Uncertainty of measurement and heteroscedasticity

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Uncertainty of measurement (hereafter referred to as uncertainty) is a parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand (that is to say the measured quantity) [1]; in other words, uncertainty is numerical information that complements a result of measurement, indicating the magnitude of the doubt about this result.

The international scientific and standardization bodies recommend that the uncertainty of patients' results obtained in clinical laboratories should be known [2, 3]; the rationale for this recommendation is that full interpretation of the value of a quantity obtained by measurement requires also evaluation of the doubt attached to its value. The common opinion of these bodies is that clinical laboratories should supply information about the uncertainty of their results of measurement, when applicable.

The uncertainty that should be written together with a clinical laboratory result is the so called expanded uncertainty, obtained by the positive squared root of the sum of the variances, corresponding to different sources of uncertainty affecting the measurement process —that is to say the combined uncertainty—multiplied by a coverage factor [1, 4, 5]. Among these causes, day-to-day imprecision is generally responsible for an important part of uncertainty.

With regard to day-to-day imprecision, the phenomenon called heteroscedasticity should be taken into account: day-to-day metrological variance depends on the value of the measurand (the opposite phenomenon is called homoscedasticity). In some cases of heteroscedasticity, in spite of variance differences with the measurand value, the coefficient of variation reminds constant; in these cases, the calculation of the variance due to day-to day impreci-

Figure 1. Imprecision profiles and variance functions of measurement procedures for the concentrations of bilirubin (a), ferritin (b) and triiodothyronine (c) in serum. Shared areas indicate the 95 % confidence interval of the fitting for imprecision profiles.
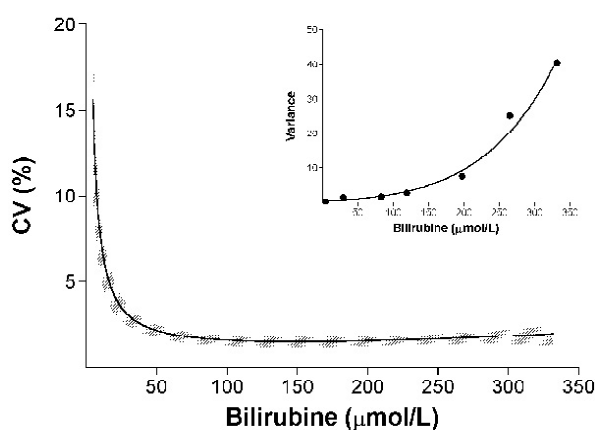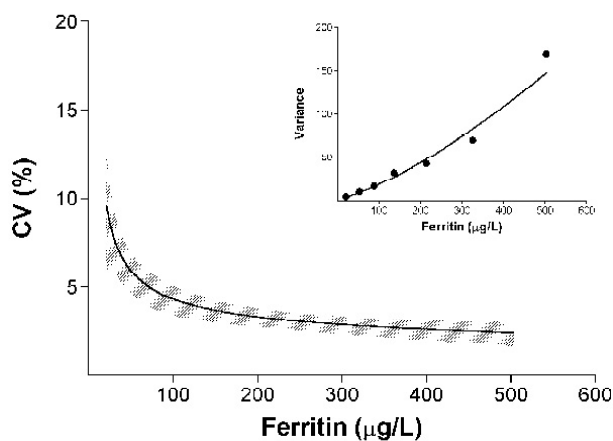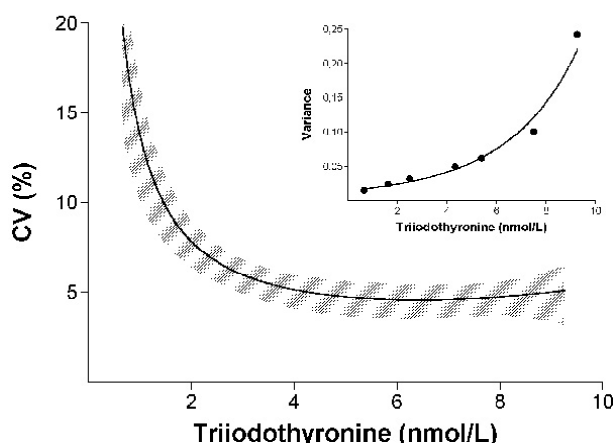

Fig. 1a

Fig. 1b

Fig. 1c

Table 1. Measurement procedures with coefficients of variation depending on the value of the measured quantity.

Quantity	Serum pool	Mean value	CV
S—Bilirubin; subst.c. [μmol/L]	1	4.7	10.0
(Hitachi 747/Jendrassik-Gróf/Roche Diagnostics)	2	29.5	4.3
	3	83.5	1.6
	4	119.7	1.4
	5	198.2	1.4
	6	265.3	1.9
	7	331.8	1.9
S—Ferritin; mass.c. [μg/L]	1	21.3	9.5
(Hitachi 917/Tina-Quant reagents/Roche Diagnostics)	2	53.4	5.9
	3	89.1	4.5
	4	136.7	4.1
	5	215.1	3.0
	6	326.5	2.5
	7	503.3	2.6
S—Triiodothyronine; subst.c. [pmol/L]	1	0.67	18.1
(Elecsys 2010/Roche Diagnostics)	2	1.64	9.5
	3	2.51	7.1
	4	4.34	5.1
	5	5.41	4.6
	6	7.51	4.2
	7	9.26	5.3
S = serum; subst.c. = substance concentration; mass c. = mass concentration.			

Variance functions may be estimated using by using the maximum approximate conditional likelihood method [6-7]. The equation used in this method is $s^2 = (\beta_1 + \beta_2 c)^J$, where s^2 is the variance of replicate measurements, c the values of the different concentrations and β_1, β_2 and J are three parameters defining the function. There is no underlying physical or chemical law for this function.

We have applied the maximum approximate conditional likelihood method using the Sadler et al. program [6] to repeated results of several measurement procedures of different quantities used in our laboratory. For each quantity, variances and coefficients of variation have been estimated with 20 replicated results, one per day, over 20 working days, in aliquots (stored at -20 oC) of seven serum pools with values representing the entire measurement range (Table 1).

The graphical outputs of the program show coefficients of variation approximately constant for several measurement procedures, such as those related to cholesterol, glucose and protein. However, other measurement procedures have clearly different coefficient of variation for each value of the measured quantity as can be appreciated in Figure 1 (the shared zone is the 95 % confidence interval).

Coming back to the uncertainty estimation, when a measurement procedure has a behavior such as represented in Fig. 1, the Sadler et al. program [6] allow us to predict, within the measurement range, the variance corresponding to the measurand value, and this variance may be used to estimate the uncertainty.

Therefore, clinical laboratories using the maximum approximate conditional likelihood method may know its imprecision profiles and variance functions in order to estimate appropriately its uncertainties.

References

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