# Novel Method for Rapid Detection of Contaminated Cough Syrup Using TD-NMR

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## Abstract

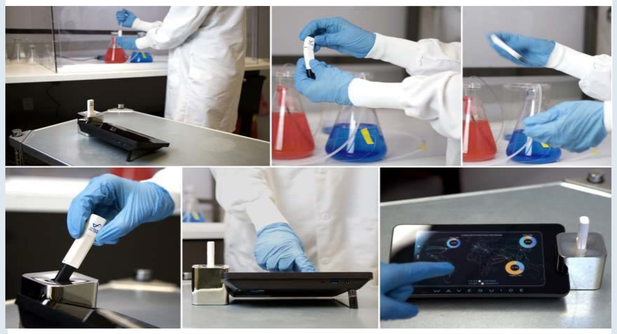
Over a four-month period from October 2022 through January 2023, more than 300 people from at least seven countries died from ingesting contaminated over the counter cough syrup.[1] Most of the fatalities were children under the age of five.[1] These countries have reported with confirmed or suspected contamination with high levels of diethylene glycol (DEG) and ethylene glycol (EG).[1] These contaminants are toxic chemicals used as industrial solvents and antifreeze agents that can be fatal even if taken in small amounts.[1] The World Health Organization (WHO) has issued global medical alerts and called on governments, regulators, and key stakeholders in medical supply to take action. WHO has urged all suppliers and distributors of medical products to always check for falsification and substandard products.[1-5] The U.S. Food and Drug Administration (FDA) has joined with WHO in the investigation of contaminated cough syrup and a call to action. The FDA acknowledges that some medicines enter the U.S. illegally and has since issued 28 warning letters to manufacturers over lax testing and failure to test raw materials and finished products for possible contamination with DEG and EG. [6,7]

Previous FDA guidance from 2007 recommended certain tests be performed on glycerin, another common ingredient in over-the-counter drugs and consumer goods, to prevent distribution of DEG-contaminated products. The FDA has recently updated its Guidance for Industry, to include other high-risk components for DEG and EG, Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, and Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol in May 2023.[8] Additionally, the U.S. Pharmacopeia (USP) has also answered the call providing a DEG and EG toolkit for manufacturers with monographs for testing raw materials.[9] Detecting and preventing contaminated products from reaching consumers is of critical importance world-wide. The contaminated cough syrups investigated by WHO showed DEG concentrations as high as 28.6%-34% versus the acceptable limit of 0.1%.[6]

A proof-of-concept study explored the feasibility of identifying DEG and EG contaminated cough syrup using Time Domain NMR (TD-NMR) with the portable and inexpensive WaveGuide Formμla™ instrument. The results show that TD-NMR can readily detect the presence of DEG and EG in cough syrup. This technique shows promise for final product testing as an importation screening tool and product safety confirmation validation. Its portability, low cost and ease of use, specifically tailored for nonscientists, make it an easy globally deployable solution for monitoring cough syrups and other compounds.

## Objective

To detect relevant levels of DEG and EG contamination in cough syrup with TD-NMR using the WaveGuide Formμla™



WaveGuide's portable TD-NMR (time domain micro-NMR) provides solutions for field testing of consumer products for contamination and counterfeiting. Testing can now be conducted on site including ports of entry where products are likely to enter the supply chain. WaveGuide's TD-NMR allows non-scientists to conduct field testing of consumer products. WaveGuide is providing a practical industry-focused solution by bringing TD-NMR to the masses.


**The WaveGuide Formμla™ portable μNMR**
Little to no sample preparation required.
Sample analysis take only minutes.
Less than 20 μL of sample typically used per test.

## Materials

The cough syrups tested in this study were purchased at the pharmacy, over the counter.

| | mg in each 5 mL | Robitussin | Robitussin CF | Mucinex | Delsym | Sudafed | CVS | Walgreens |
|---|---|---|---|---|---|---|---|---|
| Active Ingredients | Dextromethorphan HBr[a] | 7.5 | 5 | 5 | 30 | 5 | 5 | 5 |
| | Phenylephrine HCl[b] | - | 2.5 | - | - | 2.5 | 2.5 | - |
| | Guaifenesin[c] | - | 50 | 100 | - | - | - | 100 |
| | Chlorpheniramine maleate[d] | 1 | - | - | - | - | - | - |
| | Acetaminophen[e] | - | - | - | - | - | - | - |
| | Brompheniramine[a,b,d] | - | - | - | - | - | 1 | - |
| | Diphenhydramine[d] | - | - | - | - | - | - | - |
| Inactive Ingredients | Purified water | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Artificial and natural flavors | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Anhydrous citric acid[2] /Citric acid[2] * | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓* |
| | Edetate disodium[1,6] | - | - | ✓ | ✓ | ✓ | ✓ | - |
| | Glycerin[2,3,4,5] | ✓ | ✓ | ✓ | - | ✓ | ✓ | ✓ |
| | Lactic acid[2,6] | ✓ | - | - | - | - | - | - |
| | Potassium sorbate[2,3] | | - | - | - | - | - | ✓ |
| | Propyl gallate[2] | - | - | ✓ | - | - | - | - |
| | Propylen glycol[2,3,4,5] | ✓ | ✓ | ✓ | ✓ | - | ✓ | ✓ |
| | Sodium benzoate[2] | ✓ | ✓ | ✓ | - | ✓ | ✓ | - |
| | Sodium chloride[2] | - | - | - | - | - | - | - |
| | Sodium citrate[2,2,5] | ✓ | ✓ | - | - | ✓ | - | - |
| | Sodium hydroxide[2,3] | - | - | - | - | - | - | ✓ |
| | Trisodium citrate dihydrate[1,2] | - | | ✓ | - | - | - | - |
| | Carboxymethylcellulose sodium[2] | - | - | - | - | ✓ | - | - |
| | Sorbitol solution[2,5] | ✓ | ✓ | ✓ | - | ✓ | ✓ | - |
| | Sodium | 6 | 3.5 | 3 | 7 | 14 | 2 | 2 |

## Methods

The cough syrups were tested straight and after contamination with Diethylene glycol and Ethylene glycol.

Samples aliquot were placed in a glass tube configured for the TD-NMR instrument with a 3 mm outer diameter and 2.5 mm inner diameter.

The volume of sample used for each analysis was 15 μL.

All experiments were conducted at a controlled temperature of 25˚C to minimize the difference in temperature-dependencies on the relaxation time.

Six to ten replicates were measured for each cough syrup.

## Measurements & Analysis

A standard CPMG (Carr-Purcell-Meiboom-Gill) acquisition pulse sequence was utilized to measure the T2 relaxation[10,11] profile of the vaccines.

For the results reported here, the measured T2 relaxation decays were fitted with both single- and bi-exponential decay models, and the corresponding decay-times and component amplitudes were determined and analyzed.

## Conclusions

Using the WaveGuide Formμla™ μNMR instrument, WaveGuide was able to:

- ✓ Show that WaveGuide's μNMR can distinguish between different cough syrups.
- ✓ Show that WaveGuide's μNMR can detect contaminants such as Diethylene glycol and Ethylene glycol as low as 2.5%.
- ✓ TD-NMR is an inexpensive, battery operated, portable way to hit many touch points in supply chain

## References

1. World Health Organization (2023, 23 January). *WHO urges action to protect children from contaminated medicines.* WHO. https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines.
2. World Health Organization. (2023, 11 January). *Medical Product Alert N°1/2023: Substandard (contaminated) liquid dosage medicines.* WHO. https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-(contaminated)-liquid-dosage-medicines.
3. World Health Organization. (2022, 5 October 2). *Medical Product Alert N°6/2022: Substandard (contaminated) paediatric medicines.* WHO. https://www.who.int/news/item/05-10-2022-medical-product-alert-n-6-2022-substandard-(contaminated)-paediatric-medicines.
4. World Health Organization. (2022, 2 November). *Medical Product Alert N°7/2022: Substandard (contaminated) paediatric liquid dosage medicines.* WHO. https://www.who.int/news/item/02-11-2022-medical-product-alert-n-7-2022-substandard-(contaminated)-paediatric-liquid-dosage-medicines.
5. Rigby, J. (2023, 23 January). *WHO urges 'immediate action' after cough syrup deaths.* Reuters. https://www.reuters.com/business/healthcare-pharmaceuticals/who-urges-action-after-cough-syrup-deaths-2023-01-23/
6. Das, KN and Rigby, J. (2023, 13 September). *Lax testing fuelled wave of cough syrup poisonings*. Reuters. https://www.reuters.com/article/testv-health-coughsyrup-india/lax-testing-fuelled-wave-of-cough-syrup-poisonings-idUKKBN30J13N/
7. Wingrove, P. (2023, 26 September) *Cough syrup deaths overseas prompt crackdown on toxic testing*. Reuters. https://www.reuters.com/business/healthcare-pharmaceuticals/cough-syrup-deaths-overseas-prompts-us-crackdown-toxic-testing-2023-09-26/#:~:text=The%20Food%20and%20Drug%20Administration,analysis%20of%20agency%20import%20alerts
8. Food and Drug Administration. "Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol; Guidance for Industry; Availability." Regulations.Gov, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), May 2023, www.regulations.gov/docket/FDA-2023-D-1573.
9. U.S. Pharmacopeia, May 2023. "Standards Help Identify Deadly Contaminants in Allergy, Cold and Cough Medicines. ." USP Impurities-Diethylene Glycol (DEG) Resources., www.usp.org/impurities/diethylene-glycol-resources.
10. H.Y. Carr, E. M. Purcell, "Effects of Diffusion on Free Precession in Nuclear Magnetic Resonance Experiments", *Phys. Rev.*, 94, 630 (1954).
11. S.Meiboom, D. Gill, 1958. "Modified Spin-Echo Method for Measuring Nuclear Relaxation Times", *Rev. Sci. Instrum.*, 29, 688 (1958).
12. Abdallah, Salam, and Nishara Nizamuddin. "Blockchain-based solution for Pharma Supply Chain Industry." Computers & Industrial Engineering, vol. 177, Mar. 2023, p. 108997, https://doi.org/10.1016/j.cie.2023.108997.
13. Lindner, Dr. Andre. "Transforming Weak Points in Pharma-Supply Chains." LinkedIn, 19 May 2020, www.linkedin.com/pulse/transforming-weak-points-pharma-supply-chains-dr-andre-lindner-1e/.
14. Cuddy, Emily, et al. "FDA Global Drug Inspections: Surveillance of manufacturing establishments remains well below pre-covid-19 levels." Health Affairs, vol. 42, no. 12, 1 Dec. 2023, pp. 1758–1766, https://doi.org/10.1377/hlthaff.2023.00686.

## Results

**Objective 1:** Test a set of commercially available cough syrups and determine if the WaveGuide's μNMR instrument can differentiate them.

- Single-exponential model analysis - T2 values (Fig. 1 and Table 1).
- Six out of seven cough syrups are clearly distinguishable from each other (Fig. 1 and Table 1).
- Delsym and Sudafed show a similar single-exponential T2 profile.
- Bi-exponential model analysis - T2 values (Fig. 2 and Table 2).
- All seven cough syrups are clearly distinguishable from each other (Fig. 2 and Table 2).
- Delsym and Sudafed show different bi-exponential T2 profiles which allow to differentiate them from each other.

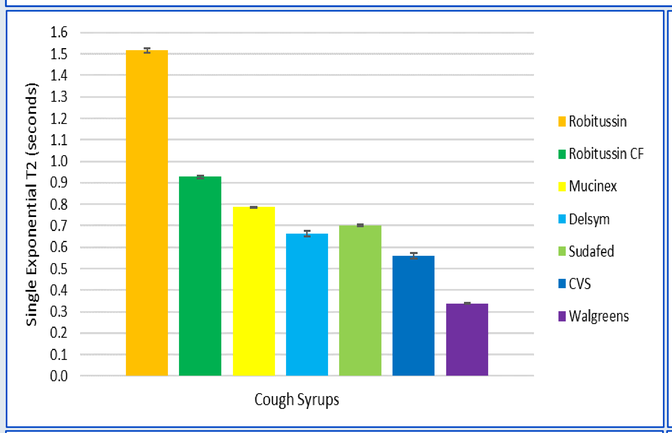



**Figure 1** and **Table 1**: Single-exponential analysis (T2) of seven commercial cough syrups. Each cough syrups show a unique T2 signature.

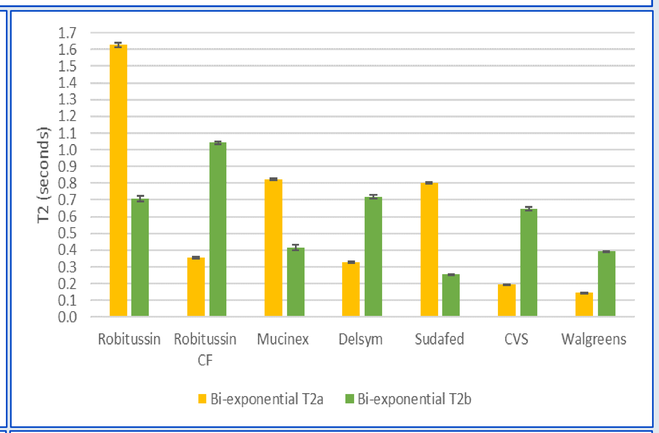



**Figure 2 and Table 2**: Bi-exponential analysis (T2) of seven commercial cough syrups. Each cough syrups show two unique T2 signatures.

| Cough Syrups | Single Exponential T2 | |
|---|---|---|
| | Mean | St. Deviation |
| Robitussin | 1.516 | 0.012 |
| Robitussin CF | 0.928 | 0.006 |
| Mucinex | 0.787 | 0.003 |
| Delsym* | 0.664 | 0.012 |
| Sudafed* | 0.703 | 0.005 |
| CVS | 0.560 | 0.013 |
| Walgreens | 0.338 | 0.002 |

*Very similar Single Exponential T2 values

| Cough Syrups | Bi-exponential T2a | | Bi-exponential T2b | |
|---|---|---|---|---|
| | Mean | St. Deviation | Mean | St. Deviation |
| Robitussin | 1.629 | 0.014 | 0.708 | 0.017 |
| Robitussin CF | 0.356 | 0.005 | 1.043 | 0.007 |
| Mucinex | 0.825 | 0.004 | 0.414 | 0.016 |
| Delsym* | 0.328 | 0.005 | 0.718 | 0.012 |
| Sudafed* | 0.801 | 0.006 | 0.255 | 0.003 |
| CVS | 0.193 | 0.005 | 0.648 | 0.013 |
| Walgreens | 0.143 | 0.002 | 0.392 | 0.002 |

*Very separable by Bi-Exponential T2 values

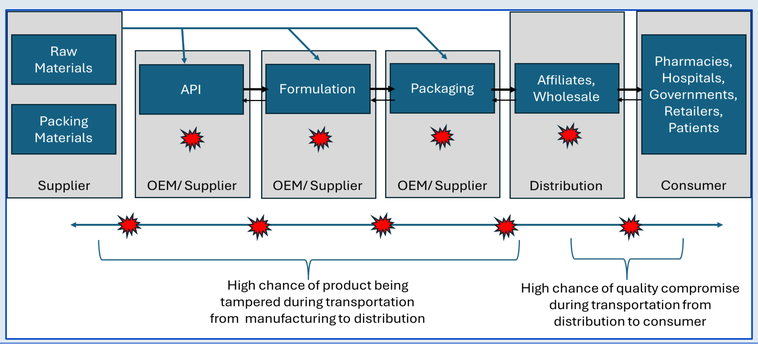
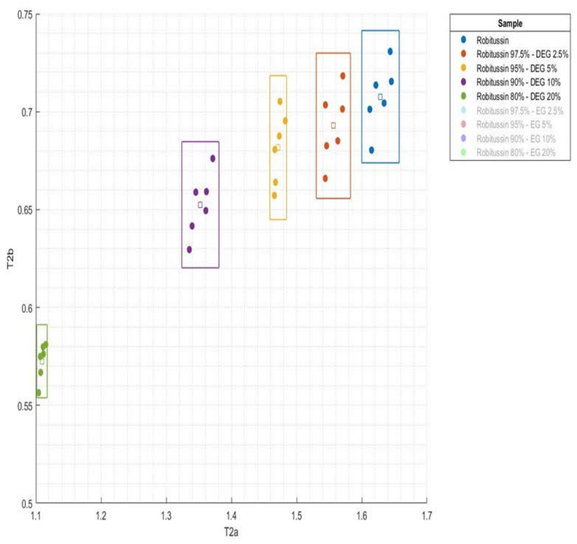
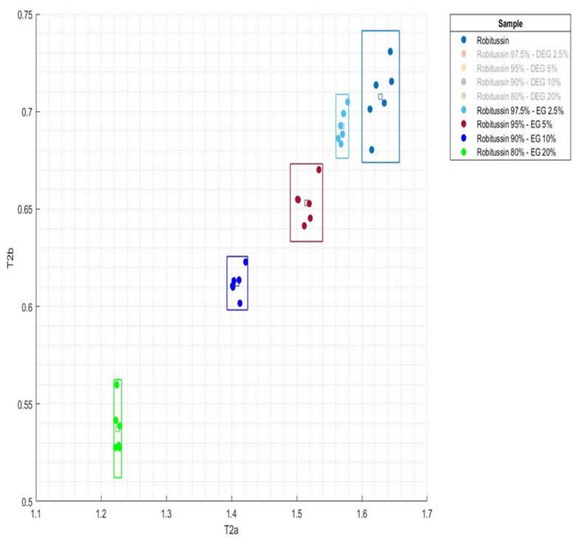



**Figure 5**: Multiple touch points exist for manipulation and/or error within the pharma sector supply chain. Low upstream visibility and control, travel delays with temperature deviations/lack of highly accurate temperature control, damage and batch splitting/product loss, and missing chain of custody.[12,13]

- Over 2/3 of US active ingredients were from India, China and Italy and >50% of finished pharma products manufactured ex-US.[14]
- Foreign FDA inspections are down 79% and domestic inspections down 35% in 2022 compared to 2019 highlighting need for easy touch point testing.[14]




**Objective 2:** Determine if the WaveGuide μNMR instrument can detect Diethylene Glycol (DEG) and Ethylene Glycol (EG) contamination in cough syrup.

- Robitussin cough syrup was spiked with Diethylene glycol and Ethylene glycol, both at 20%, 10%, 5%, and 2.5%.
- Bi-exponential model analysis - T2 values.
- Diethylene glycol and ethylene glycol contamination were both easily detectable down to 2.5%.

| Robitussin spiked with DEG | Mean (n=6) DEG Conc. (%) | | | | |
|---|---|---|---|---|---|
| | 0 | 2.5 | 5 | 10 | 20 |
| 2 exponential T2a | 1.6286 | 1.5564 | 1.4718 | 1.3524 | 1.1095 |
| 2 exponential T2b | 0.7076 | 0.6928 | 0.6817 | 0.6525 | 0.5726 |
| **Robitussin spiked with DEG** | **Standard Deviation (n=6) DEG Conc. (%)** | | | | |
| | 0 | 2.5 | 5 | 10 | 20 |
| 2 exponential T2a | 0.01437 | 0.01313 | 0.00639 | 0.01424 | 0.00397 |
| 2 exponential T2b | 0.01690 | 0.01856 | 0.01839 | 0.01610 | 0.00935 |

**Figure 3 and Table 3**: Bi-exponential analysis (T2) of Robitussin spiked with four concentrations of Diethylene glycol.

| Robitussin spiked with EG | Mean (n=6) EG Conc. (%) | | | | |
|---|---|---|---|---|---|
| | 0 | 2.5 | 5 | 10 | 20 |
| 2 exponential T2a | 1.6286 | 1.5698 | 1.5148 | 1.4089 | 1.2255 |
| 2 exponential T2b | 0.7076 | 0.6924 | 0.6532 | 0.6119 | 0.5373 |
| **Robitussin spiked with EG** | **Standard Deviation (n=6) EG Conc. (%)** | | | | |
| | 0 | 2.5 | 5 | 10 | 20 |
| 2 exponential T2a | 0.01437 | 0.00494 | 0.01239 | 0.00796 | 0.00293 |
| 2 exponential T2b | 0.01690 | 0.00820 | 0.00997 | 0.00685 | 0.01259 |

**Figure 4 and Table 4**: Bi-exponential analysis (T2) of Robitussin spiked with four concentrations of Ethylene glycol.