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CALCULATION AND APPLICATION OF COVERAGE INTERVALS FOR BIOLOGICAL REFERENCE VALUES

(Technical Report)

A supplement to the approved IFCC recommendation (1987) on the theory of reference values.
[*Clin. Chim. Acta,* 1987, **165**, 111–118; *Clin. Chim. Acta*, 1987, **170**, 1–12]
[*Clin. Chim. Acta,* 1987, **170**, 13–32; *Clin. Chim. Acta*, 1987, **170**, 33–42]

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Calculation and application of coverage intervals for biological reference values (Technical Report)

A supplement to the approved IFCC recommendation (1987) on the theory of reference values [*Clin. Chim. Acta*, 1987, **165**, 111–118; *Clin. Chim. Acta*, 1987, **170**, 1–12] [*Clin. Chim. Acta*, 1987, **170**, 13–32; *Clin. Chim. Acta*, 1987, **170**, 33–42]

Summary: In an attempt to standardize the production and publication of biological reference values (e.g. of chemical substances in biological fluids) for reference populations, the International Federation of Clinical Chemistry (IFCC) has published a series of recommendations on: the concept of reference values (*Clin. Chim. Acta*, 1987, **165**, 111–118); the selection of individuals for production of reference values (*Clin. Chim. Acta*, 1987, **170**, 1–12); statistical treatment of collected reference values - Determination of reference limits (*Clin. Chim. Acta*, 1987, **170**, 13–32); and presentation of observed values related to reference values (*Clin. Chim. Acta*, 1987, **170**, 33–42). In general, the distribution of biological measurements is not Gaussian, and IFCC recommends at least 120 reference values be used for the calculation of a reference interval (denoted the 0.95 central inter-fractile interval and defined as the interval between the 0.025 and the 0.975 fractiles of the distribution). For most purposes, non-parametric intervals are recommended by IFCC. Non-parametric confidence intervals for the estimated fractiles provide some information on the precision of the fractiles (reference limits). When using 120 or more reference values, the confidence intervals for the fractiles are reasonably narrow and it is safe to consider a measurement above the upper limit of the confidence interval for the 0.975 fractile as an unusually high value.

In recent years, the International Organization for Standardization (ISO 3534–1, 1993; ISO 3534–2, 1993) and several expert scientists have advocated calculation of a coverage interval equivalent to a prediction interval. The major advantages of coverage interval are as follows. Firstly, the probability that the interval will contain a future observation can be predicted. Secondly, the uncertainty of the coverage interval is stated in statistically well-defined terms. This latter point is of great importance when a measurement result is compared with the distribution of reference values in, for instance, clinical chemistry, or occupational or environmental health.

The costs of sampling and analysis of the samples are sometimes too high to obtain 120 or more reference values as recommended by IFCC. Here, coverage intervals should be used to give a statistically well defined measure of the uncertainty of the interval. Additionally, when many reference values are available, the coverage interval may provide useful information on the distribution. Hence, extending the IFCC recommendation, the calculation and presentation of the 0.95 coverage interval is recommended here, together with information on its coverage uncertainty with a probability of at least 0.95. Non-parametric coverage intervals can be calculated regardless of the distribution of reference values, and parametric coverage intervals can be calculated if transformation of the distribution of reference values to a normal distribution is feasible. The present paper gives guidance in calculating both types of intervals. However, in agreement with IFCC, the non-parametric intervals are recommended here, thus avoiding the transformation step.

A numerical example concerning coverage intervals for blood lead concentration is presented.

ABBREVIATIONS AND SYMBOLS

$[A;B]$	coverage interval, A is the lower limit and B is the upper limit
IFCC	International Federation of Clinical Chemistry
IUPAC	International Union of Pure and Applied Chemistry

n number of reference values

m number of reference values outside a non-parametric coverage interval

m_{low} number of reference values below the lower limit of a two-sided non-parametric coverage interval

m_{up} number of reference values above the upper limit of a two-sided non-parametric coverage interval

u_p p fractile in the normal distribution

X_i reference value

Z_i reference value after transformation to normal distribution:

- μ_Z mean of the distribution of Z
- $\overline{Z}$ estimated mean of Z
- σ_Z standard deviation of distribution of Z
- s_Z estimated standard deviation of distribution of Z

β level of expectation in coverage interval

δ $\beta + \delta$ is the coverage uncertainty of the β coverage interval

γ level of confidence of the coverage uncertainty

INTRODUCTION

Major decisions, such as those pertaining to policy on environmental and occupational health about maximum acceptable chemical exposures, depend on the availability of reliable data with well defined reference intervals. Well defined reference intervals also provide the scientific basis for biomedical research in diseases related to chemical exposure. Concentrations in reference populations of various chemical substances (e.g. trace elements, metabolites of exogenous organic compounds) are increasingly needed in occupational and environmental toxicology as well as clinical chemistry. The International Federation of Clinical Chemists (IFCC) has issued 6 publications containing recommendations on the theory of reference values. The IFCC publications deals with the concept of reference values (1); the selection of individuals for production of reference values (2); the preparation of individuals and collection of specimens for the production of reference values; the control of analytical variation in the production, transfer and application of reference values; the statistical treatment of collected reference values - Determination of reference limits (3); and the presentation of observed values related to their reference values (4).

IFCC defines a 0.95 central inter-fractile interval as the interval between the 0.025 and 0.975 fractiles. The fractiles can be estimated either non-parametrically or parametrically after transformation of the reference values to the normal distribution. The non-parametric reference interval is recommended by IFCC, since this interval is independent of the type of distribution underlying the values measured (4). To provide some information on the precision of the estimated reference limits (0.025 and 0.975 fractiles), IFCC recommends the presentation of non-parametric confidence intervals for the reference limits (3).

In general, the IFCC recommendation requires that a value be measured for at least 120 individuals (3). However, sample collection or chemical analysis of substances of toxicological relevance is frequently time-consuming and costly, and it may not always be possible to obtain the recommended large number of reference values. Such a situation is found with multi-element neutron activation analysis of trace elements in human tissues (5).

Several expert scientists (6–12) have advocated the use of a coverage interval (prediction interval) where it can be stated with a given degree of confidence, that the interval contains at least a given fraction of the population of reference values. Use of the coverage interval to predict, with a defined probability, whether a *single* future observation will fall in the interval is necessary in decision making. The term '(statistical) tolerance interval' is frequently used but according to ISO 3534–1 (13), this term should not be used because it may be confused with the definition of 'tolerance interval' given in ISO 3534–2 (14), i.e. an interval with upper and lower limits of the permissible value. IUPAC agrees with the view of ISO and

recommends the use of the term coverage interval. The coverage interval may be used not only to provide a meaningful interval when few reference values are available, but also, with many reference values, to provide useful information on the precision of the estimated interval. Hence, in addition to the non-parametric 0.95 reference interval recommended by the IFCC, the 0.95 coverage interval with a stated coverage uncertainty should be given. When the number of values, on which the coverage interval is based, is small, it may not be possible to express the coverage uncertainty with a confidence of 0.95, and in this case, a confidence of 0.90 is recommended. Scheme 1 summarizes these recommendations.

Both the reference interval of IFCC and the coverage interval recommended here can be estimated either non-parametrically or, if the distribution of reference values can be transformed to a normal distribution, parametrically. In general, the parametric intervals are narrower than the non-parametric intervals, and with a sufficiently large number of reference values, the parametric intervals may be more useful. Hence, the present paper gives guidance in calculation, presentation and use of both the parametric and non-parametric intervals. Detailed information on the underlying statistical theory and mathematical model for the calculation of coverage intervals has been published previously (6). Since the theory of two-sided intervals is similar to that of one-sided intervals, this document concentrates on the theory of two-sided intervals. However, the application of one-sided intervals may be of more practical interest when only the upper limit is of toxicological interest, or when a fraction of the reference values is below the detection limit of the measurement method (15).

Distribution of reference values

Most frequently, the distribution of biological measurements is non-central (16), and presentation of both the mean and median of the reference values is needed to give some information on the skewness.

Most of the theory for parametric intervals is based on normal distribution. For non-central distributions of the values, three steps are required to establish the parametric intervals:

(1) transformation of the values to the normal distribution

(2) calculation of the limits of the interval

(3) retransformation of the limits to obtain the final interval.

A distribution of biological values often fits well with the log-normal distribution (16). It should, however, be emphasized that any type of transformation, e.g. logarithmic, exponential, power, square root, reciprocal, which leads to an approximately normal distribution may be used (3,16). The choice of transformation is dependent solely on the distribution underlying the values, and consequently, the type of transformation used should be stated. Presentation of reference values should include the results of statistical tests for normal distribution (probability, P) performed both before and after transformation (3,16). The Anderson-Darling test has been shown to be more powerful than the Kolmogorov-Smirnov test (17,18), and may therefore be preferred. A value $P > 0.05$ may be used as a rough criterion for acceptance of normal distribution.

COVERAGE INTERVAL

The coverage interval with its coverage uncertainty at a stated confidence provides direct information on the probabilities of observed values. To harmonize the presentation of the coverage interval the 0.95 expectation level and a confidence of 0.95 should be used whenever feasible. The coverage interval at an expectation of 0.95 (denoted the 0.95 coverage interval) defines the interval between the limits A and B which *on average* covers a number fraction of 0.95 of the distribution. The uncertainty of the estimated interval is expressed in terms of the coverage uncertainty (δ) at a confidence of 0.95, i.e. the probability is at least 0.95 that the coverage interval covers $(0.95 + \delta)$ of the distribution.

Using the nomenclature presented in Appendix 1 the 0.95 coverage interval $[A;B]$ with the coverage uncertainty $[0.95\text{-}\delta;0.95+\delta]$ at a confidence of 0.95 is read:

> *'The interval [A;B] will on average cover 0.95 of the distribution and the probability is at least 0.95 that the interval covers between (0.95-δ) and (0.95+δ) of the distribution'.*

Non-parametric 0.95 coverage intervals

Estimation and presentation of non-parametric coverage intervals are preferred since they are independent of the distribution of the reference values. This is particularly necessary when there are few reference values, or if the distribution of the reference values is not amenable to transformation to a normal distribution.

The following steps are used to calculate the non-parametric coverage interval:

1. Sorting of values in ascending order

This is a standard spreadsheet facility.

2. Calculation of the limits and coverage uncertainty

The limits of a coverage interval $[A;B]$ are obtained by interpolating m from the data in Table 1 at a given number of reference values n (12); m is the number of values outside the interval at the selected level of expectation (β) and confidence (γ). For example, if a one-sided interval with an upper limit is estimated, the first reference value to be outside the interval is the mth largest value. If a two-sided interval is estimated, m_{low} is the number of values below the lower limit of the interval and m_{up} is the number of values above the upper limit of the interval. The total number of values outside the interval (m) is read from Table 1, i.e.

$m = m_{low} + m_{up}$

To obtain a central position for the coverage interval, the number of values below the interval (m_{low}) should be almost equal to the number of values above the interval (m_{up}).

Table 1. Non-parametric coverage interval. Number of reference values and size of coverage uncertainty. *Minimum number of reference values (n) such that the probability is at least γ that the β-coverage interval will cover between β-δ and β+δ of the distribution. m is the number of reference values outside the coverage interval.*

0.95 coverage interval

	Confidence 0.90 (γ)		Confidence 0.95 (γ)	
Coverage uncertainty (δ)	Number of values (n)	m	Number of values (n)	m
0.01	1361	68	1889	94
0.02	343	17	471	23
0.03	146	7	210	10
0.04	84	4	111	5
0.049	47	2	71	3

0.90 coverage interval

	Confidence 0.90 (γ)		Confidence 0.95 (γ)	
Coverage uncertainty (δ)	Number of values (n)	m	Number of values (n)	m
0.02	650	65	903	90
0.03	290	29	403	40
0.04	170	17	224	22
0.05	102	10	144	14
0.06	71	7	95	9
0.07	52	5	74	7
0.08	41	4	54	5
0.09	31	3	44	4
0.099	22	2	26	2

Adapted from Kirkpatrick (12).

For a given number of values, different combinations of level of expectation (β), level of confidence (γ) and coverage uncertainty (δ) are read from Table 1. Consider $n = 50$ as an example. Table 1 provides the following combinations:

$\beta = 0.95$; $\gamma = 0.90$; $\delta = 0.049$; $m = 2$ ($n = 47$)

$\beta = 0.90$; $\gamma = 0.95$; $\delta = 0.08$; $m = 5$ ($n = 54$)
$\beta = 0.90$; $\gamma = 0.90$; $\delta = 0.07$; $m = 5$ ($n = 52$)

In the first combination, the total number of values outside the coverage interval (m) is 2. Hence m_{low} is the lowest value and m_{up} is the highest value. The lower limit of the coverage interval is the value with the second lowest value (m_{low} being outside and below), and the upper limit is the second highest value (m_{up} is outside and above). This coverage interval will *on average* cover 0.95 of the distribution, and the interval covers between 0.901–0.999 of the distribution with a probability of at least 0.90.

In the numerical example given later (Table 4), agreement is good with many values, between the limits of the non-parametric 0.95 coverage interval and the limits of the non-parametric 0.95 reference interval recommended by IFCC (3). At n = 50, agreement is not so good. According to IFCC, the position of the reference limits should be calculated in the following manner:
Position of lower limit: $0.025(n + 1)$ Position of upper limit: $0.975(n + 1)$

If the estimated position of a limit is an integer, this value is equal to the reference limit. If the position is not an integer, the reference limit is estimated by interpolation between two values.

With few values, interpolation may be more accurate than using Table 1 to estimate the limits. However, Table 1 should still be used to estimate the coverage uncertainty.

The 0.95 parametric coverage intervals

If there are more reference values ($n > 50$) and if the distribution can be transformed to the normal distribution, a parametric coverage interval can be estimated with the following steps (see Appendix 1):

1. Transformation to normal distribution

Using, for instance, logarithmic transformation of data, the transformed data element will here after be denoted Z_i, and, similarly, $\bar{Z}$ and s_Z will denote the estimated mean and standard deviation of the transformed data.

2. Calculation of the limits

A two-sided coverage interval $[A;B]$ is given by Equation 1. Equation 1 is used for the calculation of the upper and lower limits of the coverage interval for the normal distributed, transformed reference values Z_i.

$$[A;B] = [\bar{Z} - k\,s_Z; \bar{Z} + k\,s_Z] \quad (1)$$

where A and B denote the lower and upper limit of the interval. According to Odeh et al. (9) the constant k is a function of n and the expectation β. At an expectation of 0.95 k is given by Equation 2:

$$k = (1 + 1/n)^{1/2}\, t(n-1)_{0.975} \quad (2)$$

where $t(n-1)_{0.975}$ is obtained from a table of the t distribution at $(n-1)$ degrees of freedom. Table 2 lists some relevant values for the t distribution; $t(n-1)_{0.975}$ is used in the estimation of two-sided coverage intervals with an expectation of 0.95 whereas $t(n-1)_{0.95}$ is used in estimation of one-sided 0.95 coverage intervals.

Table 2. Fractiles in the t distribution at probability 0.975. $t_{1-p} = -t_p$.

Degree of freedom (n–1)	t-value	Degree of freedom (n–1)	t-value
10	2.228	60	2.000
15	2.131	80	1.990
20	2.086	100	1.984
25	2.060	200	1.972
30	2.042	500	1.965
40	2.021	∞	1.960
50	2.009		

3. Retransformation of the limits

The coverage interval for the distribution of reference values is obtained by retransformation of the limits. For a logarithmic transformation, the retransformation of the limits is obtained simply by calculating the anti-logarithm of the limits.

4. Calculation of the coverage uncertainty (0.95 + δ)

To harmonize the presentation of coverage intervals, expectation level should be 0.95 and confidence 0.95. Table 3 lists some relevant coverage uncertainty values (δ). Table 3 contains two alternative levels of expectation (β), i.e. 0.90 and 0.95. At each level of expectation, Table 3 lists the coverage uncertainty (δ) at the recommended confidence 0.95. Oden et al. (9) have published more exhaustive tables on coverage uncertainty including different levels of expectation and confidence.

Table 3. Parametric coverage interval. Number of reference values and size of coverage uncertainty. *Minimum number of reference values (n) such that the probability is at least 0.95 that the β-coverage interval will cover between β-δ and β+δ.*

Expectation 0.90 (β)		Expectation 0.95 (β)	
Coverage uncertainty (δ)	Number of values (n)	Coverage uncertainty (δ)	Number of values (n)
0.0950	26	0.0450	50
0.0900	28	0.0400	62
0.0800	35	0.0300	110
0.0700	45	0.0250	159
0.0600	61	0.0200	250
0.0500	88	0.0150	445
0.0400	138	0.0100	1006
0.0300	245	0.0090	1242
0.0250	353	0.0080	1573
0.0200	552	0.0070	2055
0.0150	982	0.0060	2799
0.0100	2211	0.0050	4030
0.0090	2729		
0.0080	3454		
0.0070	4512		

Adapted from Odeh *et al.* (9).

At an expectation level of 0.95 and a confidence of 0.95, δ can be read for n > 50. Hence, for n > 50, the estimated 0.95 coverage interval (Equation 1) will contain [(0.95-δ);(0.95+δ)] of the distribution with a probability of at least 0.95.

The coverage uncertainty is independent of the standard deviation of the distribution, but the value of δ is dependent on the level of expectation (β), the level of confidence (γ), and the number of reference values (n), i.e. the coverage uncertainty becomes progressively larger as the number of values decreases. If the number of values is less than 50, Table 3 can be used to give coverage uncertainties (β+δ) at a lower level of expectation (β = 0.90), but estimation of non-parametric coverage intervals is then preferred.

NUMERICAL EXAMPLES

To evaluate the substance concentration of Pb^{II} in blood from a population of Danish men, age 47–51 years, a reference population of 437 individuals was selected. For each man the concentration of lead in a sample of blood was measured by atomic absorption spectrometry with Zeeman background correction and an uncertainty of measurement equal to 68 nmol/L at a confidence of 0.95 (19). A sample of 50 was selected to demonstrate the effect of sample size on the calculated intervals. Appendix 1 contains an example of the calculations.

Table 4 presents the information on the reference values and intervals in accordance with the recommendations outlined in Scheme 1.

Table 4: Numerical examples—lead in blood

Number of observations (n)	437	50
Distribution of reference values:		
Mean	392	401
Median	370	337
Test for normal distribution:		
Anderson-Darling's test for normal distribution. P	0.000	0.000
Method of transformation	Logarithmic	Logarithmic
Anderson-Darling's test for normal distribution after transformation. P	0.1283	0.6022
Intervals - IFCC recommendation:		
Non-parametric 0.95 reference interval	[160;810] nmol/L	[138;880] nmol/L
Parametric 0.95 reference interval	[174;772] nmol/L	[146;893] nmol/L
Intervals-IUPAC recommendation:		
Non-parametric 0.95 coverage interval	[160;810] nmol/L	[145;845] nmol/L
coverage uncertainty at confidence 0.95	0.95 + 0.021	0.95 + 0.049
Parametric 0.95 coverage interval	[173;774] nmol/L	[142;923] nmol/L
Coverage uncertainty at confidence 0.95	0.95 + 0.015	0.95 + 0.045

Distribution of reference values

In both examples, the mean value was higher than the median value indicating a non-central distribution with an extended right tail. Before transformation, the Anderson-Darling test revealed that both distributions (n = 437 and n = 50) deviated significantly from the normal distribution. After Logarithmic transformation, the Anderson-Darling test showed that the distributions no longer deviated significantly from normal distributions ($P > 0.05$).

Reference intervals and coverage intervals

Looking at the intervals recommended by IFCC, the non-parametric 0.95 reference interval with 437 reference values was broader than the corresponding parametric 0.95 reference interval. Similarly, the non-parametric 0.95 coverage interval recommended here by IUPAC was broader than the corresponding parametric 0.95 coverage interval.

With 437 values, the limits of the parametric 0.95 coverage interval are in reasonably good agreement with the limits of the IFCC parametric 0.95 reference interval. The small coverage uncertainty indicates a high precision in the estimate of the limits of the coverage interval. In contrast, with only 50 values, the large coverage uncertainty demonstrates the low precision in the estimate of the limits of the coverage interval.

The limits of the non-parametric coverage intervals are obtained by interpolation in Table 1. At n = 50 this gives only a rough estimate of the position of the limits, and the interpolation method used in estimating the limits of the non-parametric reference interval of IFCC may be more accurate. In general, as demonstrated by the two examples presented, the coverage uncertainty of the non-parametric coverage intervals is larger than that of the parametric coverage intervals.

Practical use of the coverage interval

Coverage interval provides useful information on the reference distribution. Hence, a comparison of limiting values for health risk from toxic substances (i.e. the values above which long-term exposure is believed to give adverse health effects) with the position of the coverage interval for healthy individuals may be useful when deciding whether there is a health risk for the general population.

The EU directive on lead specifies that occupational and environmental exposure limits be set for concentrations of lead in blood (Blood Pb) (20). In Denmark, this directive has resulted in occupational exposure limits, which in accordance with the 1993–94 suggestion of ACGIH (21), will be lowered to 965

nmol/L (20 μg/(100 mL)). With n = 437, there is a probability of at least 0.95 that the calculated 0.95 parametric coverage interval from 168 to 777 nmol/L covers between 0.935 and 0.965 of the population. Hence, there is a high certainty that the occupational exposure limit of 965 nmol/l represents an unusually high value. The same conclusion can be drawn from the reference interval estimated by the IFCC method. The parametric coverage interval of 0.95 based on a smaller sample of only 50 values (from 173 to 774 nmol/L) is broader, and the coverage uncertainty is large (between 0.905 and 0.995). Interpretation of this coverage interval means that a number fraction up to 0.095 of the population may be outside the interval, perhaps as high as the occupational exposure limit. With so few values, the IFCC parametric reference interval (from 146 to 893 nmol/L) may give a false impression that the population is well below the occupational exposure limit.

In clinical and occupational medicine, it is fairly safe to assume a 0.95 coverage interval with a confidence of 0.95 as a prediction interval (6,9,10), i.e. the probability of a future observation from the distribution being included in the interval is equal to the expectation. Consequently, an observation outside the coverage interval can then be considered unusually high (or low), and a further scrutiny of the person is needed to establish whether he or she is at increased health risk. The coverage uncertainty then gives an estimate of the reliability of the coverage interval, i.e. if the coverage uncertainty is low, the coverage interval will be reliable in practice.

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APPENDIX 1: CALCULATION OF PARAMETRIC REFERENCE INTERVALS AND COVERAGE INTERVALS

Principles

To simplify the presentation of principles, the transformed reference values Z_i of the substance are taken to belong to a normal distribution, having the mean value μ_Z and a standard deviation σ_Z, i.e.:

$Z_i \in N(\mu_Z, \sigma_Z)$

When a parametric reference interval (IFCC) or a parametric coverage interval (IUPAC) is to be calculated, estimates of the mean ($\overline{Z}$) and the standard deviation (s_Z) are obtained from a number of n reference values drawn randomly from the normal distribution. New values of $\overline{Z}$ and s_Z will appear each time a new series of reference values is drawn from the normal distribution, and the values of $\overline{Z}$ and s_Z will deviate randomly from μ_Z and σ_Z, respectively. However, *on average*, $\overline{Z} = \mu_Z$ and $s_Z = \sigma_Z$.

The parametric 0.95 reference interval (IFCC)
When n is a sufficiently high number ($n > 120$), the reference limits of the 0.95 reference interval (0.025 and 0.975 fractiles) are calculated using the approximations:

$f_{0.975} = \overline{Z} + u_{0.975}\, s_Z$

$f_{0.025} = \overline{Z} + u_{0.025}\, s_Z$

Since $u_{0.025} = - u_{0.975}$ the 0.95 reference interval is

$[\overline{Z} - u_{0.975}\, s_Z,\ \overline{Z} + u_{0.975}\, s_Z]_{0.95}$

The parametric 0.95 coverage interval (IUPAC)
A two sided 0.95 coverage interval $[A;B]$ is given by:

$[A;B] = [\overline{Z} - k\, s_Z,\ \overline{Z} + k\, s_Z]$, where

$k = (1 + 1/n)^{½}\, t(n-1)_{0.975}$

With increasing n, the constant k decreases and becomes approximately equal to $u_{0.975}$. Hence, at high number of reference values, the limits of the parametric 0.95 coverage interval (IUPAC) will be equal to the limits of the parametric 0.95 reference interval (IFCC). An excellent agreement between the two methods of calculation exists for $n > 80$. However, at low values of n the calculations according to the IFCC recommendation tend to produce narrow confidence intervals, indicating that the employed approximation may no longer be valid.

Numerical example on the calculation of a 0.95 coverage interval—Lead in blood

Number of observations (n): 437

Non-parametric 0.95 coverage interval:
Interpolation in Table 1 ($\beta = 0.95$; $\gamma = 0.95$) between 210 and 471 reference values: $m = 21$

Hence $m_{low} = 11$ and $m_{up} = 10$, i.e., the lower limit of the coverage interval is the 12th lowest reference value and the upper limit of the coverage interval is the 11th highest reference value. Thus, the 0.95 coverage interval for Pb^{II} in blood is [160;810] nmol/L.

The coverage uncertainty is also interpolated in Table 1: $\delta = 0.021$

Hence the coverage interval will cover (0.95 + 0.021) of the distribution with a confidence of at least 0.95.

Parametric 0.95 coverage interval:
Estimated arithmetic mean value ($\bar{Z}$) of logarithmic transformed data: 5.903

Estimated standard deviation (s_Z) of logarithmic transformed data: 0.3808

Equation 2: $k = (1 + 1/437)^{1/2}\, t(436)_{0.975} = 1.967$

Equation 1: The 0.95 coverage interval including retransformation of the limits:
Exp[5.903 + 1.967 (0.3808)] = [173; 774] nmol/L of Pb^{II} in blood.
The coverage uncertainty:
Using Table 3: $\delta = 0.015$.
Coverage uncertainty = 0.95 + 0.015

SCHEME 1. RECOMMENDATION ON THE PRESENTATION OF REFERENCE VALUES AND INTERVALS

1. Number of reference values

2. Distribution of reference values

Mean
Median
Test for normal distribution:
  Type and result of test (probability, P).
  Accept Gaussian distribution $P > 0.05$.
If the distribution deviates significant from Gaussian ($P < 0.05$):
  Method of transformation
  Result of test for normal distribution after transformation (P)

3. Intervals—IFCC recommendation*

At $n \geq 120$:
Non-parametric 0.95 reference interval (between the 0.025 and the 0.975 fractiles)

4. Intervals—IUPAC recommendation†

Non-parametric 0.95 coverage interval with coverage uncertainty at confidence 0.95.

*Solberg (3) and Dybkær & Solberg (4)
†The present paper.