simple random sampling model, together with 95% confidence intervals, for each of the exposure routes, for all concentration groups combined. These are the values of AMu and P95u. The other summary statistics are presented in more detail below.

Table AS9. Arithmetic mean and 95th percentile estimates from lognormal simple random sampling model for normalized exposure for All

Exposure Route	Clothing	Arithmetic Mean (95% Confidence Interval)	95th Percentile (95% Confidence Interval)
Dermal (mg/(ppm ADBAC × mins))	Long Dermal	0.00059 (0.00047, 0.00075)	0.00115 (0.00081, 0.00162)
	Short Dermal	0.00063 (0.00050, 0.00079)	0.00120 (0.00086, 0.00166)
	Long Short Dermal	0.00062 (0.00049, 0.00078)	0.00120 (0.00085, 0.00168)
	Hands Only	0.00057 (0.00044, 0.00076)	0.00121 (0.00082, 0.00179)
Inhalation Concentration ((mg/m^3)/ (ppm DDAC × mins))		4.96×10^{-8} (1.83×10^{-8}, 1.59×10^{-7})	1.91×10^{-7} (6.25×10^{-8}, 5.74×10^{-7})
Inhalation Dose (mg/ (ppm DDAC × mins))		6.47×10^{-8} (2.52×10^{-8}, 1.92×10^{-7})	2.47×10^{-7} (8.46×10^{-8}, 7.11×10^{-7})
Inhalation 8-hr TWA ((mg/m^3)/ ppm DDAC × mins))		8.09×10^{-9} (3.15×10^{-9}, 2.40×10^{-8})	3.08×10^{-8} (1.06×10^{-8}, 8.89×10^{-8})

Non-detects

For all the analyses presented in this memorandum except for Table AS10 and AS18, measurements below the LOQ or LOD were replaced by the mid-value, the midpoint of the lowest and highest possible value for that measurement. In Tables AS10 and AS18 we investigated the impact on the summary statistics of the censored values.

Table AS10. Exposure summary statistics calculated using alternative estimated exposures for values below the LOQ

Exposure Route	Method for Substituting Values Below the LOQ	Arithmetic Mean	95th Percentile
Long Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	0.00059 (0.00047, 0.00075)	0.00115 (0.00081, 0.00162)
	Substitute max value	0.00059 (0.00047, 0.00075)	0.00115 (0.00081, 0.00163)
	Substitute min value	0.00059 (0.00046, 0.00075)	0.00115 (0.00081, 0.00162)
	Censored data MLE	0.00058 (0.00047, 0.00074)	0.00113 (0.00080, 0.00157)
Short Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	0.00063 (0.00050, 0.00079)	0.00120 (0.00086, 0.00166)
	Substitute max value	0.00063 (0.00050, 0.00079)	0.00120 (0.00086, 0.00167)
	Substitute min value	0.00063 (0.00050, 0.00079)	0.00120 (0.00086, 0.00166)
	Censored data MLE	0.00062 (0.00050, 0.00078)	0.00117 (0.00085, 0.00161)
Long Short Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	0.00062 (0.00049, 0.00078)	0.00120 (0.00085, 0.00168)
	Substitute max value	0.00062 (0.00049, 0.00078)	0.00120 (0.00085, 0.00169)
	Substitute min value	0.00062 (0.00049, 0.00078)	0.00120 (0.00085, 0.00168)
	Censored data MLE	0.00062 (0.00049, 0.00077)	0.00118 (0.00084, 0.00163)

Exposure Route	Method for Substituting Values Below the LOQ	Arithmetic Mean	95th Percentile
Hands Only (mg/(ppm ADBAC × mins))	Substitute mid value	0.00057 (0.00044, 0.00076)	0.00121 (0.00082, 0.00179)
	Substitute max value	0.00057 (0.00044, 0.00076)	0.00121 (0.00082, 0.00179)
	Substitute min value	0.00057 (0.00044, 0.00076)	0.00121 (0.00082, 0.00179)
	Censored data MLE	0.00057 (0.00044, 0.00075)	0.00118 (0.00080, 0.00173)
Inhalation Concentration ((mg/m^3)/ (ppm DDAC × mins))	Substitute mid value	4.96×10^{-8} (1.81×10^{-8}, 1.57×10^{-7})	1.91×10^{-7} (6.25×10^{-8}, 5.75×10^{-7})
	Substitute max value	4.78×10^{-8} (1.96×10^{-8}, 1.31×10^{-7})	1.80×10^{-7} (6.44×10^{-8}, 4.95×10^{-7})
	Substitute min value	6.84×10^{-8} (2.63×10^{-8}, 2.03×10^{-7})	2.61×10^{-7} (8.87×10^{-8}, 7.56×10^{-7})
	Censored data MLE	5.27×10^{-8} (1.75×10^{-8}, 1.88×10^{-7})	2.04×10^{-7} (6.19×10^{-8}, 6.59×10^{-7})
Inhalation Dose (mg/ (ppm DDAC × mins))	Substitute mid value	6.47×10^{-8} (2.50×10^{-8}, 1.91×10^{-7})	2.47×10^{-7} (8.46×10^{-8}, 7.12×10^{-7})
	Substitute max value	6.06×10^{-8} (2.69×10^{-8}, 1.50×10^{-7})	2.23×10^{-7} (8.50×10^{-8}, 5.74×10^{-7})
	Substitute min value	8.48×10^{-8} (3.69×10^{-8}, 2.15×10^{-7})	3.14×10^{-7} (1.18×10^{-7}, 8.21×10^{-7})
	Censored data MLE	6.81×10^{-8} (2.45×10^{-8}, 2.19×10^{-7})	2.62×10^{-7} (8.46×10^{-8}, 7.99×10^{-7})
Inhalation 8-hr TWA ((mg/m^3)/ ppm DDAC × mins))	Substitute mid value	8.09×10^{-9} (3.12×10^{-9}, 2.38×10^{-8})	3.08×10^{-8} (1.05×10^{-8}, 8.89×10^{-8})
	Substitute max value	7.58×10^{-9} (3.36×10^{-9}, 1.87×10^{-8})	2.78×10^{-8} (1.06×10^{-8}, 7.18×10^{-8})
	Substitute min value	1.06×10^{-8} (4.62×10^{-9}, 2.68×10^{-8})	3.92×10^{-8} (1.47×10^{-8}, 1.03×10^{-7})
	Censored data MLE	8.52×10^{-9} (3.06×10^{-9}, 2.74×10^{-8})	3.28×10^{-8} (1.06×10^{-8}, 9.99×10^{-8})

The results in Table AS10 for dermal exposure show very small impacts of the alternative substitution approaches for treating values below the LOQ on the unit exposure arithmetic mean and 95th percentile. This is mainly because the dermal exposure is dominated by the hand exposures which were all above the LOQ. For inhalation exposure, the results show some large impacts of the max and min value substitution methods compared to substituting the mid value, but the results for the censored data MLE are very similar to the results for substituting the mid value.

Detailed Summary Statistics with Confidence Intervals and Fold Relative Accuracy

Tables AS11 to AS17 present the estimates, parametric and non-parametric confidence intervals and fold relative accuracy values for all the summary statistics for the All group. All these analyses use non-detects substituted by the mid-value.

Table AS11. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.61337	1.37596	1.89772	1.17	1.35467	1.82264	1.17
GMs	0.00052	0.00042	0.00066	1.25	0.00042	0.00065	1.24
AMs	0.00058	0.00046	0.00074	1.27	0.00047	0.00071	1.24
AMu	0.00059	0.00047	0.00075	1.26	0.00047	0.00072	1.24
P95s	0.00134	0.00081	0.00219	1.65	0.00073	0.00134	1.46
P95u	0.00115	0.00081	0.00162	1.41	0.00083	0.00150	1.36

Table AS12. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.58119	1.35759	1.84719	1.17	1.32819	1.78959	1.17
GMs	0.00056	0.00046	0.00070	1.24	0.00046	0.00069	1.22
AMs	0.00062	0.00050	0.00078	1.25	0.00050	0.00076	1.23
AMu	0.00063	0.00050	0.00079	1.25	0.00050	0.00077	1.23
P95s	0.00144	0.00086	0.00222	1.65	0.00076	0.00144	1.51
P95u	0.00120	0.00086	0.00166	1.39	0.00086	0.00157	1.36

Table AS13. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.60108	1.36896	1.87837	1.17	1.34327	1.81020	1.17
GMs	0.00055	0.00045	0.00069	1.24	0.00045	0.00068	1.23
AMs	0.00061	0.00049	0.00078	1.26	0.00049	0.00075	1.24
AMu	0.00062	0.00049	0.00078	1.26	0.00050	0.00076	1.24
P95s	0.00144	0.00085	0.00226	1.66	0.00076	0.00144	1.51
P95u	0.00120	0.00085	0.00168	1.40	0.00086	0.00158	1.36

Table AS14. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	1.72388	1.43815	2.07382	1.20	1.39117	1.98617	1.21
GMs	0.00049	0.00039	0.00064	1.29	0.00039	0.00062	1.27
AMs	0.00056	0.00044	0.00075	1.31	0.00044	0.00070	1.26
AMu	0.00057	0.00044	0.00076	1.31	0.00045	0.00071	1.26
P95s	0.00134	0.00081	0.00251	1.76	0.00072	0.00134	1.47
P95u	0.00121	0.00082	0.00179	1.48	0.00085	0.00159	1.38

Table AS15. 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 exposure ((mg/m^3)/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	4.668E+00	2.796E+00	7.875E+00	1.68	3.150E+00	5.938E+00	1.40
GMs	1.513E-08	7.511E-09	3.146E-08	2.05	7.692E-09	3.036E-08	1.99
AMs	4.198E-08	1.620E-08	1.346E-07	2.85	1.842E-08	7.149E-08	1.99
AMu	4.958E-08	1.827E-08	1.587E-07	2.92	1.647E-08	1.090E-07	2.60
P95s	2.302E-07	6.170E-08	1.506E-06	5.13	8.163E-08	2.302E-07	2.77
P95u	1.908E-07	6.250E-08	5.744E-07	3.03	5.728E-08	4.174E-07	2.75

Table AS16. 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 exposure (mg/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	4.388E+00	2.683E+00	7.249E+00	1.64	3.072E+00	5.331E+00	1.34
GMs	2.167E-08	1.106E-08	4.375E-08	1.99	1.134E-08	4.232E-08	1.94
AMs	5.506E-08	2.269E-08	1.678E-07	2.69	2.638E-08	8.750E-08	1.84
AMu	6.468E-08	2.520E-08	1.921E-07	2.74	2.275E-08	1.303E-07	2.41
P95s	2.302E-07	8.353E-08	1.793E-06	5.82	1.187E-07	2.302E-07	1.88
P95u	2.468E-07	8.457E-08	7.109E-07	2.90	7.788E-08	4.984E-07	2.58

Table AS17. 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 time-weighted average concentration exposure ((mg/m^3)/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	4.388E+00	2.683E+00	7.249E+00	1.64	3.072E+00	5.331E+00	1.34
GMs	2.709E-09	1.383E-09	5.469E-09	1.99	1.417E-09	5.290E-09	1.94
AMs	6.882E-09	2.836E-09	2.097E-08	2.69	3.298E-09	1.094E-08	1.84
AMu	8.086E-09	3.149E-09	2.401E-08	2.74	2.844E-09	1.628E-08	2.41
P95s	2.877E-08	1.044E-08	2.241E-07	5.82	1.484E-08	2.877E-08	1.88
P95u	3.085E-08	1.057E-08	8.886E-08	2.90	9.736E-09	6.230E-08	2.58

Tables AS11 to AS17 show that the study benchmark design value of 3 for the fold relative accuracy was met in every case, with the exception of the parametric bootstrap empirical 95th percentile for the inhalation concentration, dose, and time-weighted average concentration.

Empirical 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 lognormal models. These plots were intended to help determine whether the data supported using untransformed normalized exposure values or log-transformed values or neither. The plots are not intended to evaluate the fitted regression models for the un-normalized exposure to be described below, for which the residual quantile plots were developed.

In each case the quantile-quantile plot compared the observed quantiles of the measured values with the corresponding quantiles of a normal or lognormal distribution. A perfect fit would imply that the plotted values lie in a straight line. The quantile-quantile plots for all exposure routes are presented in Figures AS1 to AS14. In all cases the plots seem to show a better fit for the lognormal distributions, supporting the use of the log-transformed exposure values over the untransformed values.

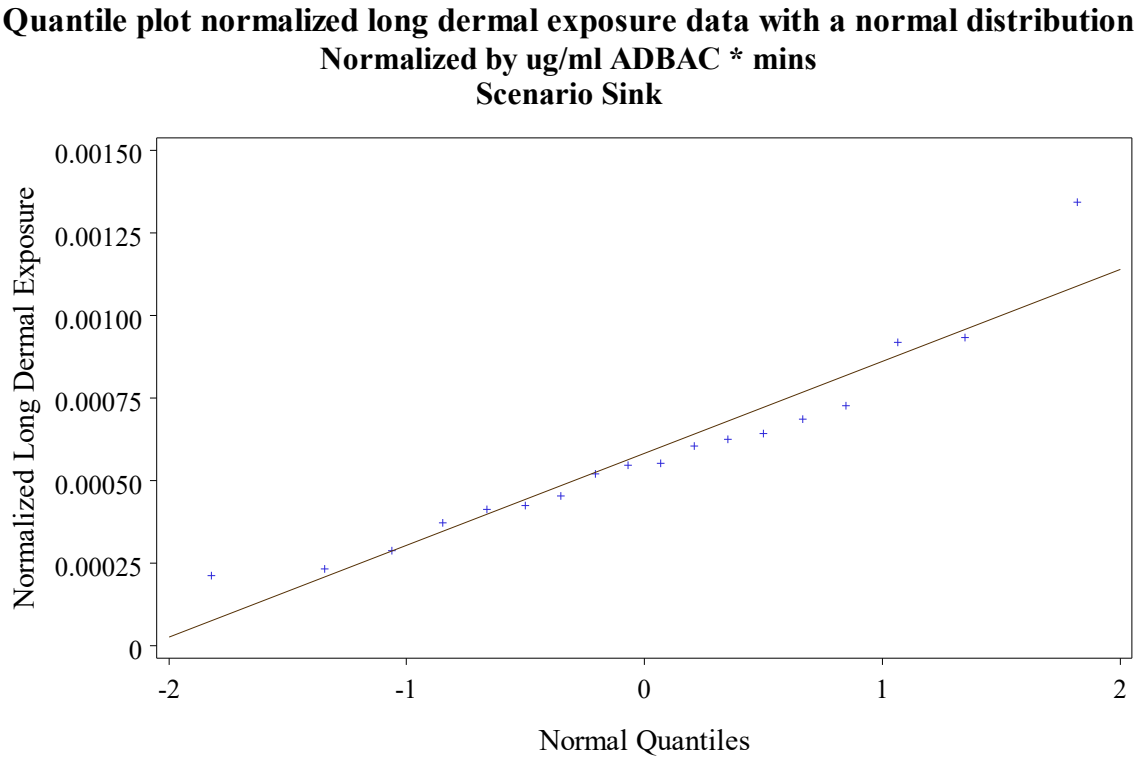

Figure AS1. Empirical quantile plot for Long Dermal, with a normal distribution

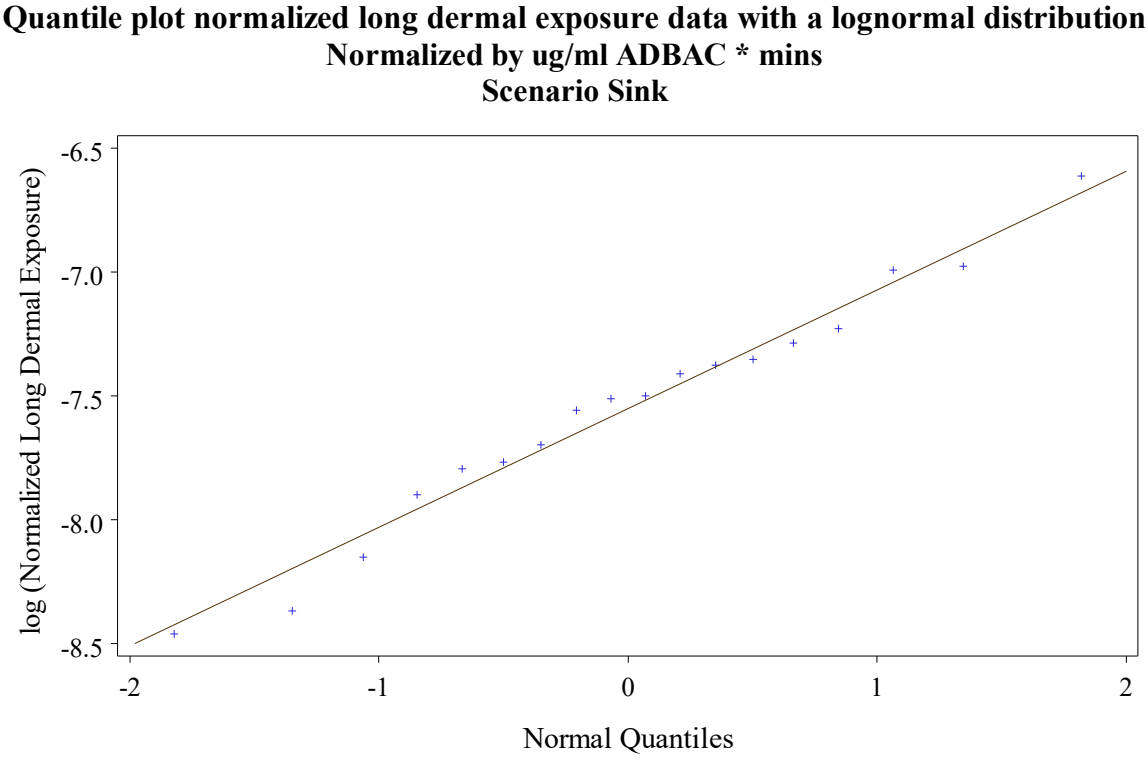

Figure AS2. Empirical quantile plot for Long Dermal, with a lognormal distribution

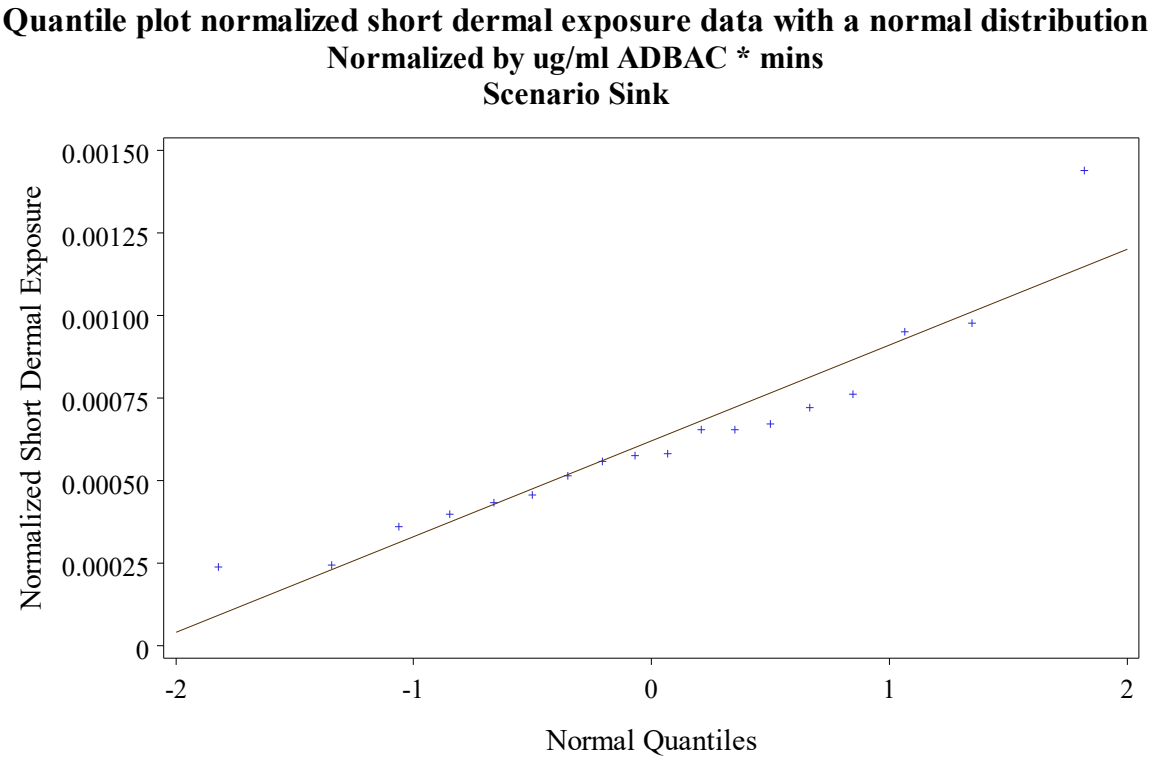

Figure AS3. Empirical quantile plot for Short Dermal, with a normal distribution

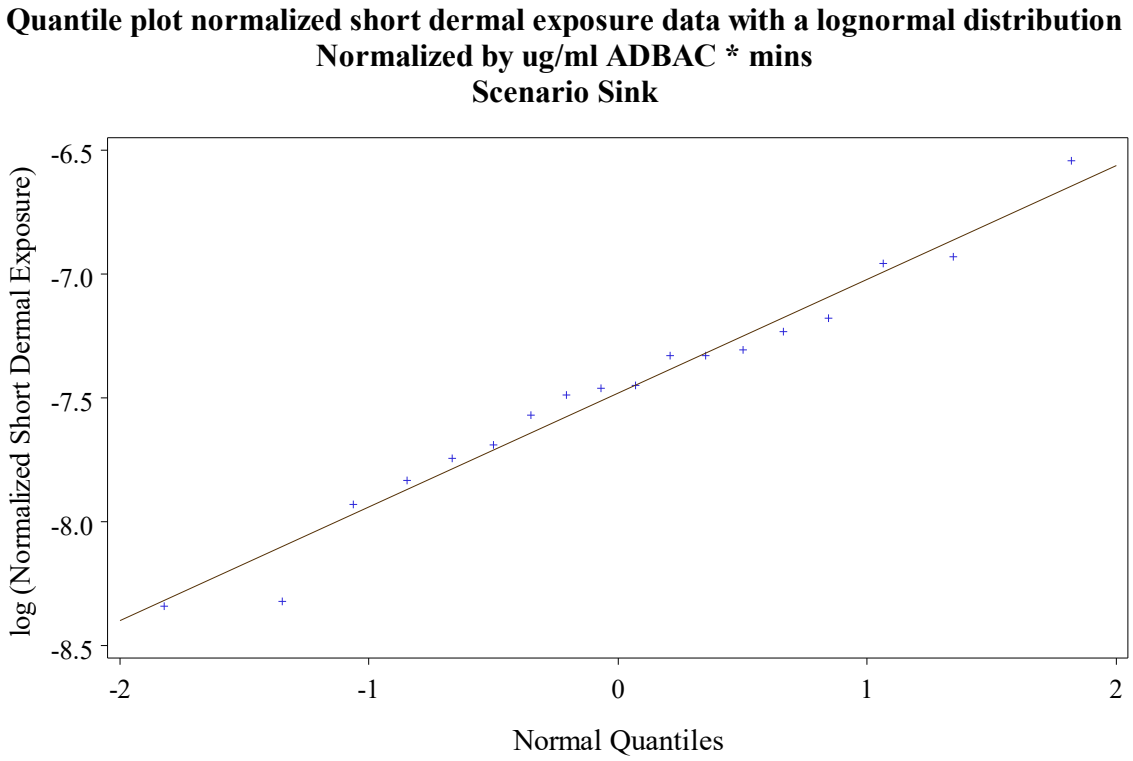

Figure AS4. Empirical quantile plot for Short Dermal, with a lognormal distribution

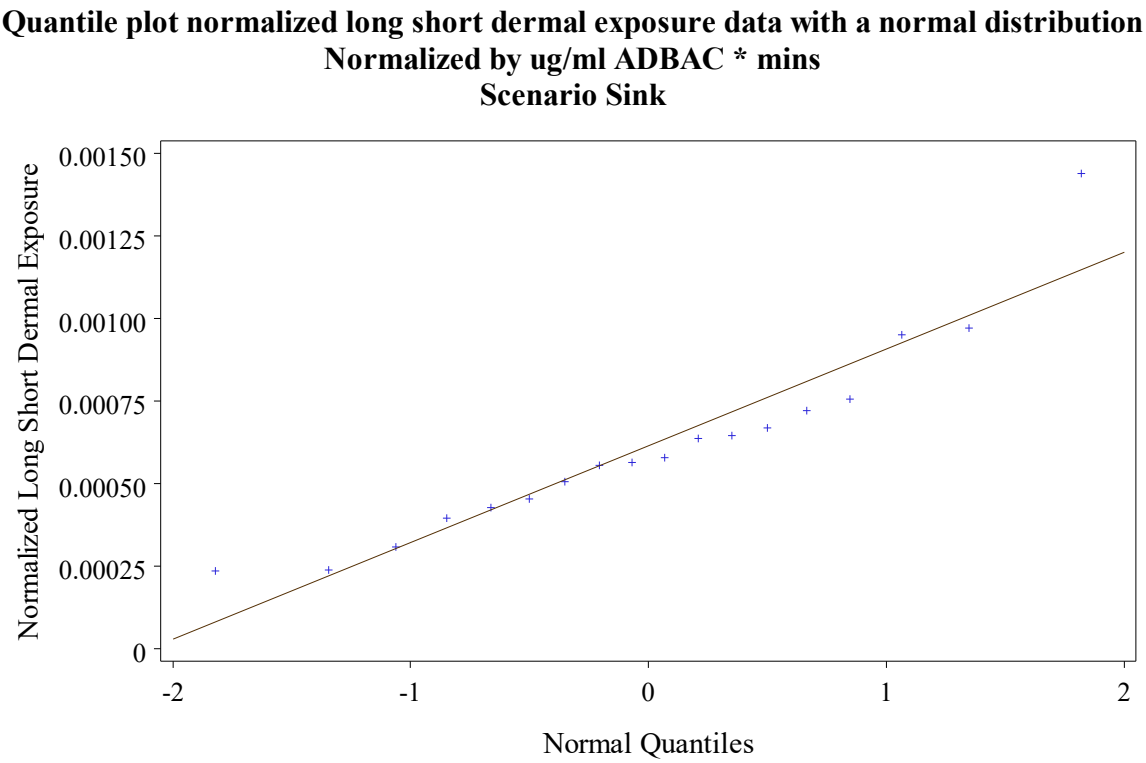

Figure AS5. Empirical quantile plot for Long Short Dermal, with a normal distribution

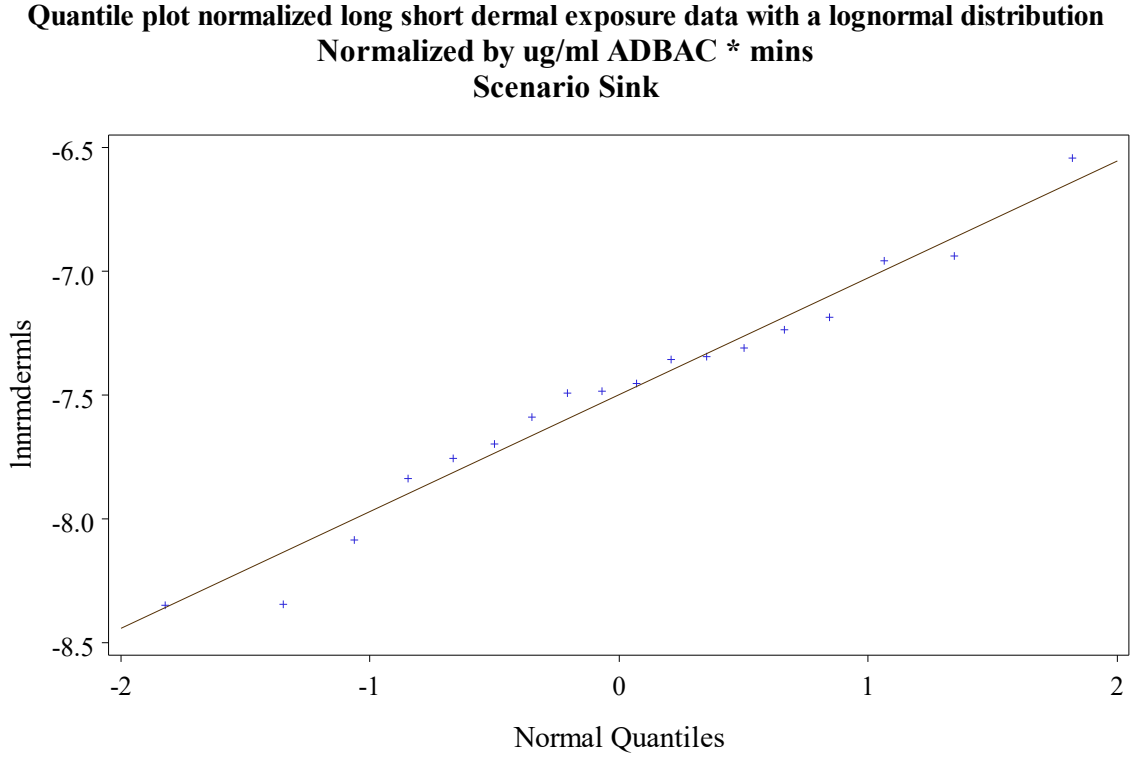

Figure AS6. Empirical quantile plot for Long Short Dermal, with a lognormal distribution

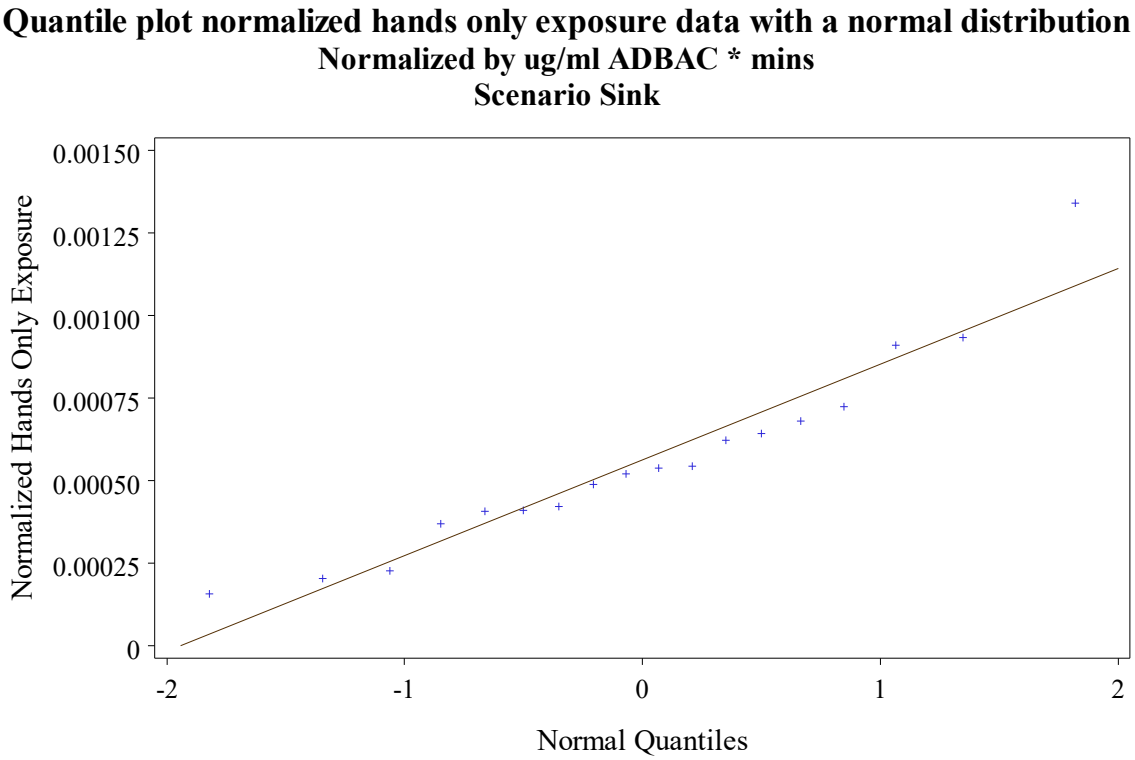

Figure AS7. Empirical quantile plot for Hands Only, with a normal distribution

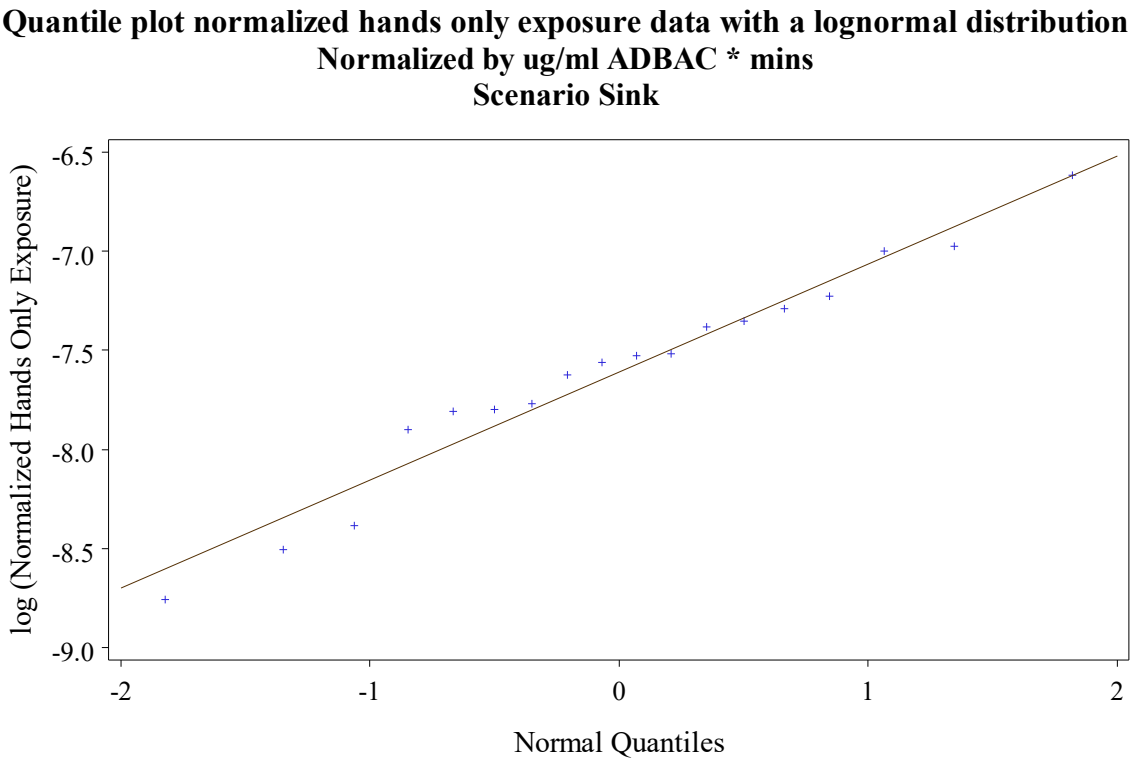

Figure AS8. Empirical quantile plot for Hands Only, with a lognormal distribution

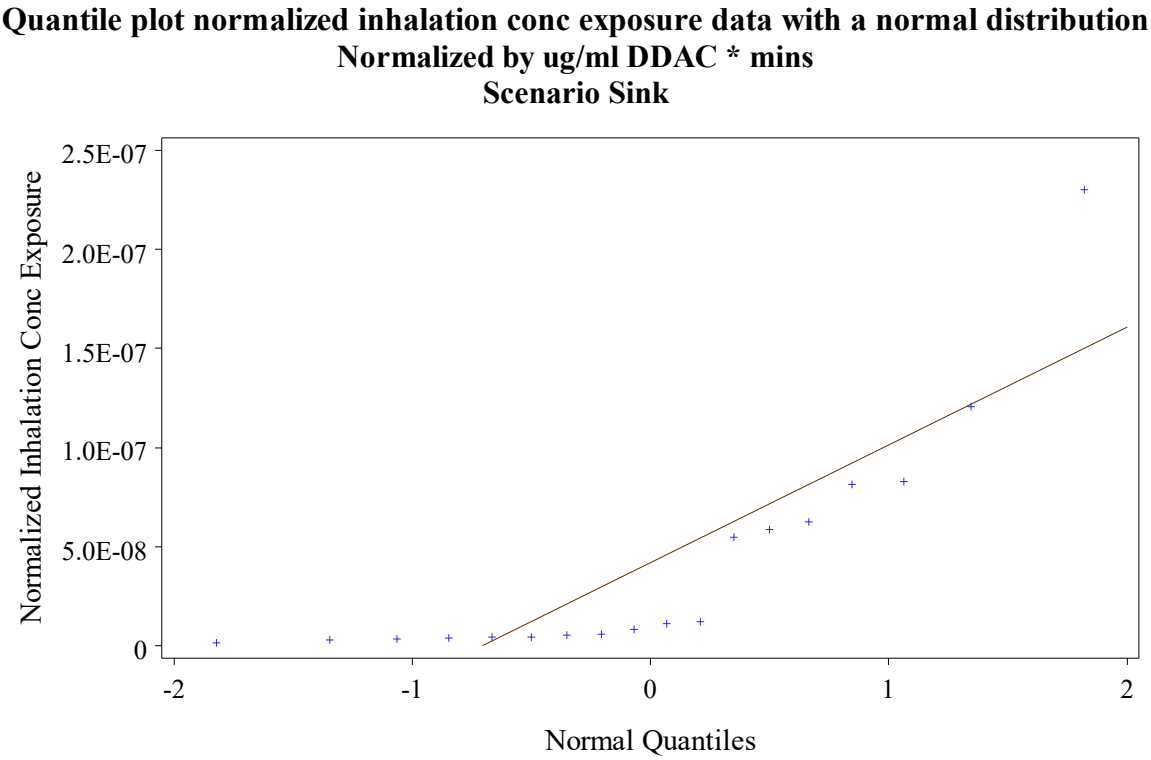

Figure AS9. Empirical quantile plot for Inhalation Concentration, with a normal distribution

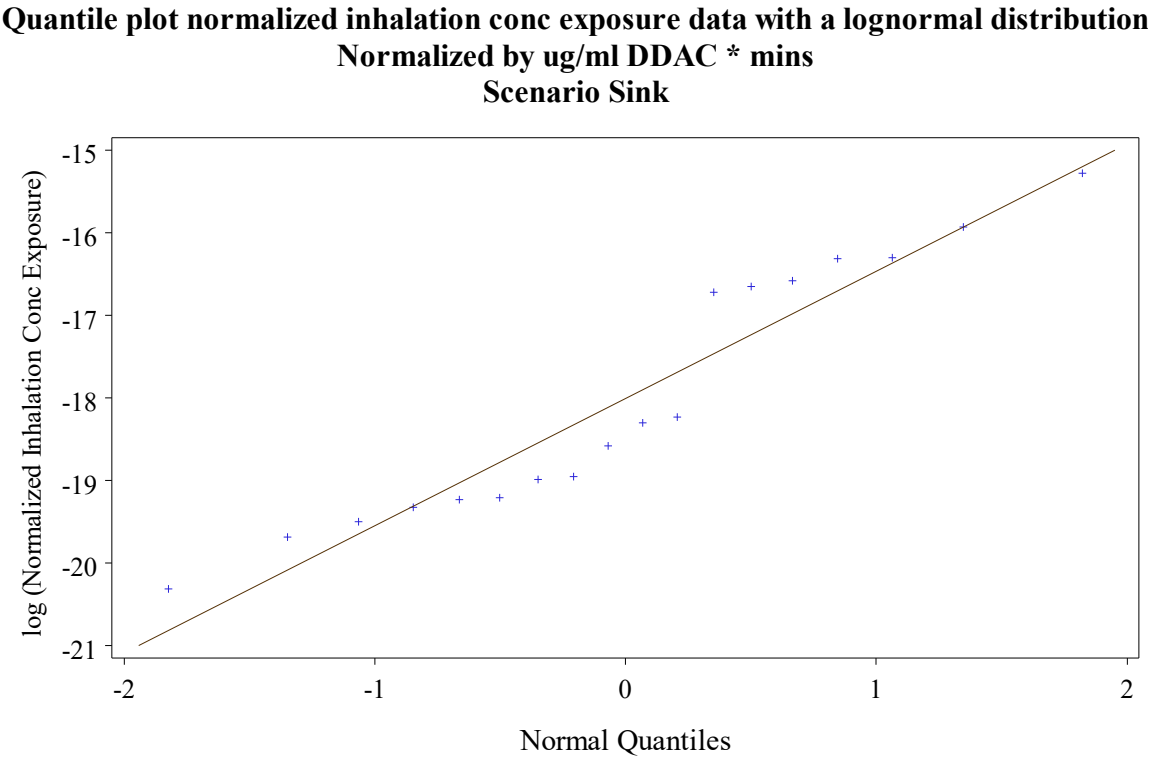

Figure AS10. Empirical quantile plot for Inhalation Concentration, with a lognormal distribution

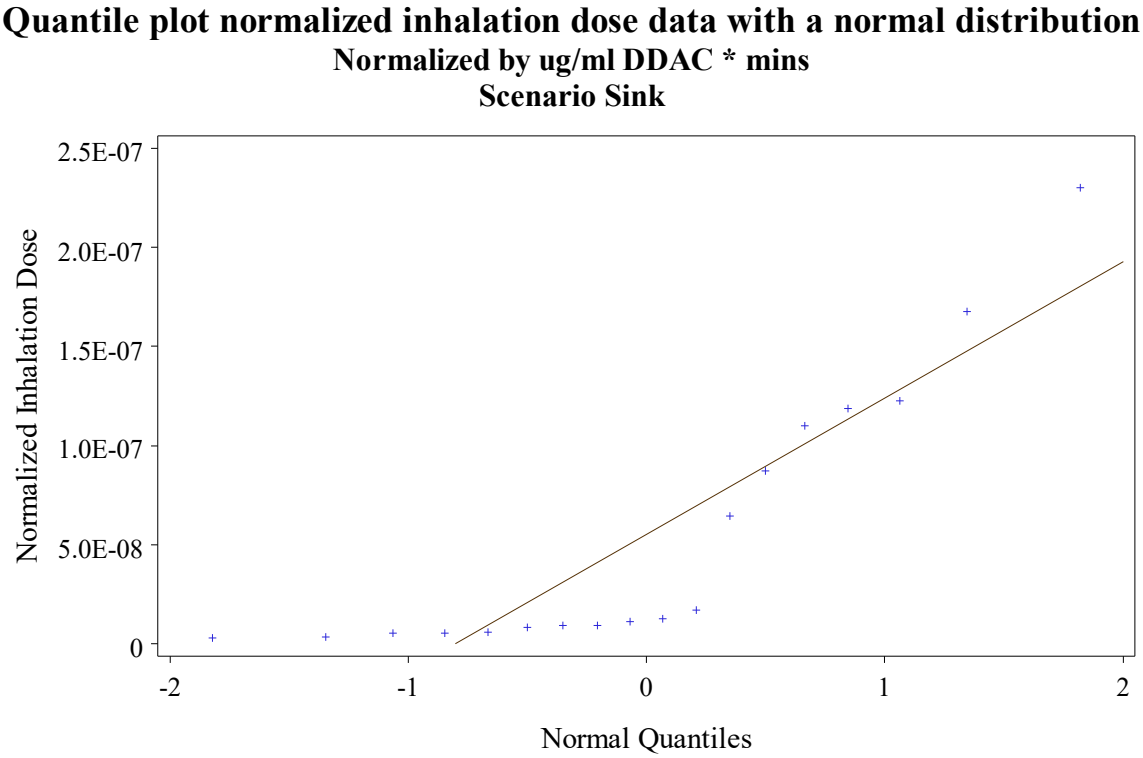

Figure AS11. Empirical quantile plot for Inhalation Dose, with a normal distribution

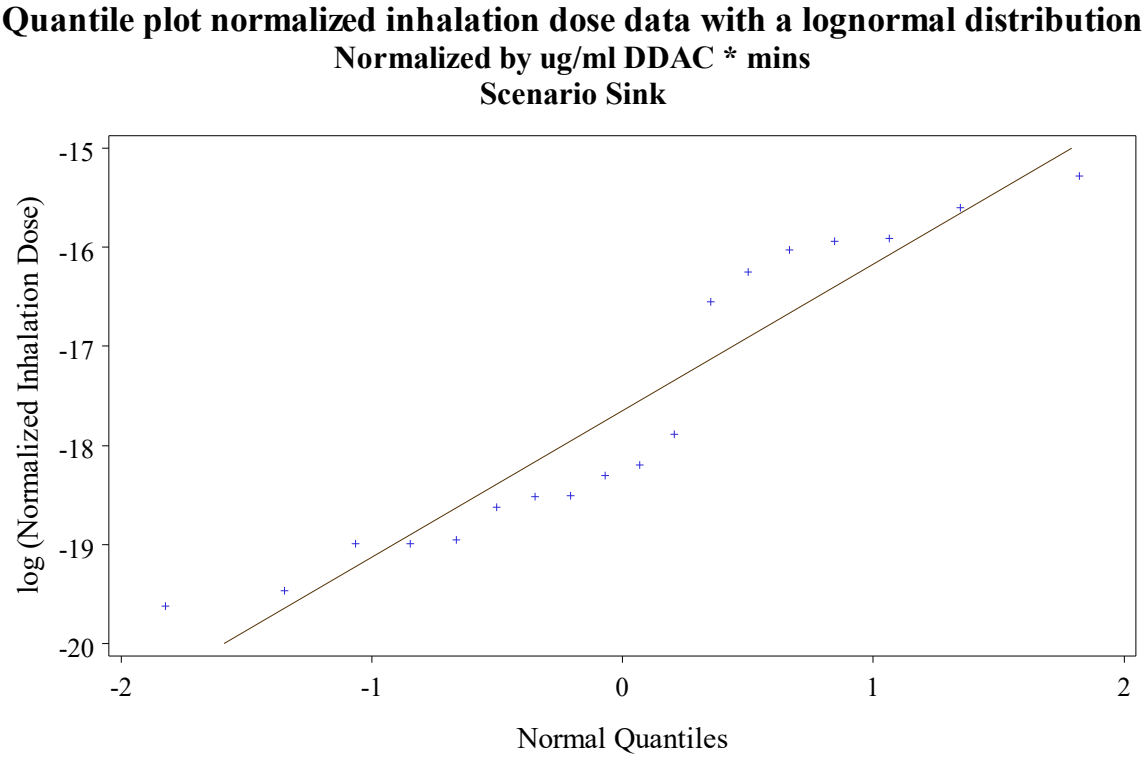

Figure AS12. Empirical quantile plot for Inhalation Dose, with a lognormal distribution

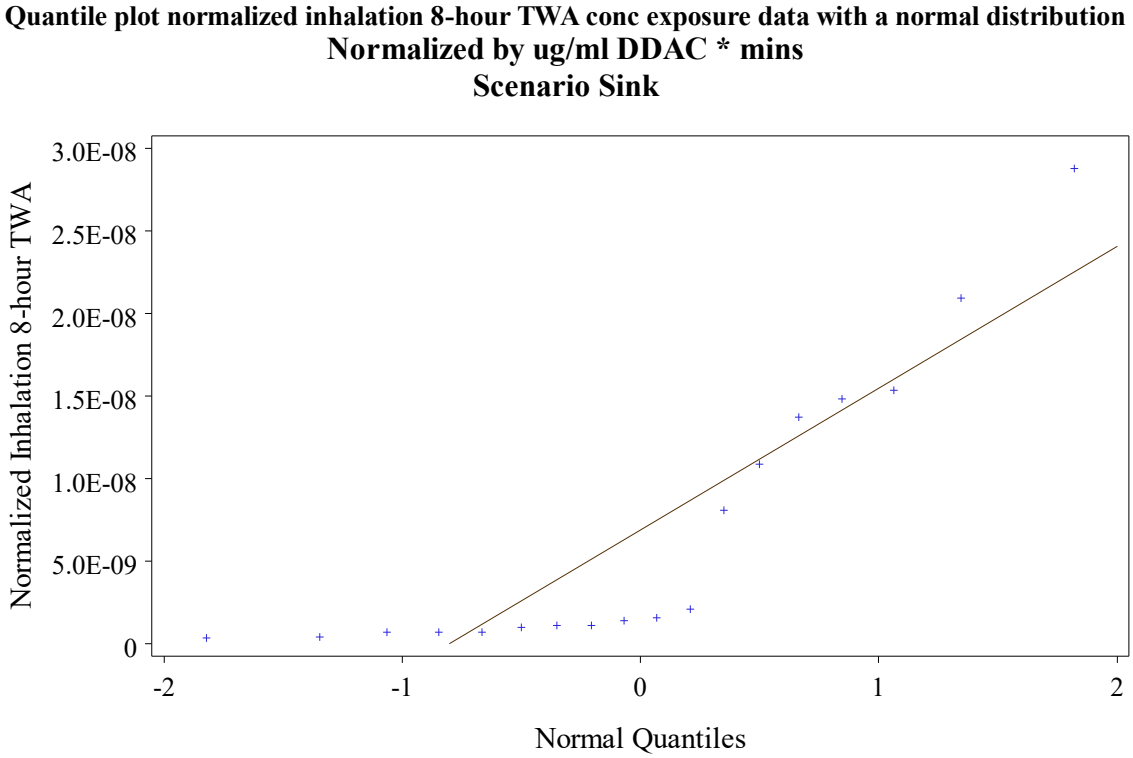

Figure AS13. Empirical quantile plot for Inhalation Time-weighted Average Conc, with a normal distribution

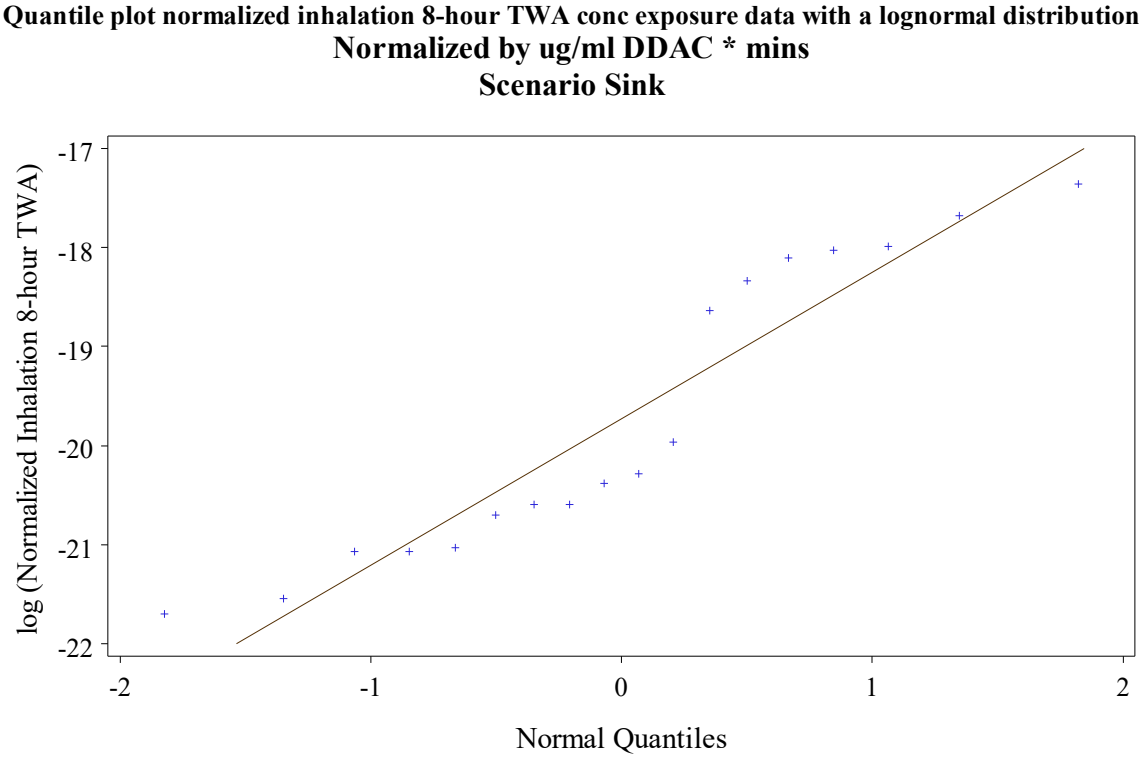

Figure AS14. Empirical quantile plot for Inhalation Time-weighted Average Conc, with a lognormal distribution

Test for log-log-linearity with slope 1

Table AS18 shows the 95% confidence intervals for the slope calculated from the above linear model. A confidence interval that includes one but not zero supports the use of unit exposures. A confidence interval that includes zero but not one suggests that the exposure does not depend on the normalizing factor. 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. This table also shows the widths of the confidence intervals used to evaluate the second benchmark for post-hoc power discussed in the next sub-section. The table also shows the values of the threshold concentration × duration (case A) or threshold concentration (case B) and the corresponding estimated exposure, to be described and discussed In the Supplement. Threshold values were not computed for the censored data models.

Table AS18. 95 percent confidence intervals for the slope of log exposure versus the log of the normalizing factor.

Exposure Route	Treatment of Non-detects	Estimate	Lower	Upper	Width	Threshold	Exposure
Long Dermal (mg)	Substitute mid value	0.915	0.683	1.147	0.464	6998	4.12
	Censored data MLE	0.915	0.713	1.117	0.404		
Short Dermal (mg)	Substitute mid value	0.912	0.691	1.134	0.443	6921	4.34
	Censored data MLE	0.912	0.719	1.105	0.386		
Long Short Dermal (mg)	Substitute mid value	0.923	0.694	1.152	0.458	7069	4.38
	Censored data MLE	0.923	0.723	1.122	0.399		
Hands Only (mg)	Substitute mid value	0.939	0.672	1.205	0.534	7586	4.35
	Censored data MLE	0.939	0.706	1.171	0.465		
Inhalation Concentration (mg/m^3)	Substitute mid value	–0.272	–0.607	0.618	0.668	3754	0.00019
	Censored data MLE	–0.245	–0.504	0.012	0.516		
Inhalation Dose (mg)	Substitute mid value	–0.174	–0.541	0.194	0.735	3993	0.00026
	Censored data MLE	–0.147	–0.425	0.131	0.556		
Inhalation Time-Weighted Average Concentration (mg/m^3)	Substitute mid value	–0.174	–0.541	0.194	0.735	3993	0.000032
	Censored data MLE	–0.147	–0.425	0.131	0.556		

Table AS18 gives the slopes for all the exposure routes.

For dermal exposures, the slopes range from 0.91 to 0.94, the confidence intervals include 1 but not 0. For inhalation exposures, the slopes are all negative and the confidence intervals include 0 but not 1. Thus for dermal exposure the assumption of independence was rejected and the assumption of log-log-linearity with slope 1 was supported. However for inhalation exposure the assumption of independence was supported and the assumption of log-log-linearity with slope 1 was rejected. The results for inhalation exposure seem to be counterintuitive.

Suppose that the study had a (post-hoc) power of at least 80% for detecting "proportionality" (i.e., log-log-linearity with a slope of 1) under the null hypothesis of independence (slope = 0). It follows that the confidence intervals have an approximate width of 1.4 or less. The results in Table AS18 show that observed widths are all below 1.4. The maximum width was about 1.2. Therefore, based on the confidence intervals, the secondary objective of meeting the 80% power for detecting proportionality was met.

Quantile plots for residuals

The quantile-quantile plots of the studentized residuals for all exposure routes are shown below in Figures AS15 to AS21.

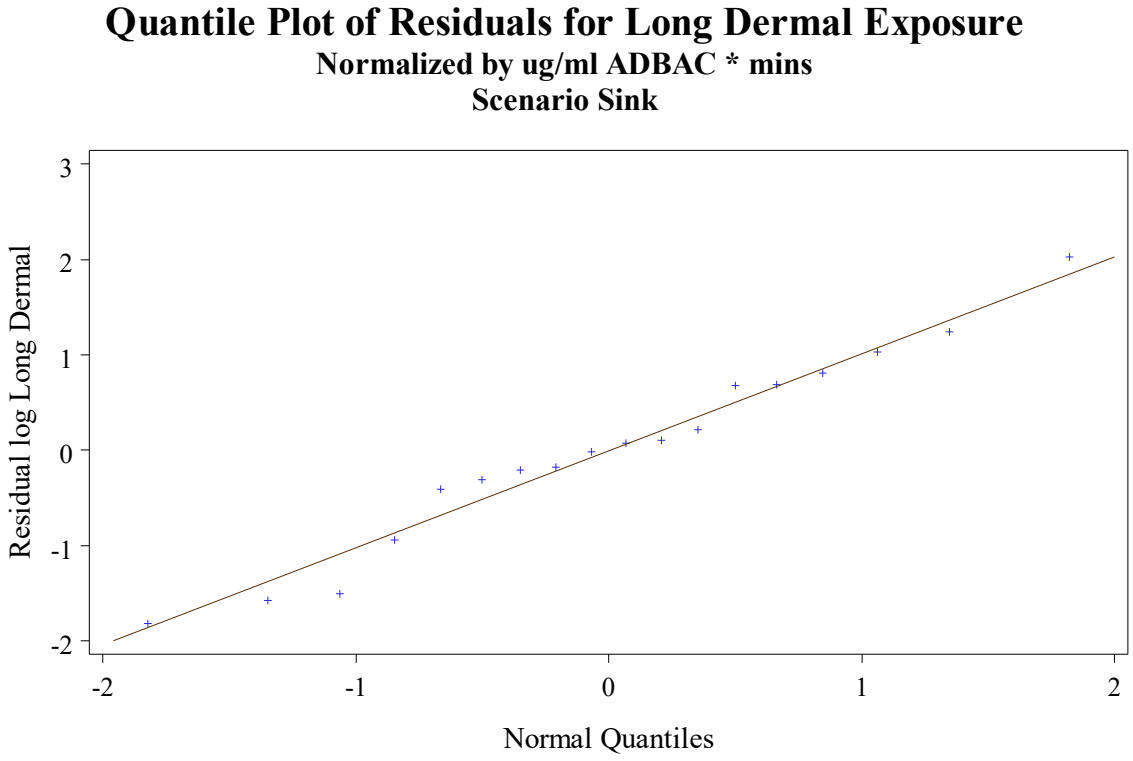

Figure AS15. Quantile plot of residuals from linear model for Long Dermal

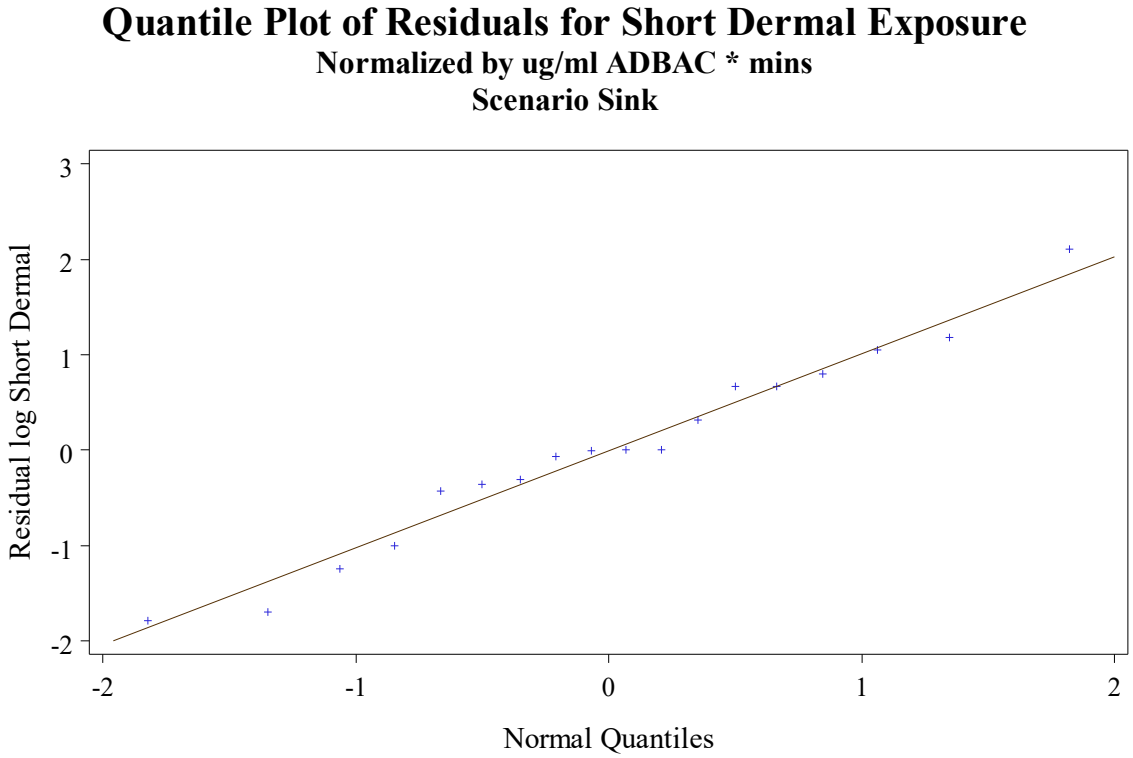

Figure AS16. Quantile plot of residuals from linear model for Short Dermal

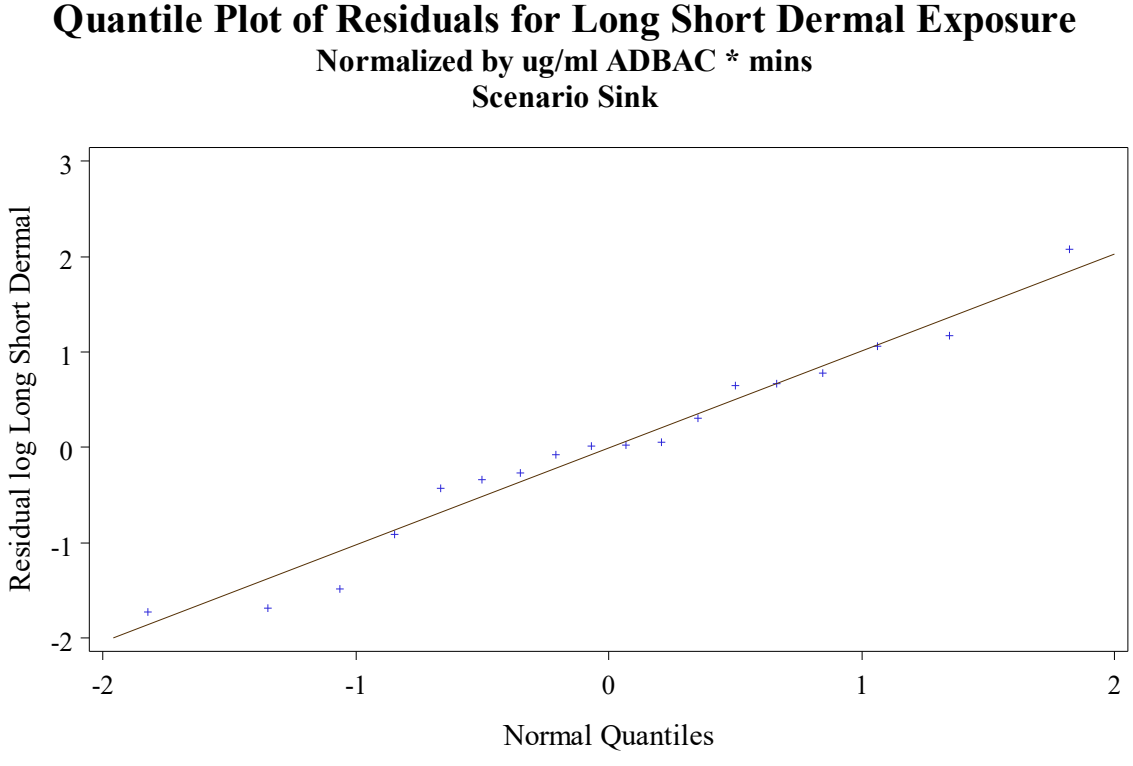

Figure AS17. Quantile plot of residuals from linear model for Long Short Dermal

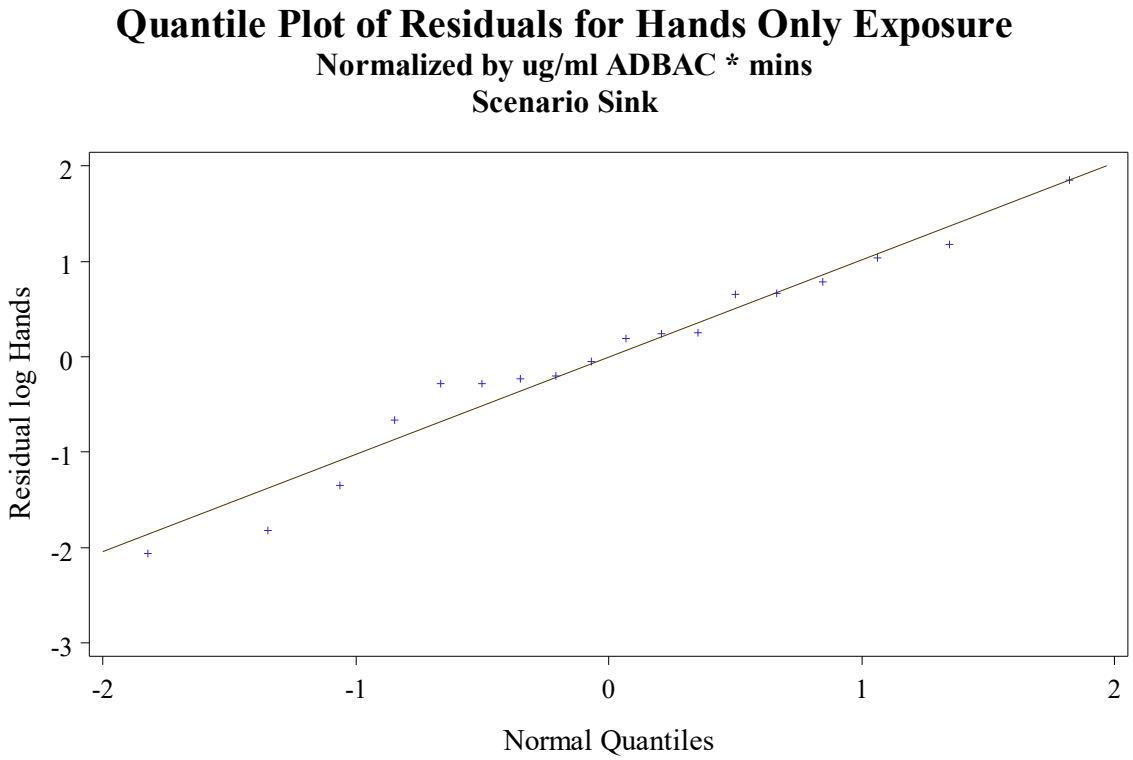

Figure AS18. Quantile plot of residuals from linear model for Hands Only

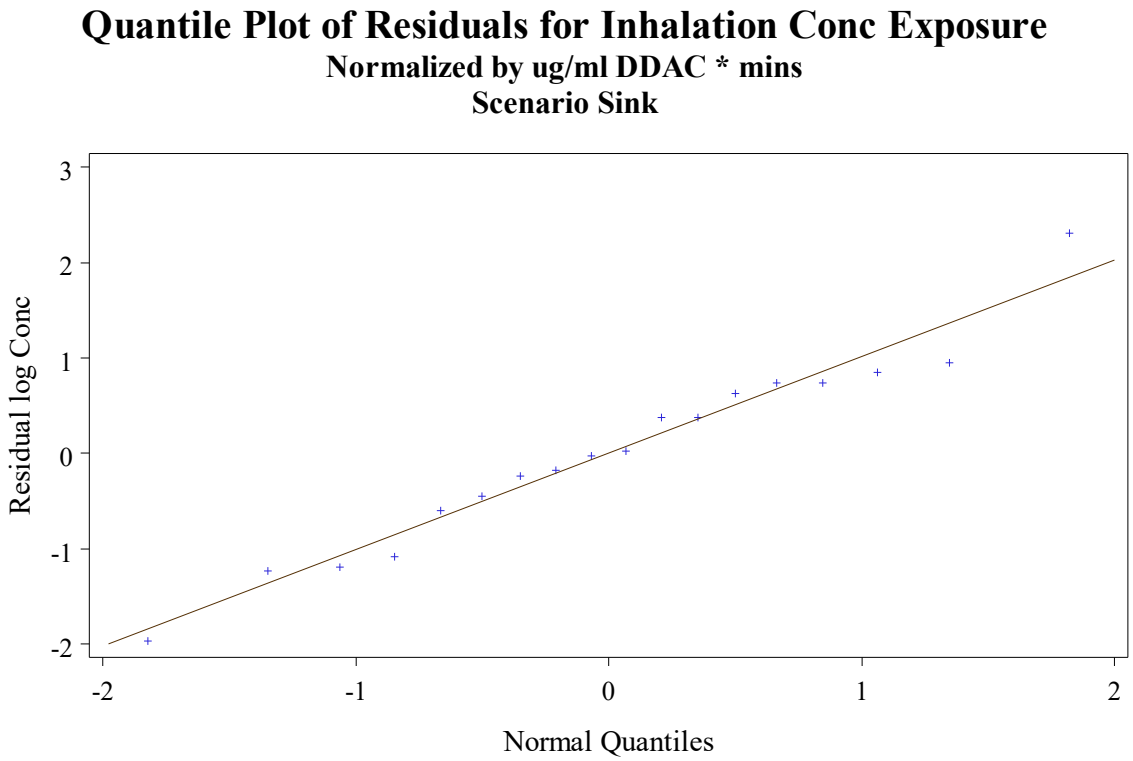

Figure AS19. Quantile plot of residuals from linear model for Inhalation Concentration

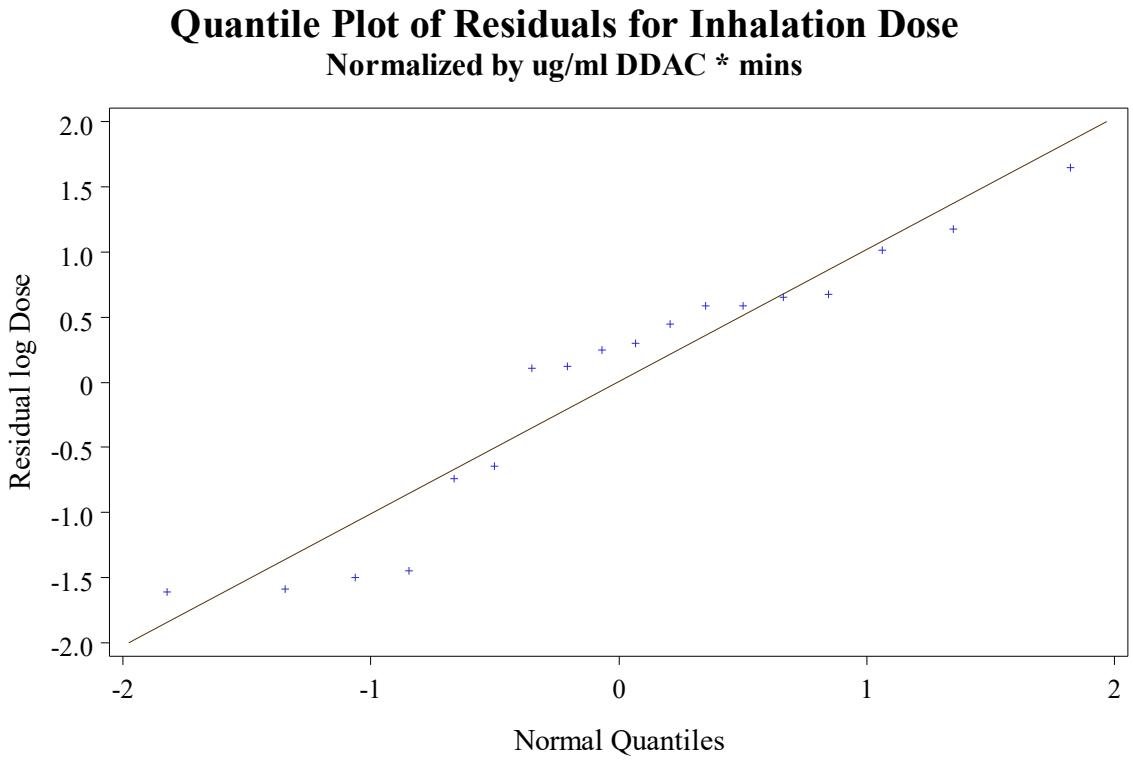

Figure AS20. Quantile plot of residuals from linear model for Inhalation Dose

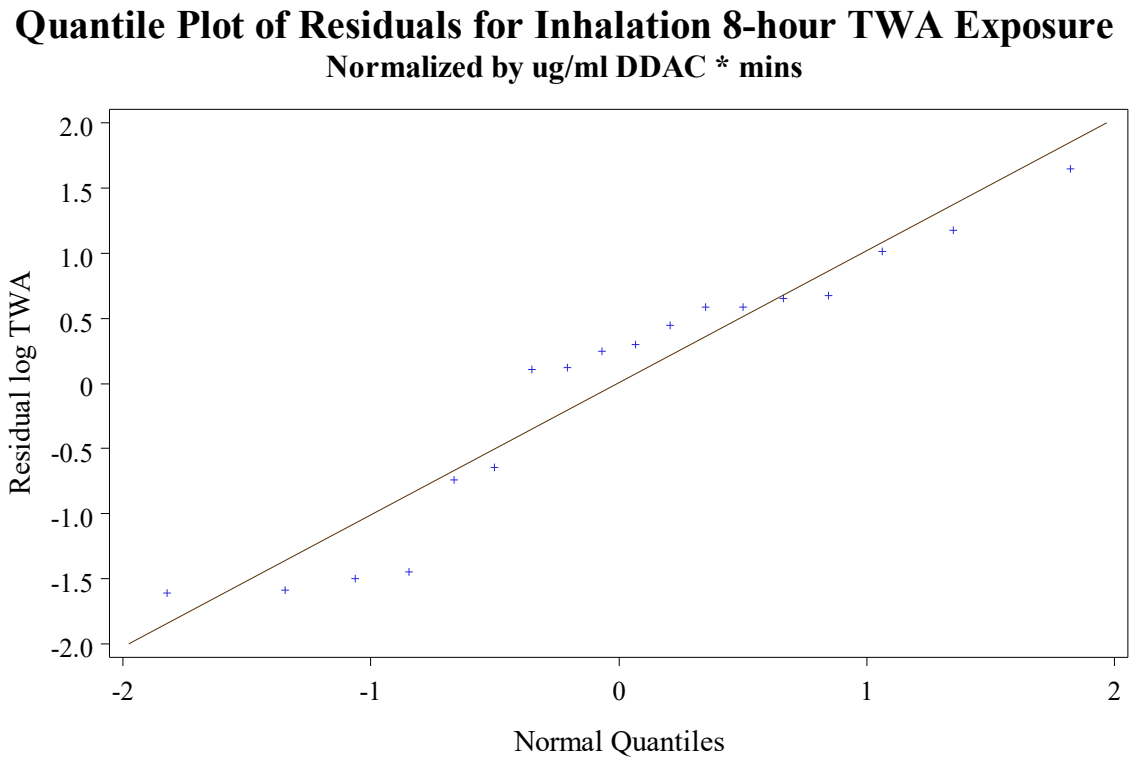

Figure AS21. Quantile plot of residuals from linear model for Inhalation Tine-Weighted Average Concentration

The quantile-quantile plots of the studentized residuals are reasonably close to the straight line except for the inhalation dose and the inhalation time-weighted average concentration. None of the studentized residuals exceeded the standard outlier cutoff of ±3.

Regression plots

The lognormal linear regression results for all the exposure routes are shown below using the mid value substitution method for non-detect values. The data points are labeled to show the targeted durations.

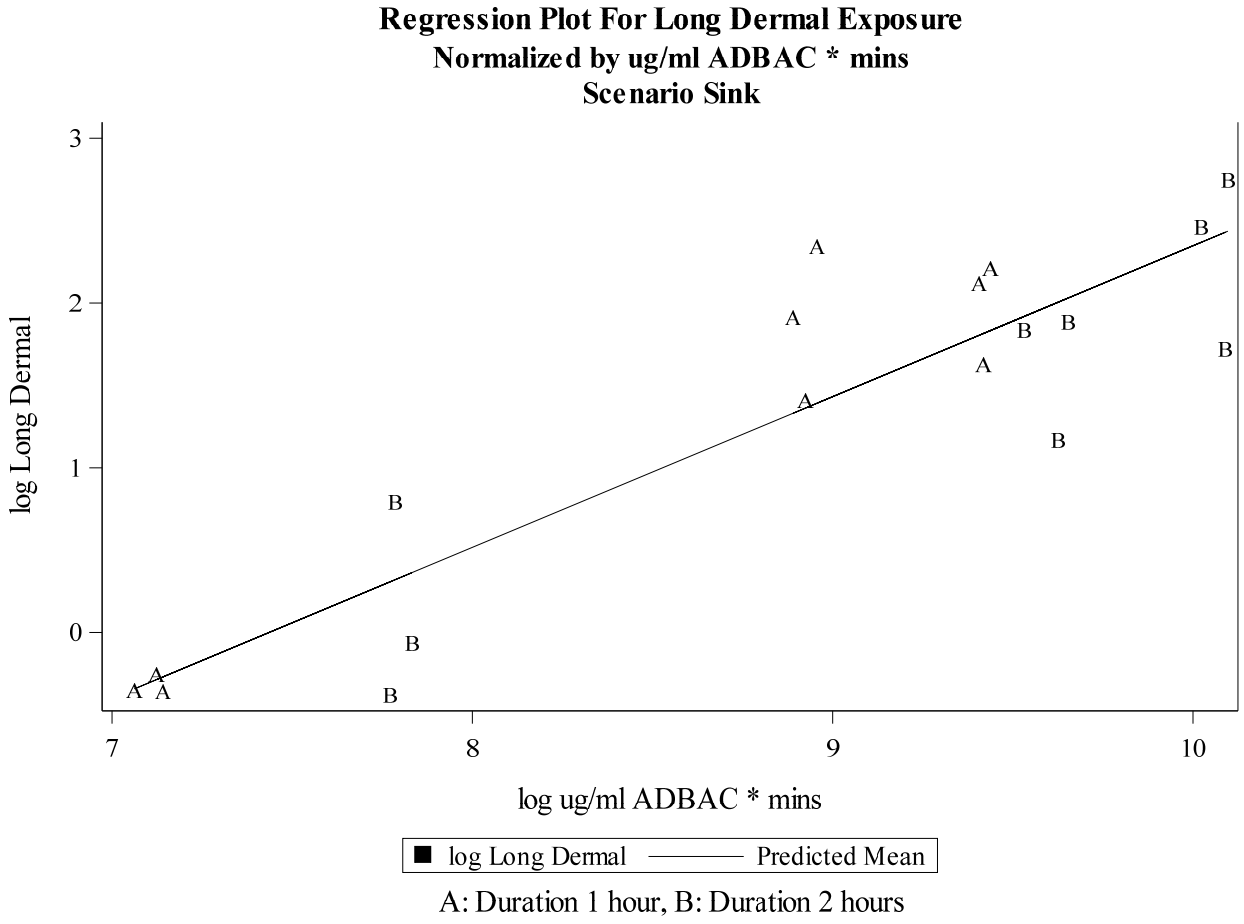

Figure AS22. Regression plot for Long Dermal Exposure (mg)

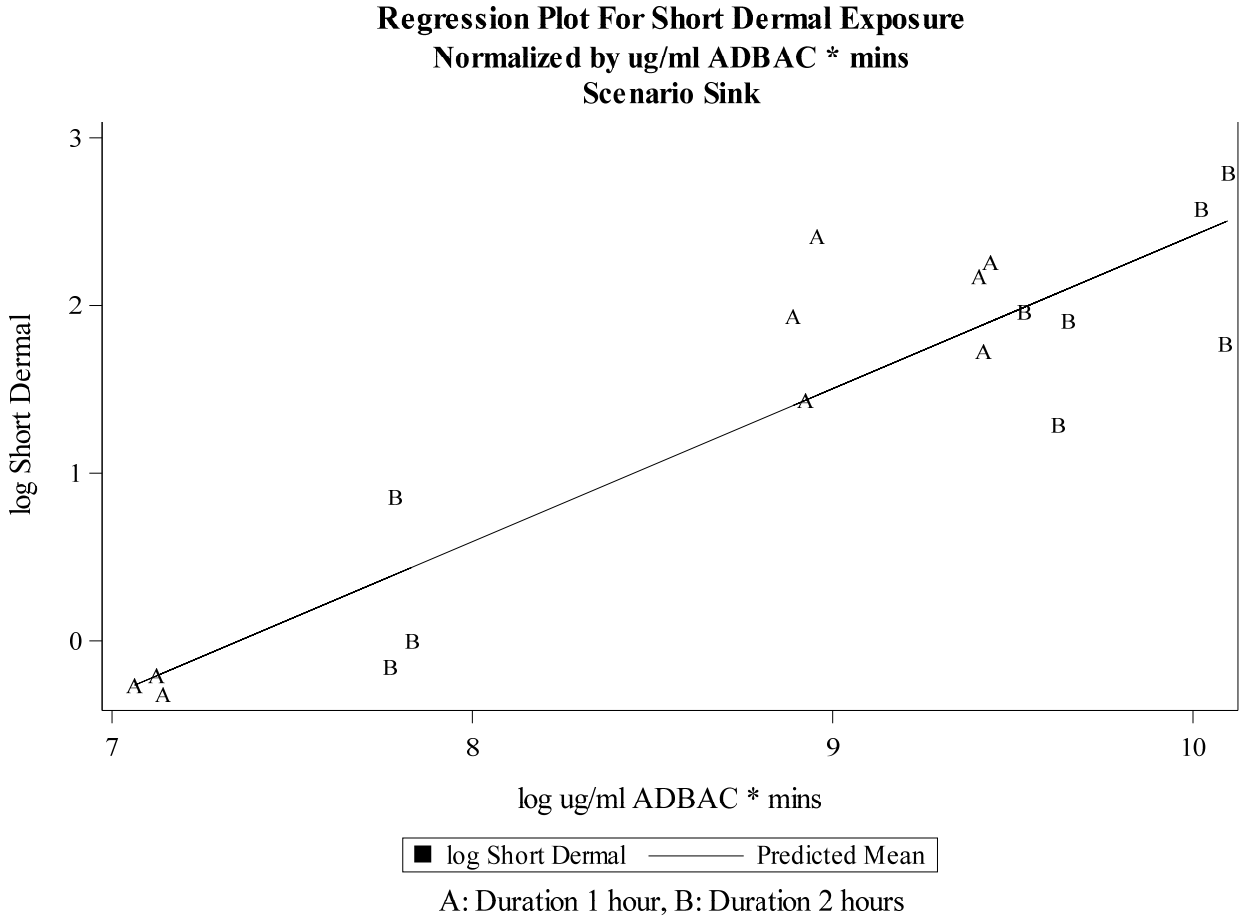

Figure AS23. Regression plot for Short Dermal Exposure (mg)

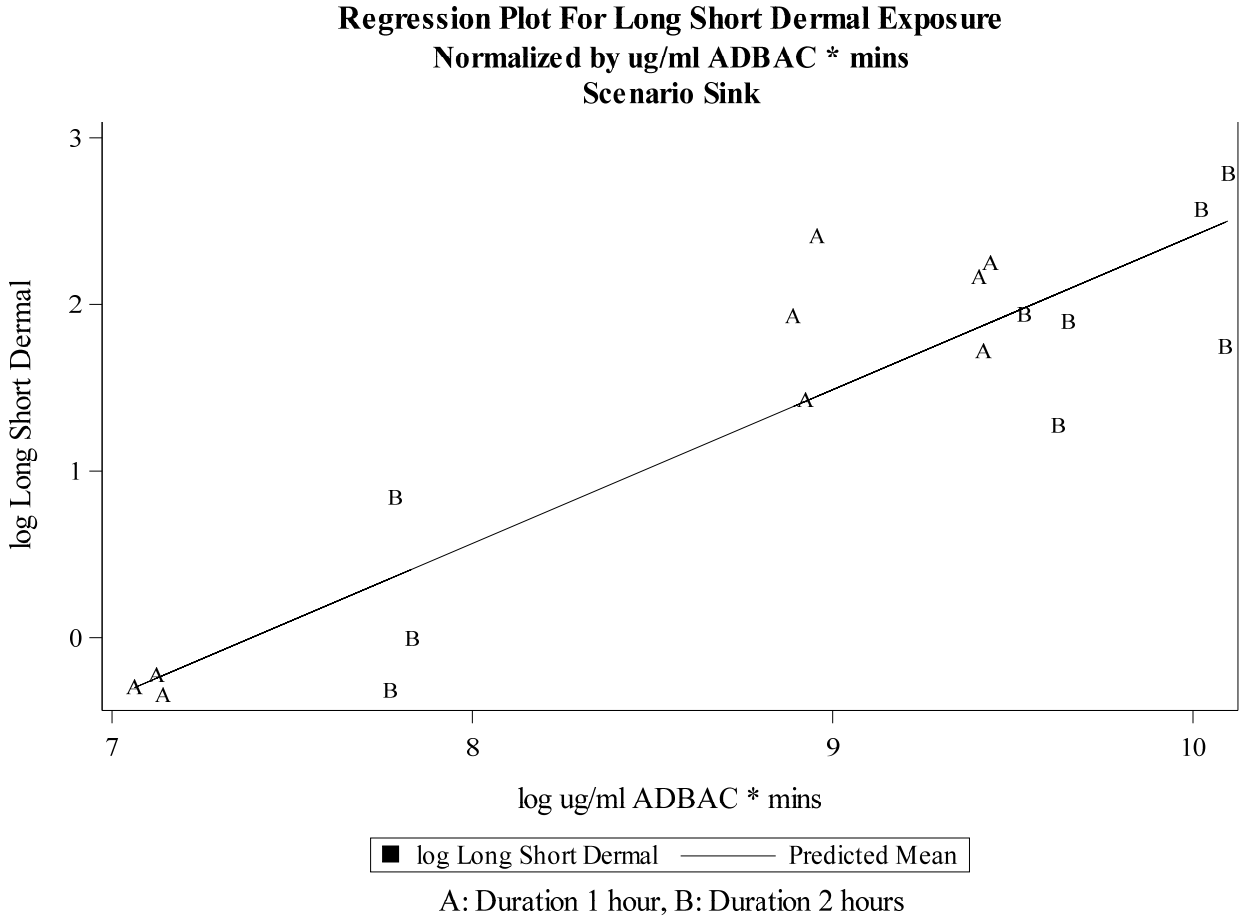

Figure AS24. Regression plot for Long Short Dermal Exposure (mg)

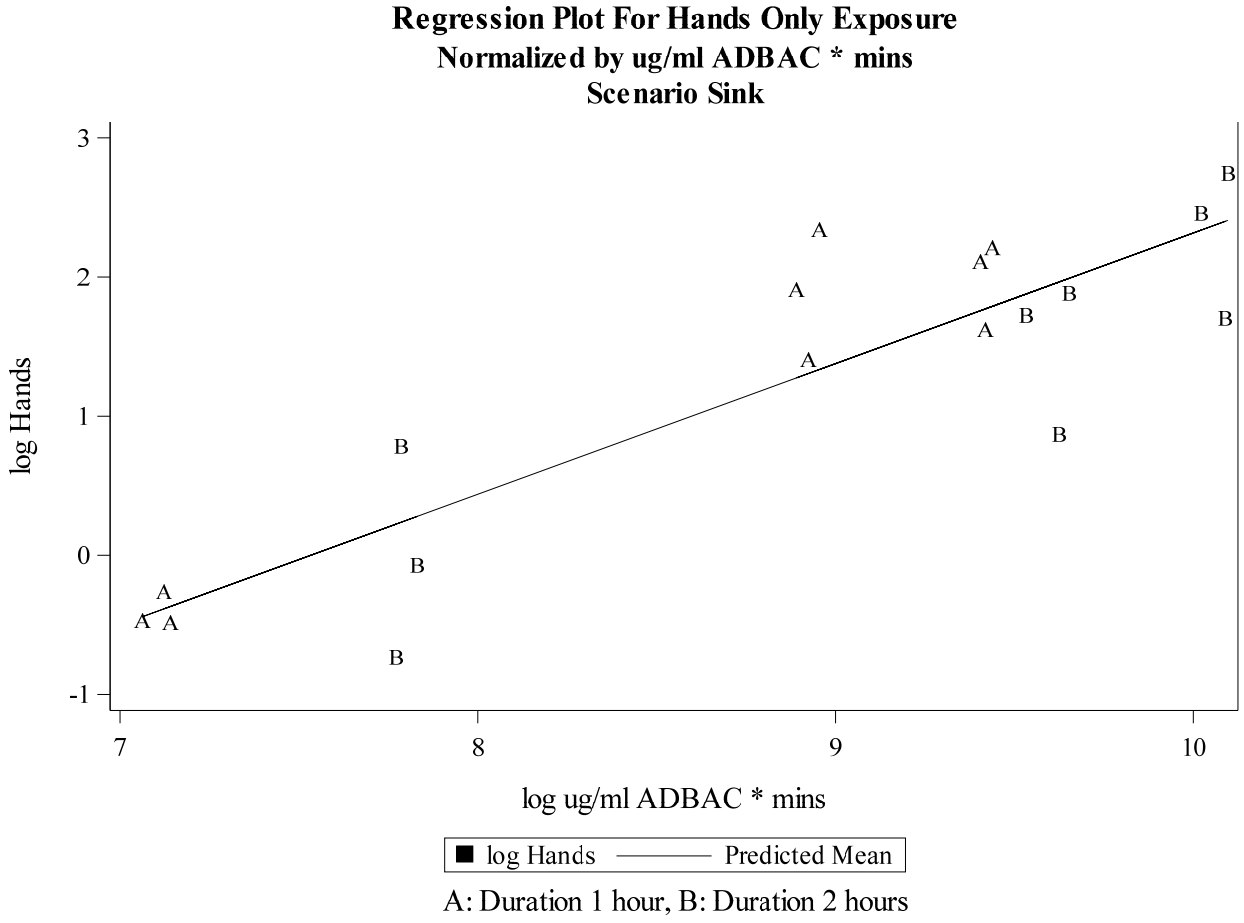

Figure AS25. Regression plot for Hands Only Exposure (mg)

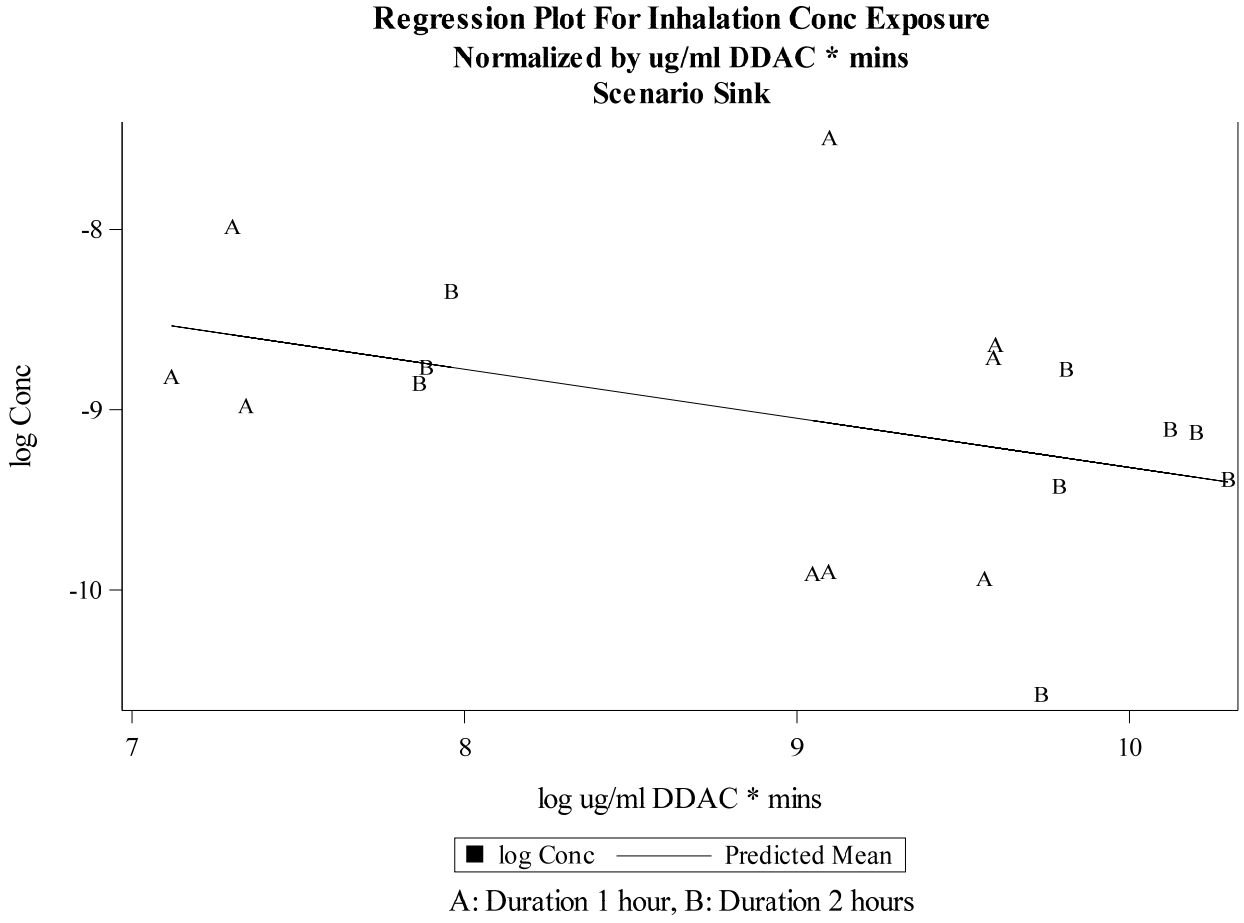

Figure AS26. Regression plot for Inhalation Concentration Exposure (mg/m^3)

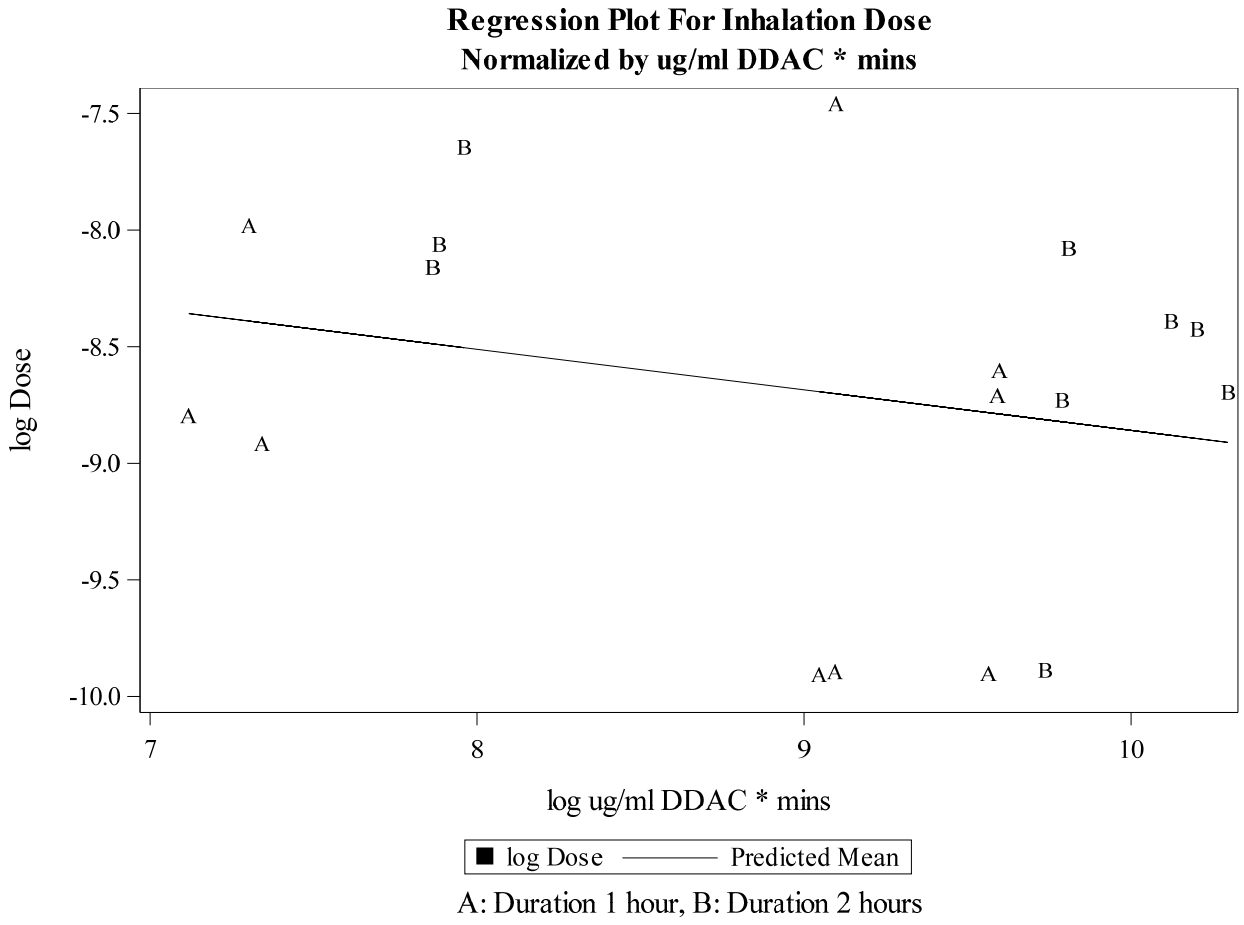

Figure AS27. Regression plot for Inhalation Dose (mg)

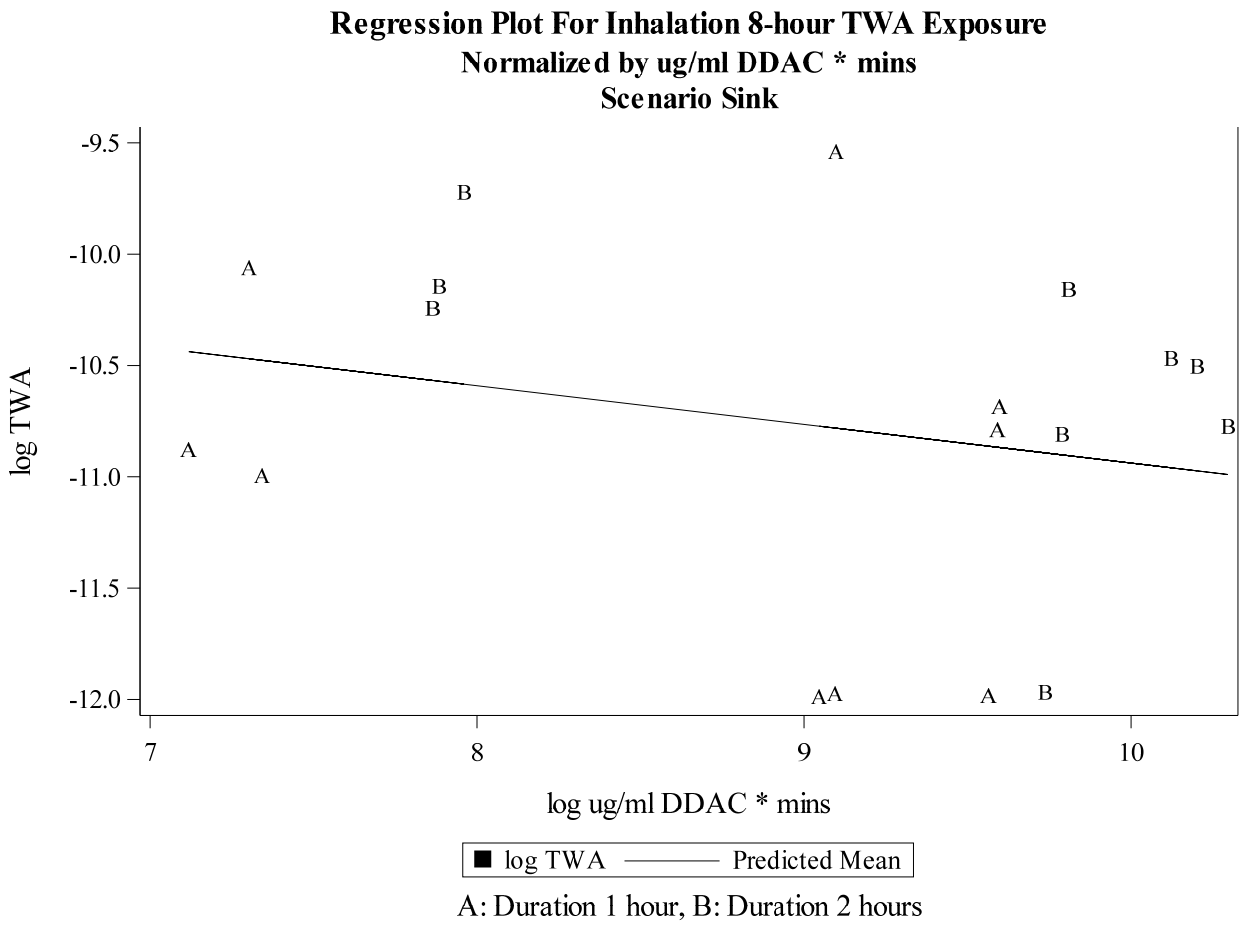

Figure AS28. Regression plot for Inhalation Time-Weighted Average Exposure (mg/m^3)

Quadratic models

Table AS19 presents the quadratic coefficient Quad from the fitted quadratic regression models for all the exposure routes using All data. Coefficients for the Intercept and Slope are shown under model 2 in Tables AS20 to AS26 below.

Table AS19. Quadratic coefficients with 95% confidence intervals for quadratic regression models for the log exposure versus log (Normalizing Factor)

Exposure Route	Estimate	Lower Bound	Upper Bound
Long Dermal	–0.17	–0.47	0.14
Short Dermal	–0.17	–0.46	0.12
Long Short Dermal	–0.17	–0.47	0.13
Hands Only	–0.17	–0.52	0.19
Inhalation Concentration	0.03	–0.44	0.50

Exposure Route	Estimate	Lower Bound	Upper Bound
Inhalation Dose	0.13	−0.38	0.64
Inhalation Time-weighted Average	0.13	−0.38	0.64

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

Alternative Statistical Approaches

In this section we present and compare some alternative statistical approaches to the linear and quadratic models.

Model Parameters

Table AS20. Alternative fitted statistical models for Long Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-6.805	-8.865	-4.746
	β	0.915	0.683	1.147
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-18.551	-40.617	3.515
	β	3.704	-1.518	8.927
	γ	-0.163	-0.468	0.142
3. Log-log logistic regression of exposure on NF	**α**			
	γ			
	β			
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-6.856	-8.726	-4.986

Model	Parameter	Estimate	Lower Bound	Upper Bound
	β	0.933	0.722	1.143
	ϕ	5.033	2.673	9.478

Table AS21. Alternative fitted statistical models for Short Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-6.708	-8.675	-4.742
	β	0.912	0.691	1.134
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-18.735	-39.669	2.199
	β	3.768	-1.186	8.723
	γ	-0.167	-0.456	0.122
3. Log-log logistic regression of exposure on NF	**α**			
	γ			
	β			
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-6.787	-8.586	-4.988
	β	0.932	0.730	1.135
	ϕ	5.428	2.878	10.234

Table AS22. Alternative fitted statistical models for Long Short Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-6.818	-8.850	-4.786
	β	0.923	0.694	1.152

Model	Parameter	Estimate	Lower Bound	Upper Bound
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-18.757	-40.471	2.957
	β	3.758	-1.381	8.897
	γ	-0.166	-0.466	0.134
3. Log-log logistic regression of exposure on NF	**α**			
	γ			
	β			
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-6.870	-8.722	-5.019
	β	0.940	0.732	1.149
	ϕ	5.133	2.725	9.669

Table AS23. Alternative fitted statistical models for Hands Only Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-7.070	-9.440	-4.699
	β	0.939	0.672	1.205
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-18.989	-44.633	6.656
	β	3.769	-2.300	9.838
	γ	-0.165	-0.520	0.189
3. Log-log logistic regression of exposure on NF	**α**			
	γ			
	β			

Model	Parameter	Estimate	Lower Bound	Upper Bound
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-7.078	-9.175	-4.982
	β	0.954	0.718	1.190
	ϕ	4.045	2.158	7.582

Table AS24. Alternative fitted statistical models for Inhalation Concentration (mg/m^3)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-6.596	-9.613	-3.578
	β	-0.272	-0.607	0.062
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-4.336	-39.136	30.465
	β	-0.800	-8.904	7.303
	γ	0.030	-0.435	0.496
3. Log-log logistic regression of exposure on NF	**α**	0.000233	0.000032	0.000434
	γ	0.000003	-0.000158	0.000164
	β	1.255499	-4.116709	6.627707
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-6.65	-9.38	-3.92
	β	-0.24	-0.54	0.06

Model	Parameter	Estimate	Lower Bound	Upper Bound
	ϕ	2.34	1.27	4.31

Table AS25. Alternative fitted statistical models for Inhalation Dose (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-7.122	-10.440	-3.805
	β	-0.174	-0.541	0.194
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	2.665	-35.235	40.566
	β	-2.460	-11.285	6.365
	γ	0.131	-0.375	0.638
3. Log-log logistic regression of exposure on NF	**α**	0.000292	-0.000179	0.000763
	γ	0.000156	-0.009339	0.009652
	β	0.836898	-4.932604	6.606400
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-7.014	-9.679	-4.349
	β	-0.160	-0.455	0.136
	ϕ	2.291	1.243	4.225

Table AS26. Alternative fitted statistical models for Inhalation Time Weighted Average Concentration (mg/m^3)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-9.202	-12.519	-5.884
	β	-0.174	-0.541	0.194

Model	Parameter	Estimate	Lower Bound	Upper Bound
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	0.586	-37.314	38.486
	β	-2.460	-11.285	6.365
	γ	0.131	-0.375	0.638
3. Log-log logistic regression of exposure on NF	**α**	0.000037	-0.000022	0.000095
	γ	0.000156	-0.009339	0.009652
	β	0.836898	-4.932641	6.606437
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-9.093	-11.758	-6.428
	β	-0.160	-0.455	0.136
	ϕ	2.291	1.243	4.225

Model Comparisons

One way to compare the fit of the 7 models presented above is to use the Akaike Information Criterion (AIC), which takes minus twice the log-likelihood and then makes an adjustment or penalty for the number of parameters in the model. The following two tables compare the AIC values for the various Dermal and Inhalation exposure measures. The smaller values of the AIC suggest a better-fitting model. AIC values for models that failed to converge are not shown.

Table AS27. Akaike Information Criteria values for alternative models for Dermal Exposure

Model	Long Dermal	Short Dermal	Long Short Dermal	Hands Only
1. Linear regression of Ln(exposure) on Ln(NF)	28.8	27.2	28.4	33.9
2. Quadratic regression of Ln(exposure) on Ln(NF)	29.3	27.5	28.8	34.8

Model	Long Dermal	Short Dermal	Long Short Dermal	Hands Only
3. Log-log logistic regression of exposure on NF				
4. 3-parameter logistic regression of exposure on NF				
5. Gamma model for exposure	29.2	27.7	28.8	33.4

Table AS28. Akaike Information Criteria values for alternative models for Inhalation Exposure

Model	Inhalation Concentration	Inhalation Dose	Inhalation Time-Weighted Average Concentration
1. Linear regression of Ln(exposure) on Ln(NF)	42.4	45.8	45.8
2. Quadratic regression of Ln(exposure) on Ln(NF)	44.4	47.4	47.4
3. Log-log logistic regression of exposure on NF	58.7	51.5	51.5
4. 3-parameter logistic regression of exposure on NF			
5. Gamma model for exposure	44.3	44.7	44.7

Based on the AIC, the best-fitting models are the linear model for the Long Dermal. Short Dermal, and Long Short Dermal models and the inhalation concentration model, and the gamma model for Hands Only, the inhalation dose, and the time-weighted average concentration.

4. COP Scenario

This entire section contains the same sets of tables and figures as Section 2. Bucket Scenario but the data and results are for the COP scenario instead of the Bucket scenario and the Table and Figure numbers start with AC instead of AB. The methods and formats are exactly the same for the Bucket and COP scenarios and so the details of the methods descriptions are not repeated. One exception is that for the COP scenario the three concentration groups are: "Target Quat: 100 ppm," "Target Quat: 600 ppm," and "Target Quat: 1000 ppm."

Summary Statistics of Exposure per Concentration Times Duration

Tables AC1 to AC7 summarize the normalized exposure data (per concentration times duration) with the summary statistics from the 18 (all concentrations), or 6 (specific concentrations) measurements for each concentration group, and each dermal and inhalation exposure route. These analyses assume that the exposure measurements within each subset come from some unspecified distribution for that subset.

Table AC1. Summary statistics for normalized long dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	1.144E-05	2.655E-05	5.605E-06	2.172E-06
Arithmetic Standard Deviation	1.423E-05	1.606E-05	3.270E-06	1.401E-06
Geometric Mean	5.911E-06	2.303E-05	4.759E-06	1.885E-06
Geometric Standard Deviation	3.342E+00	1.789E+00	1.960E+00	1.754E+00
Min	8.827E-07	1.143E-05	1.461E-06	8.827E-07
5%	8.827E-07	1.143E-05	1.461E-06	8.827E-07
10%	1.461E-06	1.143E-05	1.461E-06	8.827E-07
25%	2.056E-06	1.283E-05	4.217E-06	1.529E-06
50%	5.106E-06	2.501E-05	5.106E-06	1.815E-06
75%	1.283E-05	2.918E-05	6.373E-06	2.103E-06
90%	2.918E-05	5.584E-05	1.137E-05	4.885E-06
95%	5.584E-05	5.584E-05	1.137E-05	4.885E-06
Max	5.584E-05	5.584E-05	1.137E-05	4.885E-06

Table AC2. Summary statistics for normalized short dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	3.636E-05	5.420E-05	3.244E-05	2.243E-05
Arithmetic Standard Deviation	2.704E-05	2.606E-05	1.878E-05	2.865E-05

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Geometric Mean	2.463E-05	4.930E-05	2.643E-05	1.146E-05
Geometric Standard Deviation	2.900E+00	1.609E+00	2.195E+00	3.716E+00
Min	2.247E-06	2.818E-05	6.716E-06	2.247E-06
5%	2.247E-06	2.818E-05	6.716E-06	2.247E-06
10%	3.376E-06	2.818E-05	6.716E-06	2.247E-06
25%	1.631E-05	3.231E-05	1.810E-05	3.376E-06
50%	3.025E-05	4.803E-05	3.204E-05	1.283E-05
75%	5.508E-05	7.313E-05	4.961E-05	2.503E-05
90%	7.828E-05	9.551E-05	5.615E-05	7.828E-05
95%	9.551E-05	9.551E-05	5.615E-05	7.828E-05
Max	9.551E-05	9.551E-05	5.615E-05	7.828E-05

Table AC3. Summary statistics for normalized long short dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	2.982E-05	4.507E-05	2.506E-05	1.932E-05
Arithmetic Standard Deviation	2.498E-05	2.607E-05	1.927E-05	2.513E-05
Geometric Mean	1.853E-05	3.898E-05	1.872E-05	8.719E-06
Geometric Standard Deviation	3.234E+00	1.822E+00	2.396E+00	4.429E+00
Min	1.429E-06	1.669E-05	5.936E-06	1.429E-06
5%	1.429E-06	1.669E-05	5.936E-06	1.429E-06
10%	1.888E-06	1.669E-05	5.936E-06	1.429E-06
25%	8.754E-06	2.640E-05	8.754E-06	1.888E-06
50%	2.310E-05	3.697E-05	1.912E-05	1.090E-05
75%	4.743E-05	6.925E-05	4.743E-05	2.301E-05
90%	6.925E-05	8.416E-05	4.997E-05	6.780E-05
95%	8.416E-05	8.416E-05	4.997E-05	6.780E-05
Max	8.416E-05	8.416E-05	4.997E-05	6.780E-05

Table AC4. Summary statistics for normalized hands only dermal exposure (mg/(ppm ADBAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	8.818E-06	2.142E-05	3.714E-06	1.321E-06
Arithmetic Standard Deviation	1.307E-05	1.669E-05	3.451E-06	9.586E-07
Geometric Mean	3.451E-06	1.716E-05	2.349E-06	1.020E-06
Geometric Standard Deviation	4.434E+00	2.031E+00	3.123E+00	2.303E+00
Min	2.980E-07	9.232E-06	6.164E-07	2.980E-07
5%	2.980E-07	9.232E-06	6.164E-07	2.980E-07
10%	5.525E-07	9.232E-06	6.164E-07	2.980E-07
25%	8.706E-07	9.236E-06	6.178E-07	5.525E-07
50%	3.465E-06	1.602E-05	3.121E-06	1.189E-06
75%	9.726E-06	2.580E-05	5.083E-06	1.799E-06
90%	2.580E-05	5.222E-05	9.726E-06	2.899E-06
95%	5.222E-05	5.222E-05	9.726E-06	2.899E-06
Max	5.222E-05	5.222E-05	9.726E-06	2.899E-06

Table AC5. Summary statistics for normalized inhalation concentration exposure (mg/m^3/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	7.217E-07	1.822E-06	2.157E-07	1.273E-07
Arithmetic Standard Deviation	1.523E-06	2.380E-06	1.599E-07	1.114E-07
Geometric Mean	2.424E-07	9.023E-07	1.640E-07	9.621E-08
Geometric Standard Deviation	3.939E+00	3.763E+00	2.318E+00	2.234E+00
Min	3.657E-08	2.157E-07	6.446E-08	3.657E-08
5%	3.657E-08	2.157E-07	6.446E-08	3.657E-08
10%	5.839E-08	2.157E-07	6.446E-08	3.657E-08
25%	7.310E-08	2.397E-07	7.310E-08	5.839E-08
50%	2.277E-07	9.744E-07	1.861E-07	9.428E-08
75%	4.479E-07	2.080E-06	3.366E-07	1.428E-07
90%	2.080E-06	6.448E-06	4.479E-07	3.378E-07
95%	6.448E-06	6.448E-06	4.479E-07	3.378E-07

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Max	6.448E-06	6.448E-06	4.479E-07	3.378E-07

Tabl;e AC6. Summary statistics for normalized inhalation dose exposure (mg/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	1.089E-06	2.712E-06	3.558E-07	1.979E-07
Arithmetic Standard Deviation	2.045E-06	3.058E-06	2.950E-07	1.394E-07
Geometric Mean	4.006E-07	1.493E-06	2.681E-07	1.606E-07
Geometric Standard Deviation	3.737E+00	3.353E+00	2.268E+00	2.031E+00
Min	7.104E-08	4.782E-07	1.114E-07	7.104E-08
5%	7.104E-08	4.782E-07	1.114E-07	7.104E-08
10%	8.472E-08	4.782E-07	1.114E-07	7.104E-08
25%	1.461E-07	5.554E-07	1.461E-07	8.472E-08
50%	3.696E-07	1.134E-06	2.325E-07	1.462E-07
75%	6.260E-07	5.235E-06	5.599E-07	3.283E-07
90%	5.235E-06	7.737E-06	8.526E-07	4.109E-07
95%	7.737E-06	7.737E-06	8.526E-07	4.109E-07
Max	7.737E-06	7.737E-06	8.526E-07	4.109E-07

Table AC7. Summary statistics for normalized inhalation time-weighted average concentration exposure (mg/m^3/(ppm DDAC × mins)) using empirical sampling model

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
Arithmetic Mean	1.361E-07	3.391E-07	4.448E-08	2.474E-08
Arithmetic Standard Deviation	2.556E-07	3.822E-07	3.687E-08	1.742E-08
Geometric Mean	5.007E-08	1.866E-07	3.351E-08	2.008E-08
Geometric Standard Deviation	3.737E+00	3.353E+00	2.268E+00	2.031E+00
Min	8.879E-09	5.977E-08	1.392E-08	8.879E-09
5%	8.879E-09	5.977E-08	1.392E-08	8.879E-09
10%	1.059E-08	5.977E-08	1.392E-08	8.879E-09
25%	1.826E-08	6.943E-08	1.826E-08	1.059E-08
50%	4.620E-08	1.418E-07	2.906E-08	1.828E-08

Statistic	All	Target Quat: 100 ppm	Target Quat: 600 ppm	Target Quat: 1000 ppm
75%	7.824E-08	6.544E-07	6.998E-08	4.104E-08
90%	6.544E-07	9.672E-07	1.066E-07	5.137E-08
95%	9.672E-07	9.672E-07	1.066E-07	5.137E-08
Max	9.672E-07	9.672E-07	1.066E-07	5.137E-08

The results show fairly high proportions of the normalized Long Dermal exposure from hands only, but not as high as for the Bucket and Sink scenarios. For All and for each concentration group, based on the arithmetic means, the overall percentages of the normalized exposure from hands only range from 61 and 81% of the Long Dermal and is 77% for All, Similarly, for the unnormalized dermal exposure, the arithmetic mean hands only exposure is 69% of the arithmetic mean total dermal exposure (defined in the study report as the sum of the residues from hand wash, face/neck wipe, and the inner dosimeters, which is the definition of Long Dermal used in this memorandum). (The percentages are much lower if you include the outer dosimeters.)

Compare Concentration Groups

The results in Tables AC1 to AC7 show some differences between the normalized exposure statistics for the three concentration groups "Target Quat: 100 ppm," "Target Quat: 600 ppm," and "Target Quat: 1000 ppm." To compare these groups, an analysis of variance was performed to test whether the geometric means were statistically significantly different at the 5% significance level.

The p-values for these ANOVA tests are shown in Table AC8. These analyses show that there were statistically significant differences (at the 5% significance level) between the three concentration groups for Long Dermal, Hands Only, and the inhalation exposures.

Table AC8. P-values for testing differences in geometric means for different concentration groups

Exposure Route	ANOVA	Welch's ANOVA
Long Dermal	0.001	0.000
Short Dermal	0.115	0.070
Long Short Dermal	0.169	0.114
Hands Only	0.004	0.000
Inhalation Conc	0.022	0.032
Inhalation Dose	0.015	0.017
Inhalation 8-hr TWA	0.015	0.017

Statistical Models

Table AC9 presents the arithmetic mean and 95th percentile estimates from the lognormal simple random sampling model, together with 95% confidence intervals, for each of the exposure routes, for all concentration groups combined. These are the values of AMu and P95u. The other summary statistics are presented in more detail below.

Table AC9. Arithmetic mean and 95th percentile estimates from lognormal simple random sampling model for normalized exposure for All

Exposure Route	Clothing	Arithmetic Mean (95% Confidence Interval)	95th Percentile (95% Confidence Interval)
Dermal (mg/(ppm ADBAC × mins))	Long Dermal	1.224×10^{-5} (6.057×10^{-6}, 2.696×10^{-5})	4.301×10^{-5} (1.795×10^{-5}, 1.020×10^{-4})
	Short Dermal	4.340×10^{-5} (2.396×10^{-5}, 8.317×10^{-5})	1.419×10^{-4} (6.563×10^{-5}, 3.038×10^{-4})
	Long Short Dermal	3.690×10^{-5} (1.875×10^{-5}, 7.867×10^{-5})	1.277×10^{-4} (5.460×10^{-5}, 2.958×10^{-4})
	Hands Only	1.046×10^{-5} (4.043×10^{-6}, 3.145×10^{-5})	3.998×10^{-5} (1.360×10^{-5}, 1.160×10^{-4})
Inhalation Concentration ((mg/m^3)/ (ppm DDAC × mins))		6.203×10^{-7} (2.660×10^{-7}, 1.632×10^{-6})	2.311×10^{-6} (8.564×10^{-7}, 6.162×10^{-6})
Inhalation Dose (mg/ (ppm DDAC × mins))		9.552×10^{-7} (4.296×10^{-7}, 2.354×10^{-6})	3.503×10^{-6} (1.348×10^{-6}, 8.996×10^{-6})
Inhalation 8-hr TWA ((mg/m^3)/ ppm DDAC × mins))		1.194×10^{-7} (5.371×10^{-8}, 2.942×10^{-7})	4.397×10^{-7} (1.686×10^{-7}, 1.124×10^{-6})

Non-detects

For all the analyses presented in this memorandum except for Table AC10 and AC18, measurements below the LOQ or LOD were replaced by the mid-value, the midpoint of the lowest and highest possible value for that measurement. In Tables AC10 and AC18 we investigated the impact on the summary statistics of the censored values.

Table AC10. Exposure summary statistics calculated using alternative estimated exposures for values below the LOQ

Exposure Route	Method for Substituting Values Below the LOQ	Arithmetic Mean	95th Percentile
Long Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	1.224×10^{-5} (5.977×10^{-6}, 2.686×10^{-5})	4.301×10^{-5} (1.787×10^{-5}, 1.020×10^{-4})
	Substitute max value	1.324×10^{-5} (6.623×10^{-6}, 2.823×10^{-5})	4.591×10^{-5} (1.949×10^{-5}, 1.066×10^{-4})
	Substitute min value	1.140×10^{-5} (5.301×10^{-6}, 2.647×10^{-5})	4.103×10^{-5} (1.795×10^{-5}, 1.020×10^{-4})
	Censored data MLE	1.169×10^{-5} (5.852×10^{-6}, 2.490×10^{-5})	4.301×10^{-5} (1.633×10^{-5}, 1.015×10^{-4})
Short Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	4.340×10^{-5} (2.369×10^{-5}, 8.316×10^{-5})	1.419×10^{-4} (6.536×10^{-5}, 3.040×10^{-4})

Exposure Route	Method for Substituting Values Below the LOQ	Arithmetic Mean	95th Percentile
	Substitute max value	4.451×10^{-5} (2.486×10^{-5}, 8.288×10^{-5})	1.428×10^{-4} (6.730×10^{-5}, 2.993×10^{-4})
	Substitute min value	4.278×10^{-5} (2.250×10^{-5}, 8.587×10^{-5})	1.438×10^{-4} (6.386×10^{-5}, 3.195×10^{-4})
	Censored data MLE	4.187×10^{-5} (2.342×10^{-5}, 7.787×10^{-5})	1.342×10^{-4} (6.332×10^{-5}, 2.810×10^{-4})
Long Short Dermal (mg/(ppm ADBAC × mins))	Substitute mid value	3.690×10^{-5} (1.851×10^{-5}, 7.841×10^{-5})	1.277×10^{-4} (5.435×10^{-5}, 2.960×10^{-4})
	Substitute max value	3.795×10^{-5} (1.951×10^{-5}, 7.831×10^{-5})	1.294×10^{-4} (5.631×10^{-5}, 2.935×10^{-4})
	Substitute min value	3.607×10^{-5} (1.739×10^{-5}, 8.026×10^{-5})	1.276×10^{-4} (5.435×10^{-5}, 2.960×10^{-4})
	Censored data MLE	3.539×10^{-5} (1.820×10^{-5}, 7.302×10^{-5})	1.207×10^{-4} (5.252×10^{-5}, 2.736×10^{-4})
Hands Only (mg/(ppm ADBAC × mins))	Substitute mid value	1.046×10^{-5} (4.001×10^{-6}, 3.125×10^{-5})	3.998×10^{-5} (1.352×10^{-5}, 1.161×10^{-4})
	Substitute max value	1.046×10^{-5} (4.001×10^{-6}, 3.125×10^{-5})	3.998×10^{-5} (1.352×10^{-5}, 1.161×10^{-4})
	Substitute min value	1.046×10^{-5} (4.001×10^{-6}, 3.125×10^{-5})	3.998×10^{-5} (1.352×10^{-5}, 1.161×10^{-4})
	Censored data MLE	9.836×10^{-6} (3.902×10^{-6}, 2.794×10^{-5})	3.731×10^{-5} (1.301×10^{-5}, 1.052×10^{-4})
Inhalation Concentration ((mg/m^3)/ (ppm DDAC × mins))	Substitute mid value	6.203×10^{-7} (2.640×10^{-7}, 1.619×10^{-6})	2.311×10^{-6} (8.518×10^{-7}, 6.168×10^{-6})
	Substitute max value	6.203×10^{-7} (2.640×10^{-7}, 1.619×10^{-6})	2.311×10^{-6} (8.518×10^{-7}, 6.168×10^{-6})
	Substitute min value	6.203×10^{-7} (2.640×10^{-7}, 1.619×10^{-6})	2.311×10^{-6} (8.518×10^{-7}, 6.168×10^{-6})
	Censored data MLE	5.888×10^{-7} (2.591×10^{-7}, 1.469×10^{-6})	2.169×10^{-6} (8.222×10^{-7}, 5.630×10^{-6})
Inhalation Dose (mg/ (ppm DDAC × mins))	Substitute mid value	9.552×10^{-7} (4.256×10^{-7}, 2.345×10^{-6})	3.503×10^{-6} (1.342×10^{-6}, 9.003×10^{-6})
	Substitute max value	9.552×10^{-7} (4.256×10^{-7}, 2.345×10^{-6})	3.503×10^{-6} (1.342×10^{-6}, 9.003×10^{-6})
	Substitute min value	9.552×10^{-7} (4.256×10^{-7}, 2.345×10^{-6})	3.503×10^{-6} (1.342×10^{-6}, 9.003×10^{-6})
	Censored data MLE	9.102×10^{-7} (4.181×10^{-7}, 2.146×10^{-6})	3.295×10^{-6} (1.297×10^{-6}, 8.247×10^{-6})
Inhalation 8-hr TWA ((mg/m^3)/ ppm DDAC × mins))	Substitute mid value	1.194×10^{-7} (5.319×10^{-8}, 2.932×10^{-7})	4.379×10^{-7} (1.677×10^{-7}, 1.125×10^{-6})
	Substitute max value	1.194×10^{-7} (5.319×10^{-8}, 2.932×10^{-7})	4.379×10^{-7} (1.677×10^{-7}, 1.125×10^{-6})
	Substitute min value	1.194×10^{-7} (5.319×10^{-8}, 2.932×10^{-7})	4.379×10^{-7} (1.677×10^{-7}, 1.125×10^{-6})
	Censored data MLE	1.138×10^{-7} (5.226×10^{-8}, 2.683×10^{-7})	4.119×10^{-7} (1.621×10^{-7}, 1.031×10^{-6})

The results in Table AC10 for dermal and inhalation exposure show very small impacts of the alternative substitution approaches for treating values below the LOQ on the unit exposure arithmetic mean and 95th percentile.

Detailed Summary Statistics with Confidence Intervals and Fold Relative Accuracy

Tables AC11 to AC17 present the estimates, parametric and non-parametric confidence intervals and fold relative accuracy values for all the summary statistics for the All group. All these analyses use non-detects substituted by the mid-value.

Table AC11. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	3.342E+00	2.237E+00	5.033E+00	1.50	2.379E+00	4.223E+00	1.36
GMs	5.911E-06	3.416E-06	1.049E-05	1.75	3.452E-06	1.016E-05	1.71
AMs	1.144E-05	5.680E-06	2.543E-05	2.09	5.910E-06	1.852E-05	1.79
AMu	1.224E-05	6.057E-06	2.696E-05	2.11	5.817E-06	2.274E-05	1.99
P95s	5.584E-05	1.777E-05	2.168E-04	3.47	2.359E-05	5.584E-05	2.11
P95u	4.301E-05	1.795E-05	1.020E-04	2.38	1.740E-05	8.338E-05	2.21

Table AC12. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.900E+00	2.035E+00	4.161E+00	1.43	1.846E+00	3.812E+00	1.46
GMs	2.463E-05	1.518E-05	4.084E-05	1.64	1.514E-05	3.848E-05	1.59
AMs	3.636E-05	2.287E-05	8.103E-05	1.98	2.506E-05	4.866E-05	1.40
AMu	4.340E-05	2.396E-05	8.317E-05	1.87	2.855E-05	5.954E-05	1.46
P95s	9.551E-05	6.505E-05	5.912E-04	4.99	5.615E-05	9.551E-05	1.31
P95u	1.419E-04	6.563E-05	3.038E-04	2.15	8.145E-05	2.055E-04	1.62

Table AC13. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	3.234E+00	2.188E+00	4.817E+00	1.48	2.026E+00	4.376E+00	1.50
GMs	1.853E-05	1.087E-05	3.237E-05	1.73	1.075E-05	3.059E-05	1.68

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
AMs	2.982E-05	1.767E-05	7.499E-05	2.19	1.941E-05	4.133E-05	1.47
AMu	3.690E-05	1.875E-05	7.867E-05	2.05	2.226E-05	5.422E-05	1.58
P95s	8.416E-05	5.407E-05	6.163E-04	5.77	4.997E-05	8.416E-05	1.24
P95u	1.277E-04	5.460E-05	2.958E-04	2.33	6.792E-05	1.983E-04	1.75

Table AC14. 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/(ppm ADBAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	4.434E+00	2.701E+00	7.350E+00	1.65	2.928E+00	5.906E+00	1.45
GMs	3.451E-06	1.754E-06	7.003E-06	2.00	1.770E-06	6.706E-06	1.95
AMs	8.818E-06	3.631E-06	2.739E-05	2.72	3.875E-06	1.543E-05	2.03
AMu	1.046E-05	4.043E-06	3.145E-05	2.77	3.996E-06	2.273E-05	2.40
P95s	5.222E-05	1.343E-05	2.944E-04	4.70	1.013E-05	5.222E-05	2.38
P95u	3.998E-05	1.360E-05	1.160E-04	2.92	1.392E-05	8.748E-05	2.54

Table AC15. 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 exposure ((mg/m^3)/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	3.939E+00	2.496E+00	6.272E+00	1.59	2.288E+00	5.742E+00	1.62
GMs	2.424E-07	1.300E-07	4.650E-07	1.89	1.365E-07	4.600E-07	1.83
AMs	7.217E-07	2.446E-07	1.464E-06	2.70	2.154E-07	1.503E-06	2.87
AMu	6.203E-07	2.660E-07	1.632E-06	2.45	2.126E-07	1.758E-06	2.88
P95s	6.448E-06	8.466E-07	1.452E-05	6.65	5.606E-07	6.448E-06	4.64
P95u	2.311E-06	8.564E-07	6.162E-06	2.68	6.100E-07	6.717E-06	3.40

Table AC16. 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 exposure (mg/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	3.737E+00	2.410E+00	5.846E+00	1.56	2.166E+00	5.310E+00	1.61

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GMs	4.006E-07	2.200E-07	7.494E-07	1.85	2.300E-07	7.385E-07	1.79
AMs	1.089E-06	3.973E-07	2.164E-06	2.52	3.401E-07	2.108E-06	2.80
AMu	9.552E-07	4.296E-07	2.354E-06	2.33	3.463E-07	2.501E-06	2.70
P95s	7.737E-06	1.334E-06	2.052E-05	5.15	8.526E-07	7.737E-06	4.71
P95u	3.503E-06	1.348E-06	8.996E-06	2.58	9.370E-07	9.623E-06	3.29

Table AC17. 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 time-weighted average concentration exposure ((mg/m^3)/ (ppm DDAC × mins)) using All data

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	3.737E+00	2.410E+00	5.846E+00	1.56	2.166E+00	5.310E+00	1.61
GMs	5.007E-08	2.751E-08	9.368E-08	1.85	2.876E-08	9.231E-08	1.79
AMs	1.361E-07	4.966E-08	2.705E-07	2.52	4.251E-08	2.635E-07	2.80
AMu	1.194E-07	5.371E-08	2.942E-07	2.33	4.328E-08	3.127E-07	2.70
P95s	9.672E-07	1.667E-07	2.565E-06	5.15	1.066E-07	9.672E-07	4.71
P95u	4.379E-07	1.686E-07	1.124E-06	2.58	1.171E-07	1.203E-06	3.29

Tables AC11 to AC17 show that the study benchmark design value of 3 for the fold relative accuracy was met in every case, with the exception of the parametric bootstrap empirical 95th percentile for all exposure routes, the non-parametric bootstrap empirical 95th percentile for the inhalation exposures, and the non-parametric bootstrap lognormal empirical 95th percentile for the inhalation exposures.

Empirical 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 lognormal models. These plots were intended to help determine whether the data supported using untransformed normalized exposure values or log-transformed values or neither. The plots are not intended to evaluate the fitted regression models for the un-normalized exposure to be described below, for which the residual quantile plots were developed.

In each case the quantile-quantile plot compared the observed quantiles of the measured values with the corresponding quantiles of a normal or lognormal distribution. A perfect fit would imply that the plotted values lie in a straight line. The quantile-quantile plots for all exposure routes are presented in Figures AC1 to AC14. In all cases the plots seem to show a better fit for the lognormal distributions, supporting the use of the log-transformed exposure values over the untransformed values.

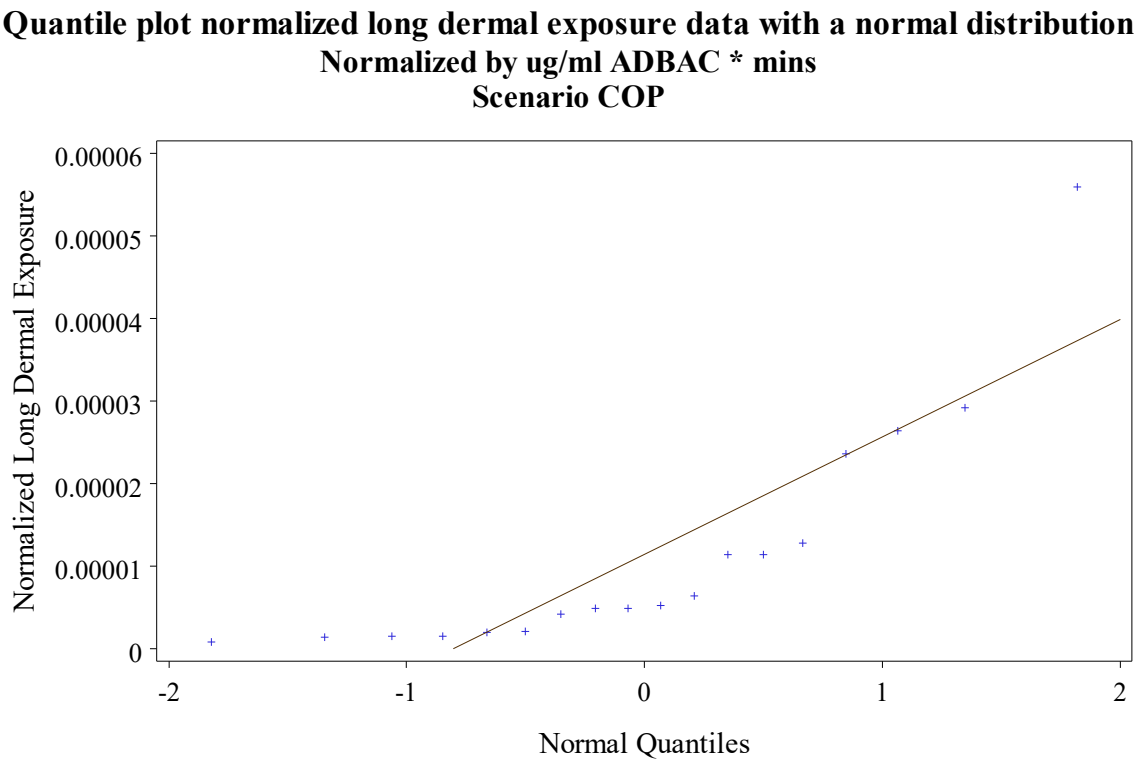

Figure AC1. Empirical quantile plot for Long Dermal, with a normal distribution

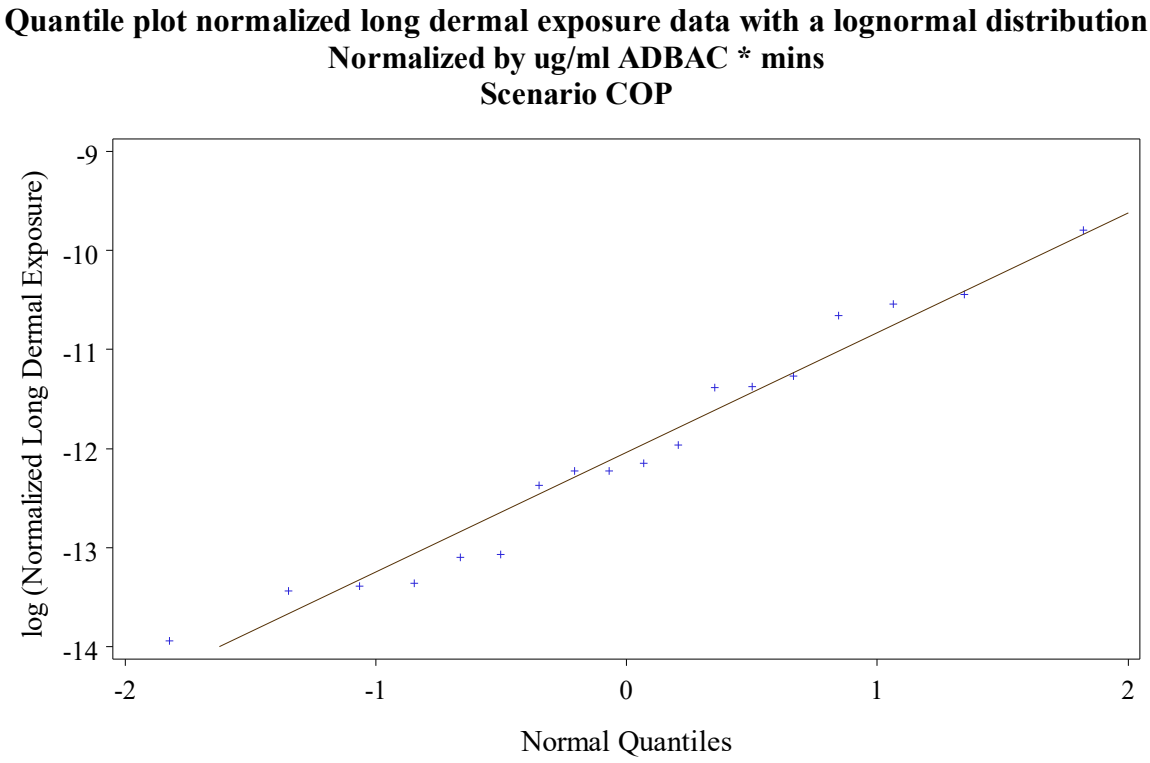

Figure AC2. Empirical quantile plot for Long Dermal, with a lognormal distribution

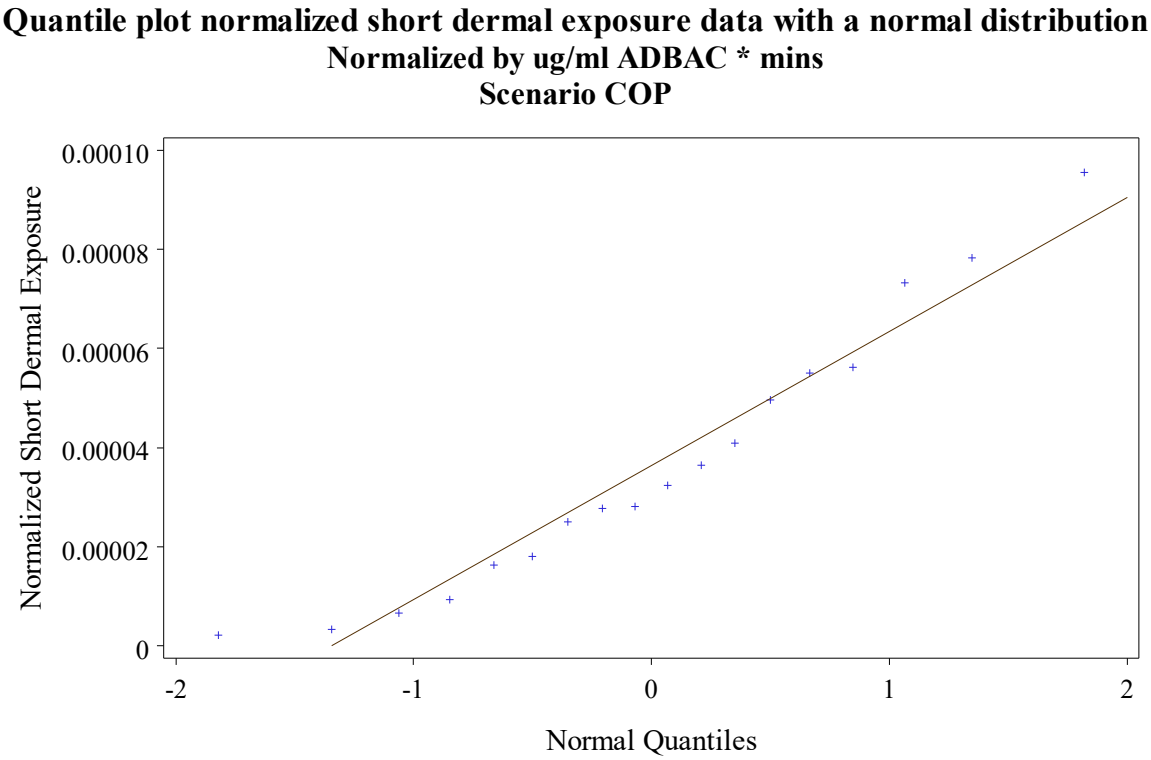

Figure AC3. Empirical quantile plot for Short Dermal, with a normal distribution

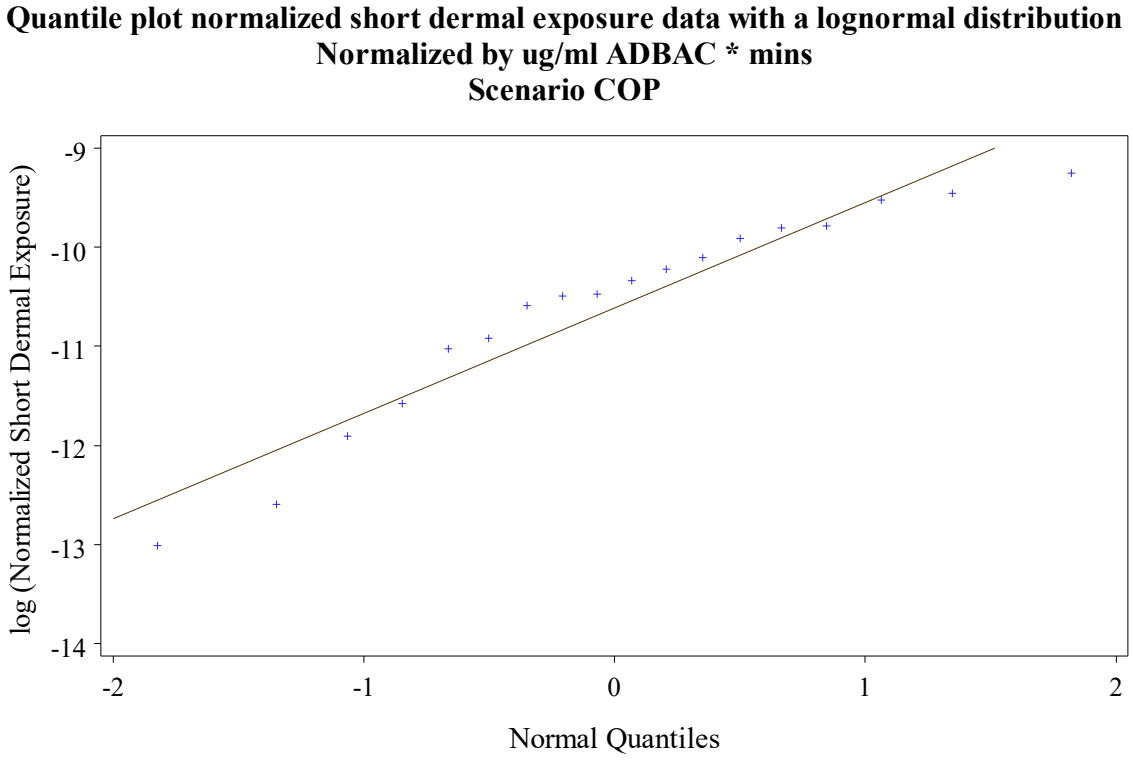

Figure AC4. Empirical quantile plot for Short Dermal, with a lognormal distribution

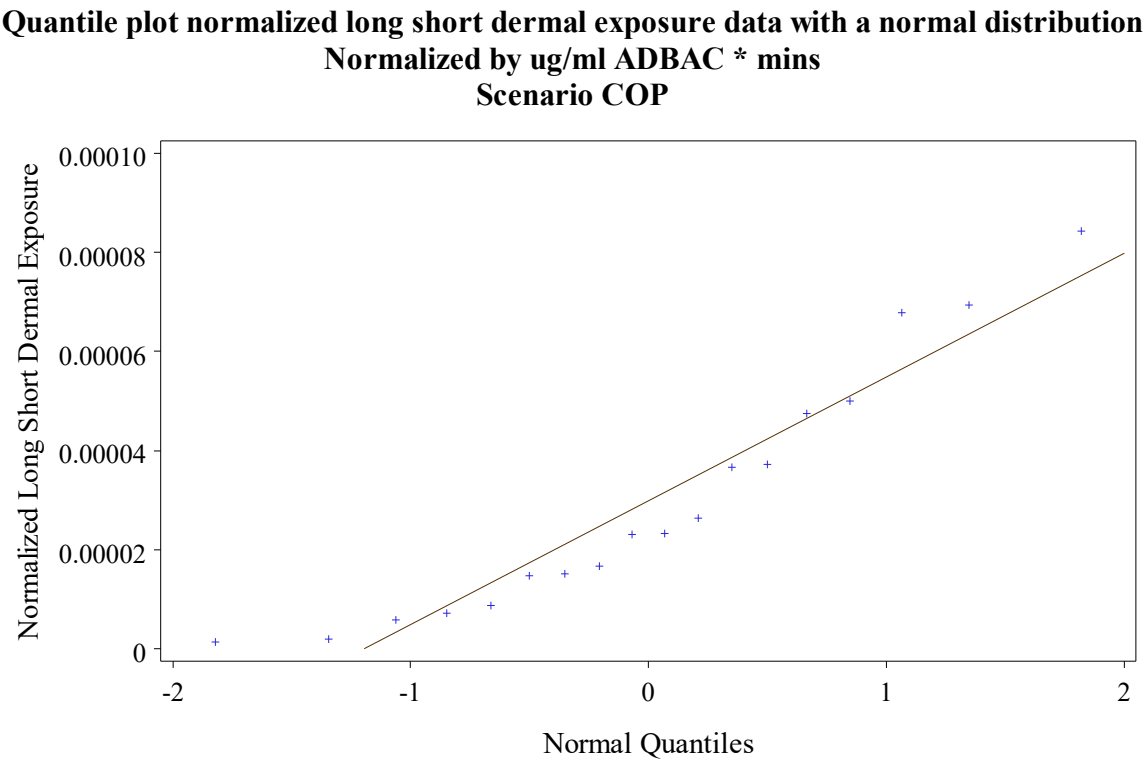

Figure AC5. Empirical quantile plot for Long Short Dermal, with a normal distribution

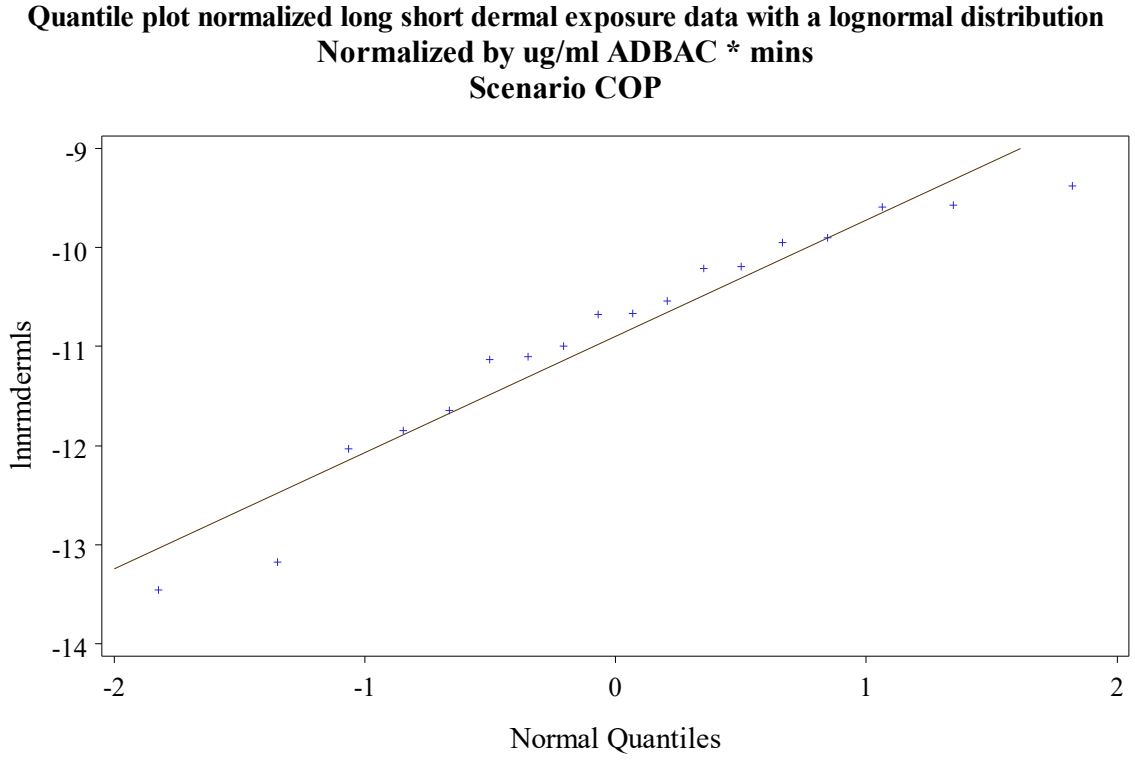

Figure AC6. Empirical quantile plot for Long Short Dermal, with a lognormal distribution

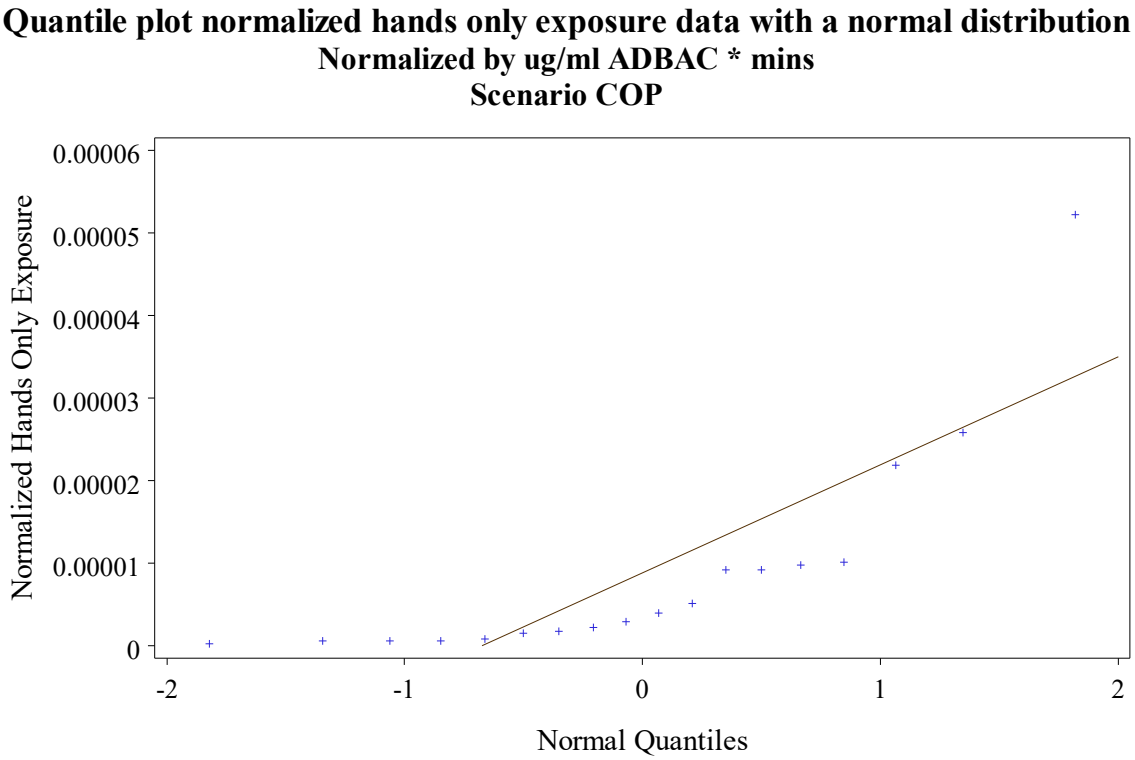

Figure AC7. Empirical quantile plot for Hands Only, with a normal distribution

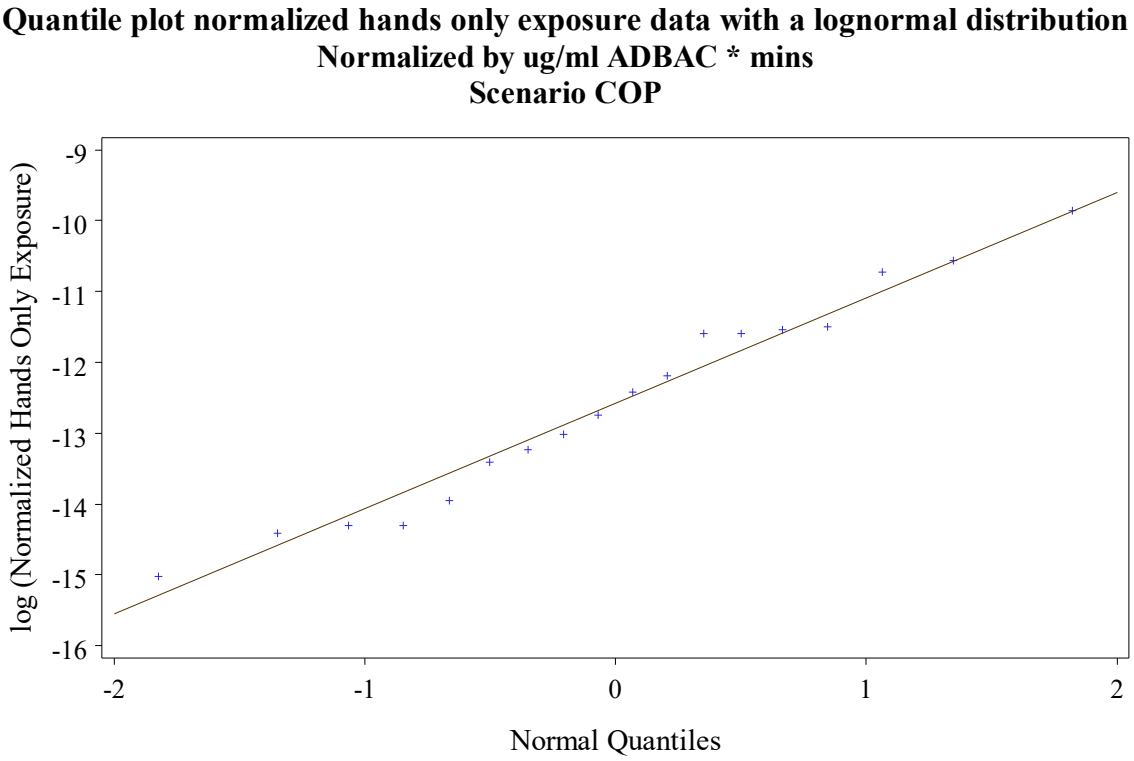

Figure AC8. Empirical quantile plot for Hands Only, with a lognormal distribution

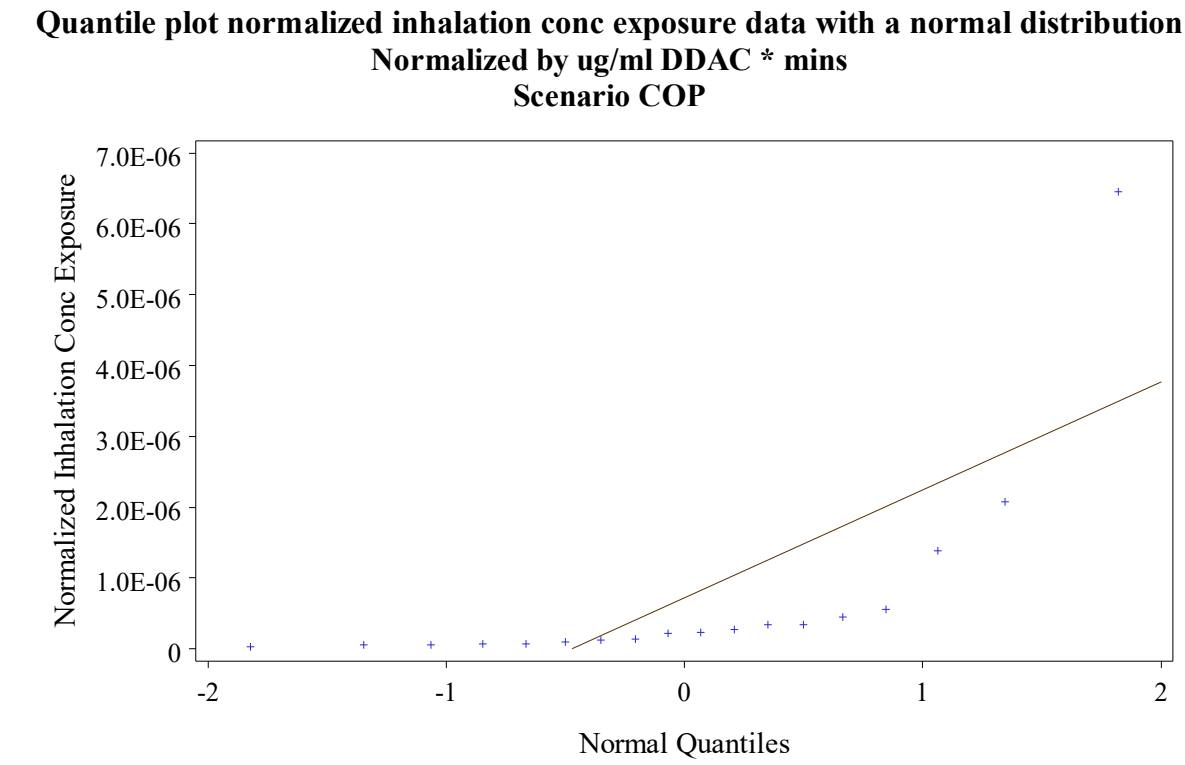

Figure AC9. Empirical quantile plot for Inhalation Concentration, with a normal distribution

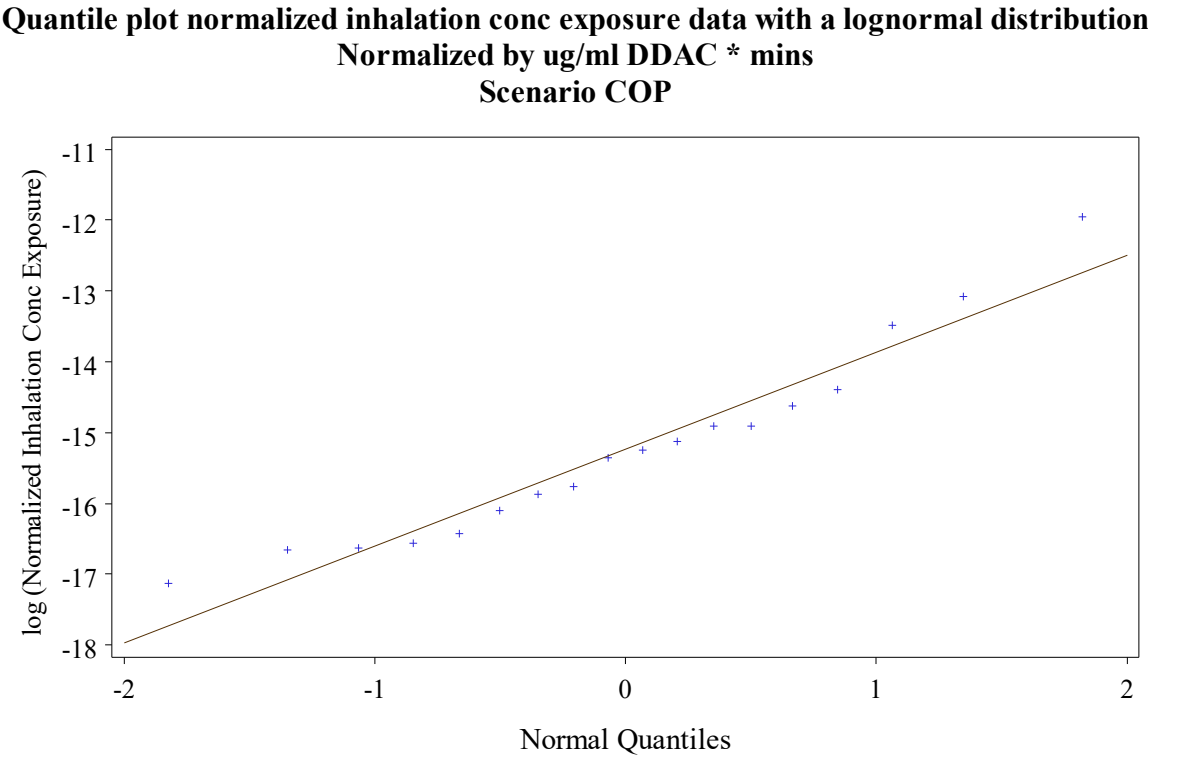

Figure AC10. Empirical quantile plot for Inhalation Concentration, with a lognormal distribution

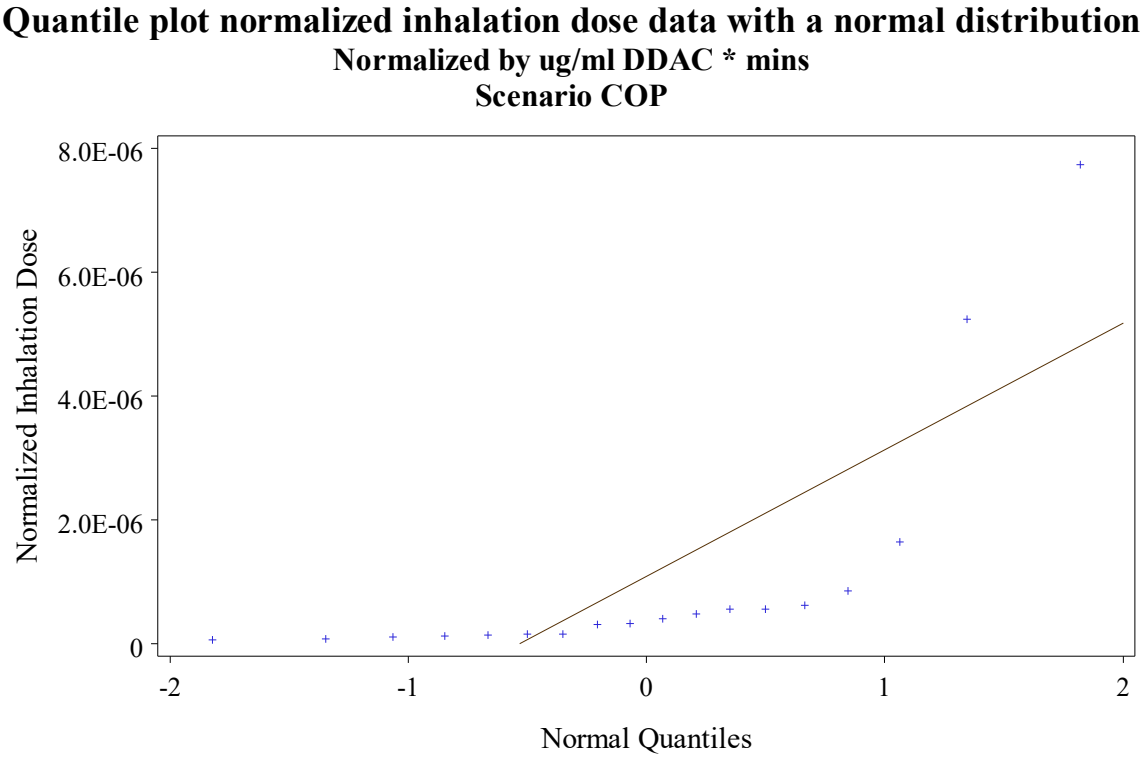

Figure AC11. Empirical quantile plot for Inhalation Dose, with a normal distribution

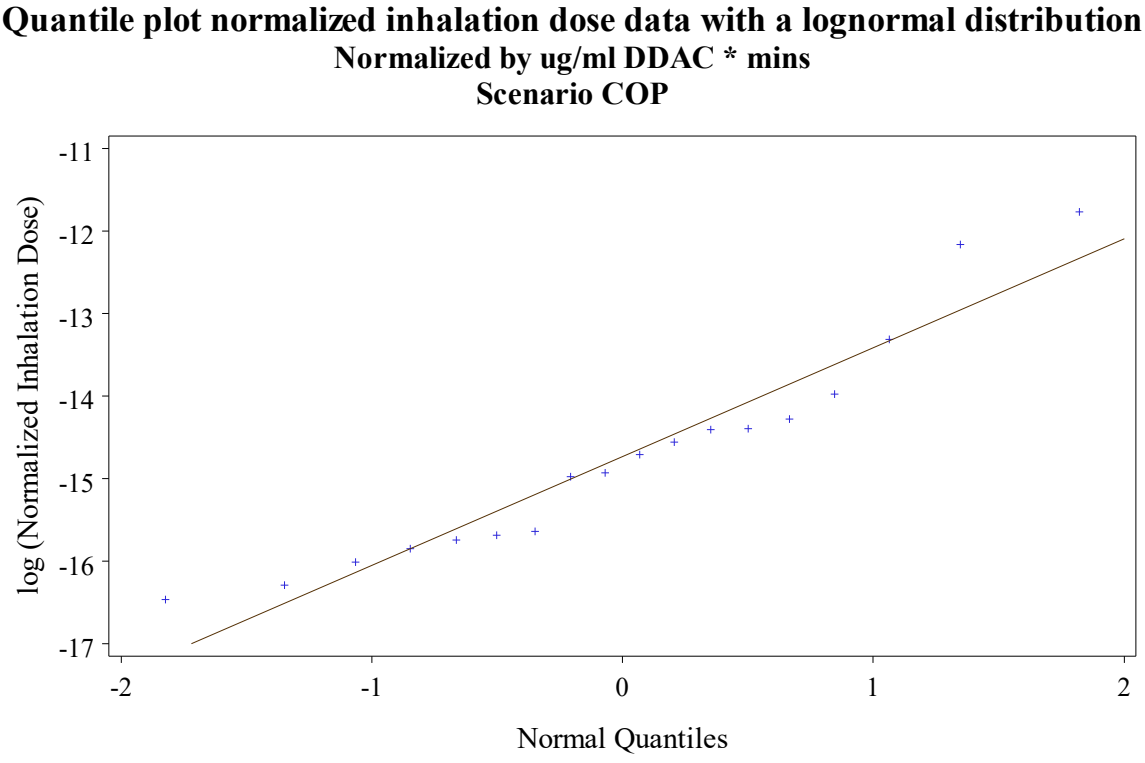

Figure AC12. Empirical quantile plot for Inhalation Dose, with a lognormal distribution

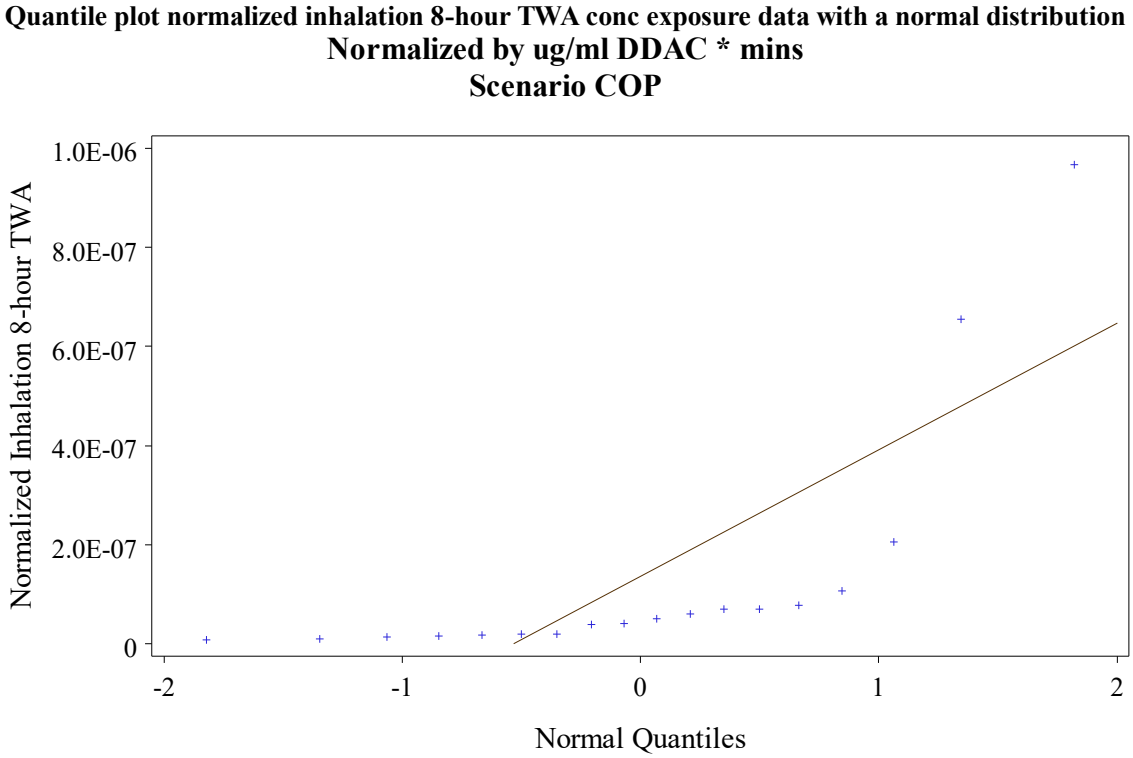

Figure AC13. Empirical quantile plot for Inhalation Time-weighted Average Conc, with a normal distribution

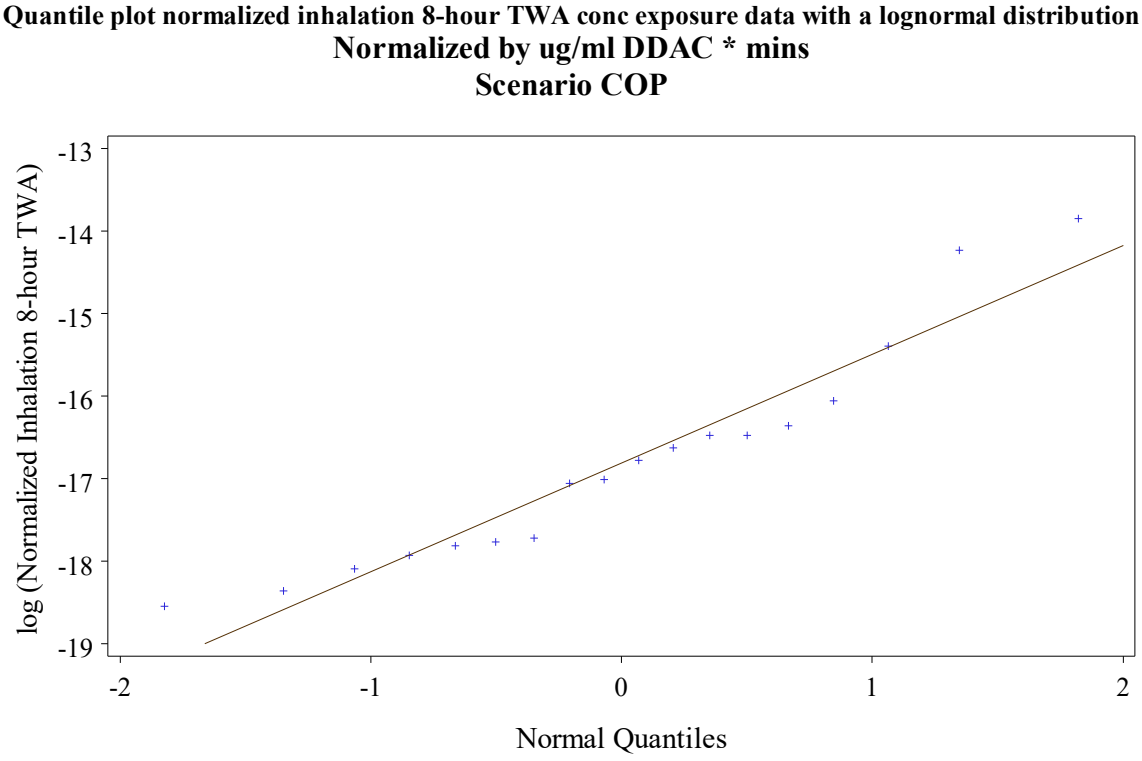

Figure AC14. Empirical quantile plot for Inhalation Time-weighted Average Conc, with a lognormal distribution

Test for log-log-linearity with slope 1

Table AC18 shows the 95% confidence intervals for the slope calculated from the above linear model. A confidence interval that includes one but not zero supports the use of unit exposures. A confidence interval that includes zero but not one suggests that the exposure does not depend on the normalizing factor. 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. This table also shows the widths of the confidence intervals used to evaluate the second benchmark for post-hoc power discussed in the next sub-section. The table also shows the values of the threshold concentration × duration (case A) or threshold concentration (case B) and the corresponding estimated exposure, to be described and discussed In the Supplement. Threshold values were not computed for the censored data models.

Table AC18. 95 percent confidence intervals for the slope of log exposure versus the log of the normalizing factor.

Exposure Route	Treatment of Non-detects	Estimate	Lower	Upper	Width	Threshold	Exposure
Long Dermal (mg)	Substitute mid value	0.038	–0.257	0.334	0.591	4389	0.054
	Censored data MLE	0.039	–0.220	0.297	0.518		
Short Dermal (mg)	Substitute mid value	0.452	0.021	0.882	0.862	5785	0.251
	Censored data MLE	0.454	0.080	0.830	0.750		
Long Short Dermal (mg)	Substitute mid value	0.416	–0.066	0.898	0.964	5708	0.211
	Censored data MLE	0.418	–0.006	0.842	0.848		
Hands Only (mg)	Substitute mid value	–0.123	–0.541	0.294	0.834	4024	0.042
	Censored data MLE	–0.123	–0.487	0.240	0.727		
Inhalation Concentration (mg/m^3)	Substitute mid value	–0.023	–0.489	0.443	0.932	5722	0.0035
	Censored data MLE	–0.023	–0.429	0.383	0.812		
Inhalation Dose (mg)	Substitute mid value	0.102	–0.394	0.598	0.992	6146	0.0059
	Censored data MLE	0.102	–0.330	0.534	0.864		
Inhalation Time-Weighted Average Concentration (mg/m^3)	Substitute mid value	0.102	–0.394	0.598	0.992	6146	0.0059
	Censored data MLE	0.102	–0.330	0.534	0.864		

Table AC18 gives the slopes for all the exposure routes.

The slopes range from –0.1 to 0.5. Except for Short Dermal, the confidence intervals include 0 but not 1, suggesting that the exposure does not depend on the normalizing factor. For Short Dermal the slope is 0.45, and the confidence interval excludes both 0 and 1 showing that the exposure increases with the normalizing factor, but the model does not support the use of unit exposures.

Suppose that the study had a (post-hoc) power of at least 80% for detecting "proportionality" (i.e., log-log-linearity with a slope of 1) under the null hypothesis of independence (slope = 0). It follows that the confidence intervals have an approximate width of 1.4 or less. The results in Table AC18 show that observed widths are all below 1.4. The maximum width was about 1.0. Therefore, based on the confidence intervals, the secondary objective of meeting the 80% power for detecting proportionality was met.

Quantile plots for residuals

The quantile-quantile plots of the studentized residuals for all exposure routes are shown below in Figures AC15 to AC21.

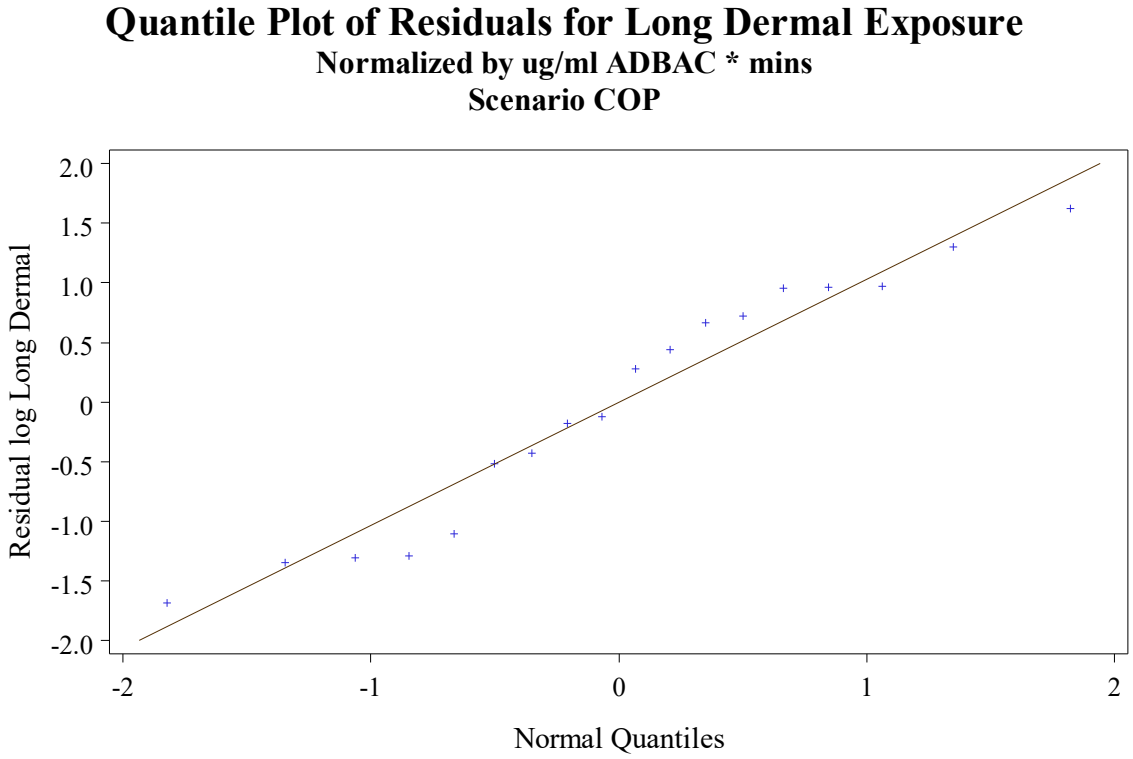

Figure AC15. Quantile plot of residuals from linear model for Long Dermal

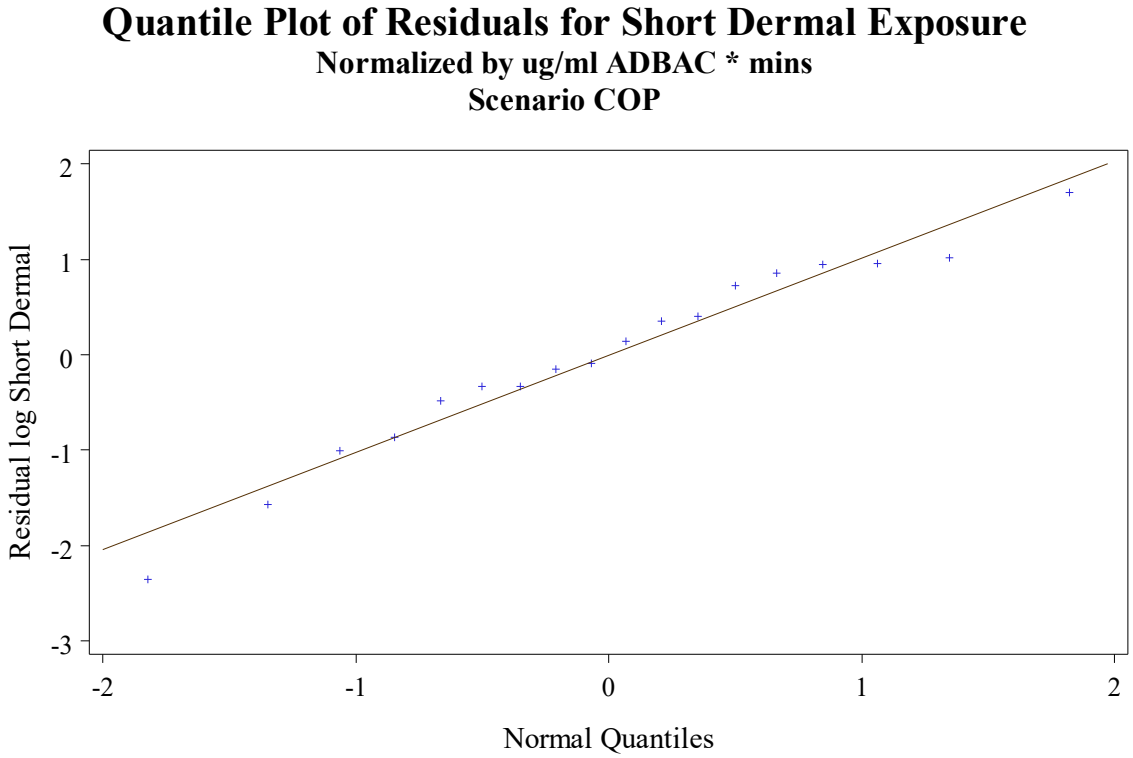

Figure AC16. Quantile plot of residuals from linear model for Short Dermal

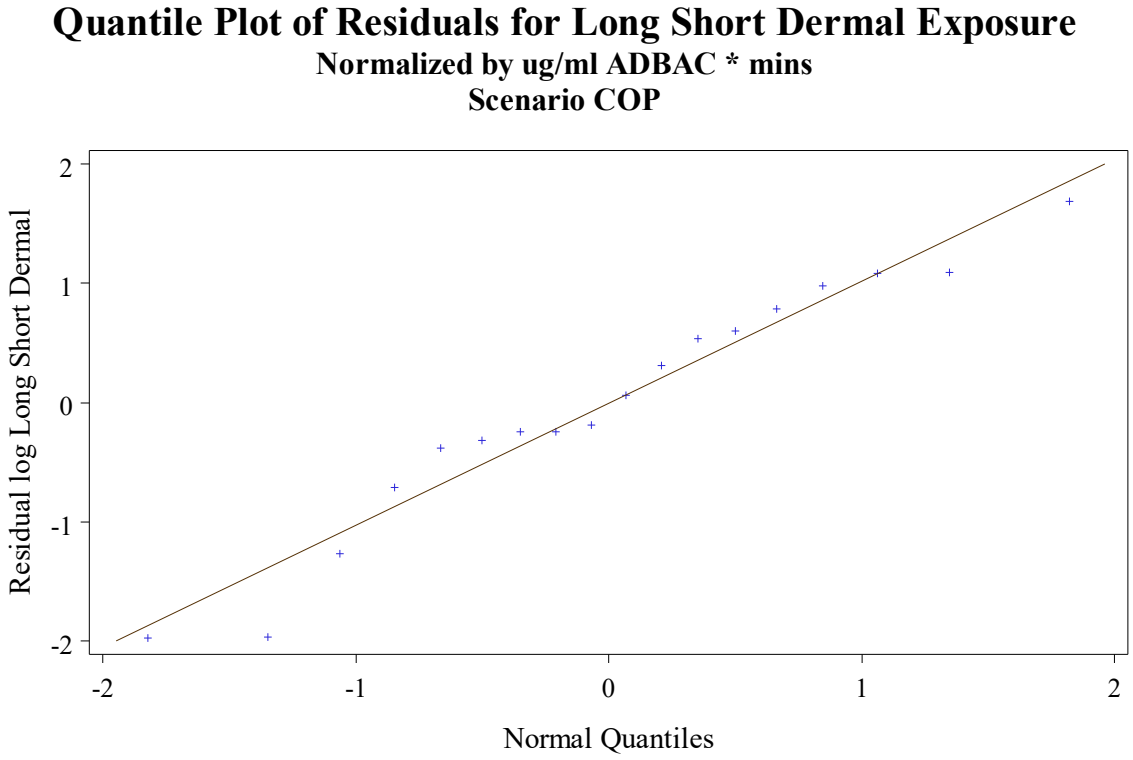

Figure AC17. Quantile plot of residuals from linear model for Long Short Dermal

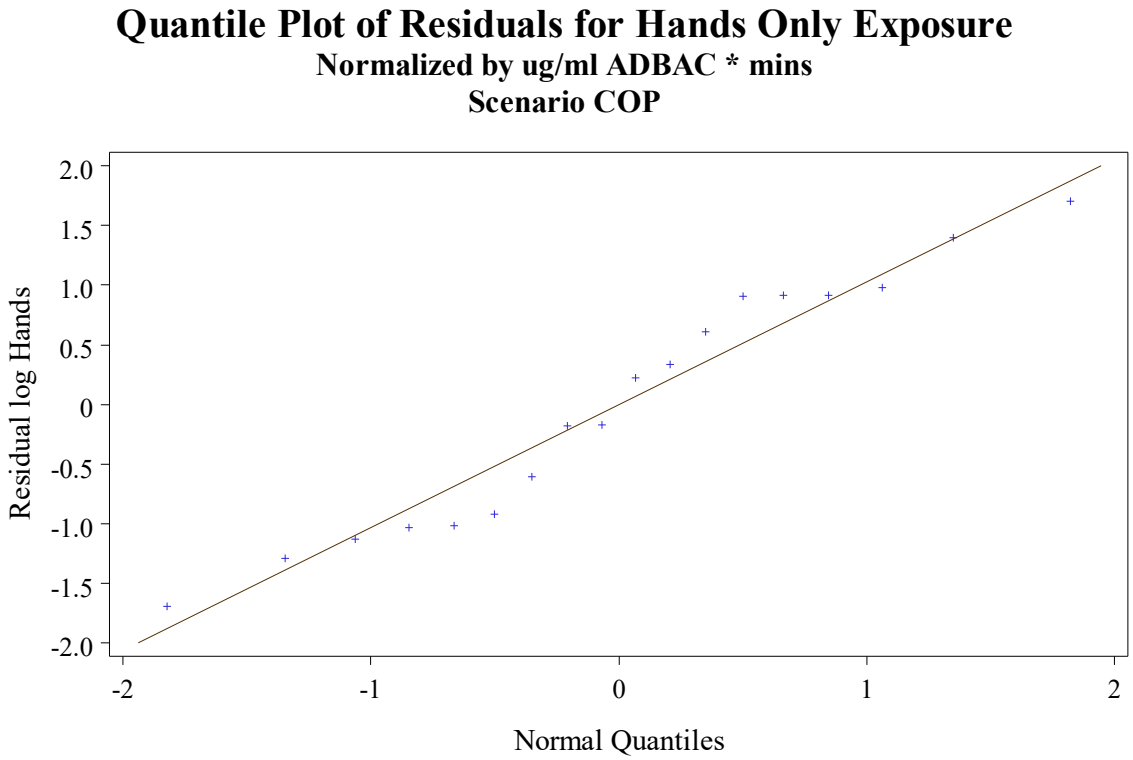

Figure AC18. Quantile plot of residuals from linear model for Hands Only

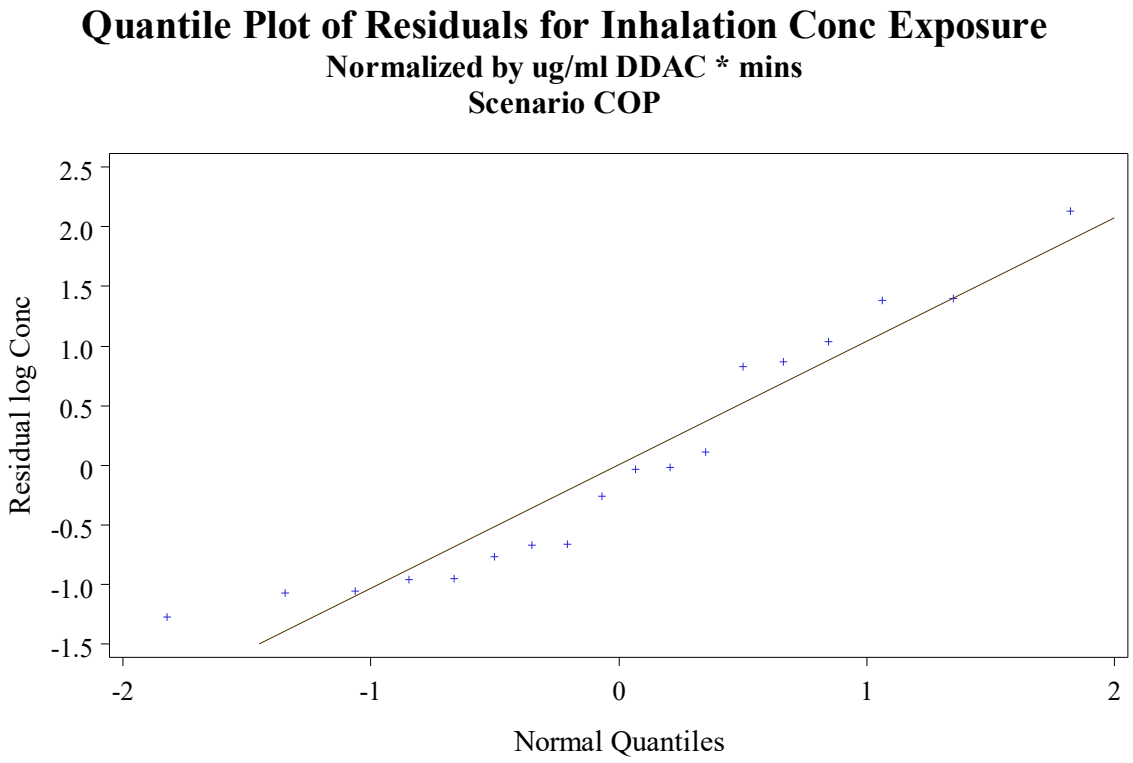

Figure AC19. Quantile plot of residuals from linear model for Inhalation Concentration

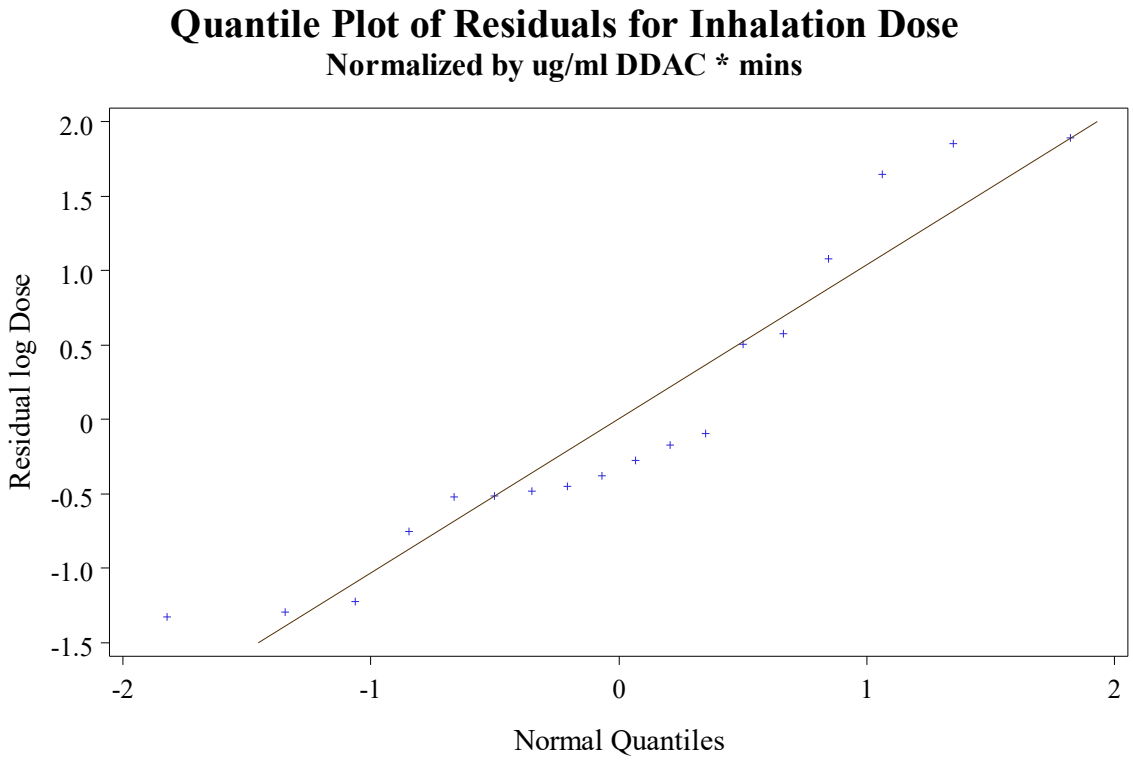

Figure AC20. Quantile plot of residuals from linear model for Inhalation Dose

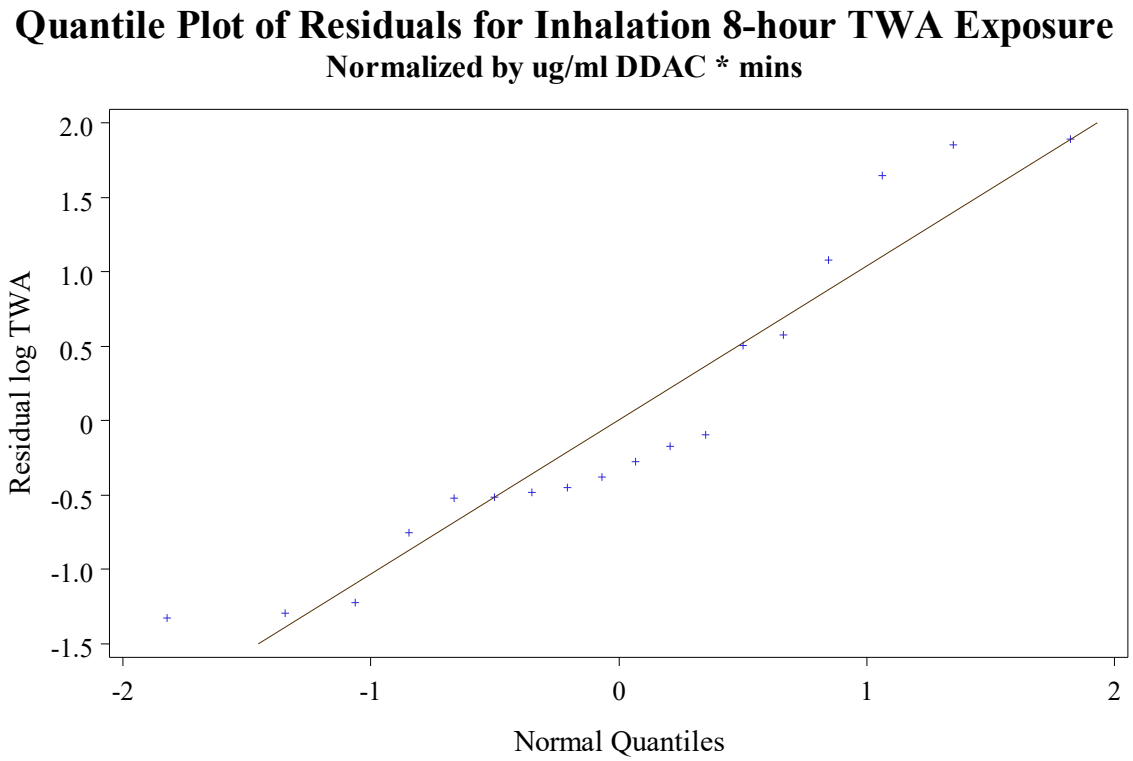

Figure AC21. Quantile plot of residuals from linear model for Inhalation Tine-Weighted Average Concentration

The quantile-quantile plots of the studentized residuals are reasonably close to the straight line except for the inhalation exposures. None of the studentized residuals exceeded the standard outlier cutoff of ±3.

Regression plots

The lognormal linear regression results for all the exposure routes are shown below using the mid value substitution method for non-detect values. The data points are labeled to show the targeted durations. Except for Short Dermal and Long Short Dermal, the regression plots show a weak relationship between exposure and the normalizing factor.

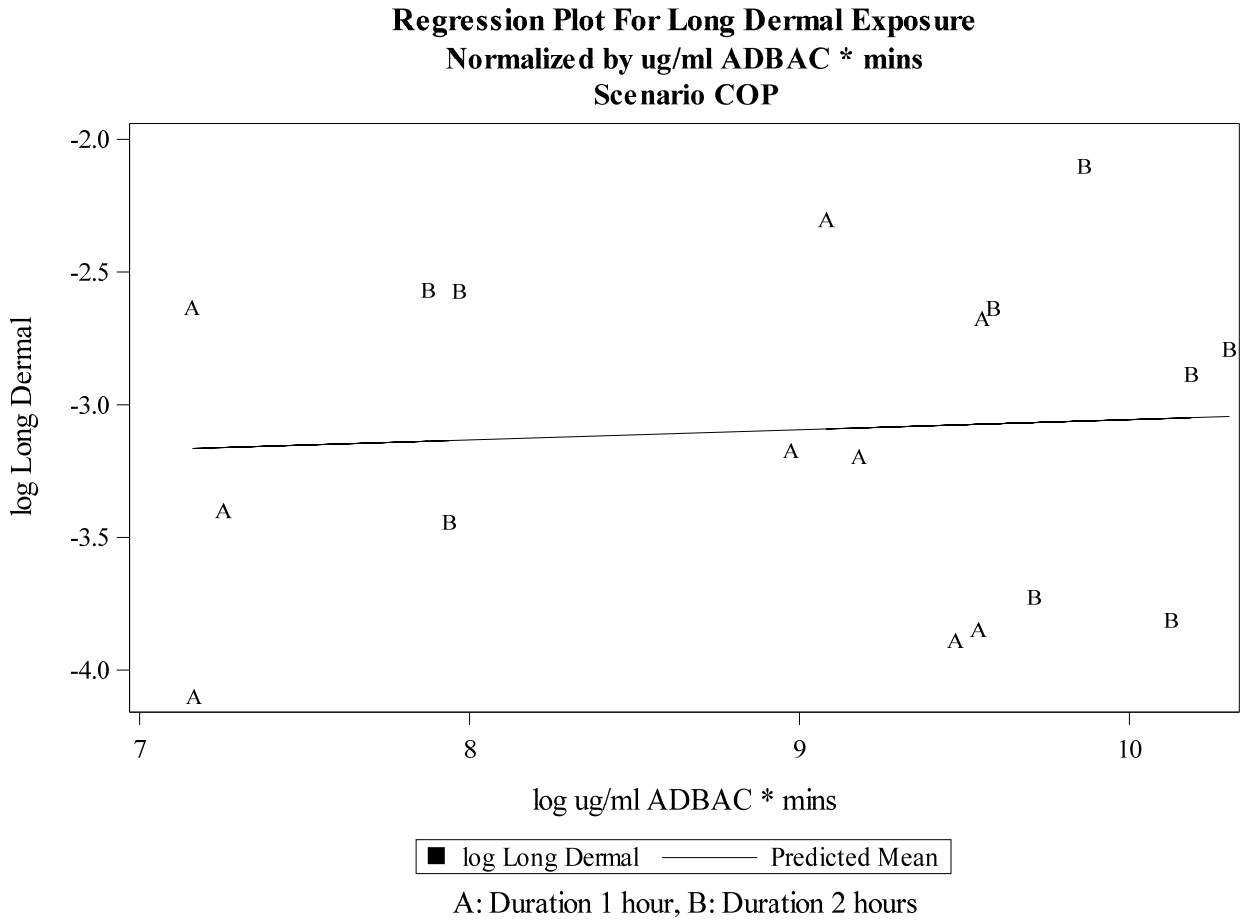

Figure AC22.

Regression plot for Long Dermal Exposure (mg)

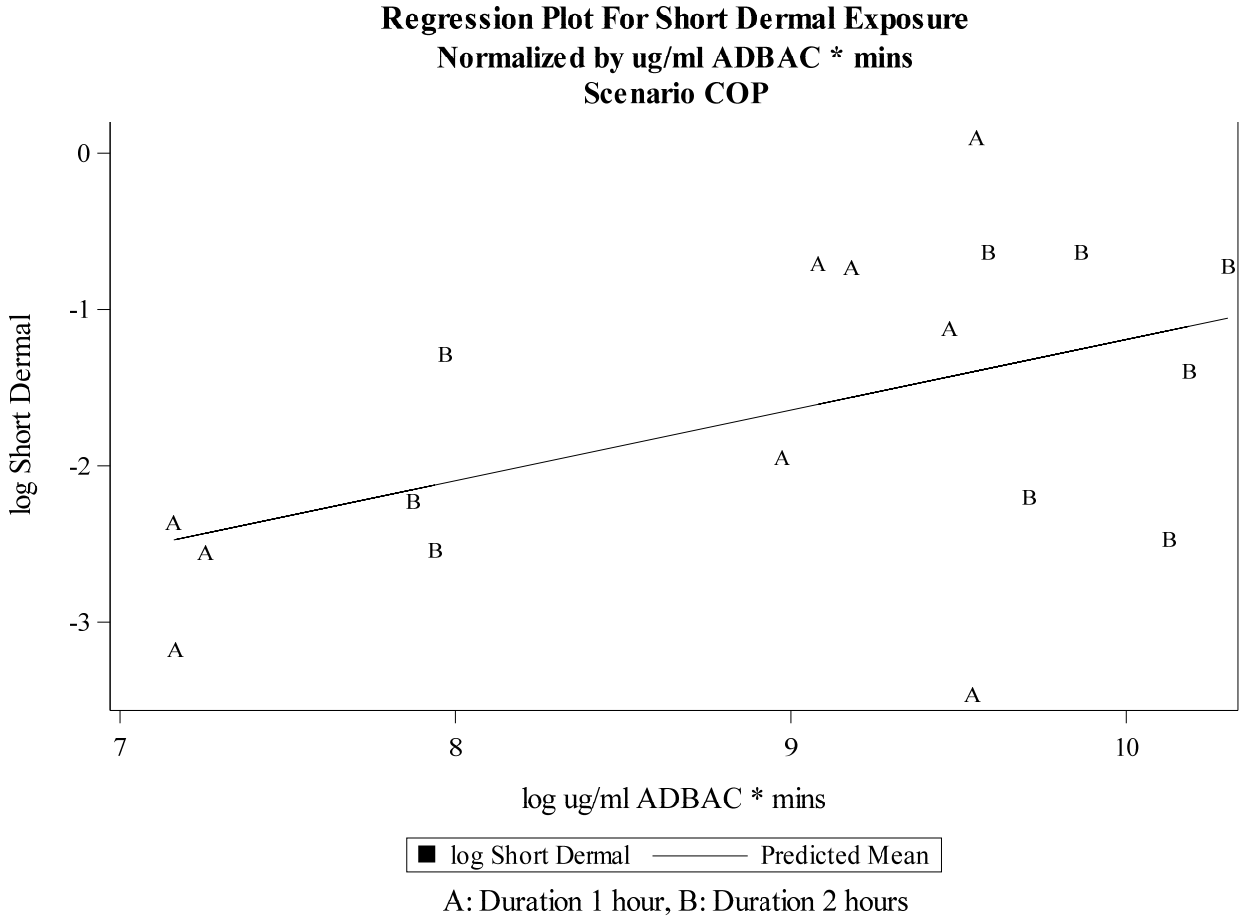

Figure AC23. Regression plot for Short Dermal Exposure (mg)

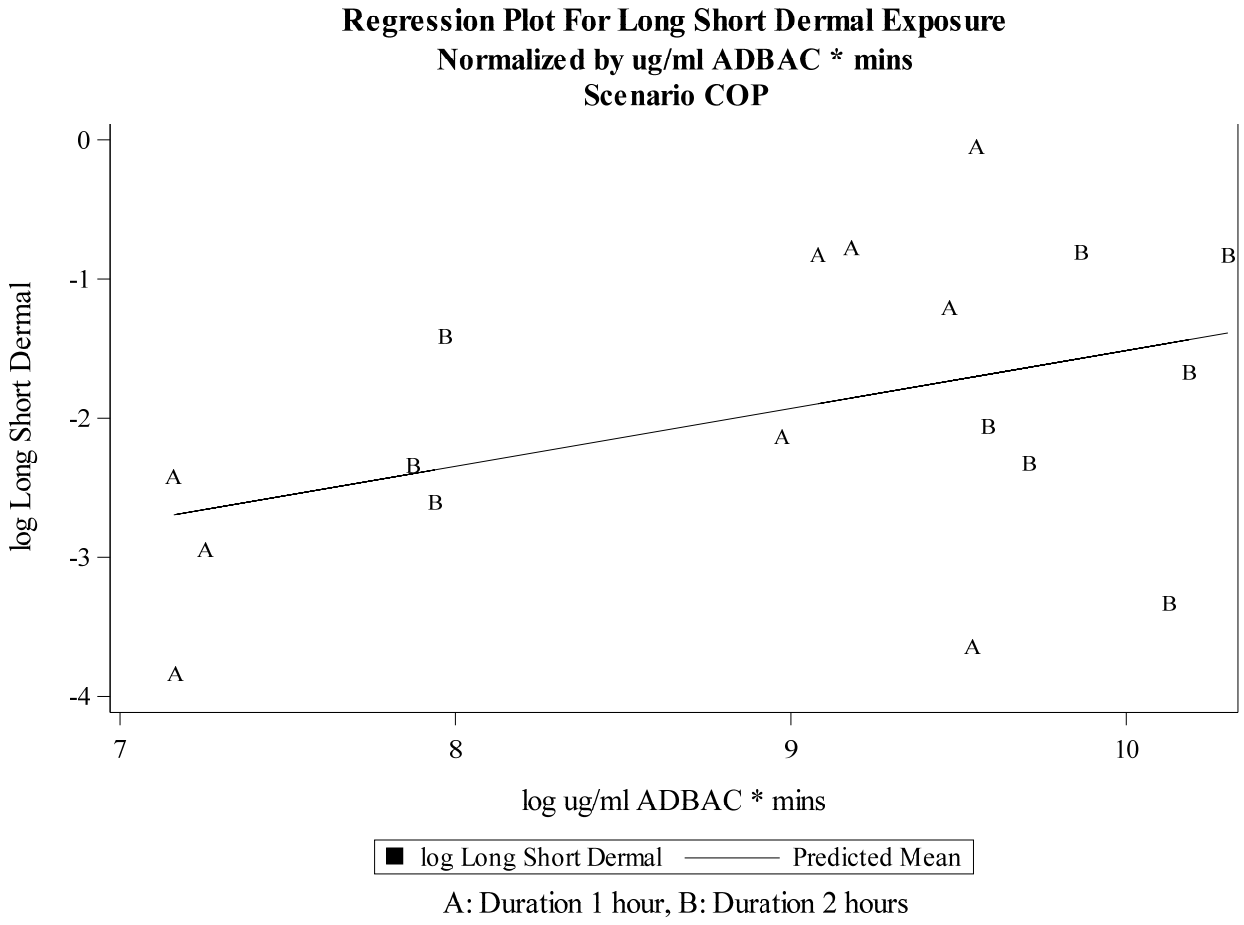

Figure AC24. Regression plot for Long Short Dermal Exposure (mg)

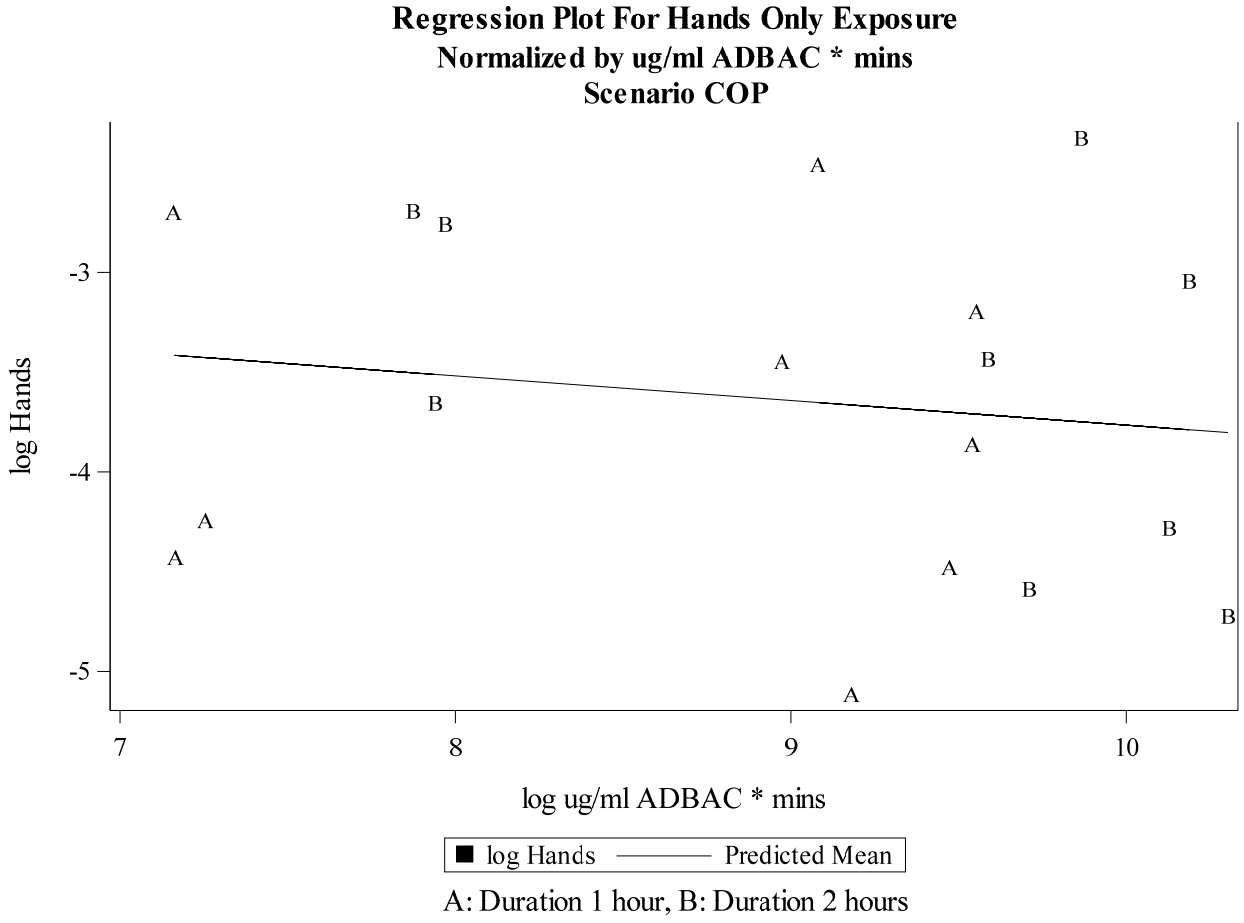

Figure AC25. Regression plot for Hands Only Exposure (mg)

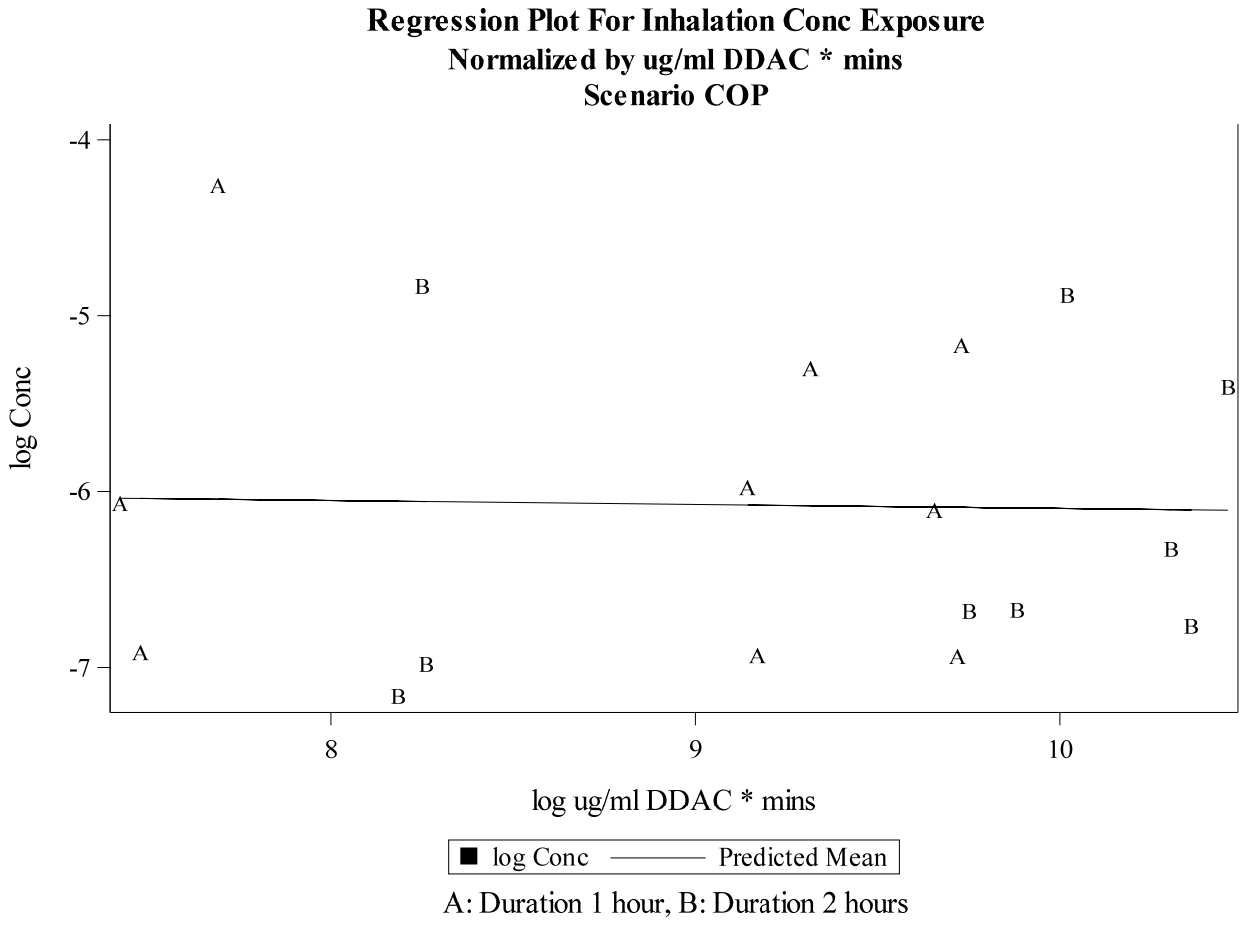

Figure AC26. Regression plot for Inhalation Concentration Exposure (mg/m^3)

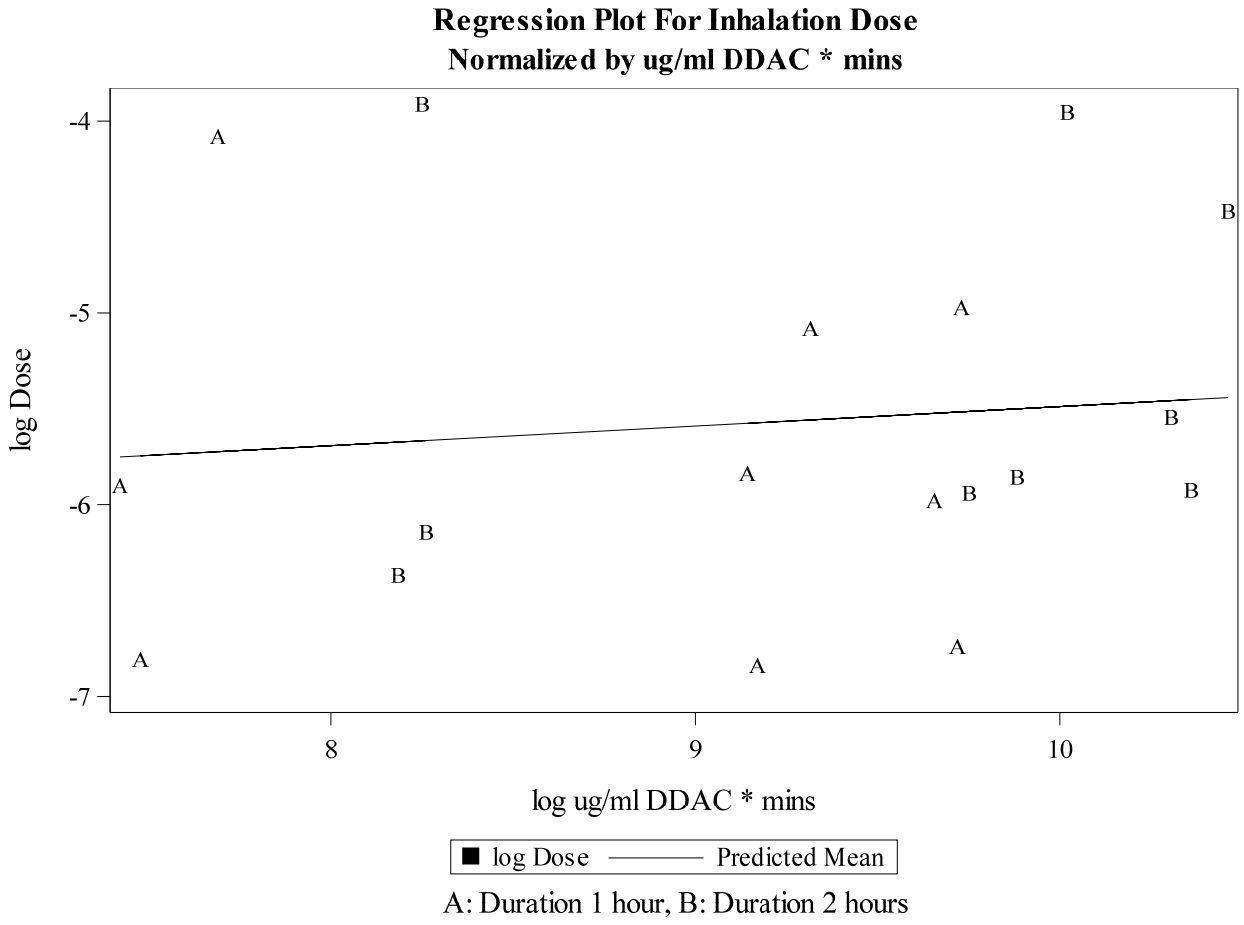

Figure AC27. Regression plot for Inhalation Dose (mg)

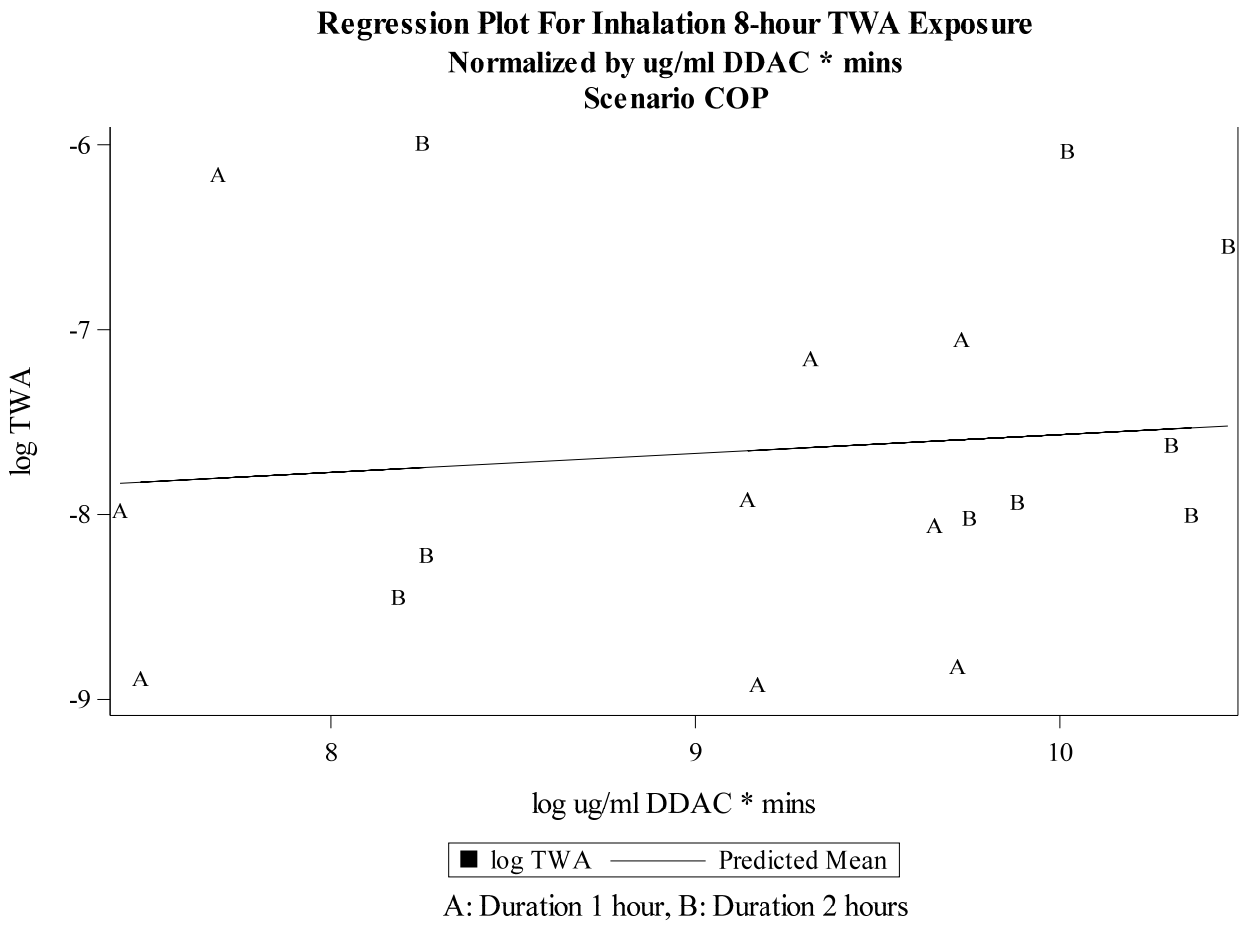

Figure AC28. Regression plot for Inhalation Time-Weighted Average Exposure (mg/m^3)

Quadratic models

Table AC19 presents the quadratic coefficient Quad from the fitted quadratic regression models for all the exposure routes using All data. Coefficients for the Intercept and Slope are shown under model 2 in Tables AC20 to AC26 below.

Table AC19. Quadratic coefficients with 95% confidence intervals for quadratic regression models for the log exposure versus log (Normalizing Factor)

Exposure Route	Estimate	Lower Bound	Upper Bound
Long Dermal	–0.09	–0.48	0.29
Short Dermal	–0.27	–0.82	0.28
Long Short Dermal	–0.36	–0.97	0.24
Hands Only	–0.19	–0.73	0.35

Exposure Route	Estimate	Lower Bound	Upper Bound
Inhalation Concentration	0.08	−0.54	0.70
Inhalation Dose	0.17	−0.48	0.82
Inhalation Time-weighted Average	0.17	−0.48	0.82

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

Alternative Statistical Approaches

In this section we present and compare some alternative statistical approaches to the linear and quadratic models.

Model Parameters

Table AC20. Alternative fitted statistical models for Long Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-3.440	-6.099	-0.782
	β	0.038	-0.257	0.334
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-10.244	-38.881	18.393
	β	1.633	-5.056	8.323
	γ	-0.092	-0.477	0.293
3. Log-log logistic regression of exposure on NF	**α**	0.054	0.031	0.077
	γ	69276.813	-44728030.378	44866584.005
	β	-1.953	-92.096	88.191
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			

Model	Parameter	Estimate	Lower Bound	Upper Bound
5. Gamma model for exposure	**μ**	-3.346	-5.595	-1.097
	β	0.046	-0.204	0.296
	ϕ	3.234	1.735	6.027

Table AC21. Alternative fitted statistical models for Short Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-5.708	-9.587	-1.829
	β	0.452	0.021	0.882
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-25.575	-66.260	15.110
	β	5.109	-4.395	14.613
	γ	-0.269	-0.816	0.279
3. Log-log logistic regression of exposure on NF	**α**	3.912E-01	1.665E-01	6.160E-01
	γ	7.761E+08	-5.810E+10	5.965E+10
	β	-2.546E+00	-1.225E+01	7.159E+00
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-6.564	-9.836	-3.293
	β	0.581	0.218	0.945
	ϕ	1.788	0.979	3.265

Table AC22. Alternative fitted statistical models for Long Short Dermal Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-5.672	-10.013	-1.332

Model	Parameter	Estimate	Lower Bound	Upper Bound
	β	0.416	-0.066	0.898
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-32.474	-77.247	12.298
	β	6.699	-3.760	17.158
	γ	-0.362	-0.965	0.240
3. Log-log logistic regression of exposure on NF	**α**	3.064E-01	1.388E-01	4.740E-01
	γ	1.236E+10	-1.287E+12	1.312E+12
	β	-2.924E+00	-1.637E+01	1.052E+01
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-6.532	-10.228	-2.835
	β	0.555	0.144	0.966
	ϕ	1.448	0.800	2.621

Table AC23. Alternative fitted statistical models for Hands Only Exposure (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-2.532	-6.288	1.225
	β	-0.123	-0.541	0.294
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	-16.318	-56.410	23.774
	β	3.109	-6.257	12.474
	γ	-0.186	-0.726	0.353
3. Log-log logistic regression of exposure on NF	**α**	0.046	-0.314	0.405
	γ	0.007	-1.338	1.352

Model	Parameter	Estimate	Lower Bound	Upper Bound
	β	0.376	-15.914	16.667
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-2.522	-5.692	0.648
	β	-0.088	-0.441	0.264
	ϕ	1.701	0.933	3.100

Table AC24. Alternative fitted statistical models for Inhalation Concentration (mg/m^3)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-5.870	-10.161	-1.579
	β	-0.023	-0.489	0.443
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	0.452	-48.164	49.068
	β	-1.458	-12.464	9.547
	γ	0.080	-0.536	0.697
3. Log-log logistic regression of exposure on NF	**α**			
	γ			
	β			
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-4.031	-7.531	-0.530
	β	-0.181	-0.561	0.199

Model	Parameter	Estimate	Lower Bound	Upper Bound
	ϕ	1.431	0.791	2.589

Table AC25. Alternative fitted statistical models for Inhalation Dose (mg)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-6.508	-11.074	-1.941
	β	0.102	-0.394	0.598
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	7.029	-44.295	58.354
	β	-2.972	-14.591	8.646
	γ	0.172	-0.478	0.823
3. Log-log logistic regression of exposure on NF	**α**			
	γ			
	β			
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-4.846	-8.570	-1.121
	β	-0.029	-0.434	0.375
	ϕ	1.227	0.683	2.202

Table AC26. Alternative fitted statistical models for Inhalation Time Weighted Average Concentration (mg/m^3)

Model	Parameter	Estimate	Lower Bound	Upper Bound
1. Linear regression of Ln(exposure) on Ln(NF)	μ	-8.587	-13.154	-4.021
	β	0.102	-0.394	0.598

Model	Parameter	Estimate	Lower Bound	Upper Bound
2. Quadratic regression of Ln(exposure) on Ln(NF)	μ	4.950	-46.375	56.274
	β	-2.972	-14.591	8.646
	γ	0.172	-0.478	0.823
3. Log-log logistic regression of exposure on NF	**α**	6.04E-01	-1.52E+04	1.52E+04
	γ	1.23E+02	-3.10E+06	3.10E+06
	β	1.99E-01	-6.93E+00	7.33E+00
4. 3-parameter logistic regression of exposure on NF	**α**			
	c			
	β			
5. Gamma model for exposure	**μ**	-6.925	-10.649	-3.201
	β	-0.029	-0.434	0.375
	ϕ	1.227	0.683	2.202

Model Comparisons

One way to compare the fit of the 7 models presented above is to use the Akaike Information Criterion (AIC), which takes minus twice the log-likelihood and then makes an adjustment or penalty for the number of parameters in the model. The following two tables compare the AIC values for the various Dermal and Inhalation exposure measures. The smaller values of the AIC suggest a better-fitting model. AIC values for models that failed to converge are not shown.

Table AC27. Akaike Information Criteria values for alternative models for Dermal Exposure

Model	Long Dermal	Short Dermal	Long Short Dermal	Hands Only
1. Linear regression of Ln(exposure) on Ln(NF)	38.0	51.6	55.6	50.4
2. Quadratic regression of Ln(exposure) on Ln(NF)	39.6	52.3	55.7	51.8

Model	Long Dermal	Short Dermal	Long Short Dermal	Hands Only
3. Log-log logistic regression of exposure on NF	43.3	66.9	73.3	60.8
4. 3-parameter logistic regression of exposure on NF				
5. Gamma model for exposure	37.8	49.9	54.4	51.0

Table AC28. Akaike Information Criteria values for alternative models for Inhalation Exposure

Model	Inhalation Concentration	Inhalation Dose	Inhalation Time-Weighted Average Concentration
1. Linear regression of Ln(exposure) on Ln(NF)	52.0	54.2	54.2
2. Quadratic regression of Ln(exposure) on Ln(NF)	53.9	55.9	55.9
3. Log-log logistic regression of exposure on NF			77.4
4. 3-parameter logistic regression of exposure on NF			
5. Gamma model for exposure	54.7	58.1	58.1

Based on the AIC, the best-fitting models are the linear model for the Hands Only, and the three inhalation exposure routes, and the gamma model for Long Dermal, Short Dermal, and Long Short Dermal.