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STUDY OF "LAW OF PROPAGATION OF UNCERTAINTY" ON THE ISO-GUM APPLICATION TO THE BLOOD CHEMICAL ANALYSIS

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Abstract – Generally, analysis of variance (ANOVA) has been using for the data analysis of the measured value. On the other hand, J.W. Tukey had studied the exploratory data analysis (EDA)[1] in 1977. Therefore, the ISO (International organization for standardization) made the ISO-GUM (Guide to the expression of Uncertainty) that is a guidebook adopted EDA in 1993. In the ISO-GUM, the dispersion of data is evaluated as the uncertainty with the error. In the medical field, ISO-GUM was also taken up it. Nowadays, the improvement of accuracy of the measurement data on the blood chemical material analysis (BCA) is done by WHO standard based on ANOVA. ANOVA is said as the classical data analysis as well (CDA).

The purpose of this study is to make the improvement of the accuracy in the quality control (QC) of the measured value and to make an accuracy assurance. So, it was verified how it was different when ISO-GUM rule and WHO standard were applied to BCA.

Keywords: EDA. ISO-GUM, uncertainty

1. BASIC INFROMATION

ISO-GUM can be adapted to the immunity response about using BCA.

In the BCA, A calibration curve by the check standard is necessary for the quantitative analysis. A calibration curve makes by more than one test reagents for calibrating. A test reagent is the calibrator.

Therefore, this study is confirmed that ISO -GUM was useful for the setting of working reference. In the purpose of this study, to be more important is to search a problem of uncertainty, For example, it is detection of the new error factor and the improvement of accuracy, and it is link to the improvement of accuracy for measured data.

In the BCA, The object of this study is the accuracy improvement of the calibrators for check reference. The multi calibrators are estimated by principal assigned value for check point. The accuracy of calibrator is very important as an intermediate accuracy in the measurement system.

An official approval test is used to on the 2 ways design nest method due to the repetition for computation of repeatability, and it is estimated on levrl-2 standard deviation (SD).

In the therapy of medical clinical, the data of uncertainty will be comes the result which delays medical treatment by hesitating the distinction of the diagnosis. In the delay of the clinical treatment, the waste of medical resource is made to arise, and then the clinical cost is increasing about it.

This paper is reported when ISO-GUM rule applied for BCA and the difference when WHO standard applied

A difference in ANOVA and EDA is shown in the table 1.[1].

Table.1	EDA(ISO-GUM)	CDA(classical data analysis)
Model	Suggest admissible model	impose model (ANOVA)
Distribution	abnormal distribution	normal or pseudo normal
Techniques.	general graphic	general quantitative in statistics
Focus	on data	on model
Rigor	subjective and interpretation	probabilistic function
Data treatment	all of available data	underlying assumption
Evaluation	uncertainty (noise/signal)	error (bias and dispersion)

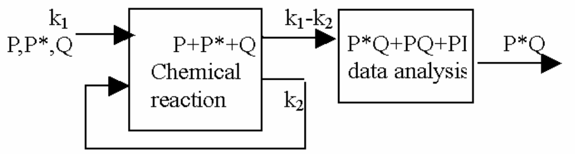
2. MEASUREMENT THEORY OF BCA

The test reagent of the radioimmunoassy (RIA) in BCA was used for this experiment. As for the immunology reaction, a chemical reaction follows "the law of action mass" in the base of the same configuration about measurement.

The RIA has used for marker of measurement with radioactive substance of I-125.

The reaction modeling is shown the model of the immunology reaction in the Fig.1. As for the sign in the Fig 1 and (1), Q is antibody, P is antigen, P* is labeled antigen, PQ is reaction compounds, P*Q is a reaction compound with P* and PI is an abnormal reaction compound. In the "the law of action mass", Total quantity of antigen P_0= P*Q+ PQ + PI is always constant.

The quantity of reaction compound is estimated by the calibration function (calibration curve) that is converted into the computation dose from the affinity coefficient. A calibration curve is made of multi calibrators what were prepared in multi dose values of test reagents. The concentrations of calibrators are the principal assigned dose values as well.



$$P+P^{*}+Q \underset{k_2}{\overset{k_1}{\rightleftarrows}} P^{*}Q+PQ+PI \quad (1)$$

k_1: association constant
k_2: disassociation constant
k: affinity((P*Q /P*+Q)

Fig.1. Chemical reaction model of immunoassay

3. METHOD

The design of experiments (DOE) is planned on QC of a 6 sigma and level-2 SD. In the ISO GUM, a procedure of uncertainty analysis is classified the type A evaluation and the type B evaluation.

In the type A and the type B, the traceability, the transferability and the comparability used to the technology of uncertainty analysis. The " Law of propagation uncertainty " is carried out on the total process of uncertainty analysis. (See Fig. 7)

In the type A evaluations, impose model is made only the normal frequency distribution. Then a distribution is analyzed by fundamental statistics method that is standard deviation (SD), variance, skewness and Kurtosis. If it is abnormal frequency distribution, that is analyzed by other methods by the type B evaluations. Then it is suggest admissible model. The technology of other method is used as nonparametric (or softcomputing). The latent uncertainty factor is extracted by the analysis of the abnormal frequency distribution. And result of analysis is useful to setting of reference for calibration curve.

The accuracy improvement of the calibration curve is done about the accuracy of the regression analysis. In the uncertainty analysis, after it guesses the model form of the measurement data, a distribution is analyzed with ISO-GUM (EDA) for quantity basic statistic evaluations.

The calibrator used for the experiment is the reagent of Elastese-1 of RIA. The Elastese-1 is one of the pancreas hormones, and RIA is being general used for the routine daily test.

4. RESULT OF EXPERIMENT

In the Fig.2 (a)-(f) series, the six figures of frequency distribution are made to Pareto charts that are data of six kind doses. The bar graph (A) is indicative of a measured data, and the line graph (B) is indicative of a calculated data. All of bar graph shows an abnormal distribution. A line graph was calculating from measured data by regression analysis. Then, a regression analysis is made to pseudo-normal distribution from the abnormal distribution according to the WHO standard.

Table.2 is listed nine quantities of basic statistics for selection of a working reference value. Reference value is used as working true value for check standard. The quantity of basic statistics evaluation was calculated by the measured value. In the table 2, chaos and fuzzy data are contained with marking of * a sign,.

Therefore four calculation values (a mean value, RSS value peak value and fuzzy theory) in the table 2 are validated as a working reference value, because it was the about same value. The working reference value of the test reagents for calibration can be use to the intermediate reference value in the total measurement systems or the second standard value intra laboratory.

The table 3 shows the difference between in statistics value of the measured data (A) and the calculated data (B). Fig.3 (a) - (d) series show four main results by the line graph by the table 3. Fig.3 (a) is shown a stewness. Fig.3 (b) is shown a kurtosis. Fig.3 (c) is shown a variance. Fig.3 (4) is a SD. In the Fig.3, though a calculated graph (B) is improved than to compared with measured value (A), but still dispersion in data are large, because, dispersion of SD detected from in higher dose value area (same as in the low affinity area) than in lower dose value on the graphs. Fig.2 and Fig.3 are made as new result in this study series.

The illustration of “law of propagation on uncertainty” is interpreted for a process of uncertainty analysis in the Fig.7. The process has nine steps, and included already reported the data of results in this study series.

In the Fig.4, a scatter chart of time series data of Elastese-1 0 value is shown a made of measured data [3]. SD of between day variability during the deposit is shown in Fig.5 that is made of data by Fig.4. An analysis of time series data is useful technology of applied tracerbility [3] (see sixth step in Fig.7).

In the Fig.6, data of applied comparability is shown an interaction on calibration curves in eighth step of Fig.7 [4]. Accuracy assurance is estimated by coverage factor in ninth step of Fig.7. In the ISO, coverage factor is recommended to use 2 [6]. Fig.4-Fig.6 series had been already reported at last time [5]. All of the data are very important for setting of working reference value.

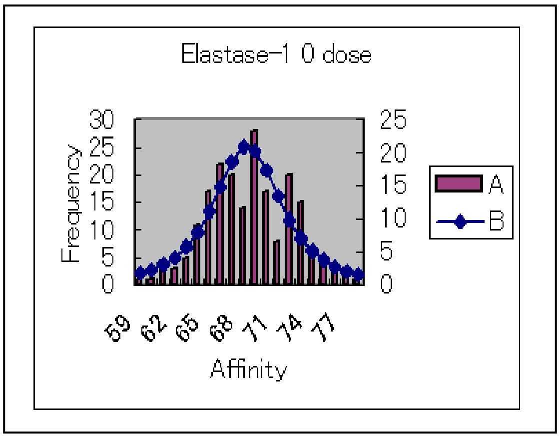


Fig.2(a) Elastase-1 0 d0se Frequency curve

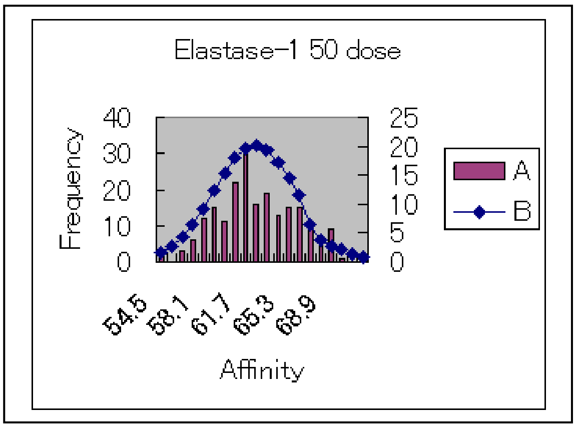


Fig.2(b) Elastase-1 50 d0se Frequency curve

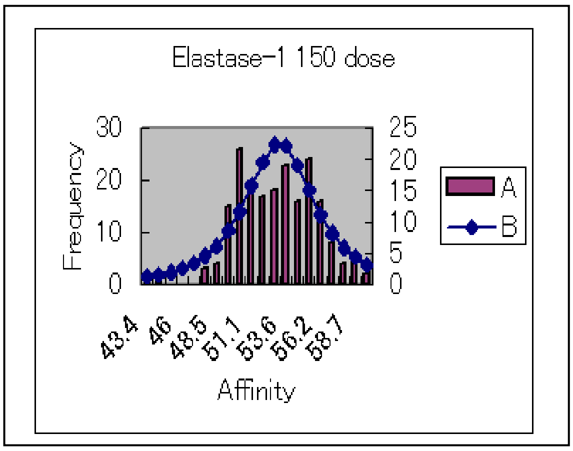


Fig2(c) Elastase-1 150 dose Frequency curve

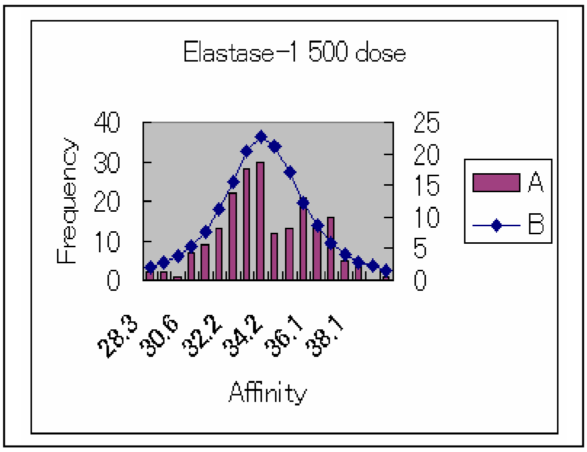


Fig.2(d) Elastase-1 500 dose Frequency curve

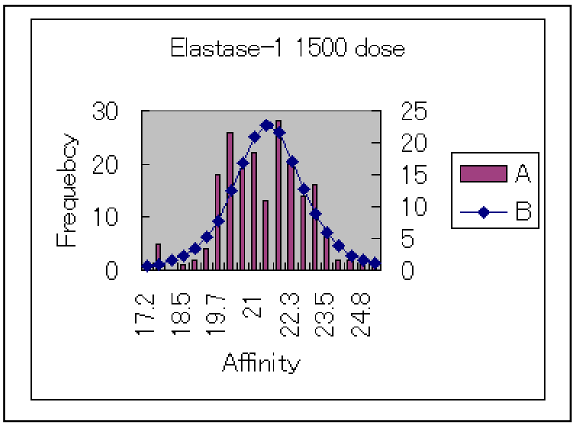


Fig2(e) Elastase-1 1500 dose Frequency curve

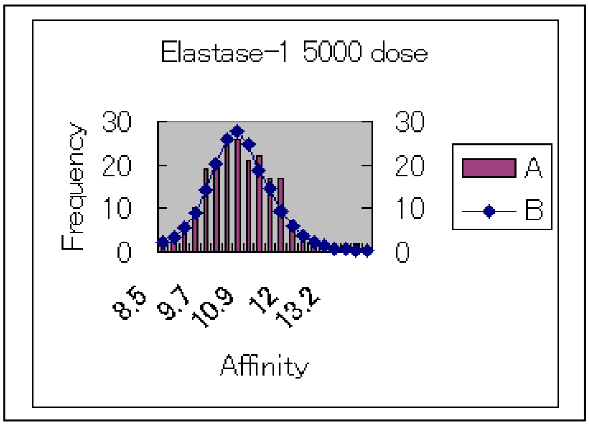


Fig.2(f) Elastase-1 5000 dose Frequency curve

Table.2 Calculation value

Dose	0 dose	50 dose	150 dose	500 dose	1500 dose	5000 dose
Mean	68.31	61.90	52.20	34.70	20.80	10.57
RMS	68.27	61.95	52.09	34.69	20.68	10.38
Fuzzy*	68.35	61.85	52.09	34.72	20.68	10.41
Median	68.25	61.7	52.1	34.93	20.6	10.4
Curve peak	68.31	62.2	53.14	34.93	21.7	10.57
Mode	70.3	62	50.2	35.1	21.7	9.8
Chaos*	71.4	65.4	54.3	37.4	23.2	17.1
Maximum	78.2	71.8	60.0	43.1	28.9	17.1
Minimum	46.7	41.1	34.4	21.7	12.4	6.9

Table.3 Calibration value

Dose position	0 dose 1	50 dose 2	150 dose 3	500 dose 4	1500 dose 5	5000 dose 6
Correlation	0.854	0.885	0.858	0.854	0.853	0.965
Kurtosis A B	-0.880 -0.995	-0.451 62.2	-1.434 -1.029	-0.316 -0.741	-1.229 -0.934	-1581 -1.806
Skewness A B	0.588 0.68	0.259 0.688	0.367 0.632	0.819 0.824	0.522 0.741	0.438 0.795
Variance A B	70.306 44.412	67.924 49.879	82.2 52.217	87.674 52.572	90.029 58.051	90.621 88.749
Residual	27.58	28.18	21.95	31.05	34.95	8.585
95% Coefficient of determination	27 19.25	31 19.42	26 21.15	30 21.46	28 22.1	26 27.54
Coefficient of determination	0.963	0.892	0.921	0.828	0.964	0.971
Probability P<	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Standard A deviation B	8.385 6.663	8.241 7.063	9.066 7.226	9.363 7.251	9.488 7.678	9.519 9.421
Standard A error B	1.875 1.490	1.843 1.579	2.027 1.616	2.094 1.622	2.122 1.717	2.129 2.107
Frequency peak A B	28 20.4	31 18.13	26 22.58	30 22.63	28 22.8	26 27.87

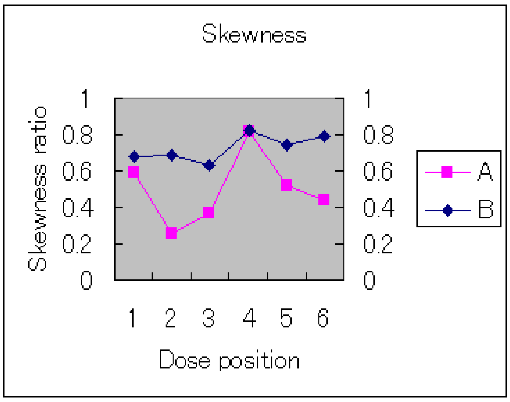


Fig.3(a) Skewness

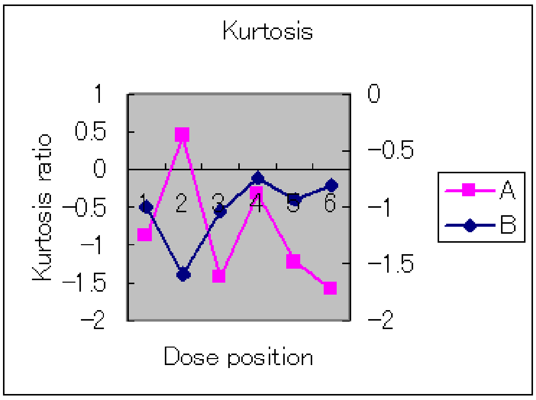


Fig.3(b) Kurtosis

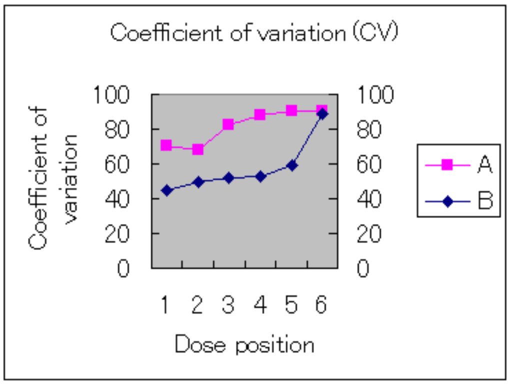


Fig.3 (c) Variance

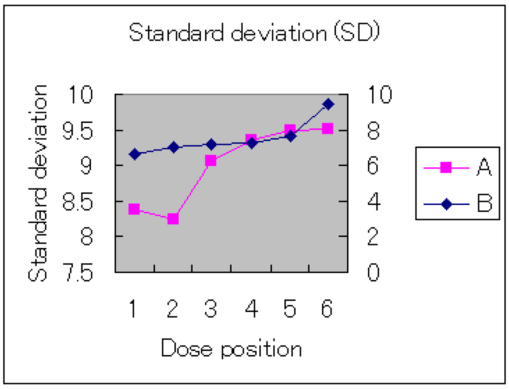


Fig.3(d) Standard deviation

5. CONCLUSION

1. The working reference value of the routine test level in the intra-laboratory can establish even a present WHO standard only in the special time period. Because the daily repeatability is influenced by a deposit period of variance.[3]

2. "Law of propagation the uncertainty" (see Fig.7) is important because the process of technology was useful for the decision of accuracy assurance on the working reference value [2].

3. A special time period is needed to select for using of test reagent, because dispersion in data

is changing a period of the deposit days. ISO-GUN shall be making a change of time series data such as in between day variability. By comparison, WHO standard has regulated only a manufacture official assay day and unregulated after shipping.

4. An official approval by EDA must be regulated on all of dose areas of the calibrating reagent value. In the WHO standard, it is only about quartile point check (25th, 50th, 75th percentiles), and 25th percentile under of affinity (same as high dose areas in the Table.2) become the outside of the regulation, and this problem is big poor [5.]
5. WHO standard is taken as the satisfactory correlation factor that data is all right. If there is detected an interaction with ISO-GUM rule, it comes defective to handle. Particularly when medical activities are done an important influence in the systematically intersection action of surveillance exerts. Therefore, it has a problem in the accuracy guarantee between the laboratories.
6. In the evaluation of SD [4]. Dispersion of data was still stay as the random error-ability. because ISO-GUM (EDA) and WHO (CDA) are evaluated on SD. Random error is unfavorable for patient of personal data.

These random errors are the factor that becomes disadvantageous at the start time of IT in the medical data. Then, more study is necessary for the evaluation of the random error.

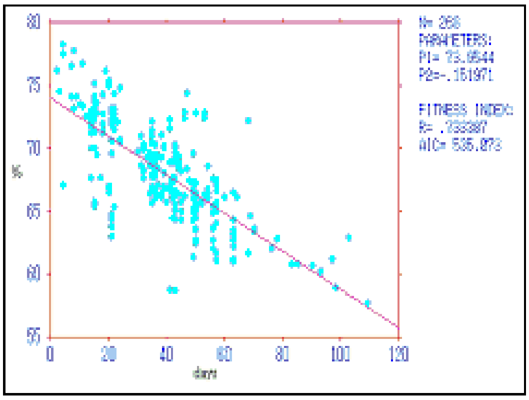


Fig.4 time series data of days variance

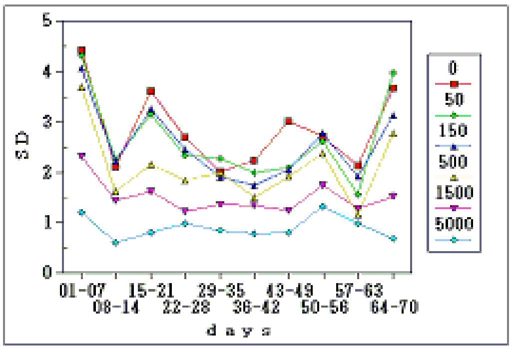


Fig.5 SD of day variance during the deposit

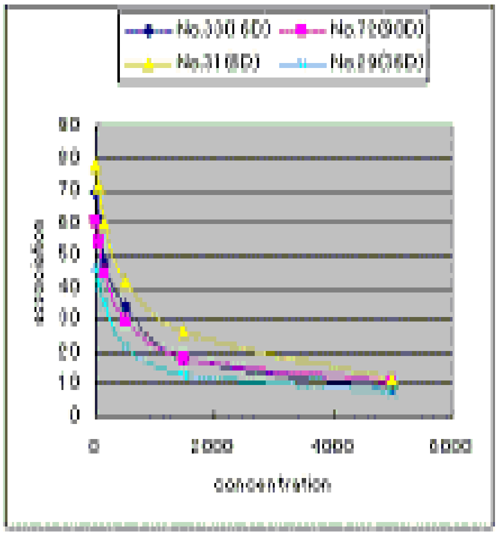


Fig 6 interaction between bi-calibration curve

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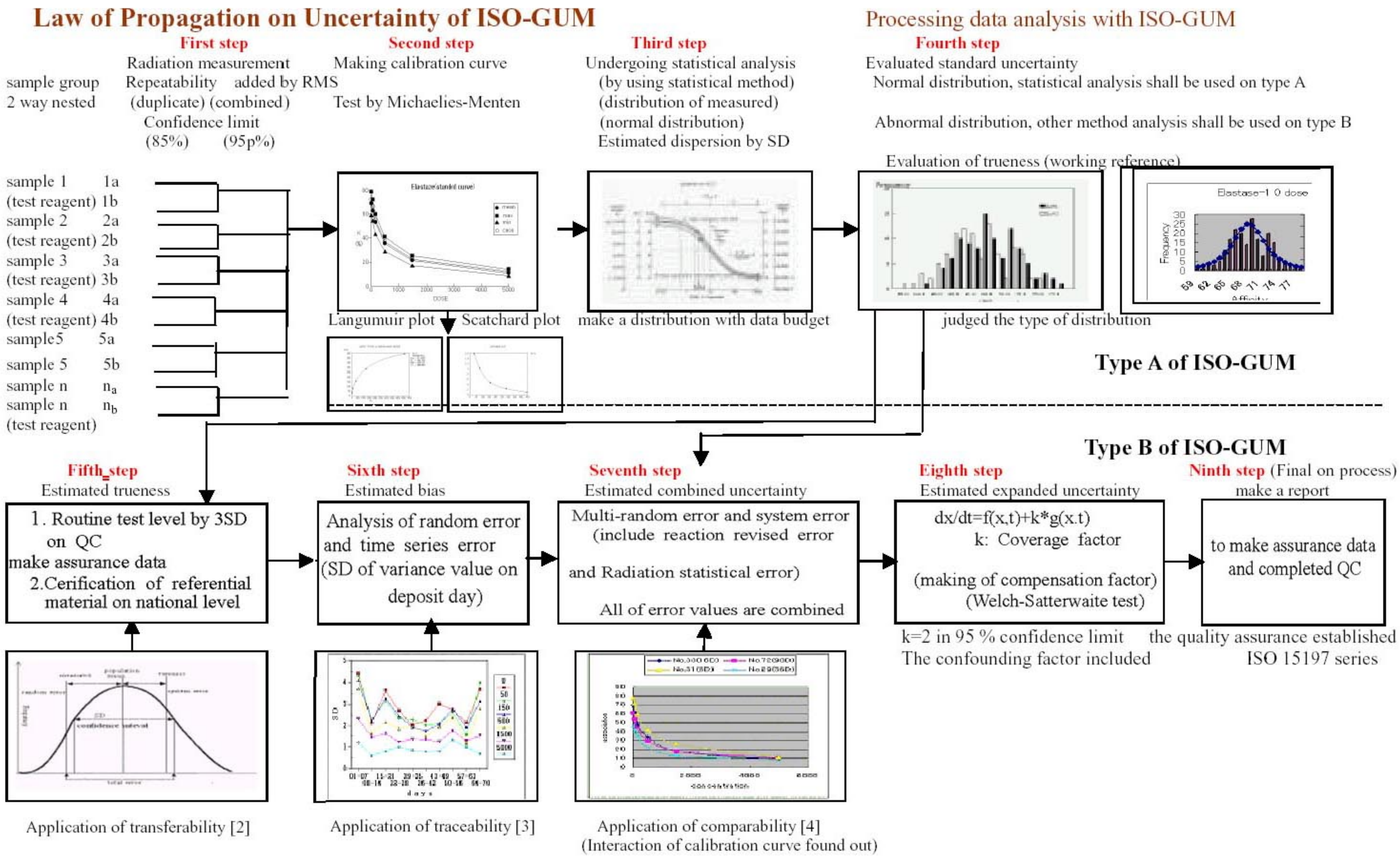

Fig.7 Interpretation of "Law of Propagation on Uncertainty" for BCA [6]