

## Quality Control in chemical industry: Quantitative NMR Spectroscopy

Quantitative NMR spectroscopy (qNMR) has become an invaluable tool for the exact content assignment and quantitative determination of impurities.

A main property of  $^1\text{H}$ -qNMR is that it is a relative primary method. This means that the signal intensity is directly proportional to the number of protons contributing to the resonance. It is therefore possible to directly compare the signal intensities of a substance of interest and a reference standard. Therefore, a direct traceability to an internationally recognized reference standard can be achieved. Chromatographic techniques such as HPLC or GC usually do not provide this traceability, because they require a highly pure standard of the substance of interest, which is often not available.

Sigma Aldrich Switzerland uses a 600 MHz NMR instrument for the purity determination of organic substances under ISO accreditation (ISO/IEC 17025 and ISO Guide 34). Based on metrological weighing using an ultramicro balance the exact amounts of sample and reference are weighed into the same vial. After solvation in an appropriate deuterated solvent the mixture is measured by  $^1\text{H}$ -qNMR. The signal ratio of two different protons can be measured with tremendous accuracy and precision. Measurement uncertainties down to 0.1% can be achieved. This technique is used for the exact determination of the purity (content as % mass fraction) of a broad variety of organic substances. Together with homogeneity and stability data these substances are then certified to become CRMs (certified reference materials).

### References:

- Reichmuth et al., *MicroChimica Acta* (2004) 148 (3-4): 133-141
- Schoenberger T., *Anal. Bioanal. Chem.* (2012) 403: 247-254
- Saito et al., *Accred. Qual. Assur.* (2009) 14: 79-86

### Additional web-info:

- Poster Analytica: [http://www.sigmaaldrich.com/content/dam/sigmaaldrich/docs/Fluka/Posters/1/poster\\_analytica.pdf](http://www.sigmaaldrich.com/content/dam/sigmaaldrich/docs/Fluka/Posters/1/poster_analytica.pdf)
- Analytix article: [http://www.sigmaaldrich.com/content/dam/sigmaaldrich/docs/Fluka/General\\_Information/1/analytix\\_orgcrm.pdf](http://www.sigmaaldrich.com/content/dam/sigmaaldrich/docs/Fluka/General_Information/1/analytix_orgcrm.pdf)
- Example certificate: [www.sigmaaldrich.com/organiccrm](http://www.sigmaaldrich.com/organiccrm)

**Questions:**

1. Traditionally content determinations (purity) of organic substances are performed using chromatographic methods (GC, HPLC). Alternatively, purities can also be measured by qNMR. Please elaborate the advantages and disadvantages of both techniques with regard to the quality of the measurand (content determination / purity) and possible restrictions.
2. Substances that are used as internal standards for qNMR have to fulfill certain chemical and physical properties. Please name the most important properties that a “good” qNMR reference has to show.
3. Based on the described process of quantification by NMR, please identify components that have major or minor influence on the measurement uncertainty within a qNMR measurement. Please try to show this in a diagram. Where do you expect major contributions and why?
4. Purity determinations that are carried out by different techniques may lead to different results. Which differences (qualitative and quantitative) would you expect if you compare qNMR with traditional chromatographic techniques and what could be the reasons?