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DATA MINING OF UNCERTAINTY DATA IN THE BLOOD CHEMICAL ANALYSIS FOR QC

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Abstract - This study is mining the error factors in the uncertainty measurement data. The purpose is to be advanced the accuracy control for QC (Quality control) of BCA (Blood Chemical Analysis). BCA is often taken as uncertainty data [1]. On the QC of calibration curve, it is important to securing an intermediate accuracy in the measuring system of ISO-GUM (International Organization for Standardization-Guide to the express of Uncertainty Measurement) [2].

In the technology of ISO-GUM, the analysis method of traceability, transferability and compatibility are applied. Already we have reported the uncertainty problems as series of three times in the IMEKO world congress.

1〕 1997.in Finland. The reference value was chosen by transferability of ISO-GUM [3].

2) 1999.in Japan. The error factor was taken in time series data by traceability of ISO-GUM [4].

3) 2000.in Austria. The Michaels-Menten test should be practiced by using the compatibility of ISO-GUM [5].

These reports were studied by using only one of test reagent of Elastase-1 [6], which is a kind of human pancreas hormone. The study has been continuing by using other 4 kinds similar sample. Then the purpose of this study is an experiment to get more high reliability. In this thesis, a new result on uncertainty problem is reported.

Keywords: ISO-GUM, Uncertainty data, Blood chemical analysis,

1. INTRODUCTION

The study of uncertainty is to analyze the measurement error and "Law of Propagation on uncertainty" with ISO-GUM is applied. The classification of the uncertainty has two sections of a type A and a type B with ISO-GUM.

The evaluation of the standard uncertainty in the type A should be estimated by the effective statistics method for the measurement data. And the type A is approximately same with WHO standard [7] in the present time.

The evaluation of standard uncertainty in the type B should be done by other method which is possible to do more effectively the input information.

The elements of uncertainty are greatly divided in to two class had "random effect" and " system effect", and are formed as the type A and the type B commonly.

Fig.1 shows the conception of type A and type B in ISO-GUM.

ISO-GUM
- Type A: statistical analysis method. (Parametric method)
- Type B: another analysis method. (Non-parametric method)

Fig.1 Conception of ISO-GUM.

In this study, RIA (Radi-Immuno-Assay) [8] has been using as analysis method of BCA. And the radioisotopes are used as a measuring maker. On the papers already reported, Elastase-1 which is a kind of test reagent of RIA was used. And here, the occurrence of a cycle swing in the measurement uncertainty data of Elastase-1 was detected. The QC of BCA is influenced large by the occurrence of a cycle swing in time series data. We confirmed also occurred cycle swing in the other test reagents of RIA.

2. THEORY OF CALIBRATION CURVE IN THE RIA

An immunity reaction of RIA is usually supposed as "Both of the antigen and the antibody are a complexes of mono -valence and reacted reversibly in one to one "[12]. The model of the dynamic chemical reaction rate is used for the explanation about the measurement theory of RIA. (See

Eq.1)。

This model follows the ”law of the action mass” and in proportion to the activated concentration of the reaction material. That model must be used in constant temperature based on the same condition

There are, the symbols indicate labeled antigen [P*], non-labeled antigen [P], an antibody [Q], non-labeled reaction compound [PQ], labeled reaction compound [PQ*] and abnormal reaction product [PI]. A labeled material is the radioisotope I^{125}

$$[P]+[P^*]+[Q] \underset{k2}{\overset{k1}{\rightleftarrows}} [PQ^*]+[PQ]+[PI] \qquad (1)$$

k1: association constant
k2: dissociation constant
k=k1/k2: affinity

Total antigen P_0 is always constant with PQ+PQ*+PI. Affinity value increases due to the progress of the reacting time. Affinity is a characteristic association constant

3. ERROR THEORY IN THE UNCERTAINTY

If the statistics value frequency distribution is an abnormal distribution [8], the nonparametric analysis of the type B of ISO–GUM must be used as the analysis method.

In the nonparametric analysis method, a softcomputing method which is called as a present topic was used. Here, chaos theory [9] and fuzzy theory [10] were used

The measuring value is obtained from the ordinary difference equation dx/dt by time t. That is equal with sensitivity coefficients. Here, x is input.

The trueness value exists in the data is shown with null statistical hypothesis as on the observation independent function f(x,t). Then the trueness value is estimated by the population mean or the standard deviation (SD) of the type A.

In the analysis of uncertainty data, the formula y=f (x1, x2 ……and xN) which developed approximately one dimension Tayler series is used. Because, multi variance quantity analysis needs. When more than one error element were contain in the uncertainty data. N is the input quantity number of the independent elements. "The law of propagation uncertainty” is used more effectively as the method of ISO-GUM. (See Fig 2)

An uncertainty element contains the error time function Ag(x.t) of time series as an independent observation element. Here, A is coverage factor in the ISO-GUM.

y (t) =dx / dt is constructed by two element, one is an element of the trueness value and other is an element of the error value. And the measured value is evaluated with an Eq. (2).

$$dx/dt = f(x,t) + Ag(x.t) \qquad (2)$$

An improvement of accuracy for QC shall be minimized Ag(x.t) element

A non-linear analysis or nonparametric analysis is necessary for the analysis method of the abnormal distribution. Then the two-dimensional difference movement equation d^2x / dt_2 is the most suitable for the measurement value y (t). (See Eq.2.)

A non-linear analysis or non-parametric analysis is necessary with the type B for the analysis of the error. y (t) is self-recurrence of second differential equation d2x/dt2 (See Eq.3). The example is a self-recurrence model which is based on the central limited theorem and it is agreed in the theorem of re-yoke of logistic mapping with in the chaos theory.

$$Y_n=ay_{n-1}(1-y_{n-1}) \qquad (3)$$

4. METHOD

Four kinds of new sample are progesterone of human androgenic hormone, testosterone of human female hormone, plasma rennin active of human kidney hormone and thyroxin T4 of human thyroid hormone. The adding samples are same with the theory of chemical reaction of Elastase-1. The reason is that the five hormones oposit to five main hormones in the human body.

In the RIA, a calibration curve is made by multi calibrators. A group of the calibrators is composed theoretically by a consistent by some kinds of test reagent which are most suitable reference value. As the example of the test reagent of Elastase-1, the reagent concentrations are the value of dose of 0.50.150.500.1500 and 5000. A concentration of the principal assigned value is decided by the reference value character which is the standard value of the routine blood test

The error factors are taken come out from an abnormal distribution and are estimated as the combined standard uncertainty factor. Here the " law of propagation on uncertainty" of ISO-GUM can apply to the calculation of an analysis method of the error.

The result of the uncertainty measurement completes by the fixed quantity of uncertainty. In the quantity-analysis, a proper of the fixed quantity result obtained only under the same measurement condition.

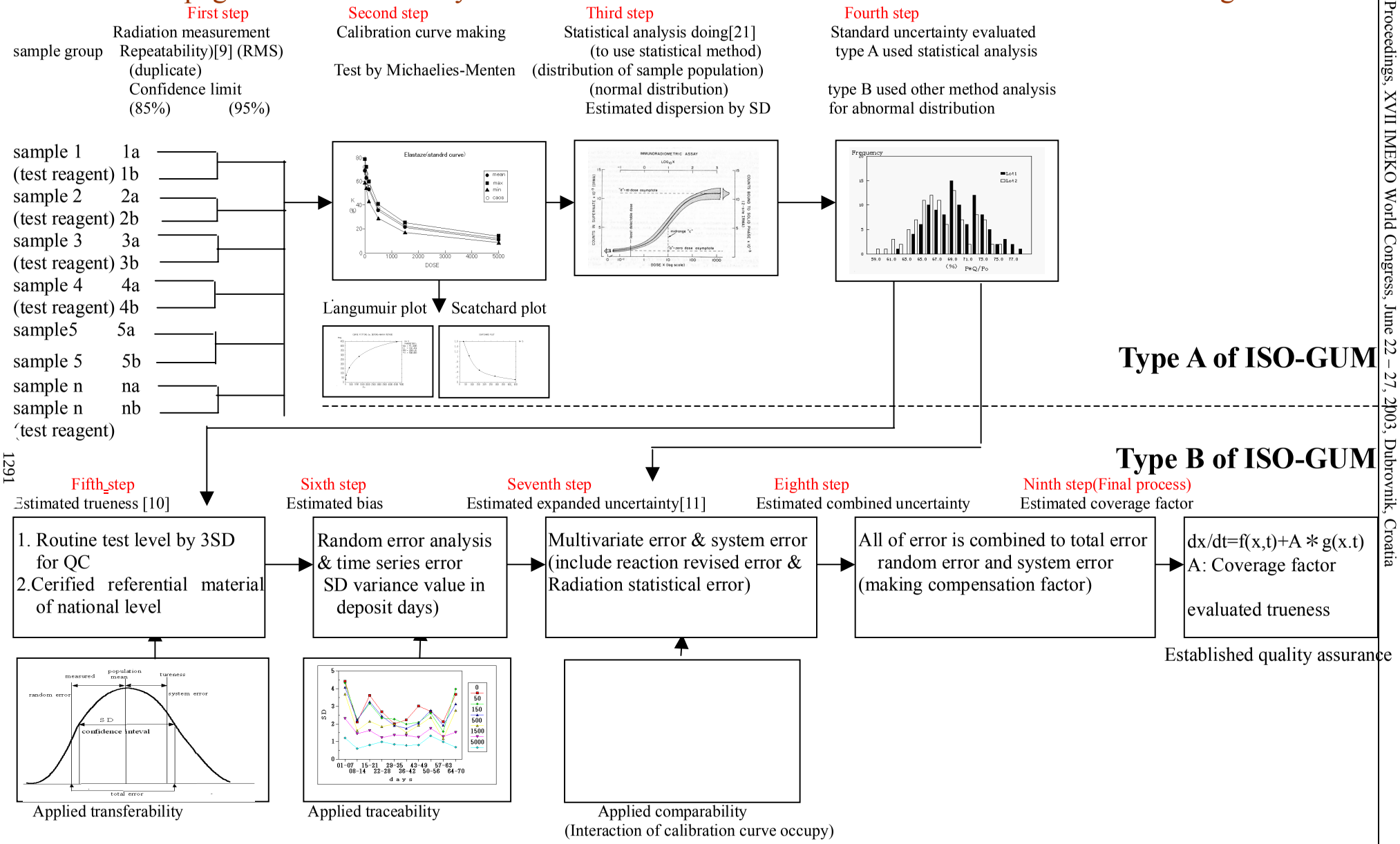

Fig. 2 Law of Propagation on Uncertainty for RIA

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Fig.2 shows the procedure of the calculation of error by the ”Law of propagation on uncertainty” of ISO-DUM. This figure is indicated as a measurement standard system of RIA. Each stage in the chart is doing to the next work.

In the first-step works, About the more than one sample, the radiation is counted by reproducibility and repeatability. The radiation count is necessary to hold in the confidence interval. Namely it is desirable to becomes same count under the same measurement condition,

In the second-step works, a calibration curve is made by the counting result of the previous step and a regression analysis. And the completed curve is judged by the official summary of Michaelies-Menten test.

In the third-step works, a frequency density distribution curve is made by using the result in the second process, and calculates the population mean in one group by the statistics method.

In the fourth-step works, a frequency distribution is made by a result of first-step for each test reagent. And it judges which are the normal distribution or the abnormal distribution. Then if it is abnormal distribution, it is analyzed by the type B of ISO-GUM.

In the fifth-step works, the trueness value of the test reagent is calculated from the result of fourth-step.

In the sixth-step works, then standard deviation (SD) or coefficient of variation (CV) is estimated by the uncertainty data of time series from fourth-step result, which is leaded from the abnormal distribution by tracerbility technology.

In the seventh-step works, the result of measurement of the multivariate quantity is combined with the sixth-step result, and standard combination uncertainty is evaluated.

In the eighth-step works, a random error and a system error are added by root mean square, and it is evaluated as expanded uncertainty.

In the ninth-step works, All process is completed by calculating a coverage coefficient k. Then the outline is calculated with k=2. The report of this uncertainty is made as the final step.

5. RESULTS

5.1 The fundamental data already have published.

To the principal assigned test reagents of elastase-1, the reference values are calculated by the affinity of each test reagent. Calculated result is line up in the Table 1.

Fig. 3 shows the frequency distribution of the measured value of test reagent had 0 dose value of calibrator of test reagent of elastase-1. Here, the abnormal distribution had the multiple peaks is confirmed. The cause occurs by the time series data in deposit days. The number of samples is 300. In this figure, the all sampls are divided into two rot sample according to a calendar days.

Table 1 Calculated result of analysis

Dose	Chaos	Fuzzy	RMS	Mean	Max
0	71.4	68.35	68.27	68.3	78.2
50	65.4	61.85	61.95	61.9	71.8
150	54.3	52.09	52.09	52.2	60.0
500	37.4	34.72	34.68	34.7	43.1
1500	23.2	20.58	20.58	20.7	28.9
5000	17.1	10.41	10.38	10.5	17.1

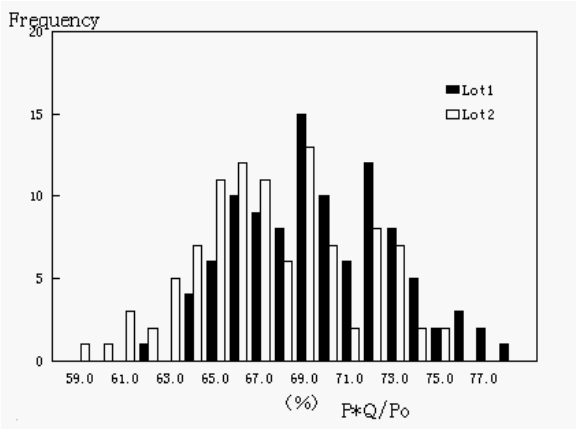

Fig.3 Frequency distribution of 0 dose of Elastase-1

Fig.4 shows the change of reaction ability by the deposit days of the test reagent, and the deterioration of reaction ability was confirmed. This is a typical result of the time series data.

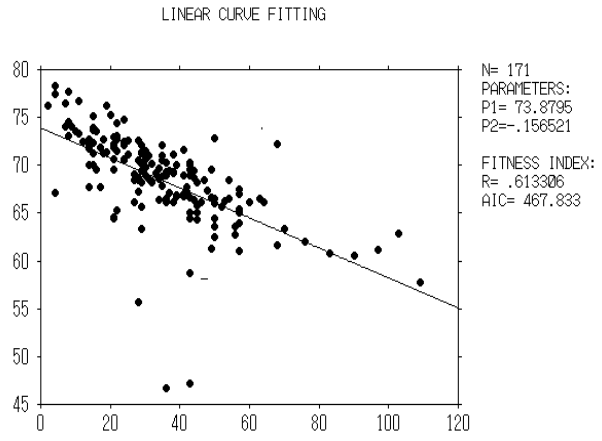

Fig.4 Time series scatter chart of 0 dose of Elastase-1

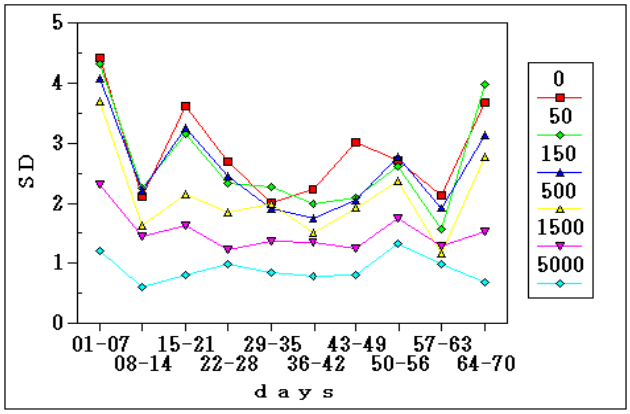

Fig.5 Variance of SD value on deposit day of Elastarse-1

Fig.5 shows the change of SD value on every between 7 days group and the result shows the cycle swing like biological rhythm. The largest SD value occurred in the peak graph of cycle swing at near the production day and peak of the swing. The cycle period is about 28 days. Y-axis is change of SD value. X-axis is deposit days. The deposit days show the deposit term from product assay day to the use day of blood test as test reagent. Test reagents are sampled within 70 deposit days.

5.2 New result

The Fig. 6-9 groups show the change of SD value. Fig.6 shows the change of SD value on plasma rennin active. Fig.7 shows the change of SD value on thyroxin T4. Fig.8 shows the change of SD value on the testosterone. Fig.9 shows the change of SD value on progesterone. All of figures show fluctuation curve and cycle swing. Fig 9 shows suddenly higher up SD curves in 80-86 days area. Because, the sample size is small, and then added the frequency density distribution of bar graph in with the change of SD curve.

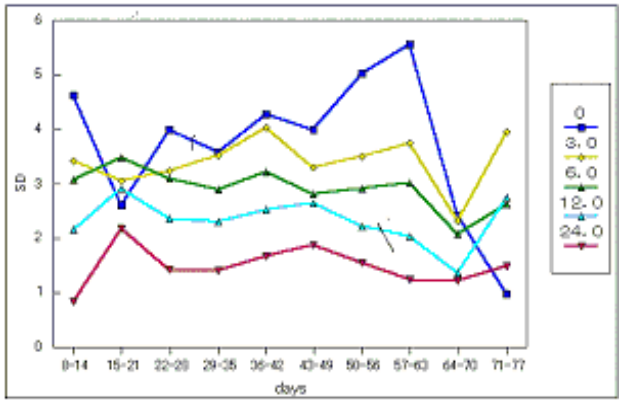

Fig.6. The change of SD value of on thyroxin T4.

An uncertainty value is calculated by cycle swing. The cycle swing is likes with biological rhythm, and the calculation value of error element is estimated by nonparametric function. Then the combined standard uncertainty is estimated by the sum of squares mean within the change of SD data

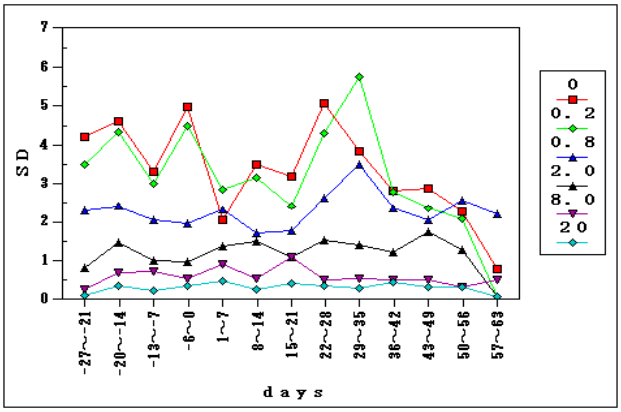

Fig.7. The change of SD value of on plasma rennin active

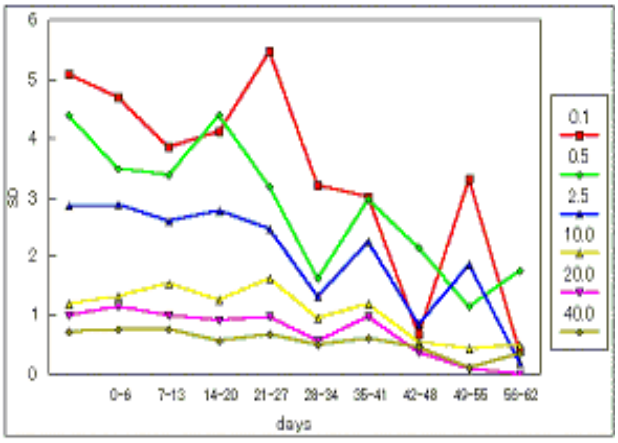

Fig.8. The change of SD value of on testosterone.

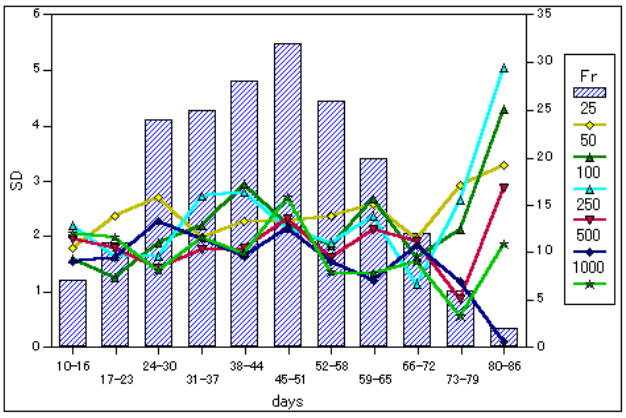

Fig.9. The change of SD value of on progesterone

6. CONCLUSION

The proper of error in blood chemical analysis is much influenced by deposit days of test reagent. The reason is that time series data of test reagent have biological swing rhythm. However, there is a place where exceeds 3SD. Still 3SD is routine test level. The test regent must be decided by used day that the dispersion becomes smallest.

It is important that the relations between the precisions and the concentrations are shown. And the accurate domain becomes higher as much as concentration is high. And when the concentration is low, the accuracy becomes low.

In cycle swing, the time series data of a dynamic blood chemical reaction exist. Then the cycle swing gives a large influence to the real QC. This phenomenon is proved the existence of the available reverse reaction by the official answer dissociation constant k2. (See Eq. (1))

Generally, the chemical reaction analysis method has the same problem on the uncertainty.

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