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WHITE PAPER · CALIBRATION IN PRACTICE

MATRIX EFFECTS · INSIGHTS 34

Matrix-matched, solvent or standard addition: choosing the calibration the sample needs.

A solvent curve can pass every test and still read a sample a third low, because the sample does not ionise like the solvent. The calibration has to match what the detector actually sees.

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SUMMARY

Signal suppression and enhancement mean a standard in solvent and the same amount in a sample extract can give different responses. This paper shows how to measure that difference as a matrix effect, sets out the 20% threshold in the EU pesticide guidance SANTE 11312/2021 and the matrix effect test in ICH M10, and works an illustrative set of analytes and commodities. It compares solvent, matrix-matched, procedural and standard addition calibration and when each one fits.

THE SHORT VERSION

01 Measure the matrix effect as the difference between a standard in blank extract and the same standard in solvent.

02 A solvent-calibrated result is off by roughly the matrix effect, and the ICAL cannot show it.

03 SANTE 11312/2021 asks labs to address effects above 20% in calibration; ICH M10 tests them across six matrix lots.

The solvent curve that passed.

The solvent curve is clean. Five levels, RSD under 5%, every standard inside ±10% on refit. The spiked tea sample comes back at 59% recovery. The spiked lettuce comes back at 94%.

The curve did nothing wrong. It showed how the detector sees the analyte in solvent. Tea extract is not solvent. In tea, the same amount of analyte gives a much smaller signal.

Measure the matrix effect first.

SANTE 11312/2021 v2 defines the matrix effect as the difference in response between a standard in matrix extract and a standard in solvent [1]. In practice, compare the slopes of the two curves, or the responses at one concentration.

Matrix effect, in percent, is the slope in blank extract divided by the slope in solvent, minus one, times 100.

A negative value means the matrix cuts the signal. A positive value means it adds to it. A sample calibrated against solvent standards is biased by roughly that amount. Its response sits on the matrix slope, but the result is read from the solvent one.

Four analytes, three matrices.

Here are illustrative matrix effects for four analytes in three commodities.

MATRIX EFFECT	LETTUCE	CITRUS	BLACK TEA
Analyte A	−6% PASS	−18% PASS	−41% ADDRESS
Analyte B	+4% PASS	+12% PASS	+27% ADDRESS
Analyte C	−11% PASS	−24% ADDRESS	−58% ADDRESS
Analyte D	−2% PASS	−5% PASS	−9% PASS

Illustrative values constructed for this article, not instrument data. Flags apply the SANTE 11312/2021 threshold of 20% signal suppression or enhancement.

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COMBINATIONS ABOVE 20%

−58%

WORST MATRIX EFFECT, READ AS SOLVENT BIAS

One

ANALYTE SAFE IN EVERY MATRIX

Analyte D could be calibrated in solvent in all three matrices. Analyte C could be calibrated in solvent only in lettuce. In tea, a solvent curve would report it at less than half its true value.

The pattern matters as much as the numbers. The effect belongs to the pair, not to the analyte or the method alone. One test matrix does not settle it for every crop a lab will see.

Matrix effect belongs to the pair of analyte and matrix, not to the analyte alone.

Four ways to calibrate against a matrix.

01 **Solvent calibration.**
Fine where the matrix effect is shown to be small. The simplest to prepare and keep stable.

02 **Matrix-matched calibration.**
Standards in blank extract, preferably of the same type as the sample [1]. It needs a steady supply of truly blank matrix.

03 **Procedural calibration.**
Blank test portions spiked before extraction and taken through the whole method. It also corrects for recovery, but only for samples of the same type in the same batch [1].

04 **Standard addition.**
At least three test portions of the sample, with additions of about one to five times the estimated level [1]. It fits the matrix of that one sample, at the cost of extra runs and an answer read off the end of the line.

In an illustrative standard addition with a sample at 20 µg/kg and a suppressed slope, the extrapolated result comes out at 19.3 µg/kg. The matrix loss is gone. The price is that the answer sits below the lowest addition. Small errors in the slope move it more than they would move an interpolated result.

What SANTE and ICH M10 expect.

SANTE 11312/2021 v2 asks for matrix effects to be assessed at initial method validation. Where suppression or enhancement exceeds 20%, matrix effects need to be addressed in calibration. Back-calculated concentrations of calibration standards should not deviate by more than ±20% [1].

ICH M10 tests matrix effect across different sources. It uses at least three replicates of low and high QCs, each prepared in matrix from at least six sources or lots. Accuracy should be within ±15% and precision within 15% [2].

A matrix calibration checklist.

01 **Measure the matrix effect.**
Per analyte, per matrix type, at validation.

02 **Apply the threshold.**
Above 20%, address it in the calibration.

03 **Match the calibration to the samples.**
Same matrix type, or procedural standards.

04 **Recheck for new commodities.**
One validated matrix does not cover the rest.

05 **Use standard addition for the odd sample.**
And treat its result as an extrapolation.

06 **Record which approach was used.**
For every batch, with the matrix effect data behind it.

Where WLTR fits.

A calibration can be statistically perfect and still describe the wrong matrix. Seeing every standard back-calculated under every model is the first check. Matching the calibration to the sample is the second, and no statistic replaces it.

WLTR is calibration data integrity infrastructure for regulated analytical laboratories. For each analyte, it derives nine calibration regression models: average response factor, plus linear and quadratic fits across four weightings each. It scores every model against fifteen ICAL parameters, including RSE. All of it is computed orthogonally to the CDS, under U.S. Patent 12,038,448 B2 [P].

CALIBRATION VERIFICATION

See every calibration standard back-calculated under every regression model and weighting, computed orthogonally to your CDS.

GET COMPLIANCE GAP ASSESSMENT

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SOURCES

1. European Commission, Analytical Quality Control and Method Validation Procedures for Pesticide Residues Analysis in Food and Feed, SANTE 11312/2021 v2, implemented 1 January 2024, paras. C17, C21, C24, C28 and Table 4. food.ec.europa.eu/document/download/d4786faf-c574-4222-a5c6-45086b3920b8_en
2. ICH, M10: Bioanalytical Method Validation and Study Sample Analysis, final version adopted 24 May 2022, Sec. 3.2.3. www.pmda.go.jp/files/000246792.pdf
3. U.S. Patent 12,038,448 B2, inventor Walter “Chip” Hinchman Sr. patents.google.com/patent/US12038448B2

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