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Increasing the Precision of Probability of Causation
A Summary of Research

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03/03/2026	00	New document (first developed in July 2023) summarizing the main findings from the DCAS-RPT-011, DCAS-RPT-012, and DCAS-RPT-013 reports, on the comparison of several percentile definitions, the effect of alternative percentile definitions on PC values, and the settings to achieve a desired precision for the 99th percentile of Probability of Causation in NIOSH-IREP. The document provides a list of recommendations for settings and operations to be implemented in v.6.0 and subsequent versions of the NIOSH-IREP software.

ABSTRACT

Claims filed under the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) are awarded compensation when the estimated **P**robability of cancer **C**ausation (PC) for exposed workers exceeds the decision threshold of 50%. The NIOSH-IREP (NIOSH Interactive Radio-Epidemiological Program) software estimates PC as a probability distribution function (pdf) from multiple samples produced using Monte-Carlo computations to account for uncertainties in radiation dose and risk parameters representing the exposure situation. The 99th percentile of that distribution is used in decision making. In the NIOSH-IREP v.5.9 and earlier versions, 2000 samples (iterations) are used to determine the 99th PC values. When the 99th PC values are between 45% and 52%, 30 repetitions (runs) of 10,000 iterations each are carried out using IREP Enterprise Edition v.5.9 (IREP-EE) to improve precision and the average of the resulting thirty 99th percentiles (Avg. 99th PC value) is used for compensation. However, even at 30 runs of 10,000 iterations each, the Avg. 99th PC value can vary with changing random seeds by up to $\pm$0.5, a variability that is significant when 99th percentiles of PC are close to 50%.

This report summarizes a series of studies dedicated to further increasing precision in the estimated 99th percentile of PC, when expected values are close to the threshold of 50.0%.

As a first step, ten commonly used methods to estimate a percentile (e.g., 99th) of a pdf described by multiple samples were identified and tested on hypothetical cases and real claims. The performance of a percentile method differs, depending on the percentile level, sample size, type of underlying distribution, and magnitude of uncertainty and of positive skewness, but, in general, the larger the sample size, the smaller the difference between the values of the same percentile produced by different methods. For all tested scenarios, the sample percentile method used by default in the SAS software had the smallest relative bias and smallest relative root mean squared error at all the sample sizes, when estimating the 99th percentile. The sample percentile method used in NIOSH-IREP v.5.9 and earlier versions tends to underestimate the theoretical 99th percentile in all the scenarios tested, especially for sample sizes lower than 20,000 values. For sample sizes greater than 20,000 the difference between methods becomes small enough and can be neglected. Thus, it is preferable to use 20,000 or more samples in NIOSH-IREP v.6.0 and subsequent versions for the PC computations, in evaluating the claims filled under EEOICPA.

Secondly, the convergence of the 99th PC values as well as of the Avg. 99th PC values, as the number of iterations increases was shown for multiple cases with PC values close to 50%, and for each of these cases there is a clear trend for both quantities to converge to a stable value that represents the theoretical 99th percentile from the distribution of PC values for that case.

The theoretical 99th PC value of the PC probability distribution for a case cannot be determined exactly, but a 95% confidence interval for the estimated 99th PC value can be calculated. The larger the number of iterations used in the computation, the smaller the length of the 95% confidence interval for the 99th PC value will be, where the length is defined as the upper bound minus the lower bound of the 95% confidence interval. For a large enough sample size, a length of the 95% confidence interval of less than 0.15 or 0.10 can be achieved.

The 95% confidence intervals for the Avg. 99th PC values with a length lower than 0.15 were obtained in IREP-EE for all tested cases when using 200 runs at 50,000 iterations. Lengths of the 95% confidence intervals for the Avg. 99th PC values lower than 0.10 were obtained for all tested cases when using 300 runs at 100,000 iterations.

To increase efficiency and minimize IREP running time, a Predictive Tool was developed to determine the minimum number of iterations needed to achieve a desired precision measured by the length of the 95% confidence interval of the Avg. 99th PC values. For a 0.15 precision level, the number of iterations needed in a set of 23 test cases with Avg. 99th PC values between 49.00% and 50.01% varied between 5,000 and 35,000 iterations, and for the 0.10 precision level, the number of iterations needed for the 23 cases varied between 15,000 and 60,000 iterations. The largest IREP running time observed for the 23 cases was less than one hour for a precision level of 0.15 and less than 1.75 hours for a precision level of 0.10.

By increasing the number of runs in IREP-EE from 30 to 300, and by increasing the number of iterations per run to values predicted by the IREP Predictive Tool, the length of the 95% confidence interval of the Avg. 99th PC values can be efficiently and reliably reduced below the desirable precision levels of 0.15 or 0.10.

Based on the analyses described in this report, the following new settings and operational changes are recommended starting with version v.6.0 of NIOSH-IREP and NIOSH-IREP Enterprise Edition.

1. The default number of 2,000 iterations used in IREP v.5.9 should be increased to 20,000 iterations in IREP v.6.0 and subsequent versions.

2. The default number of 10,000 iterations per run used in IREP-EE v.5.9 should be increased to 20,000 iterations per run in IREP-EE v.6.0 and subsequent versions.

3. The range for the cases selected to run on the IREP-EE version will remain the same as in IREP v.5.9 version, i.e. [45.0%, 52.0%], but the determination will be based on the 99th PC value obtained in IREP v.6.0 (or subsequent versions) at 20,000 iterations.

4. Incorporate the IREP Predictive Tool into the IREP-EE v.6.0 and subsequent versions and change IREP-EE to run cases with either 30 random seeds or 300 random seeds. IREP-EE v.6.0 and future versions would feel and operate just like the IREP-EE v.5.9 version, with no discernible difference for a user.

5. The IREP Predictive Tool should be used for cases with Avg. 99th PC values obtained from the IREP-EE v.6.0 and subsequent versions in the range of [49.5%, 50.5%], to determine the minimum number of iterations required to achieve a precision of less than or equal to 0.10 around the Avg. 99th PC value. Those cases will then be rerun with 300 runs and the number of iterations suggested by the IREP Predictive Tool.

All these recommendations were adopted and implemented starting in 2024 for IREP and IREP-EE v.6.0 and subsequent versions.

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ACRONYMS AND ABBREVIATIONS

Sampling Methods

MLH	Median Latin Hypercube sampling method
RLH	Random Latin Hypercube sampling method
MC	Monte-Carlo sampling method

Distribution types

Lognormal	Lognormal probability distribution defined by parameters GM and GSD
GM	Geometric Mean
GSD	Geometric Standard Deviation
Normal	Normal probability distribution defined by parameters mean and SD
mean	Mean of a Normal (Gaussian) probability distribution
Std. Dev.	Standard deviation
Triangular	Triangular distribution defined by parameters min, mode and max
min	Minimum of a Triangular probability distribution
mode	Mode of a Triangular probability distribution
max	Maximum of a Triangular probability distribution
Uniform	Uniform distribution defined by parameters min and max
min	Minimum of a Uniform probability distribution
max	Maximum of a Uniform probability distribution
Weibull	Weibull distribution defined by parameters shape and scale
shape	Shape parameter of a Weibull probability distribution
scale	Scale parameter of a Weibull probability distribution

Other terms

99th PC value	99th percentile of probability of causation (PC)
Avg. 99th PC value	Average of the 99th percentiles of PC obtained in sets of 30, 100, 200, or 300 runs.
ABRWH	Advisory Board on Radiation and Worker Health
C.I.	Confidence Interval
DCAS	Division of Compensation Analysis and Support
DOL	Department of Labor
EEOICPA	Energy Employees Occupational Illness Compensation Program Act
IREP	Interactive Radio-Epidemiological Program
IREP-EE	Interactive Radio-Epidemiological Program Enterprise Edition
NIOSH	National Institute of Occupational Safety and Health
NOCTS	NIOSH DCAS Claims Tracking System
PC	Probability of Causation
RB	Relative Bias
RRMSE	Relative Root-Mean Squared Error
S.E.	Standard Error

1.0 INTRODUCTION

A series of studies dedicated to further increasing precision in the estimated 99th percentile of Probability of Causation (PC) has been completed and documented in: DCAS-RPT-011 "Comparison of Several Percentile Definitions" (Stancescu et al. 2026), DCAS-RPT-012 "Effect of Alternative Percentile Definition on PC Values" (Stancescu et al. 2026), and DCAS-RPT-013 "Methods for Increasing Precision of the 99th Percentile of PC" (Stancescu et al. 2026). This report is a summary of findings from those three reports and covers the comparison of several percentile definitions, the effect of alternative percentile definitions on PC values, the variability of PC at different number of iterations in the NIOSH-IREP software, the convergence of the 99th PC values as the number of iterations is increased, the settings that can be used to achieve a desired precision for the 99th PC values, the use of an IREP Predictive Tool to minimize the number of iterations, and a validation of the 99th PC values from the IREP and IREP Enterprise Edition versions.

This report (first developed in 2023) is a summary of the main findings from the DCAS-RPT-011, DCAS-RPT-012, and DCAS-RPT-013 reports.

A list of recommendations is provided in this report regarding new settings that were adopted and implemented in 2024 starting with version v.6.0 of NIOSH-IREP and NIOSH-IREP Enterprise Edition. Guidance for updated operations on the new versions is provided as well.

2.0 COMPARISON OF SEVERAL PERCENTILE DEFINITIONS

There is no standard method to estimate a percentile (quantile) from multiple samples obtained from a probability distribution. Multiple definitions are currently in use, with each software package using different methods to compute the percentiles. Probabilistic modeling and risk analysis software packages like Crystal Ball (Oracle 2010), @Risk (Lumivero 2020), Analytica (Lumina 2015), and Model Risk (Vose 2012) include a single method to compute the percentiles, different for each package. Starting with the Microsoft Office 2010 version, Excel offers two methods. Statistical software packages like SAS or R have multiple definitions implemented for computing percentiles, with one method being used by default.

In the absence of a standard method to compute a percentile, there is a need to clarify how the 99th percentile is estimated in the NIOSH-IREP software (which uses Analytica as the computational engine), and how accurate this estimation is during the process of the Monte Carlo computations used for the purpose of estimating the Probability of Causation (PC) values.

There are several articles in statistical literature dealing with the issue of which percentile definition to use. Hyndman and Fan (1996) evaluated nine different methods for computing the quantiles relative to six desirable properties. Their goal was to advocate for a standardized definition of percentiles so that percentiles reported by different statistical software will be computed according to the same formula. While this goal hasn't been achieved yet, the Hyndman and Fan (1996) paper is the most widely cited article regarding this issue, and most of the statistical software use one of the nine methods described by Hyndman and Fan (1996). These nine methods are presented here, and some of the software packages that use those methods as default are identified. Often software packages have more than one method implemented, with one method being used by default, unless the user specifically selects a different method (Analytica has only one of these methods implemented, current versions of Microsoft Excel have two methods implemented, SAS has five, and R has available all nine methods).

Table 1 shows a summary of the nine sample quantile definitions from Hyndman and Fan (1996). In Table 1, N represents the number of values in the data set, $x_1, \ldots, x_N$ represent the sorted data values, and p is the percentile level. The nearest-rank method is the most common definition of a percentile, as introduced in elementary statistics, and determines the percentile as the value from the data that splits the sorted data set into two parts, where the lower part contain p percent of the data, and the upper part contains the rest of the data, i.e., (100 – p) percent of the data. The first three methods estimate the percentiles using a discrete rounding scheme, while the other six methods use a continuous interpolation scheme.

All the methods used for computing the percentiles are non-parametric, meaning that no assumption is made about the distribution for the population from which the samples are taken.

Figure 1 shows an example of estimating the 90th percentile using ten different methods. The estimates for the 90th percentile computed using the ten methods range anywhere between the last two values in the data set, which are 5 and 9. The nearest-rank method (Type 1 method) assigns the lowest of the two values ($Q_{0.9}$ = 5), while the method used in the Vose software assigns the highest of the two values ($Q_{0.9}$ = 9). The default method in SAS (Type 2 method) assigns the middle of the two values ($Q_{0.9}$ = 7), the default method in R, which is also used by the Analytica software (Type 7 method), assigns the value $Q_{0.9}$ = 5.4, while the newer method implemented in Excel (Type 6 method) assigns $Q_{0.9}$ = 8.6 as the 90th percentile. Other values assigned by the remaining methods for the 90th percentile are $Q_{0.9}$ = 7.53 for Type 8 method, and $Q_{0.9}$ = 7.4 for Type 9 method. As it can be seen in this example, some of the methods produce identical values for the 90th percentile. For this particular data set and the 90th percentile, Type 3 and Type 4 methods produce the same result as Type 1 method, and Type 5 method produce the same result as Type 2 method.

Table 1. Summary of the nine sample quantile definitions, from Hyndman and Fan (1996)[a].

Method	h	Estimated percentile (Q_p)	Description
Type 1 (nearest-rank)	Np	$x_{\lceil h \rceil}$	Inverse of empirical cumulative distribution function
Type 2 (default in SAS)	$Np + 1/2$	$(x_{\lceil h - 1/2 \rceil} + x_{\lfloor h + 1/2 \rfloor}) / 2$	Same as Type 1, but with averaging at discontinuities
Type 3	$Np - 1/2$	$x_{\lfloor h \rceil}$	The observation numbered closest to Np
Type 4 (@Risk, Crystal Ball)	Np	$x_{\lfloor h \rfloor} + (h - \lfloor h \rfloor)(x_{\lceil h \rceil} - x_{\lfloor h \rfloor})$	Linear interpolation of the empirical distribution function
Type 5	$Np + 1/2$	$x_{\lfloor h \rfloor} + (h - \lfloor h \rfloor)(x_{\lceil h \rceil} - x_{\lfloor h \rfloor})$	Piecewise linear function where the knots are the values midway through the steps of the empirical distribution function
Type 6 (Excel PERCENTILE.EXC)	$(N + 1)p$	$x_{\lfloor h \rfloor} + (h - \lfloor h \rfloor)(x_{\lceil h \rceil} - x_{\lfloor h \rfloor})$	Linear interpolation of the expectations for the order statistics for the uniform distribution on [0,1]
Type 7 (default in R, Analytica, Excel PERCENTILE)	$(N - 1)p + 1$	$x_{\lfloor h \rfloor} + (h - \lfloor h \rfloor)(x_{\lceil h \rceil} - x_{\lfloor h \rfloor})$	Linear interpolation of the modes for the order statistics for the uniform distribution on [0,1]
Type 8	$(N + 1/3)p + 1/3$	$x_{\lfloor h \rfloor} + (h - \lfloor h \rfloor)(x_{\lceil h \rceil} - x_{\lfloor h \rfloor})$	Linear interpolation of the approximate medians for order statistics
Type 9	$(N + 1/4)p + 3/8$	$x_{\lfloor h \rfloor} + (h - \lfloor h \rfloor)(x_{\lceil h \rceil} - x_{\lfloor h \rfloor})$	Quantile estimates are approximately unbiased for the expected order statistics if data is normally distributed

[a] All methods compute Q_p, the estimate for the P-quantile ($p = P/100$), from a sample of size N by computing a real-valued index h. When h is an integer, the h-th smallest of the N values, x_h, is the quantile estimate. Otherwise, a rounding or interpolation scheme is used to compute the quantile estimate from h, $x_{\lfloor h \rfloor}$, and $x_{\lceil h \rceil}$. The symbols $\lceil\ \rceil$ and $\lfloor\ \rfloor$ are the ceiling and floor functions, respectively and $\lfloor\ \rceil$ indicates rounding to the nearest integer, choosing the even integer in case of a tie.
See also: https://en.wikipedia.org/wiki/Quantile.

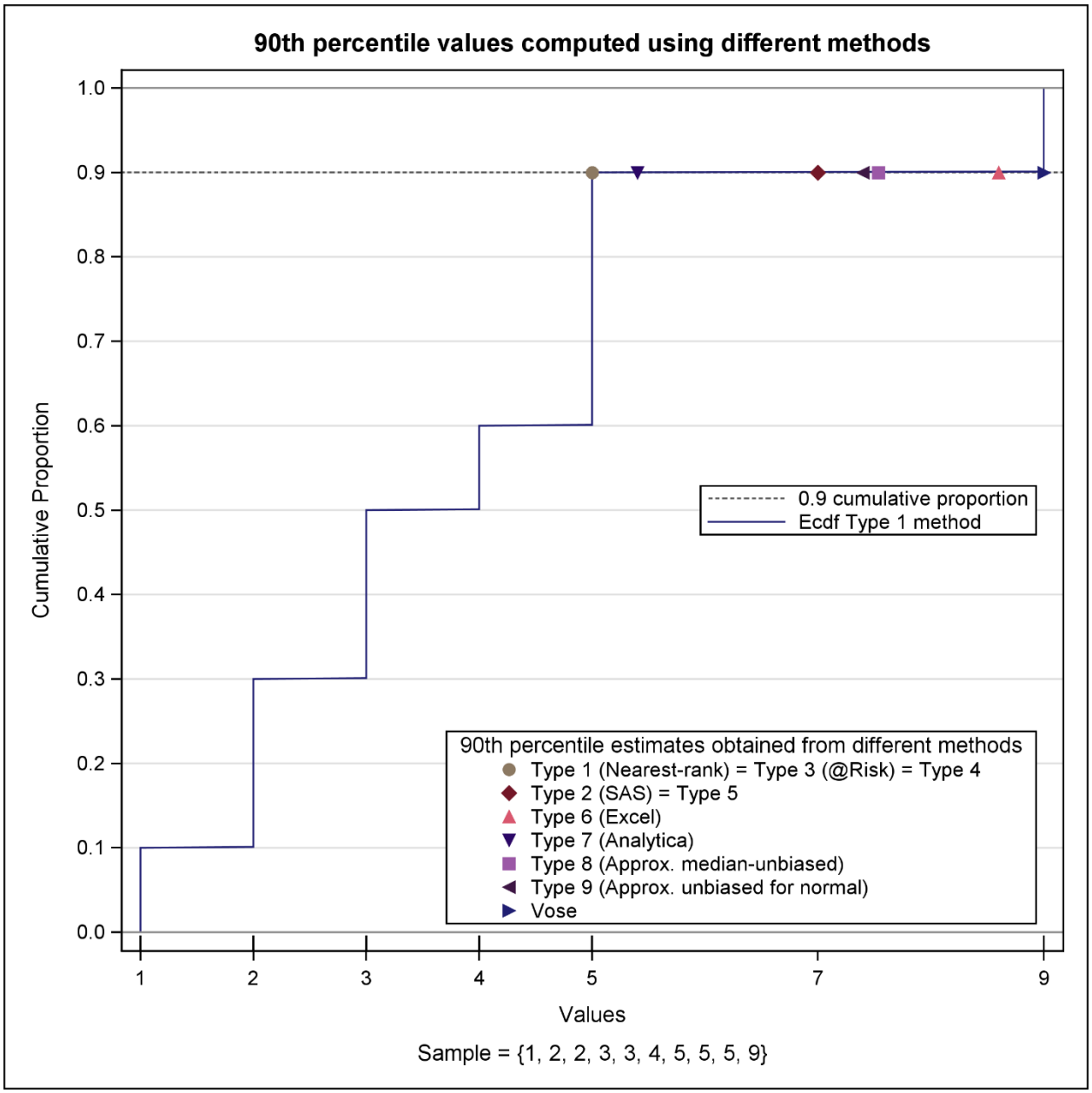


Figure 1. Estimates of the 90th percentile from 10 different methods, for a data set with 10 values.

To better understand the behavior of some of the methods used to compute percentiles in different software packages, two simulations were conducted for the most common distributions used in NIOSH-IREP. The first simulation involves sampling from a single distribution, and the second simulation involves combining (adding and multiplying) values that are simulated from two different distributions. In both simulations, the percentiles obtained using the chosen methods are compared among themselves and against theoretical percentiles.

In the first simulation, five different continuous distributions were tested (these are the most common distributions used in the NIOSH-IREP software), each with different parameters settings, for a total of 10 combinations: Uniform (1,6), Triangular (1,3,5), Triangular (1,1,5), Weibull (2,1),

Weibull (1,10), Normal (5,1), Normal (25,5), LogNormal (1,3), LogNormal (3,6), and LogNormal (3,10).

There are different sampling methods that can be used to select random samples from a known distribution, with the most common methods being Median Latin Hypercube (MLH), Random Latin Hypercube (RLH), and Monte Carlo (MC) sampling. In the first simulation, only MLH and RLH sampling methods were used.

To analyze the distribution of values for each of the percentile definitions used, multiple repetitions were used to select samples from each distribution. For the RLH sampling method, $R = 500$ repetitions were used to assess the distribution of percentiles computed from the samples. For the MLH sampling method, the resulting samples of the same size always have the same values when sorted. As a result, the percentiles are the same for all MLH samples of the same size, and thus only one repetition was performed for MLH sampling.

Six different sample sizes were used: 2,000, 5,000, 10,000, 20,000, 30,000, and 50,000 iterations. A sample size of 2,000 is used as default in NIOSH-IREP v.5.9, and a sample size of 10,000 is used in NIOSH-IREP Enterprise Edition, where 30 runs (repetitions) are performed, and the results are averaged to determine the final PC value.

Six different methods of computing the percentiles were chosen for this simulation, including the methods implemented in the most common software packages: Type 1 method (Nearest-Rank method), Type 2 (default method used in the SAS software), Type 4 (used in the @Risk software), Type 6 (used by the Excel PERCENTILE.EXC function), Type 7 (used in the Analytica software), and the method used by the Vose software.

Figure 2 shows box plots for the 99th percentile computed based on the six different methods, using MLH and RLH sampling, at different sample sizes, sampled from the LogNormal (3,6) distribution. The method used by the SAS software has the smallest bias in estimating the 99th percentile at each sample size. Three of the methods used (Nearest-Rank, @Risk, and Analytica) underestimate the 99th percentile computed from the samples when compared with the theoretical 99th percentile of the distribution, and two methods (Excel, and Vose) overestimate the 99th percentile. For all methods used, the bias in estimating the 99th percentile decreases as the sample size increases from 2,000 to 50,000.

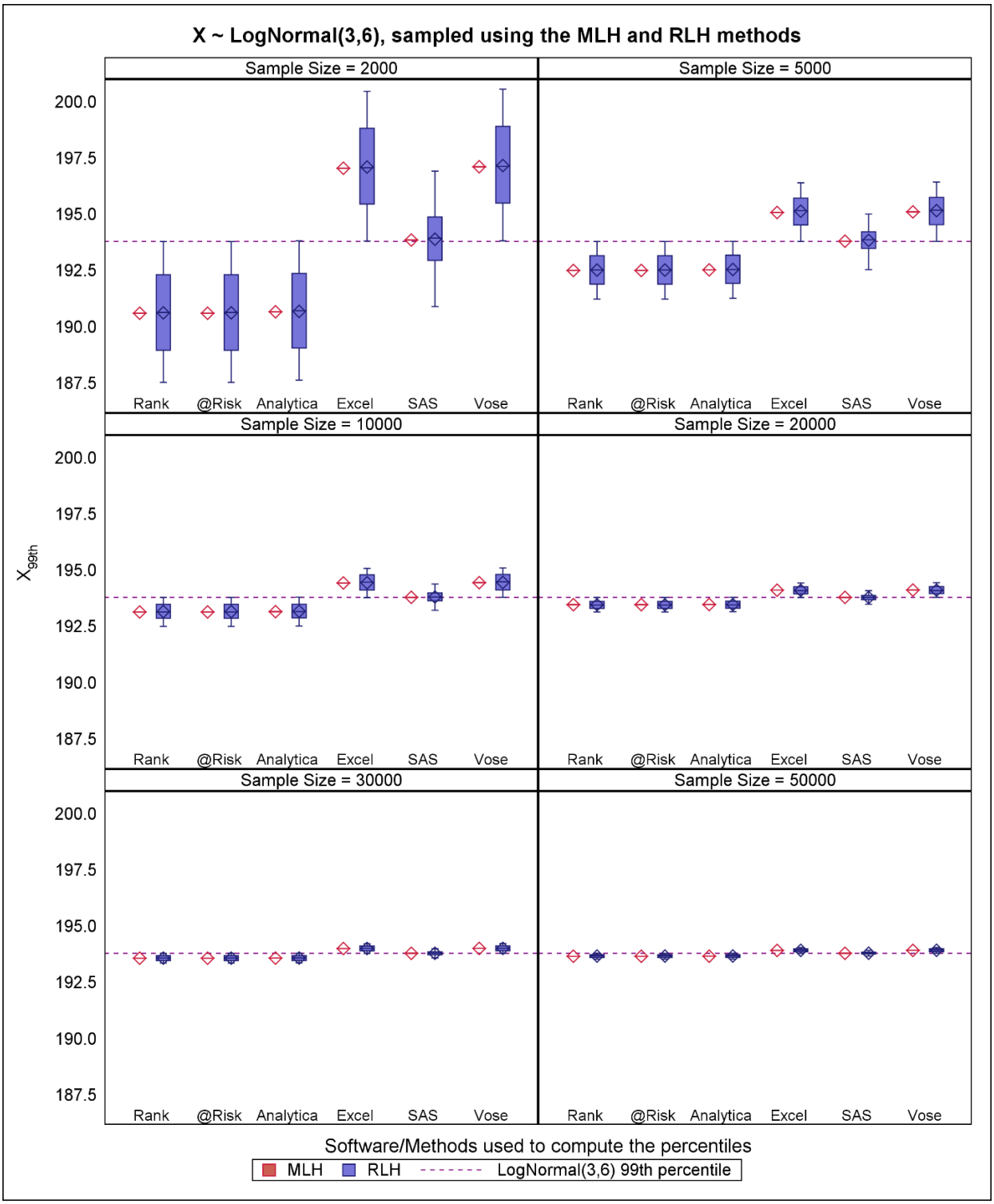


Figure 2. 99th percentile computed using different methods, for the LogNormal(3,6) distribution.

Table 2 shows the absolute bias at three different sample sizes (2,000, 10,000, and 20,000), based on the method used in the Analytica software of estimating the 99th percentiles, for the 10 simulated scenarios. The bias reported in Table 2 is obtained using the MLH method, but the RLH method produces very similar results. For all the distributions tested at all sample sizes, Type 7 method used by Analytica to estimate percentiles produces negative biases, meaning that this method is underestimating the theoretical quantiles. Skewed distributions with the largest uncertainty have the largest bias, and the bias decreases at the sample size increases.

Table 2. Bias at different sample sizes, based on MLH sampling and the method used in the Analytica software for the estimation of the 99th percentiles.

Distribution	Bias at 2,000 sample size	Bias at 10,000 sample size	Bias at 20,000 sample size
Uniform (1,6)	-0.0012	-0.0002	-0.0001
Triangular (1,3,5)	-0.0034	-0.0007	-0.0003
Triangular (1,1,5)	-0.0049	-0.0010	-0.0005
Weibull (2,1)	-0.0056	-0.0011	-0.0006
Weibull (1,10)	-0.2419	-0.0489	-0.0245
Normal (5,1)	-0.0091	-0.0018	-0.0009
Normal (25,5)	-0.0455	-0.0092	-0.0046
LogNormal (1,3)	-0.1280	-0.0259	-0.0130
LogNormal (3,6)	-3.1305	-0.6359	-0.3186
LogNormal (3,10)	-13.1705	-2.6806	-1.3433

Figure 3 shows the relative bias of the 99th percentile computed based on ten different methods (the 9 methods from Hyndman and Fan (1996), and the method implemented in Vose software), at different sample sizes, sampled from the LogNormal (3,6) distribution, and using the RLH sampling. For all the methods the relative bias approaches 0, as the sample size increases to 50,000, but for Types 2 and 5 methods the bias is the closest to 0 at any sample size. The relative bias of the 99th percentile computed using the MLH sampling method (not shown) is almost identical to the relative bias from the RLH sampling method.

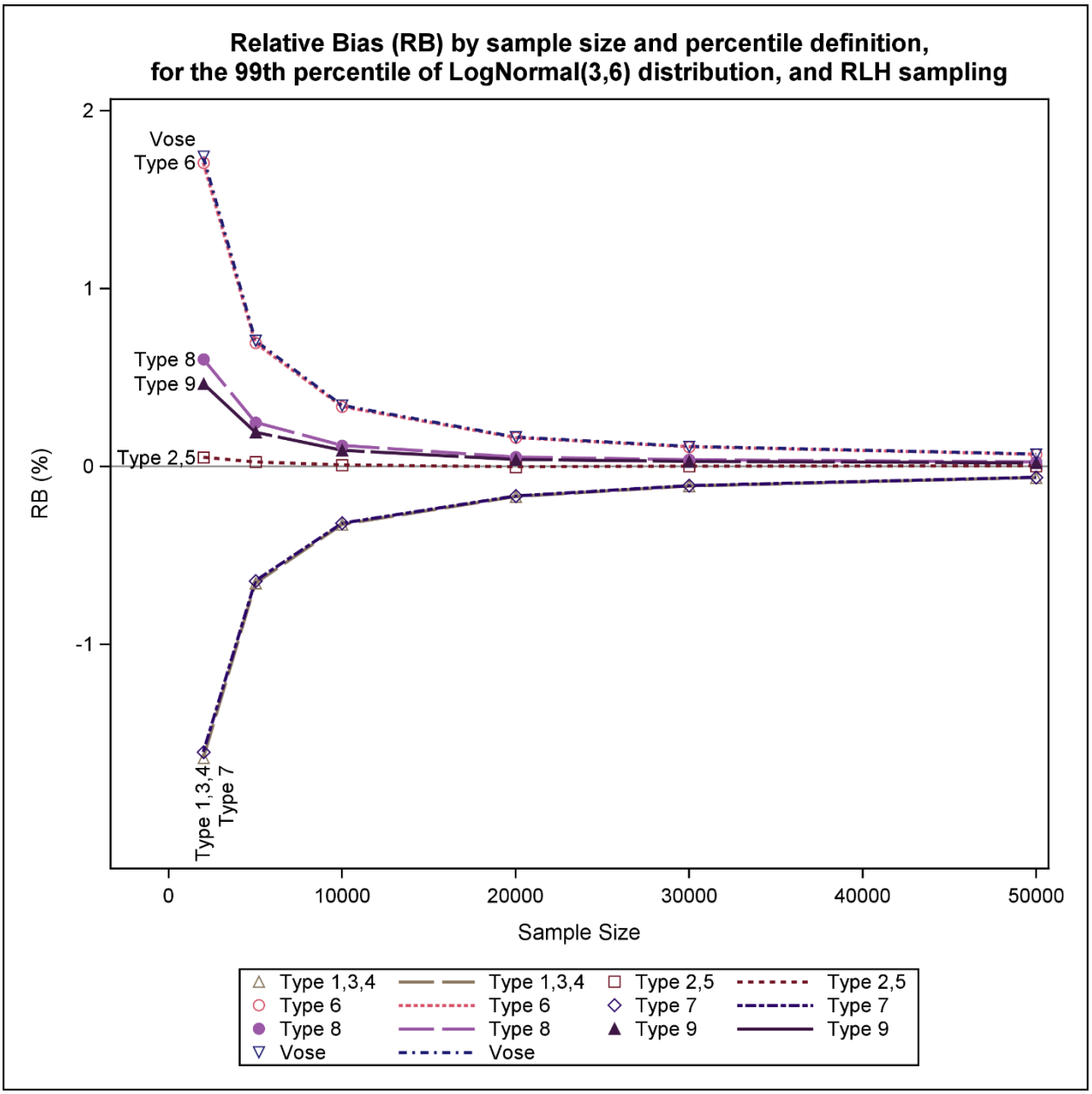


Figure 3. Relative Bias for the 99th percentile computed for different percentile definitions, and RLH sampling, for the LogNormal (3,6) distribution.

From the tested methods used to compute the 99th percentile in the first simulation, Type 2 and Type 5 methods are the ones with the smallest relative bias and smallest relative root mean squared error at all the sample sizes, and for all the distributions scenarios tested. While for the relative bias both sampling methods produce similar results, the MLH sampling has an advantage versus the RLH sampling, due to lower RRMSE values at all sample sizes.

To investigate which method of computing the 99th percentile is better in terms of bias and variability when two distributions are combined, a second simulation was set up.

Since the normal and lognormal distributions are the most common distributions used in NIOSH-IREP, these distributions with either small or large standard deviations were used in this

simulation, for both additive and multiplicative interactions, and a mixed interaction between the normal and lognormal distributions was also analyzed. A total of 20 scenarios were considered, obtained by either adding or multiplying two distributions from the following list: Normal (5,1), Normal (5,25), LogNormal (1,3), and LogNormal (3,6).

When two normal distributions are added, or when two lognormal distributions are multiplied, the distribution obtained is known to be either normal or respectively lognormal, and its parameters can be determined based on the parameters of the two input distributions. Therefore, in 6 out of the 20 scenarios, the theoretical 99th percentile of the combined distribution could be easily determined. For the remaining 14 scenarios, where the combined distribution is not known, the theoretical 99th percentile of the combined distribution cannot be determined exactly, however a confidence interval can be computed for the estimated 99th percentile.

Figures 4 and 5 show the 99th percentile computed based on two different methods (Type 2 method, used by default in SAS, and Type 7 method used in Analytica), for the Y1 = X1 + X2 distribution, where X1 ~ LogNormal (1,3), and X2 ~ LogNormal (3,6), and for all three sampling methods. The blue circles represent the average of the 99th percentile over the number of repetitions indicated before, and the vertical error bars shows the 95% confidence interval for the 99th percentile estimate. The red dotted horizontal lines in each plot represent the 95% confidence limits for the theoretical 99th percentile of the Y1 = X1 + X2 distribution. Type 7 method (used in Analytica) underestimates the theoretical 99th percentile at all sample sizes up to 20,000 iterations (especially for MLH and RLH sampling). Since all the MLH and RLH estimates obtained using Type 2 method are within the 95% C.I. of the theoretical 99th percentile at all sample sizes (when compared with the estimates obtained using Type 7 method), Type 2 method produce estimates that are the closest to the theoretical 99th percentile at all sample sizes.

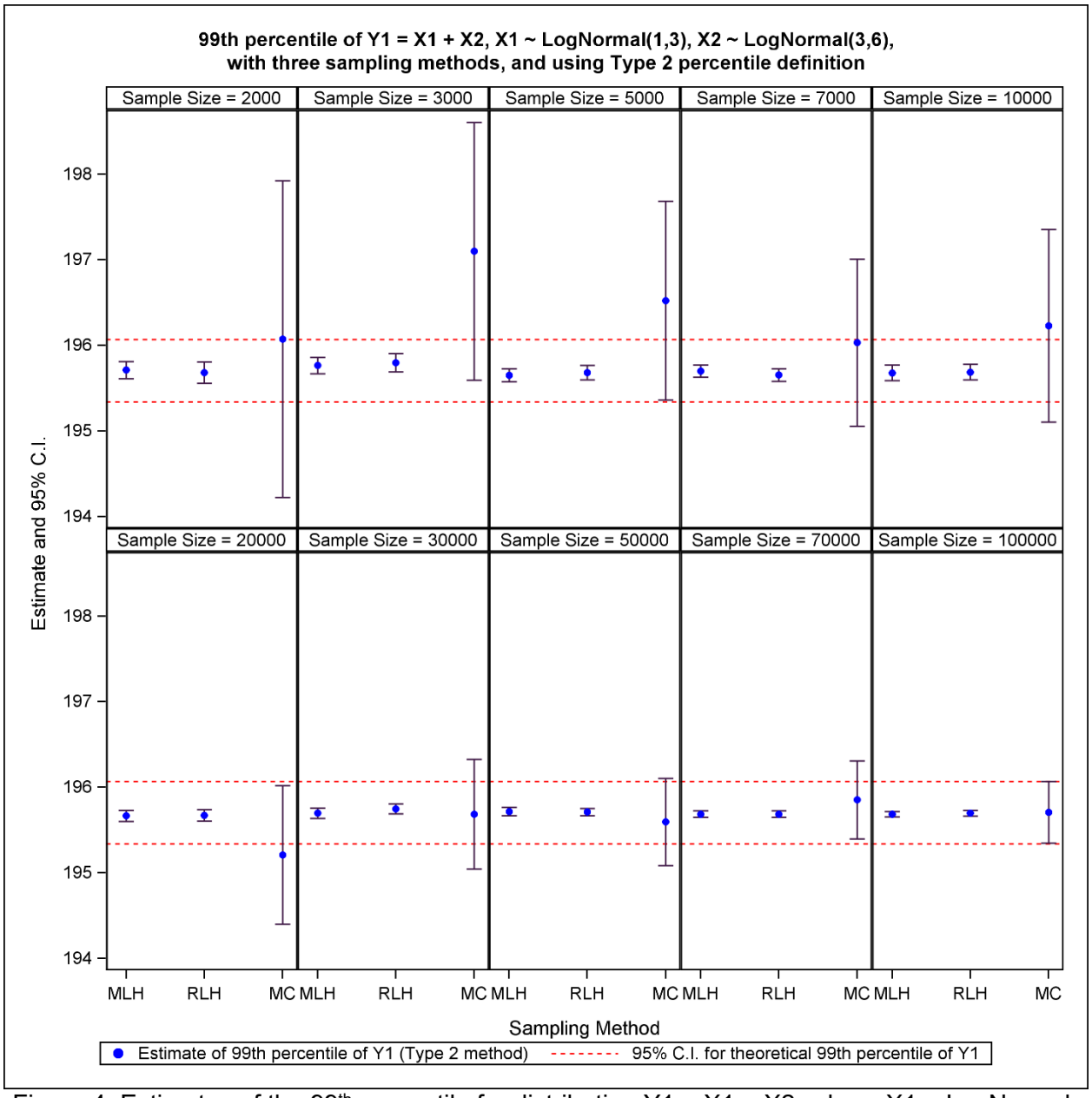


Figure 4. Estimates of the 99th percentile for distribution Y1 = X1 + X2, where X1 ~ LogNormal (1,3), and X2 ~ LogNormal (3,6), from different sampling methods, and using Type 2 percentile definition.

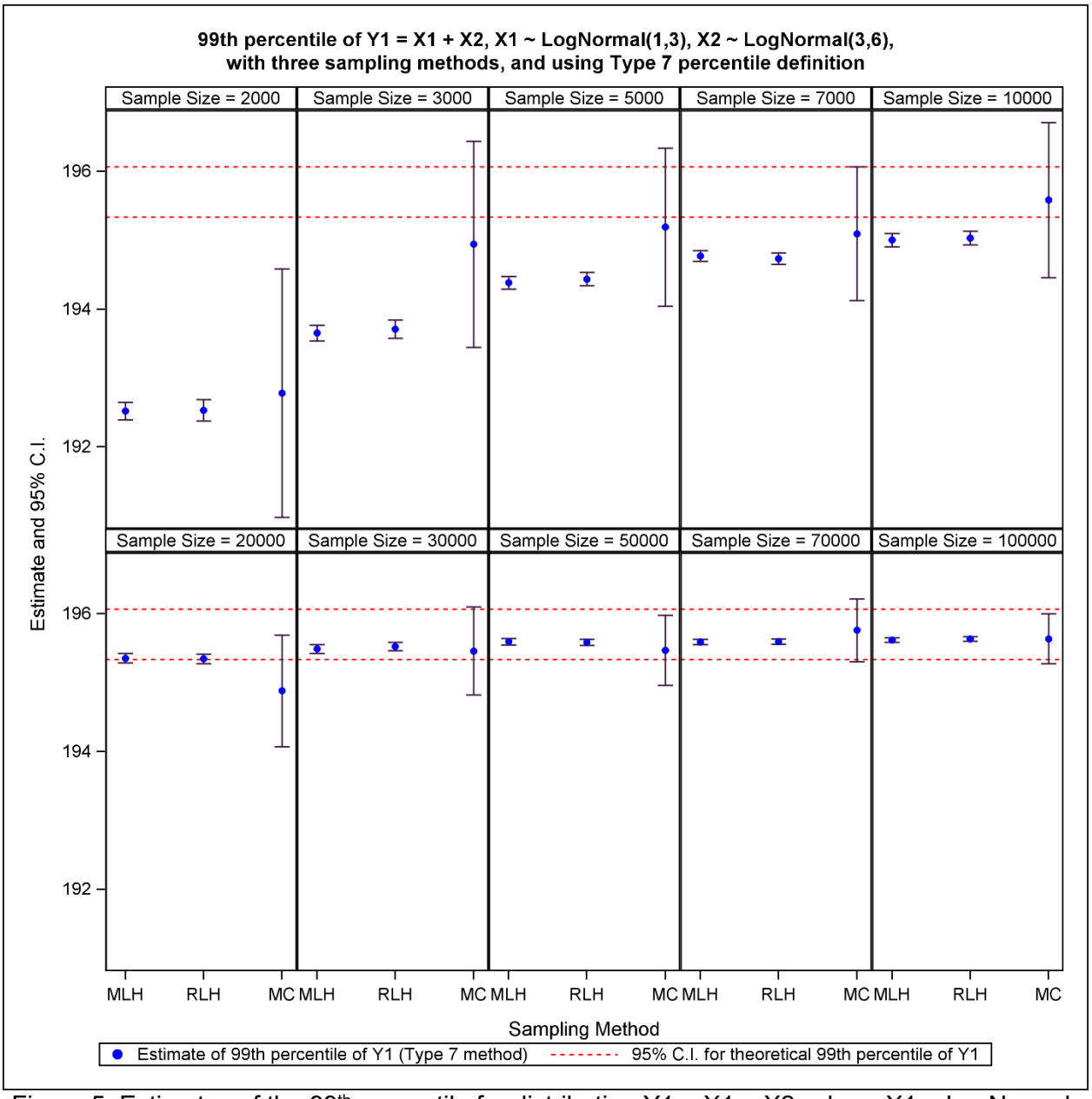


Figure 5. Estimates of the 99th percentile for distribution Y1 = X1 + X2, where X1 ~ LogNormal (1,3), and X2 ~ LogNormal (3,6), from different sampling methods, and using Type 7 percentile definition.

From the tested methods used to compute the 99th percentile in the second simulation, Type 2 method used by default in SAS, seems to be the one with the smallest relative bias and the MLH sampling seems to have an advantage over the RLH sampling in terms of the RRMSE for some of the scenarios tested. The Type 7 method used in Analytica underestimates the theoretical 99th percentile of the combined distribution in all scenarios, for most sample sizes, and for sample sizes up to 20,000 values the bias can be significant.

In conclusion, there is no standard definition of a percentile, however there are multiple definitions currently in use, with each software package using different methods to compute the percentiles. The performance of the percentile methods differs, depending on the percentile level, sample

size, type of distribution, magnitude of uncertainty and of positive skewness; however, the larger the sample size, the less important the effect of the percentile definition used. This section summarized and compared several percentile definitions and clarified which of these definitions is used in the NIOSH-IREP software, for the purpose of computing the PC values.

For all the simulations scenarios tested, the Type 2 method, used by default in the SAS software, seems to be the method with the smallest relative bias and smallest relative root mean squared error at all the sample sizes, in estimating the theoretical 99th percentile.

The Type 7 method, currently used in Analytica, underestimates the theoretical 99th percentile in all the scenarios tested, especially for sample sizes less than 20,000 values. It is thus preferrable to use 20,000 or more samples in PC calculations in future NIOSH-IREP versions (starting with version v.6.0) for EEOICPA claim evaluations.

3.0 EFFECT OF AN ALTERNATIVE PERCENTILE ON PC VALUES

Based on the two simulations described before, it was determined that Type 2 percentile definition, used by default in the SAS software, is the method with the smallest relative bias and smallest relative root mean squared error at all the sample sizes, in estimating the theoretical 99th percentile. The Type 7 percentile definition, which is used in Analytica, and in the NIOSH-IREP software, will be denoted as the Default percentile, and the Type 2 percentile definition, used in the SAS software, will be denoted as the Alternative percentile. This section analyzes the effect of using the Alternative percentile instead of the Default percentile on the 99th PC values (99th percentile of PC).

Five sets of claims were selected from the NOCTS database to test the effect of using the Alternative percentile instead of the Default percentile (query date is December 17, 2019). Each set of cases were randomly selected based on the following ranges of the 99th PC values:

- Set 1: 45 single cancer cases with 99th PC values between 44.00% and 44.99%
- Set 2: 25 single cancer cases with 99th PC values between 45.00% and 48.99%
- Set 3: 22 single cancer cases with 99th PC values between 49.00% and 49.99%
- Set 4: 36 multiple cancer cases with Combined 99th PC values between 49.00% and 49.99%
- Set 5: 25 single cancer cases with 99th PC values between 50.00% and 51.99%.

Only partial results for Set 1, Set 3, and Set 4 are included in this report, with detailed results included in the main report.

Of the 283 single cancer cases with 99th PC values of record between 44.00% and 44.99%, 45 cases were randomly selected in Set 1 for testing purposes. Figure 6 shows the 99th PC values computed using both the Default percentile and the Alternative percentile for all 45 cases at 2,000 iterations. Since all cases were rerun on the IREP v.5.9 version, only a fraction of the recomputed PC values falls in the 44.00% and 44.99% range, with most of them being outside this range. Results obtained using the Alternative percentile are greater than those obtained using Default percentile for all cases at 2,000 iterations. The difference between the Alternative percentile and

the Default percentile has an average increase of 0.26, with a maximum increase of 1.46 at 2,000 iterations.

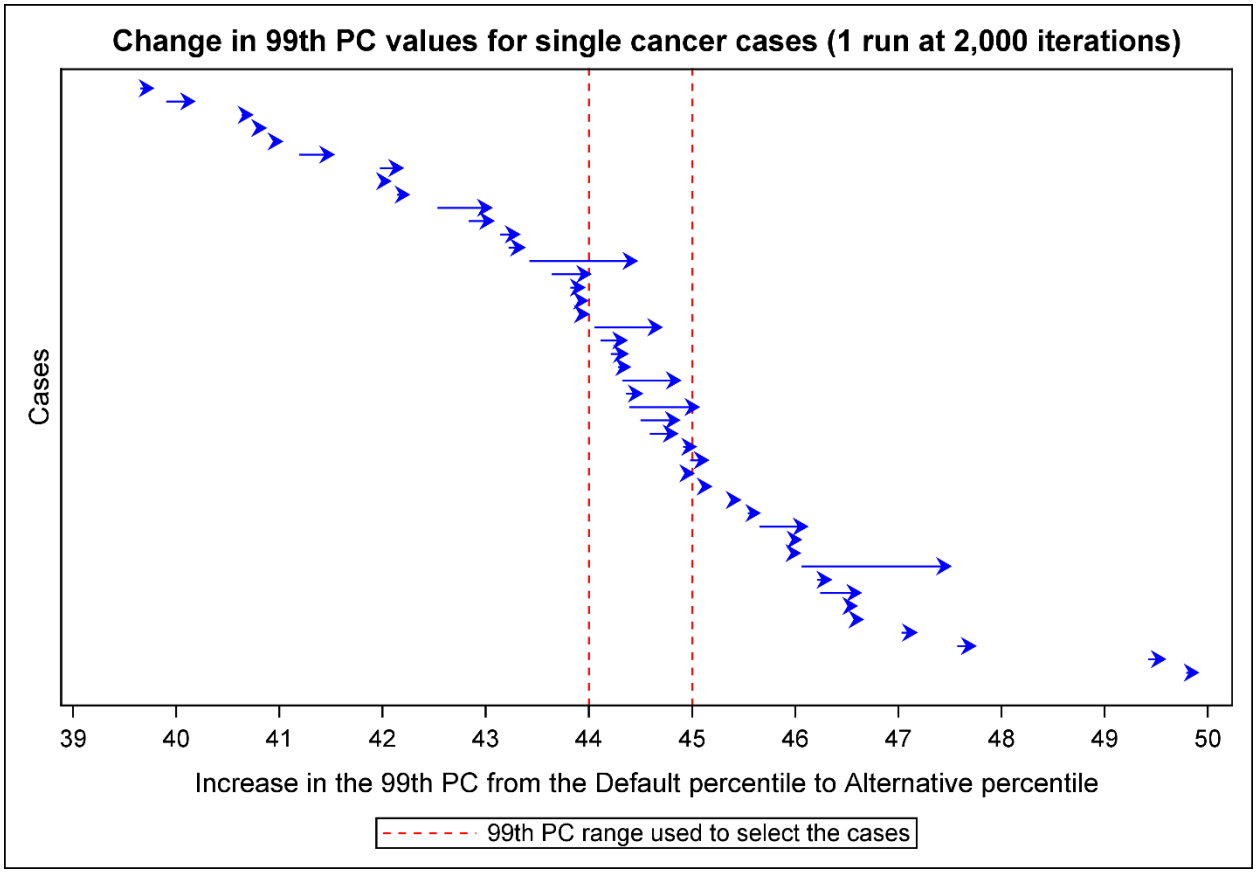


Figure 6. Increase in the 99th PC values from using the Default percentile to using the Alternative percentile at 2,000 iterations, for the 45 cases from Set 1 (PC values between 44.00% and 44.99%).

All 22 single cancer cases with 99th PC values between 49.00% and 49.99% were selected in Set 3 for testing purposes. The Alternative percentile produces greater 99th PC values than the Default percentile for all cases and each number of iterations. The difference between Alternative percentile and the Default percentile has an average increase of 0.04, with a minimum increase of 0.02, and maximum increase of 0.07 at 10,000 iterations, an average increase of 0.02, with a maximum increase of 0.04 at 20,000 iterations, and an average increase of 0.015, with a maximum increase of 0.02 at 30,000 iterations. Figure 7 shows the Avg. 99th PC values computed using both the Default percentile and the Alternative percentile for all 22 cases, based on 30 runs at 10,000 iterations.

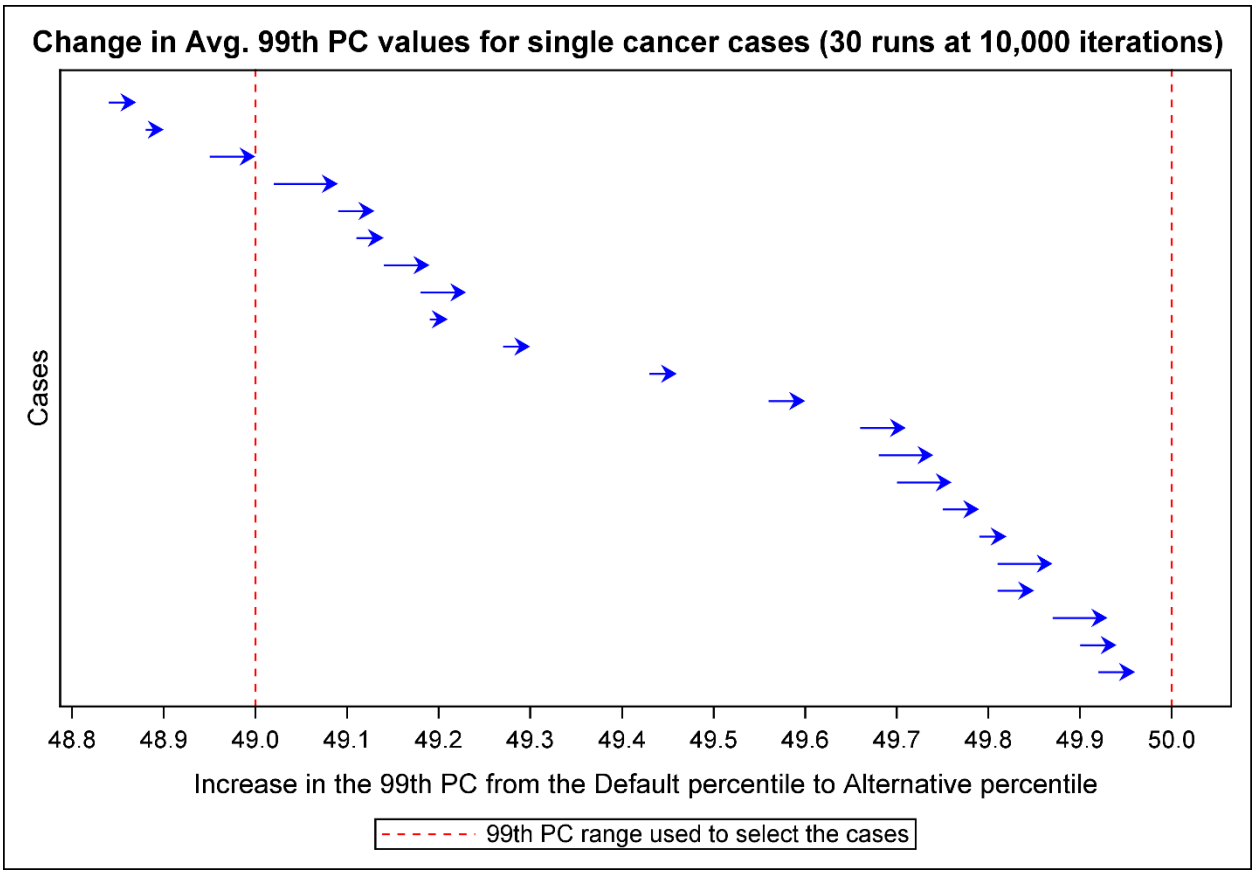


Figure 7. Increase in the Avg. 99th PC values from using the Default percentile to using the Alternative percentile, for the 22 single cancer cases from Set 3 (PC values between 49.00% and 49.99%), based on 30 runs at 10,000 iterations.

Figure 8 shows the Avg. 99th PC values computed using both the Default and the Alternative percentiles for all 22 cases in Set 3 based on 30 runs using 20,000 iterations. The lengths of the arrows in Figure 8 are smaller than in Figure 7, showing smaller increases in PC values using 20,000 iterations compared to 10,000 iterations. By running the 22 cases with 20,000 iterations, two of the 22 cases reach or surpass the 50.0% compensation threshold using either the Default percentile or the Alternative percentile.

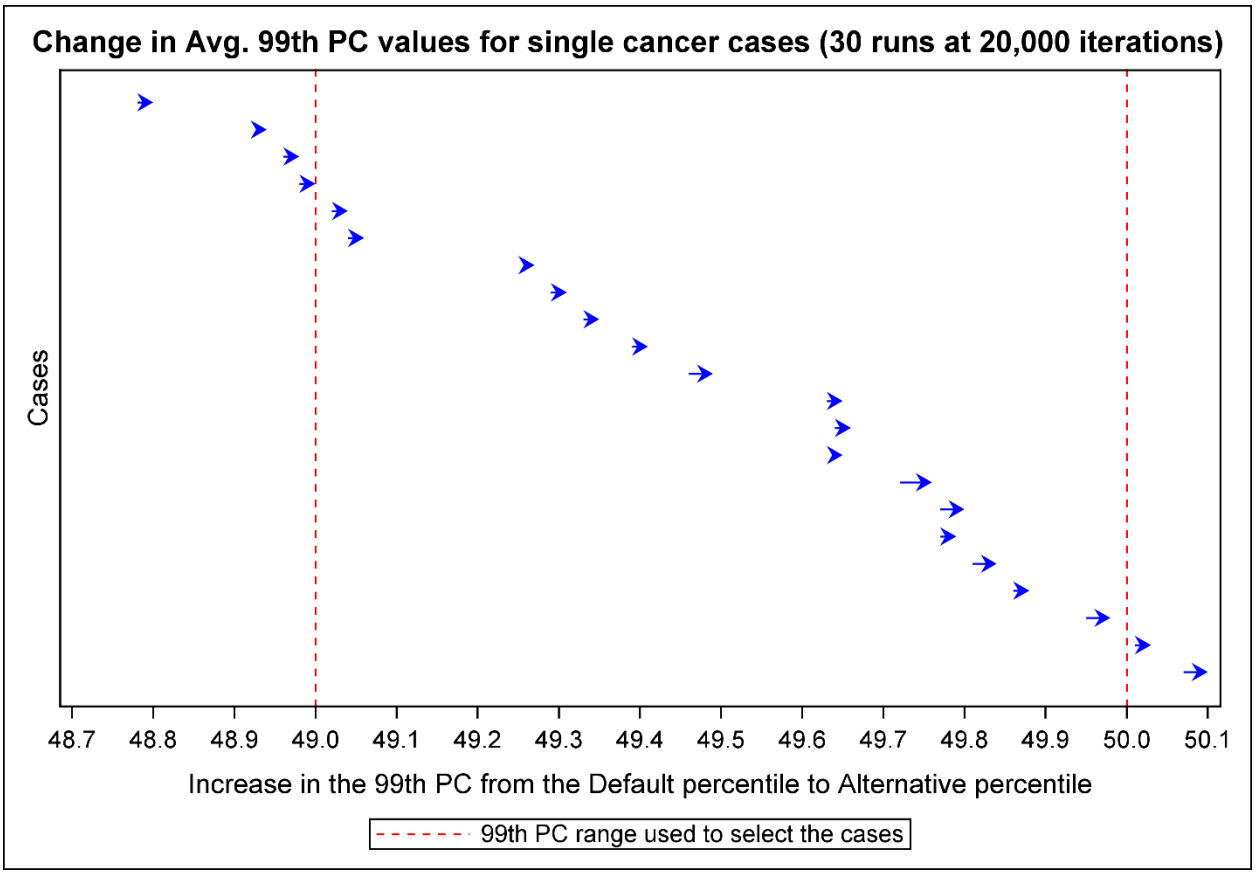


Figure 8. Increase in the Avg. 99th PC values from using the Default percentile to using the Alternative percentile, for the 22 single cancer cases from Set 3 (PC values between 49.00% and 49.99%), based on 30 runs at 20,000 iterations.

Figure 9 shows the Avg. 99th PC values computed using both the Default and the Alternative percentiles for all 22 cases in Set 3 based on 30 runs of 30,000 iterations each. The lengths of the arrows in Figure 9 have slightly smaller magnitudes than the lengths of the arrows in Figure 8, showing smaller increases in PC values using 30,000 iterations compared to 20,000 iterations. By running the 22 cases with 30,000 iterations, two of the 22 cases reach or surpass the 50.0% compensation threshold using either the Default percentile or the Alternative percentile.

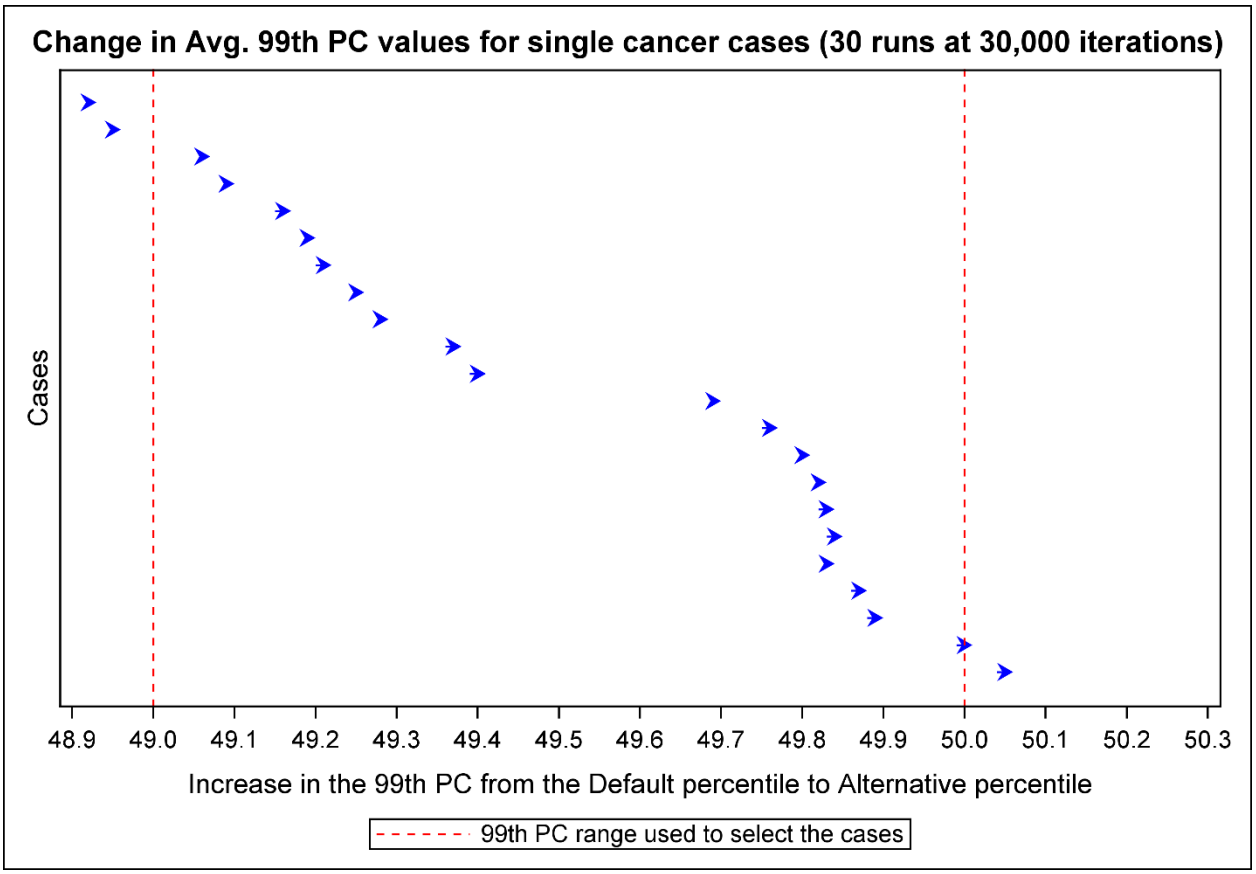


Figure 9. Increase in the Avg. 99th PC values from using the Default percentile to using the Alternative percentile, for the 22 single cancer cases from Set 3 (PC values between 49.00% and 49.99%), based on 30 runs using 30,000 iterations.

In addition to the single cancer cases with 99th PC values between 49.00% and 49.99%, all the 36 multiple cancer cases with Combined 99th PC values between 49.00% and 49.99% were also selected in Set 4 for testing purposes. The number of cancers varied between 2 and 13 cancers, for the cases selected. The Alternative percentile produced 99th PC values greater than the Default percentile for all cases and each number of iterations, and the difference between Alternative and the Default percentile has an average increase of 0.05, with a minimum increase of 0.03, and a maximum increase of 0.09, at 10,000 iterations.

Figure 10 shows the Combined Avg. 99th PC values computed using both the Default and the Alternative percentiles for all 36 cases, based on 30 runs of 10,000 iterations each. The lengths of the arrows in Figure 10 are larger than the lengths of the arrows in Figure 7, showing the larger increases in PC values for multiple cancer cases versus the single cancer cases. As it can be seen from the plot, two cases reach or surpass the 50.0% compensation threshold using the Alternative percentile.

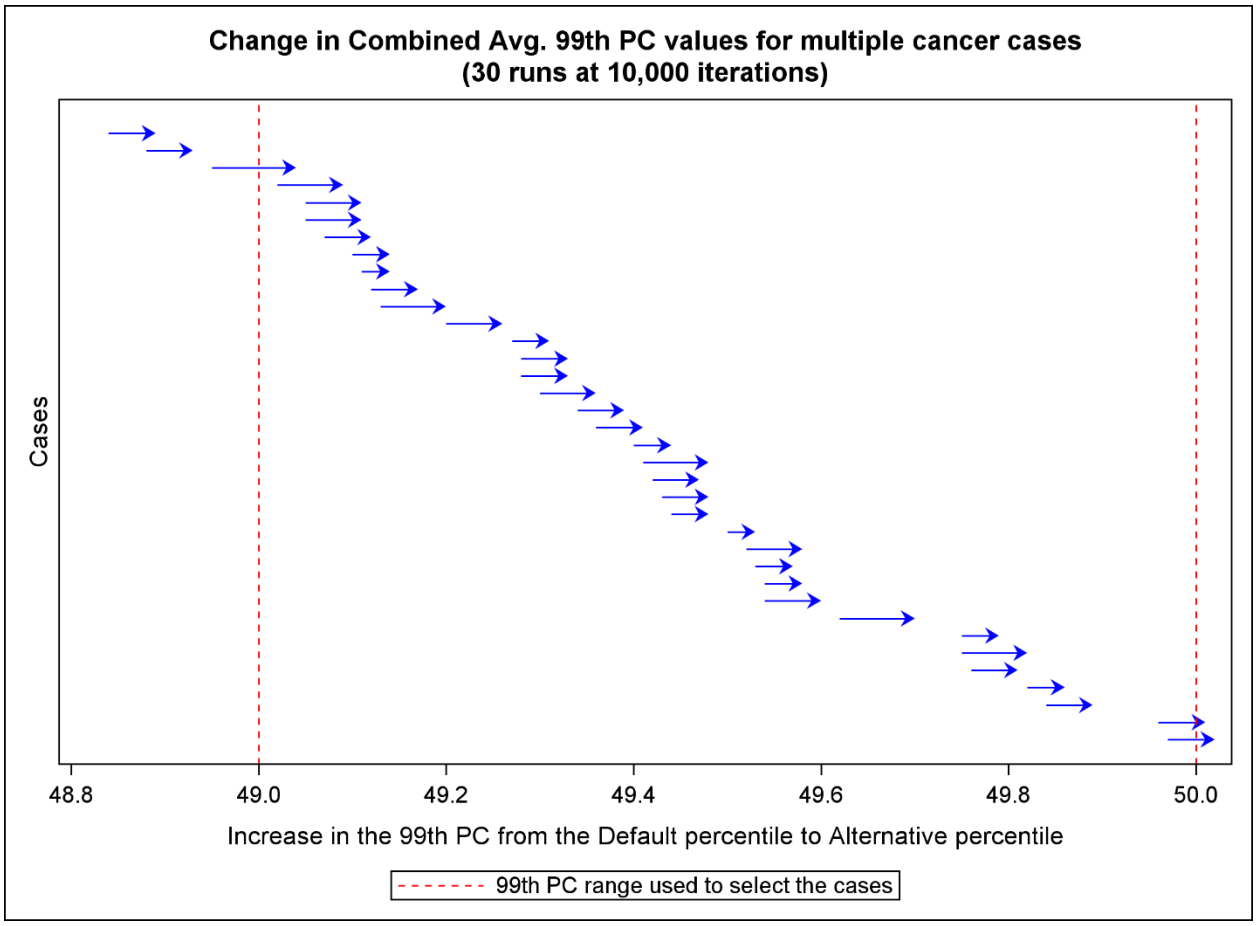


Figure 10. Increase in the Combined Avg. 99th PC values from using the Default percentile to using the Alternative percentile, for the 36 multiple cancer cases from Set 4 (Combined Avg. PC values between 49.00% and 49.99%), based on 30 runs of 10,000 iterations each.

Figure 11 shows a plot with the running times at 10,000, 20,000, and 30,000 iterations versus the number of exposures for all 72 cases with Avg. 99th PC values between 45.00% and 51.99%. The largest number of exposures among the 72 cases is 724 exposures. The filled circles in the plot correspond to cases with Lung cancers, which usually take longer to complete because two lung cancer models are run in parallel. These running times were obtained using a research version of IREP-EE, which is faster than the public IREP-EE version; it is expected that the running times can be longer by up to one order of magnitude if cases were run on the public IREP-EE version.

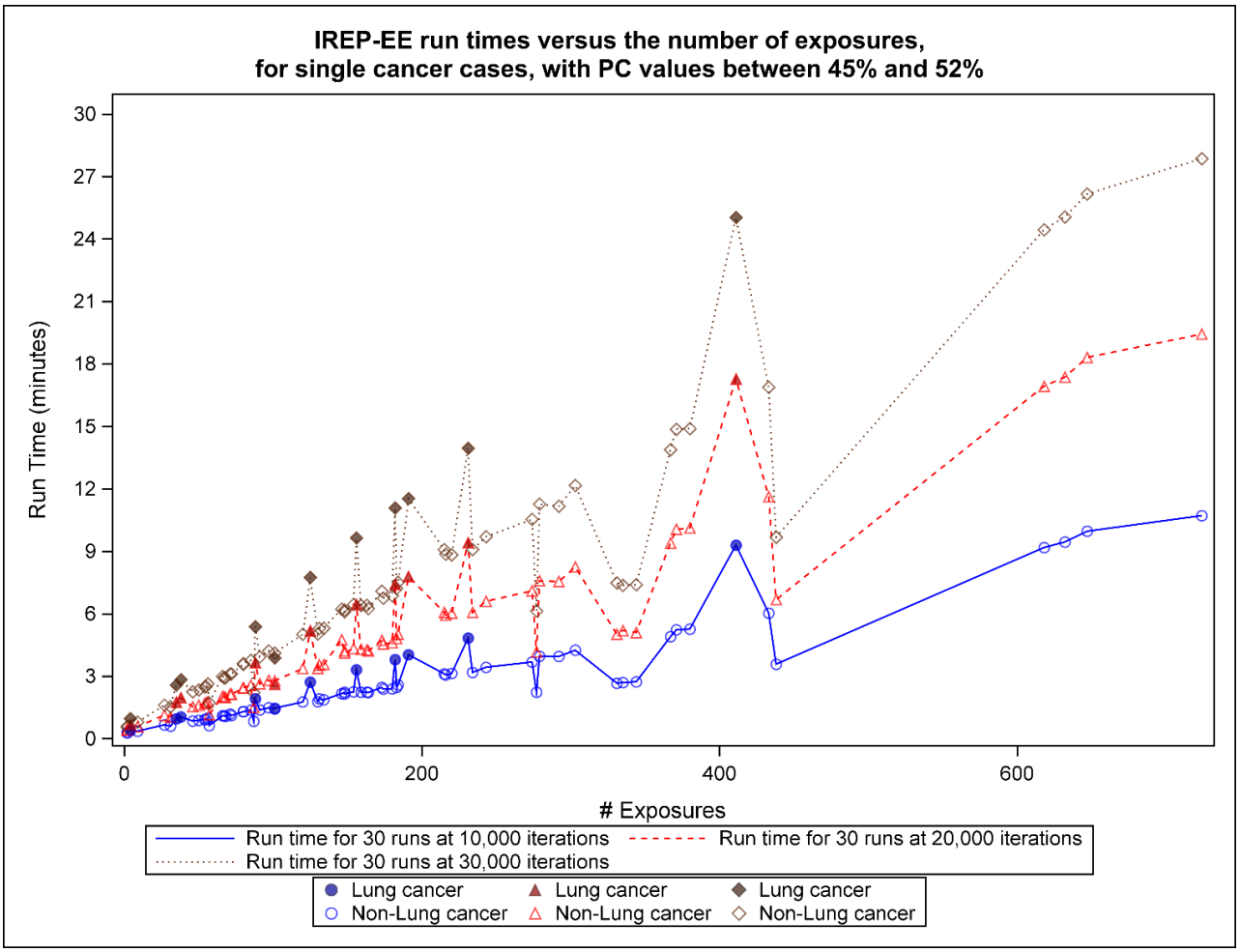


Figure 11. IREP-EE run times (minutes) at 10000, 20000, and 30000 iterations versus the number of exposures for the 72 cases with Avg. 99th PC values between 45.00% and 51.99%.

In conclusion, there are significant differences in the 99th PC values obtained using the Default percentile (computed using the Type 7 percentile definition, currently used in the NIOSH-IREP software) and the Alternative percentile (computed using the Type 2 percentile definition) for the NOCTS cases tested, with the Alternative percentile always producing higher values than the Default percentile.

For the 45 cases with the 99th PC values between 44.00% and 44.99%, there is an average increase in the 99th PC values of 0.27, with a maximum increase of 1.46 using 2,000 iterations, from the Default percentile versus the Alternative percentile, an average increase of 0.06, with a maximum increase of 0.27 using 10,000 iterations, and an average increase of 0.02, with a maximum increase of 0.17 using 20,000 iterations.

For the 72 cases with the 99th PC values between 45.00% and 51.99%, there is an average increase in the 99th PC values of 0.04, with a maximum increase of 0.11 using 10,000 iterations, when switching from the Default percentile to the Alternative percentile. Using 20,000 iterations, there is an average increase of 0.02 (maximum increase of 0.05), while using 30,000 iterations, the average increase is 0.015 (maximum 0.04).

To improve the estimates of 99th PC values, either the Alternative percentile definition can be implemented in future NIOSH-IREP versions, or the number of iterations used should be increased, to minimize the underestimation effect on the 99th PC values.

The number of iterations used in the IREP version should be increased in future NIOSH-IREP versions (starting with version v.6.0) to a minimum of 10,000 iterations, but preferably to 20,000 iterations or more. The number of iterations used in in future NIOSH-IREP Enterprise Edition versions (starting with version v.6.0) should be increased to a minimum of 20,000 iterations, but preferably to 30,000 iterations or more.

4.0 PC VARIABILITY AT DIFFERENT NUMBER OF ITERATIONS

Each case in NOCTS is run in IREP v.5.9 using 2,000 iterations and a default random seed of 99, and if the resulting 99th PC value is between 45.00% and 51.99%, the case is rerun on IREP-EE v.5.9 with 30 runs of 10,000 iterations, and each run having a different random seed. Estimates of 99th percentile of PC obtained from 2,000 iterations can vary significantly depending on the random seed used. To better determine the variability of 99th PC values obtained at different numbers of iterations, an analysis was conducted for all cases with the 99th PC values between 45.00% and 51.99%. Altogether, a total of 77 cases with 99th PC values between 45.00% and 51.99% were selected for this analysis, and each of the 77 cases was run on IREP-EE with 2,000, 10,000, 20,000, and 30,000 iterations.

Individual 99th PC values obtained from each set of 30 runs have a considerable higher variability when using 2,000 iterations, and the variability decreases as the number of iterations increases to 10,000, 20,000, and 30,000 iterations. For each set of 30 runs performed for a case at any number of iterations, the individual 99th PC values are approximately normally distributed, with the mean given by the Avg. 99th PC value.

Figure 12 shows the fitted normal distributions of individual 99th PC values using 2,000, 10,000, 20,000, and 30,000 iterations for one case with the Avg. 99th PC value at 30 runs and 10,000 iterations selected between 49.00% and 49.99% (the Avg. 99th PC value on record in NOCTS for this case is 49.87%). The Avg. 99th PC values for each number of iterations are shown as vertical lines in the plot. This example shows a high probability that one 99th PC value using 2000 iterations could have been generated above 52%, making this case not eligible for a run on IREP-EE (which would have been an incorrect decision, and the compensability would have been incorrectly decided for this case).

Figure 13 shows the fitted normal distributions of the individual 99th PC values using 2000, 10000, 20000, and 30000 iterations for one case with the Avg. 99th PC value at 30 runs and 10000 iterations selected between 50.00% and 51.99% (the Avg. 99th PC value on record in NOCTS for this case is 50.47%). This example shows a small probability that one 99th PC value using 2000 iterations could have been generated below 45%, making this case not eligible for a run on IREP-EE (which would have been an incorrect decision, a decision that would have been incorrectly affected the compensability for this case).

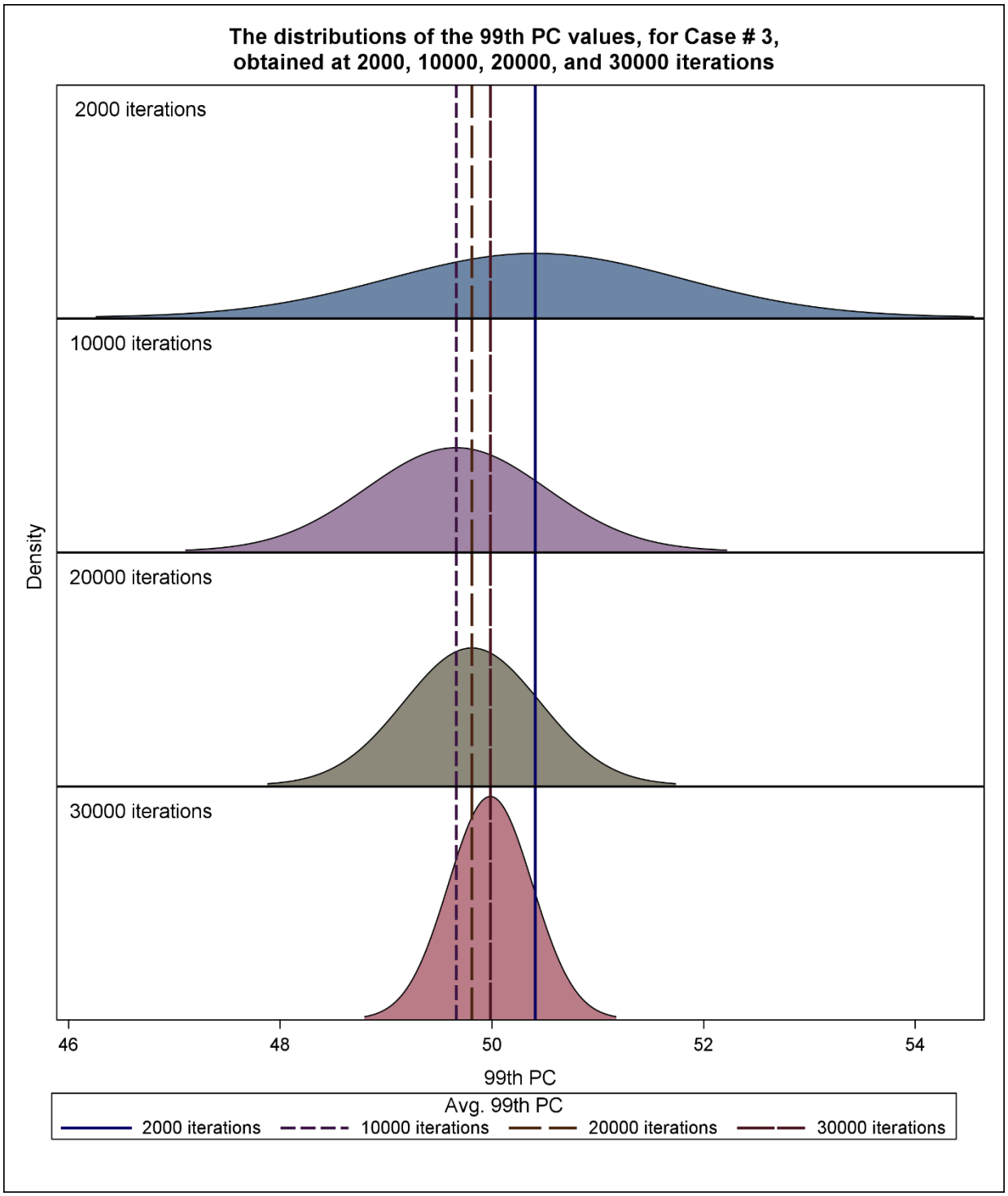


Figure 12. Fitted normal distributions for the individual 99th PC values using 2,000, 10,000, 20,000, and 30,000 iterations for a case with Avg. 99th PC value (obtained with 30 runs and 10,000 iterations) between 49% and 50%.

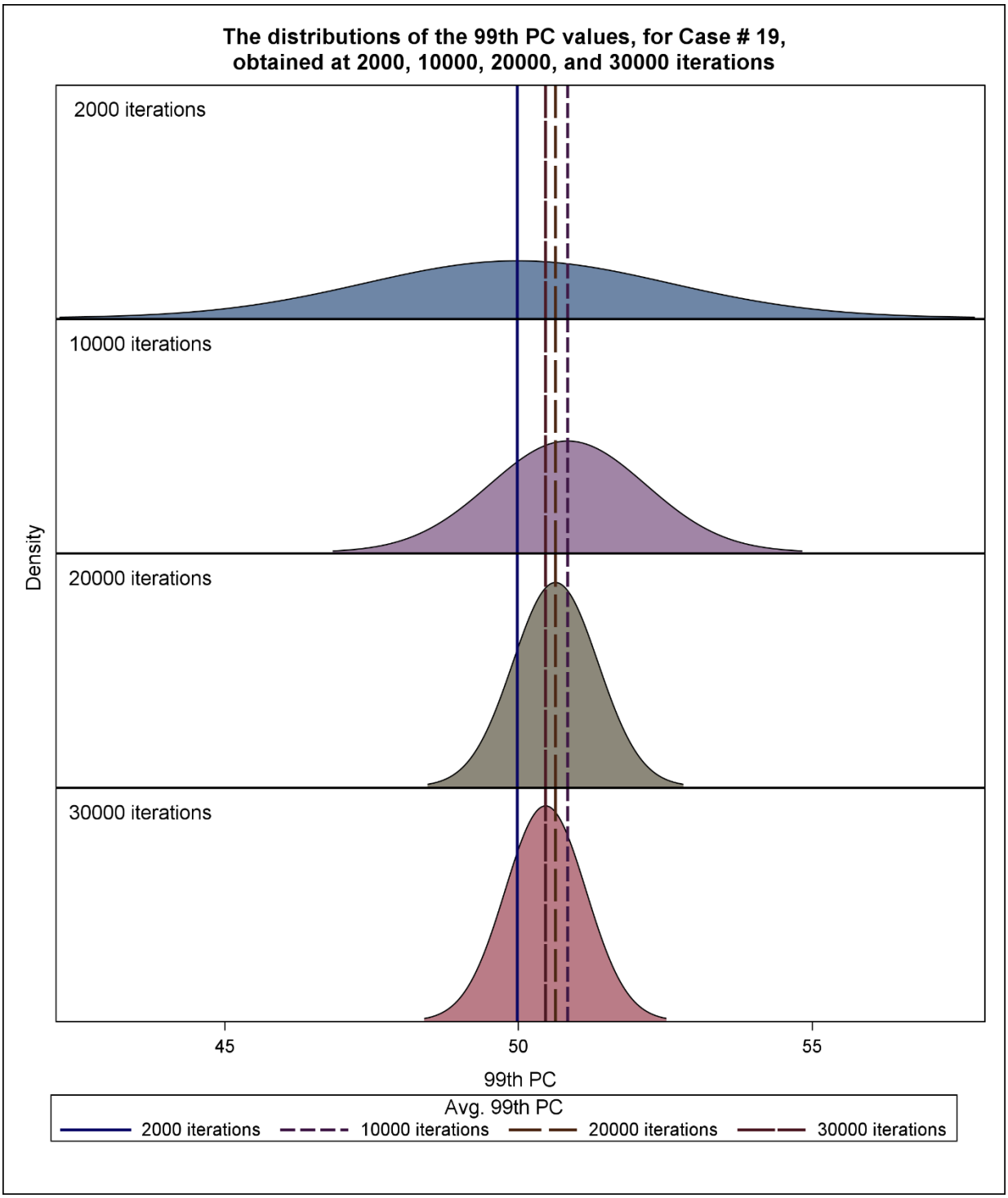


Figure 13. Fitted normal distributions for the individual 99th PC values using 2,000, 10,000, 20,000, and 30,000 iterations for a case with Avg. 99th PC value (obtained using 30 runs and 10,000 iterations) between 50% and 52%.

Analyzing the 77 cases with PC values between 45.00% and 51.99% shows a large range of values for the individual 99th PC values, especially for the individual 99th PC values obtained using 2,000 iterations. While the individual 99th PC values have a very large variability, the Avg. 99th PC values have a much smaller variability, and so there is a big advantage in using the Avg. 99th PC values instead of the individual 99th PC values, due to the lower variability and the more stable values generated in the sampling process.

The examples shown in Figures 12 and 13 show the peril of choosing one individual 99th PC value for determining a case outcome, and the fact that one individual 99th PC value obtained using 2,000 iterations might not always be a reliable indicator for deciding which cases to run on the IREP Enterprise Edition, especially with the setting of 2,000 iterations used in the IREP v.5.9 version. The current rule in use is that if the individual 99th PC value obtained using 2,000 iterations and default random seed is between 45.00% and 51.99%, corresponding to a range of (-5.0, 2.0) around the compensation threshold of 50.00%, then the case is rerun on IREP Enterprise Edition with 30 runs of 10,000 iterations each. Based on the analysis with 76 cases (after excluding one outlier case), the range at 2,000 iterations around the 50% threshold to be used in selecting which cases need to run in the IREP Enterprise Edition would need to be increased to (-8.8, 8.8). If the 99th PC value are obtained using the IREP version at 10,000 iterations, then the range used should be approximately (-4.4, 4.4), and if the 99th PC value are obtained using the IREP version at 20,000 iterations, then the range used should be approximately (-2.8, 2.8).

In conclusion, while the number of iterations used in the IREP v.5.9 and IREP v.5.9 Enterprise Edition versions need to be increased, the ranges around the 50% compensation threshold to be used in selecting which cases to run in the IREP Enterprise Edition, based on 99th PC value obtained using the IREP version, should be adjusted accordingly, and several ranges are provided to be used depending on the number of iterations used in the IREP version.

5.0 PC CONVERGENCE AT 30 RUNS IN IREP ENTERPRISE EDITION

The convergence of the 99th PC values as well as of the Avg. 99th PC values, as the number of iterations increases, can be seen in Figure 14, which shows the 99th PC values obtained for a case with the 99th PC value between 49% and 50% (the Avg. 99th PC value on record in NOCTS for this case is 49.87%). The plot shows the individual 99th PC values, as well as the Avg. 99th PC values from 30 runs, obtained at 7 different sample sizes ranging between 10,000 and 200,000 iterations. For each sample size, four sets of 30 random seeds were used (the same 4 sets of 30 random seeds were used at each sample size). The plot clearly shows that, for each sample size, there is much more variation in the individual 99th PC values than in the Avg. 99th PC values obtained from each set of 30 random seeds. Also, as the sample size increases, the Avg. 99th PC values obtained are much more stable with respect to changing the set of 30 random seeds. There is a clear trend of the individual 99th PC values, as well as the Avg. 99th PC values, to converge to a stable value that represents the theoretical 99th PC value of the distribution of PC values for this case.

The theoretical 99th PC value of the distribution of PC values for a case cannot be determined exactly, but a 95% confidence interval can be estimated for the theoretical 99th PC value. The larger the number of iterations used in the computation, the smaller the length of the 95% confidence interval for the 99th PC value will be. For the case shown in Figure 14, the 95% confidence interval for the 99th PC value based on 1,000,000 iterations is (49.63, 50.02), and the 95% confidence interval for the theoretical 99th PC value based on 5,000,000 iterations is (49.76, 49.93). As the sample size increases, the 95% confidence interval for the 99th PC value will be

narrower. In this case the length of the 95% confidence interval for the theoretical 99th PC value obtained from 1,000,000 iterations is 0.39, and the length of the 95% confidence interval for the theoretical 99th PC value obtained from 5,000,000 iterations is 0.17, and these lengths remain almost unchanged if different random seeds are used.

Figure 15 shows the 95% confidence intervals for the Avg. 99th PC values at each sample size, obtained using both the default and the alternative percentile definitions (Stancescu et al. 2026, DCAS-RPT-012), as well as the 95% confidence limits for the theoretical 99th PC value obtained based on a 5,000,000 iterations (blue dotted lines), for the same case shown in Figure 14. The Avg. 99th PC value obtained based on the alternative percentile definition is always greater or equal than the Avg. 99th PC value obtained based on the default percentile, but the differences between the Avg. 99th PC values obtained using the two percentile definitions get smaller as the sample size increases. The 95% confidence intervals lengths around the Avg. 99th PC values decrease as the sample size is increasing. The lengths of the 95% confidence intervals for the Avg. 99th PC values using 200,000 iterations are smaller or equal than 0.17, which is the length of the 95% confidence interval for the theoretical 99th PC value obtained from 5,000,000 iterations. For both percentile definitions, the Avg. 99th PC values from the four random seeds sets become less spread out as the sample size increases, showing the convergence trend.

Figure 16 shows the 95% confidence intervals for the Avg. 99th PC values at each sample size, obtained using both the default and the alternative percentile definitions, as well as the 95% confidence limits for the theoretical 99th PC value, for a different case with the 99th PC value slightly above 50% (the Avg. 99th PC value on record in NOCTS for this case is 50.01%). The 95% confidence interval for the theoretical 99th PC value for this case was obtained by using a non-parametric method (Meeker 2017) from a data set with 6,000,000 individual PC values. This data set was obtained by combining 3 samples of 2,000,000 individual PC values, since IREP cannot directly compute the 95% confidence limits for a case with large number of exposures and for a large sample size, due to computer memory limitations. The 95% confidence interval for the theoretical 99th PC value is (49.96, 50.05), which shows that for this particular case, even with a large sample size, the compensability of the case might be hard to decide. Since the length of the 95% confidence interval for the theoretical 99th PC value is 0.09, this case suggests that there is a limit of the precision with which the theoretical 99th PC value for a case can be bounded.

In Figures 15 and 16, the Avg. 99th PC values from the four random seeds sets are getting closer to each other as sample size increases, showing an increased precision. At larger sample sizes, the Avg. 99th PC values from the four random seeds sets are within the confidence interval limits for the theoretical 99th PC value indicating also a tendency for improved accuracy with increasing sample size. The increased precision and accuracy apply for any given model assumptions used in IREP.

In conclusion, there is a clear trend of the individual 99th PC values, as well as the Avg. 99th PC values, to converge to a stable value that represents the theoretical 99th PC value of the distribution of PC values for that case. The theoretical 99th PC value of the distribution of PC values for a case cannot be determined exactly, but a 95% confidence interval for the theoretical 99th PC value can be estimated. The larger the number of iterations used in the computation, the smaller the length of the 95% confidence interval for the theoretical 99th PC value will be, and for a sample size large enough, a length for the 95% confidence interval of less than 0.15 or even less than 0.10 can be achieved.

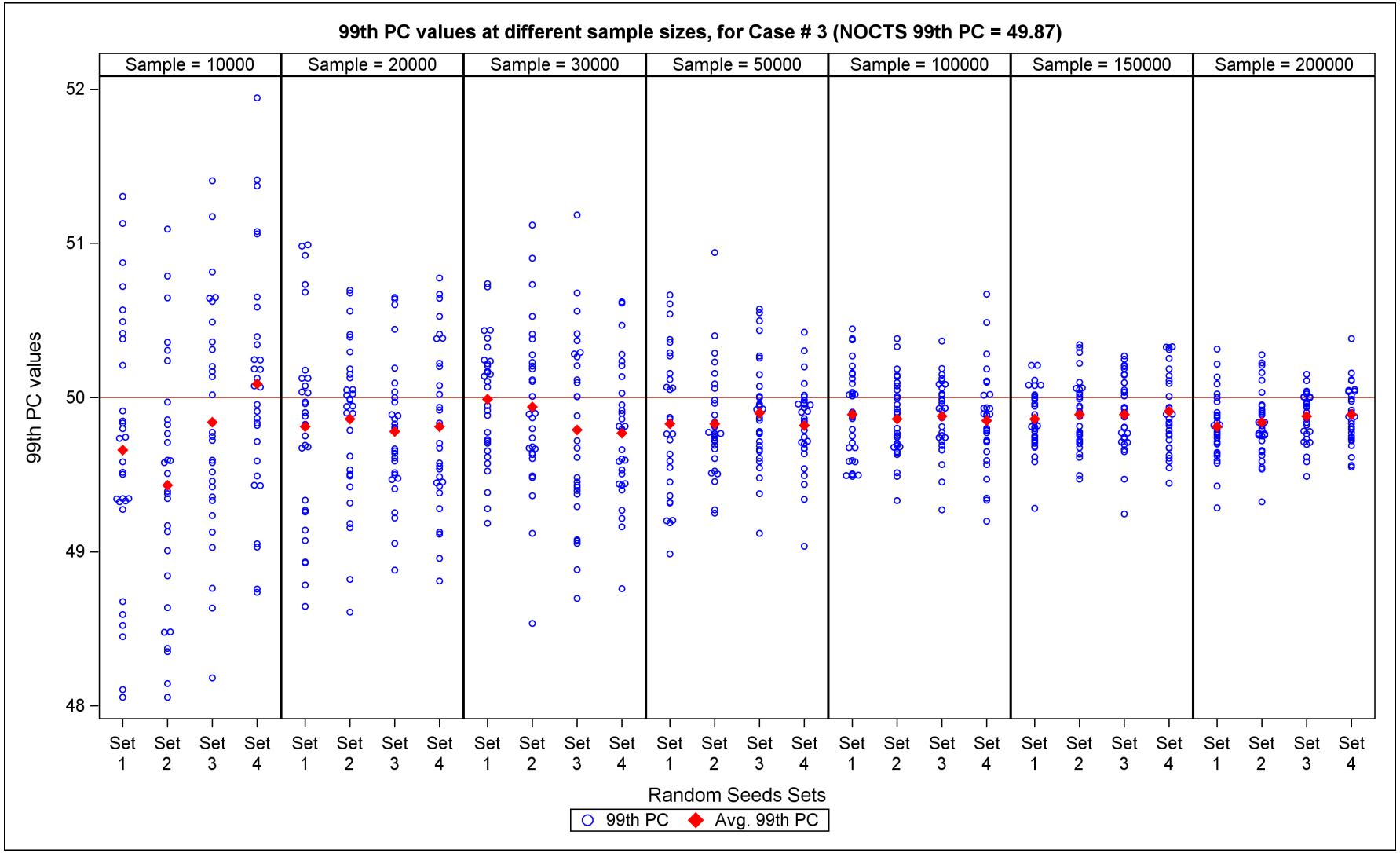


Figure 14. The 99th PC values obtained at different sample sizes, for a case with the Avg. 99th PC value between 49% and 50%.

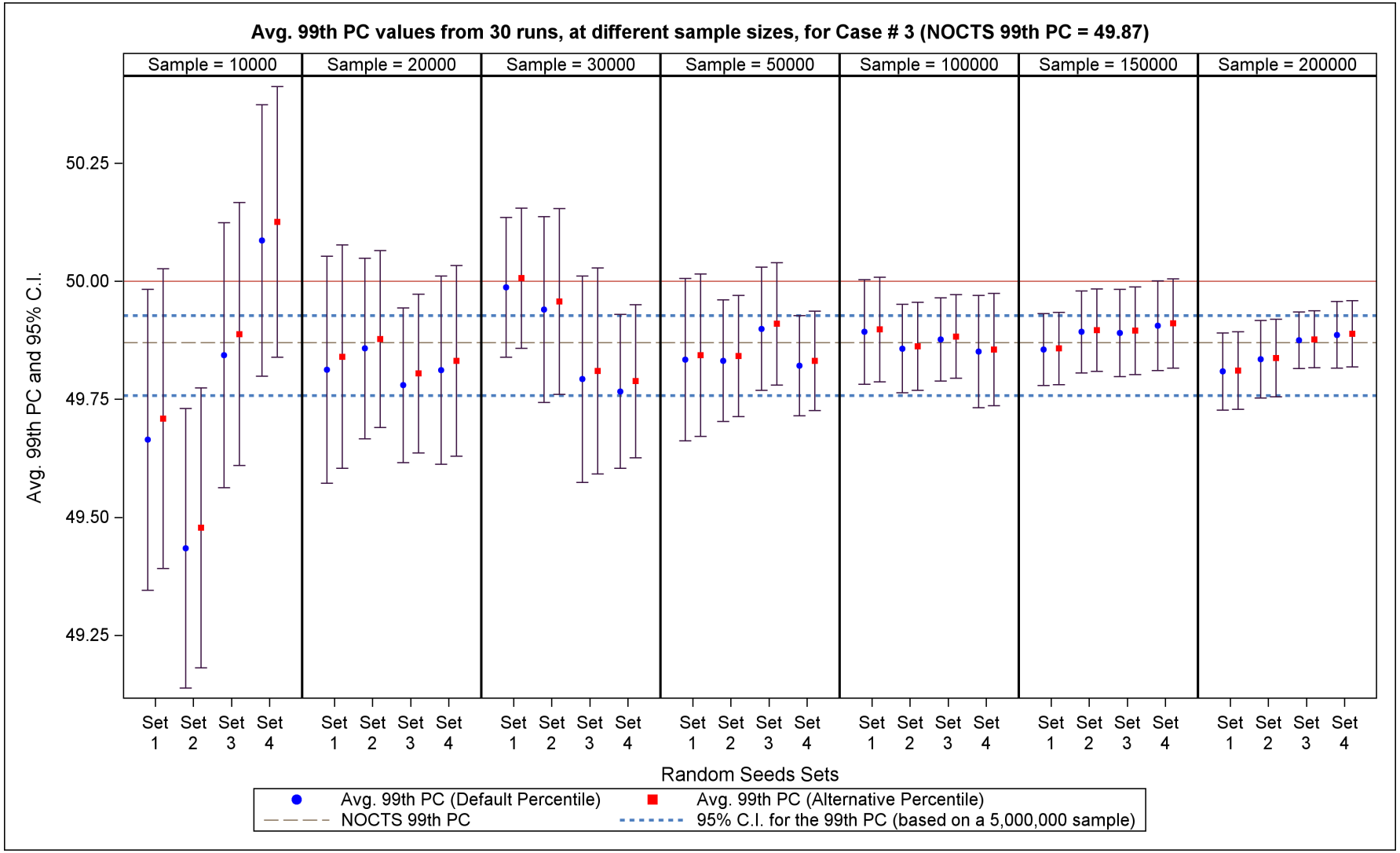


Figure 15. The Avg. 99th PC values from 30 runs, and their 95% confidence intervals, obtained using the default and alternative percentiles.

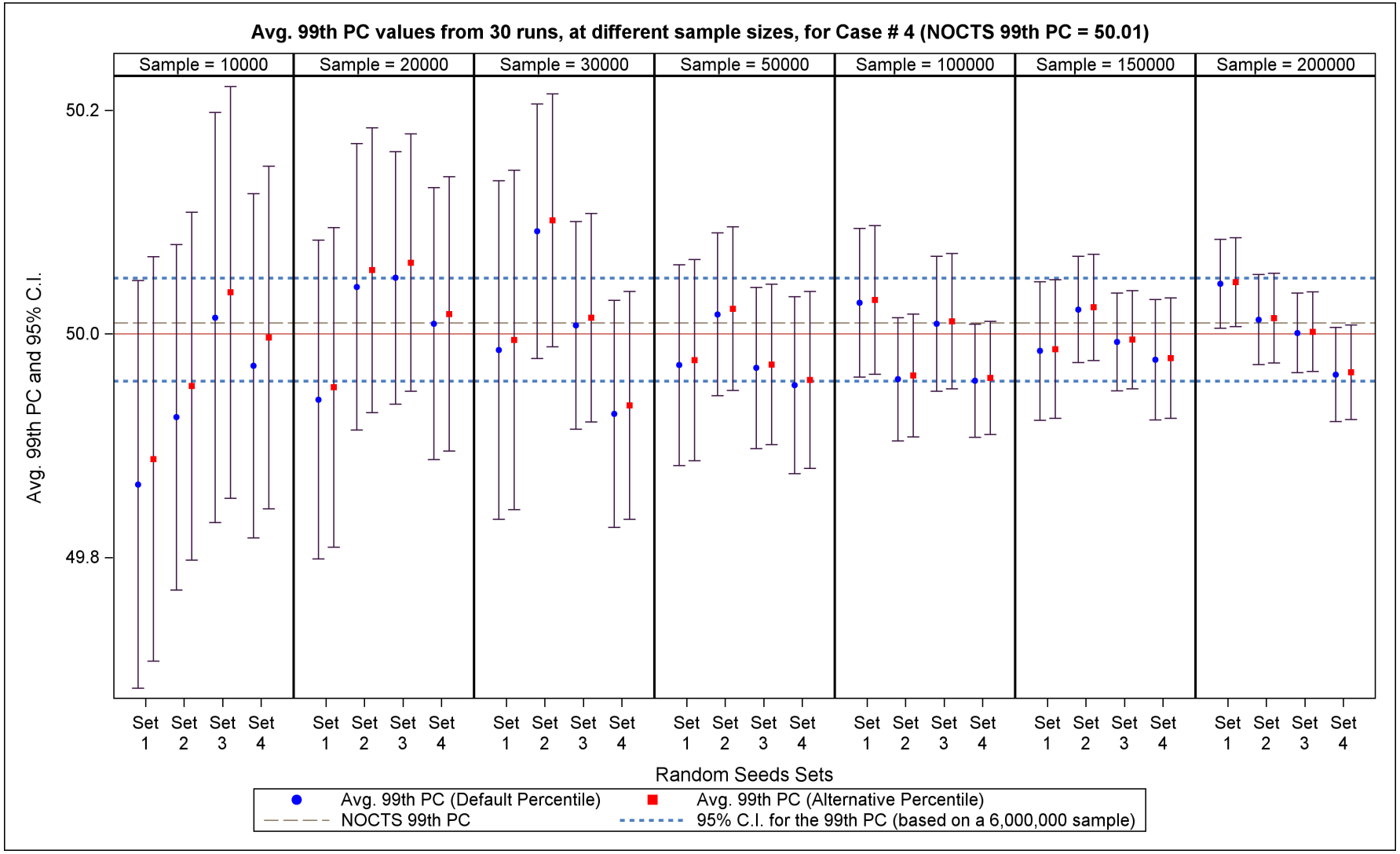


Figure 16. The Avg. 99th PC values from 30 runs, and their 95% confidence intervals, obtained using the default and alternative percentiles.

6.0 PC CONVERGENCE AT MORE THAN 100 RUNS IN IREP ENTERPRISE EDITION

In the previous section, it was shown that the Avg. 99th PC values converge to a stable value that represents the theoretical 99th PC value of the distribution of PC values for that case. In order to achieve convergence for the Avg. 99th PC values (i.e., the Avg. 99th PC values to become relatively stable with respect to changing the set of random seeds), the number of iterations needs to be increased to at least 50,000 iterations for each of the 30 runs used in the IREP v.5.9 Enterprise Edition, for most of the tested cases. To speed up the convergence of the PC values and to reduce the length of the 95% confidence intervals for the Avg. 99th PC values, either the number of iterations, the number of runs or both need to be increased.

The goal is to reduce the 95% confidence intervals for the Avg. 99th PC values to be less than or equal to a desired precision level (e.g., a length of the 95% confidence interval of 0.15 or 0.10), for cases with Avg. 99th PC values in the 49.00% to 49.99% range. Increasing the number of iterations is not always a good option, especially for cases with larger number of exposures, since the IREP runs can get interrupted due to the high memory usage. The option of increasing the number of runs is more feasible in practice, since it just adds additional runs to the 30 runs previously used in the IREP Enterprise Edition. To look for the optimal combination of the number of runs and iterations that are enough to reduce the length of the 95% confidence intervals for the Avg. 99th PC values below the desirable lengths of either 0.15 or 0.10, several different combinations of number of runs and iterations were considered. Another factor in choosing the optimal combination of the number of runs and iterations is the total time it takes in IREP-EE to compute the Avg. 99th PC value for each combination of runs and iterations; ideally, a single cancer case should be completed in no more than 2 or 3 hours.

Twenty-three cases with the Avg. 99th PC values between 49.00% and 50.01% were selected for this analysis, and each case was run on a modified version of the IREP Enterprise Edition for the following four scenarios:

- Scenario 1: 100 runs with 50,000 iterations (for a total of 5,000,000 iterations)
- Scenario 2: 200 runs with 50,000 iterations (for a total of 10,000,000 iterations)
- Scenario 3: 300 runs with 50,000 iterations (for a total of 15,000,000 iterations)
- Scenario 4: 300 runs with 100,000 iterations (for a total of 30,000,000 iterations).

Figure 17 summarizes the lengths of all the 95% confidence intervals obtained for the 23 cases from each of the four scenarios, and it also shows the standard errors for each case obtained in the four scenarios (the length of the 95% confidence intervals as well as the standard errors were obtained from a bootstrap analysis). The plot shows that the lengths of the 95% confidence intervals are smaller than 0.15 for all cases in Scenarios 2 and 3, and less than 0.10 for all cases in Scenario 4.

For the analyses in which 30 runs were used in the IREP Enterprise Edition, even with 200,000 iterations per run, there were cases for which the lengths of the 95% confidence intervals were higher than 0.15, and none of two desired precision levels can be achieved. This is the main reason why the number of runs need to be increased to at least 100 runs or more.

The convergence of the Avg. 99th PC values obtained using 100, 200, and 300 runs, as the number of iterations increases, can be seen in Figure 18, which shows the Avg. 99th PC values obtained for the case shown in Figure 15. The plot shows the Avg. 99th PC values obtained from the four tested

scenarios. For each scenario, four sets of either 100, 200, or 300 random seeds were used, and the same sets of random seeds were used at 300 runs for both 50,000 and 100,000 iterations. The plot shows that as the number of total iterations increases, the Avg. 99th PC values obtained become more stable with respect to changing the sets of random seeds. The lengths of the 95% confidence intervals for the Avg. 99th PC values from Scenario 2 are less than 0.15, and the lengths of the 95% confidence intervals for the Avg. 99th PC values from Scenarios 3 and 4 are less than 0.10. There is a clear trend of the Avg. 99th PC values to converge to a stable value that represents the theoretical 99th PC value of the distribution of PC values for this case. The length of the 95% confidence interval for the theoretical 99th PC value obtained from a 15,000,000 sample is 0.10.

Figure 19 illustrates the convergence of the Avg. 99th PC values, as the number of iterations increases, for the case in Figure 16. The plot shows that as the number of total iterations increases, the Avg. 99th PC values obtained become more stable with respect to changing the sets of random seeds. The lengths of the 95% confidence intervals for the Avg. 99th PC values from Scenarios 2 and 3 are less than 0.06, and the lengths of the 95% confidence intervals for the Avg. 99th PC values from Scenario 4 are less than 0.04. There is a clear trend of the Avg. 99th PC values to converge to a stable value that represents the theoretical 99th PC value of the distribution of PC values for this case. The length of the 95% confidence interval for the theoretical 99th PC value obtained from a 15,000,000 sample is 0.06. However, in all four scenarios, for which between 5,000,000 to 30,000,000 iterations were used, the compensability of this case is still hard to decide, since the Avg. 99th PC values bounce around the 50.0% compensability threshold.

In Figures 18 and 19, the Avg. 99th PC values from the four random seeds sets are getting closer to each other as sample size increases, showing an increase in precision. At larger sample sizes, the Avg. 99th PC values from the four random seeds sets are within the confidence interval limits for the theoretical 99th PC value indicating also a tendency for improved accuracy with increasing sample size. The increased precision and accuracy apply for any given model assumptions used in IREP.

In conclusion, in order to speed up the convergence of the PC values and to reduce the length of the 95% confidence intervals for the Avg. 99th PC values, four different scenarios with different number of runs and iterations were tested, and it was concluded that the lengths of the 95% confidence intervals for the Avg. 99th PC values are smaller than 0.15 for all tested cases in Scenario 2 (200 runs with 50,000 iterations) and Scenario 3 (300 runs with 50,000 iterations), and less than 0.10 for all cases in Scenario 4 (300 runs with 100,000 iterations). The largest IREP running time observed for the 23 cases using Scenario 2 is around 2 hours, using Scenario 3 is around 3 hours, and using Scenario 4 is slightly less than 5.7 hours.

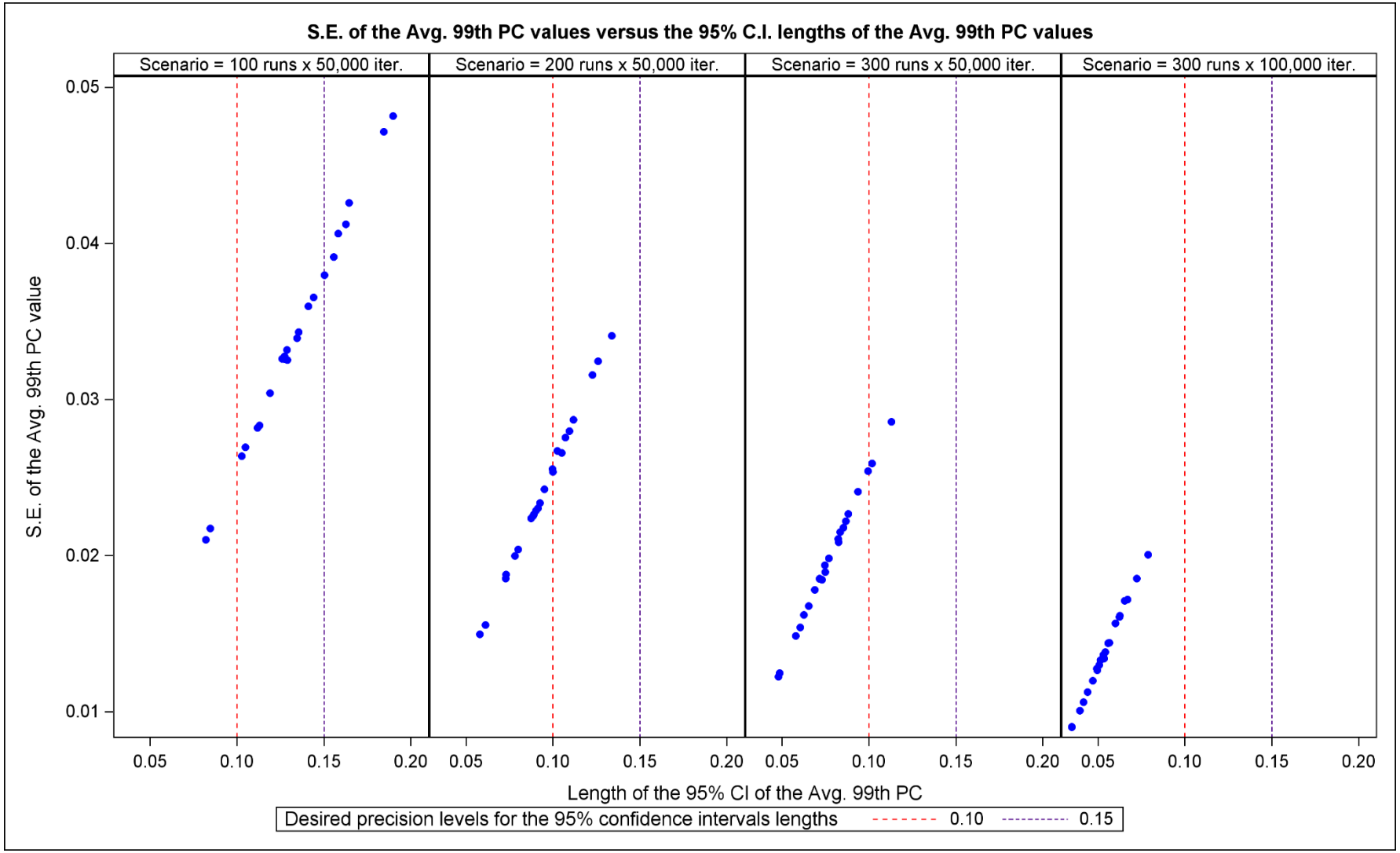


Figure 17. Standard errors (S.E.) versus 95% C.I. lengths in four scenarios with different number of runs and iterations.

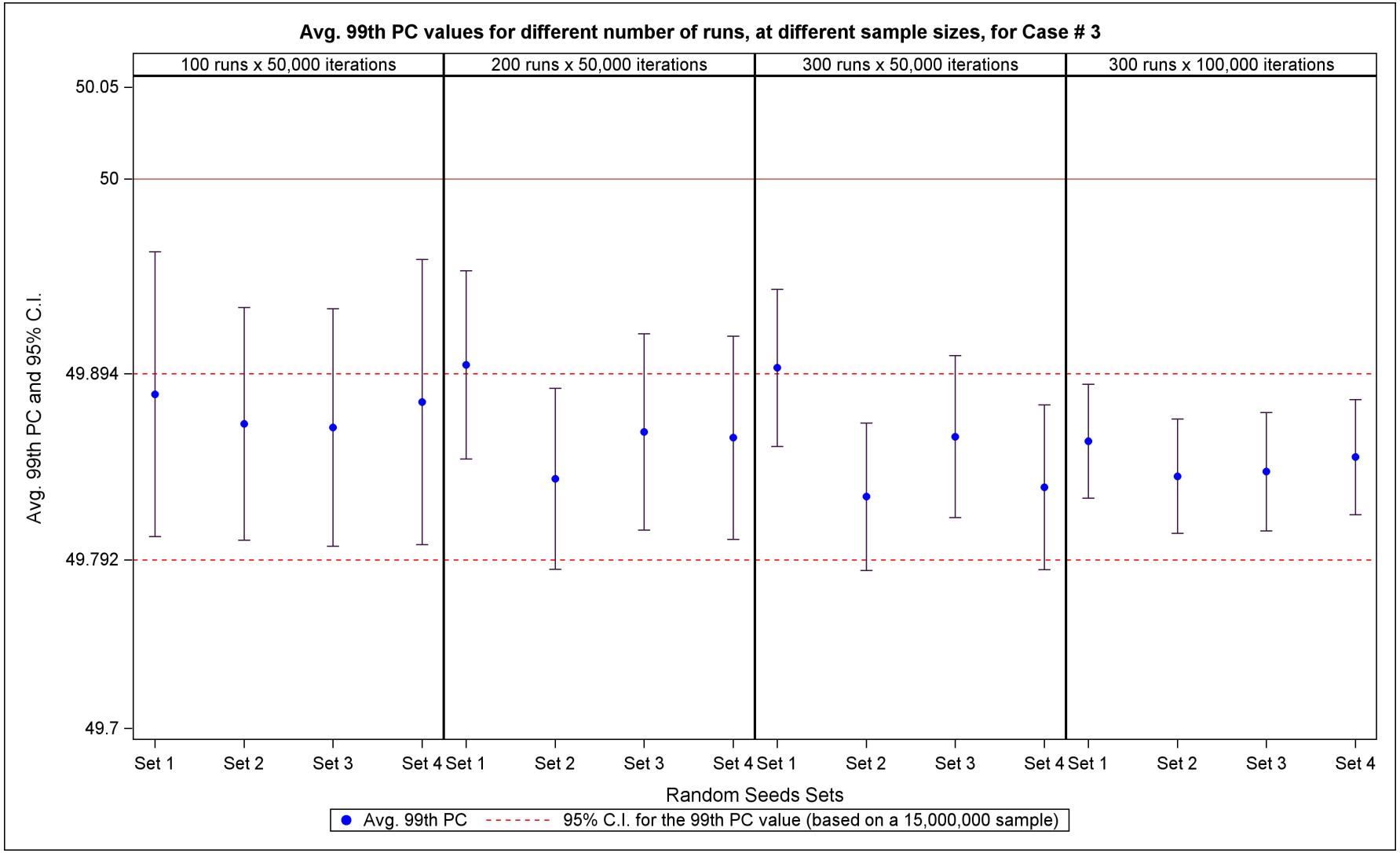


Figure 18. Avg. 99th PC values from 100, 200, 300 runs, and their 95% C.I., and confidence limits for the theoretical 99th PC value.

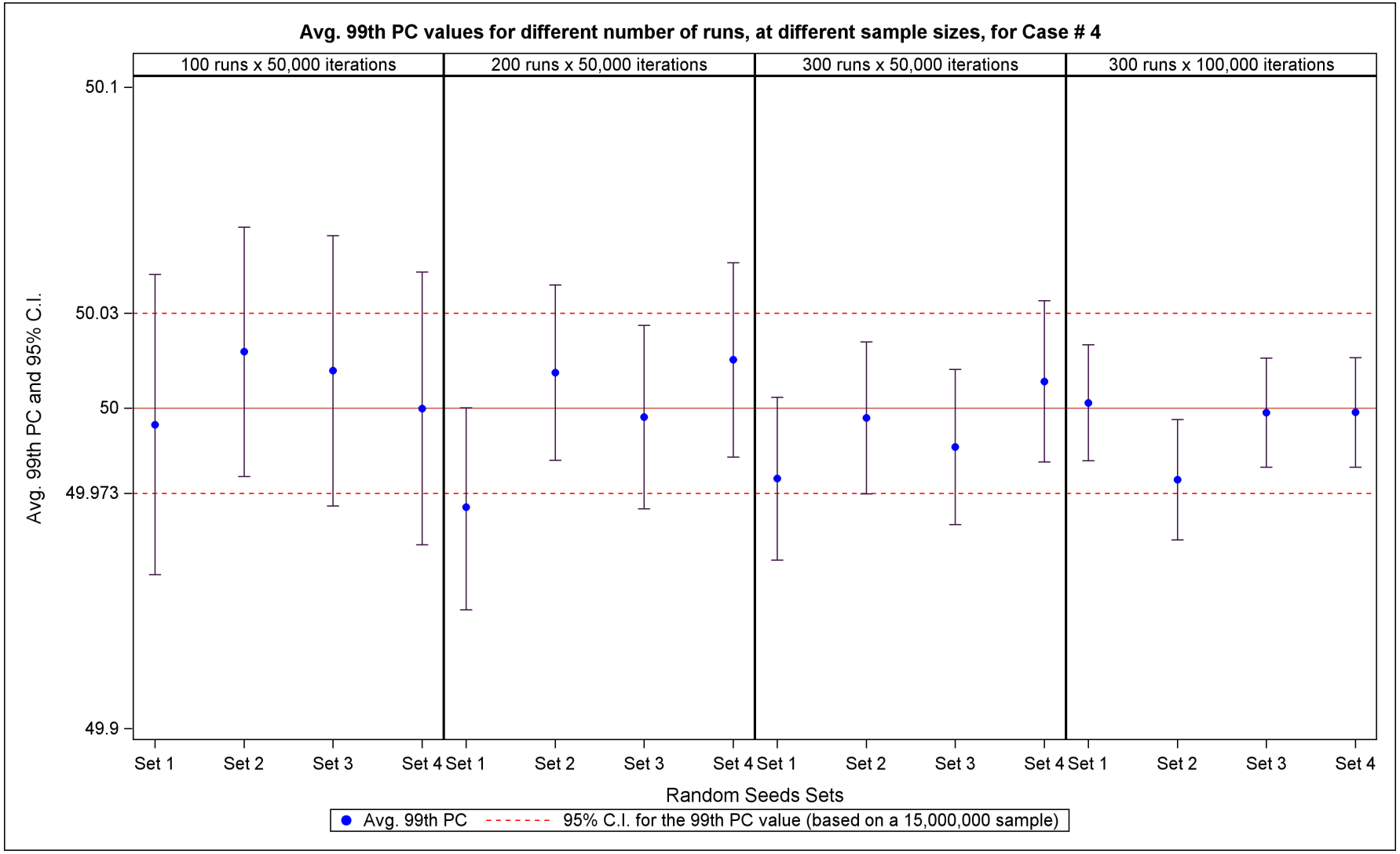


Figure 19. Avg. 99th PC values from 100, 200, 300 runs, and their 95% C.I., and the confidence limits for theoretical 99th PC value.

7.0 IREP PREDICTIVE TOOL TO MINIMIZE THE NUMBER OF ITERATIONS

In the previous section, it was shown that for the 23 tested cases with Avg. 99th PC values between 49.00% and 50.01%, the lengths of the 95% confidence intervals are smaller than 0.15 for all cases in Scenarios 2 and 3, and less than 0.10 for all cases in Scenario 4. However, in each of these scenarios, the lengths of the 95% confidence interval are sometimes much smaller than the desired precision levels, which suggests that the actual number of iterations needed might be even smaller than the fixed number of iterations used in these four scenarios, depending on factors specific to each case. Reducing the number of iterations for a case, and still being able to achieve the desired precision for the 95% confidence interval of the Avg. 99th PC values, will help with reducing the IREP running times associated with completing each case, which for Scenario 2 was around 2 hours for the case with the largest number of exposures, and for Scenario 3 was around 3 hours for the case with the largest number of exposures.

To minimize the number of iterations needed to achieve the desired precision for the length of the 95% confidence interval for the Avg. 99th PC values, a predictive tool was built into the research version of IREP Enterprise Edition. This IREP predictive tool uses an observed decreasing power function relating the length of the 95% confidence interval of the Avg. 99th PC values to the number of iterations, that was fitted based on multiple trials with different number of iterations for the tested cases. The function has an estimated exponent of -0.5. To use the IREP predictive tool, the following two steps are needed:

1) Run IREP Enterprise Edition using 300 runs with a small number of iterations (e.g., 1,000 iterations). If the precision level is not already met, the built-in tool will display a recommended number of iterations that will help to reach the desired precision level.

2) Run IREP Enterprise Edition using 300 runs and with the recommended number of iterations (or larger) to obtain Avg. 99th PC values with the desired precision for the 95% confidence interval.

Each of the 23 cases previously selected were also tested using the IREP Predictive Tool, in order to determine the minimum number of iterations needed to reach the 0.15 and the 0.10 precision criteria for each case.

Figure 20 shows a plot with the IREP-EE running times obtained for the two desired precision levels using the number of iterations determined according to the IREP Predictive Tool. The plot shows the IREP-EE (with 300 runs) times versus the number of exposures for all 23 cases with Avg. 99th PC values between 49.00% and 50.01%, and there is a clear trend for the IREP-EE running times to increase as number of exposures increase. The largest IREP-EE running time observed for the 23 cases when the precision level was 0.15 is less than 1 hour, and the largest IREP-EE running time observed when the precision level was 0.10 is around 1.75 hours.

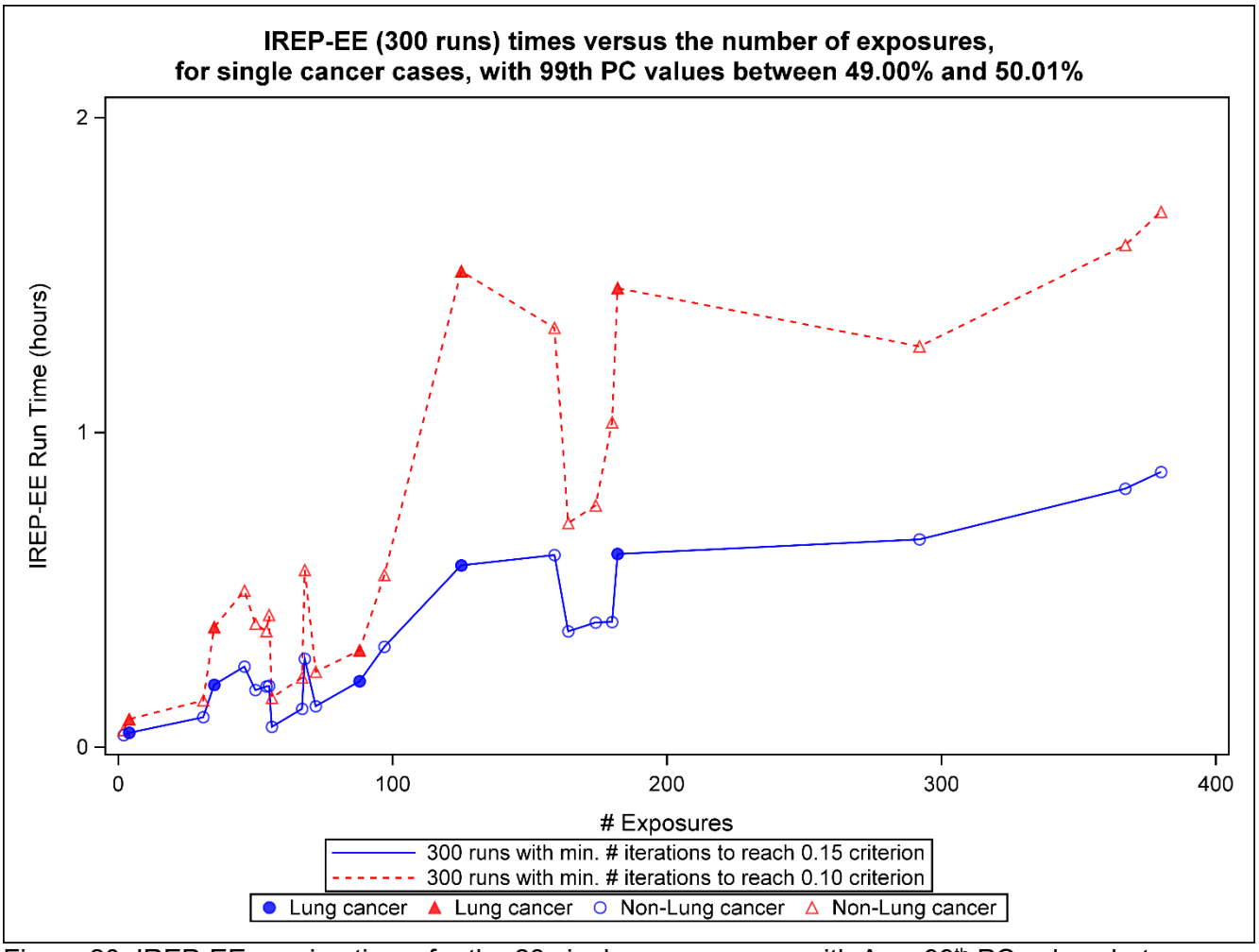


Figure 20. IREP-EE running times for the 23 single cancer cases with Avg. 99th PC values between 49.00% and 50.01%.

Figure 21 shows the minimum number of iterations needed for each case to reach the two desired precision levels. For the 0.15 precision level, the number of iterations needed for the 23 cases varies between 5,000 and 35,000 iterations, which is a much smaller number of iterations than the number of iterations used in Scenario 2, in which a fixed number of 50,000 iterations were used for all cases, and which was enough to reach the 0.15 precision level for all cases. For the 0.10 precision level, the number of iterations needed for the 23 cases varies between 15,000 and 60,000 iterations, which also represent a much smaller number of iterations than the number of iterations used in Scenario 4, in which a fixed number of 100,000 iterations were used for all cases, and which was enough to reach the 0.10 precision level.

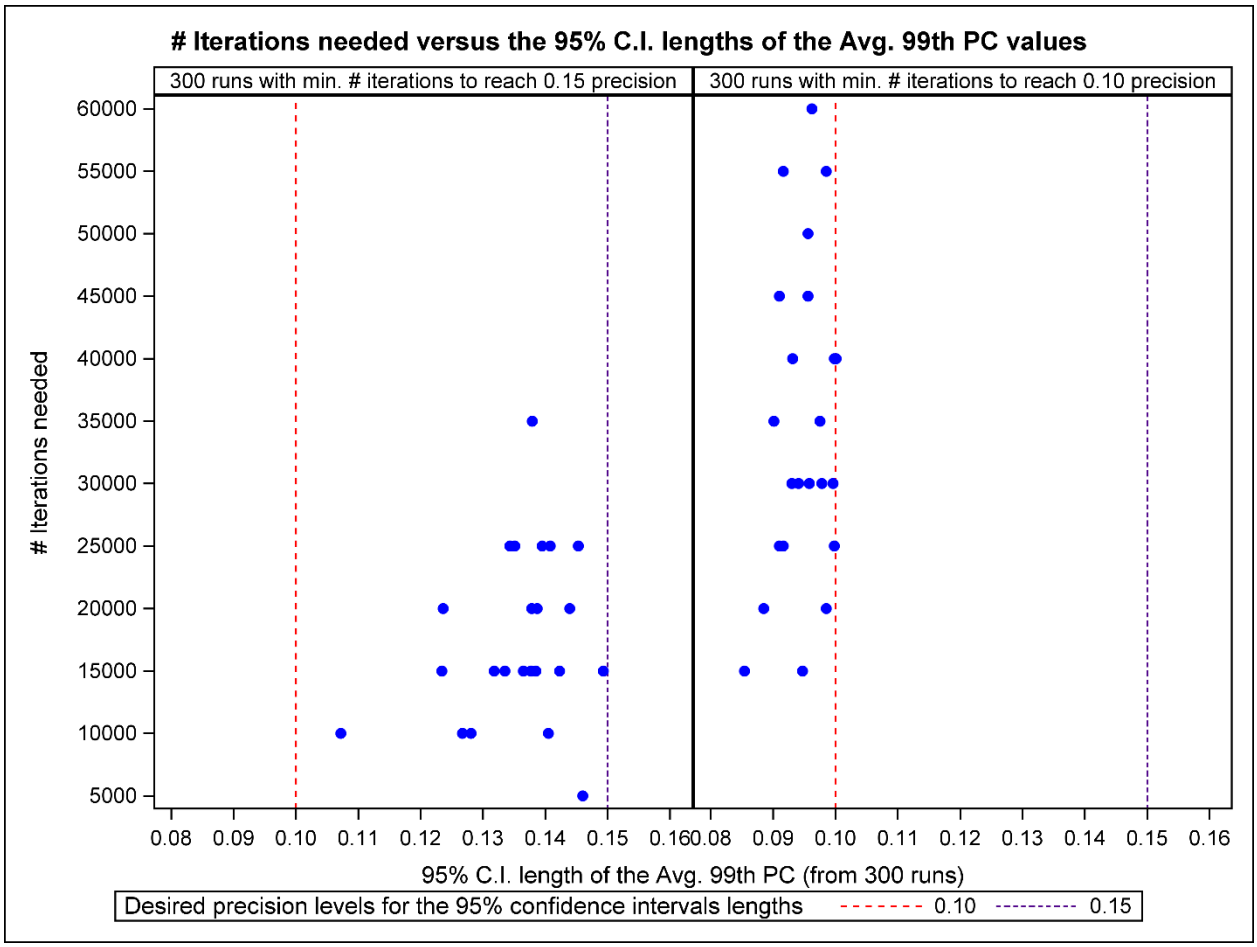


Figure 21. Minimum number of iterations necessary to reach the desired precision levels for 23 single cancer cases with 99th PC values between 49.00% and 50.01%.

The precision reached for the 95% confidence intervals of the Avg. 99th PC values, from the IREP-EE scenarios tested, and the largest IREP-EE running times obtained for the 23 tested cases are shown in Table 3. Any of these five combinations of runs and iterations can be used in practice to achieve the desired precision level for the 95% confidence intervals of the Avg. 99th PC values.

For cases with Avg. 99th PC values between 49.50% and 50.50%, one of the 5 scenarios of number of runs and iterations described in Table 3 can be used to reduce the variability of the Avg. 99th PC values that is occurring by changing the sets of random seeds, and increase the precision of the Avg. 99th PC values.

Table 3. Precision reached for the 95% confidence intervals of the Avg. 99th PC values and the largest IREP-EE runtimes obtained for the 23 tested cases.

IREP-EE Scenario	# Runs	# Iterations	Length of 95% C.I. of Avg. 99th PC	IREP-EE Runtime
Scenario 2	200	Fixed (50,000)	< 0.15	< 2.1 hours
Scenario 3	300	Fixed (50,000)	< 0.15	< 3.1 hours
Scenario 4	300	Fixed (100,000)	< 0.10	< 5.7 hours
IREP Predictive Tool	300	Variable (5,000 - 35,000)	<= 0.15	< 1 hour
IREP Predictive Tool	300	Variable (15,000 - 60,000)	<= 0.10	< 1.75 hours

For cases with multiple cancers, a slightly modified procedure to use the IREP Predictive Tool will guarantee that the Combined Avg. 99th PC value (obtained using the Multiple Primary Cancers formula in IREP) will have the desired precision for the 95% confidence interval. This procedure relies on identifying the needed number of iterations for each cancer separately and using the largest of these number of iterations for all cancers.

In conclusion, an alternative way to reduce the length of the 95% confidence intervals for the Avg. 99th PC values and also to minimize the IREP-EE running times, is to use the IREP Predictive Tool to determine the minimum the number of iterations needed to achieve the desired precision in the Avg. 99th PC values.

For the cases with PC values between 49.5% and 50.5%, one of the 5 scenarios of number of runs and iterations described in Table 3 is recommended to reduce the variability and increase the precision of the Avg. 99th PC values. By increasing the number of runs in the IREP Enterprise Edition from 30 runs to 300 runs, and by increasing the number of iterations per run, the length of the 95% confidence interval of the Avg. 99th PC values should be smaller than one of the desired precision levels of 0.15 or 0.10.

By running a case with 300 runs and 50,000 to 100,000 iterations per run, we expect that the length of the 95% confidence interval around the Avg. 99th PC values will be between 0.05 and 0.10, and this is the lowest precision that can achieved for most of the cases. So, the precision around the Avg. 99th PC values obtained in IREP-EE can be estimated somewhere between 0.05 and 0.10, if enough number of iterations are used. This indicates there is a practical limit with which the precision around the Avg. 99th PC values in IREP-EE can be estimated. A precision lower than 0.05 will be either difficult or even impossible to reach for most of the cases, since it will require an extensive running time in IREP that becomes prohibitive.

8.0 VALIDATION OF 99TH PC VALUES FROM IREP AND IREP-EE VERSIONS

As a validation exercise, comparisons between the 99th PC values obtained from the IREP version and the Avg. 99th PC values obtained from the IREP-EE version were conducted for six different cases with small number of exposures and four different scenarios with a total of 300,000, 5,000,000, 10,000,000, and 15,000,000 iterations.

That analysis showed that as the number of total iterations increases, there are no significant differences between the 99th PC values obtained from a single run with very large number of iterations in IREP versus the Avg. 99th PC values obtained from multiple runs in IREP-EE, for the same number of total iterations used.

Also, it was concluded that there is a slightly better precision in the 99th percentile of PC (smaller lengths for the 95% confidence interval in the Avg. 99th PC values obtained from IREP-EE, versus the 99th PC values obtained from IREP) for the same number of total iterations used.

The IREP-EE version also has the advantage that it can work with either 30 or 300 samples, and each of these samples can have 50,000 iterations or more, so overall the IREP-EE version can use a much larger number of total iterations than the IREP version for any case, regardless of the number of exposures.

9.0 RECOMMENDATIONS

Based on the analyses described in this report, the following new settings and operational changes are recommended starting with version v.6.0 and subsequent versions of NIOSH-IREP and NIOSH-IREP Enterprise Edition.

1. The default number of 2,000 iterations used in IREP v.5.9 should be increased to 20,000 iterations in IREP v.6.0 and subsequent versions.

2. The default number of 10,000 iterations per run used in IREP-EE v.5.9 should be increased to 20,000 iterations per run in IREP-EE v.6.0 and subsequent versions.

3. The range for the cases selected to run on the IREP-EE version will remain the same as in IREP v.5.9 version, i.e. [45.0%, 52.0%], but the determination will be based on the 99th PC value obtained in IREP v.6.0 (or subsequent versions) at 20,000 iterations.

4. Incorporate the IREP Predictive Tool into the IREP-EE v.6.0 and subsequent versions and change IREP-EE to run cases with either 30 random seeds or 300 random seeds. IREP-EE v.6.0 and future versions would feel and operate just like the IREP-EE v.5.9 version, with no discernible difference for a user.

5. The IREP Predictive Tool should be used for cases with Avg. 99th PC values obtained from the IREP-EE v.6.0 and subsequent versions in the range of [49.5%, 50.5%], to determine the minimum number of iterations required to achieve a precision of less than or equal to 0.10 around the Avg. 99th PC value. Those cases will then be rerun with 300 runs and the number of iterations suggested by the IREP Predictive Tool.

All these recommendations were adopted and implemented starting in Aug. 2024 for IREP and IREP-EE v.6.0 and subsequent versions.

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