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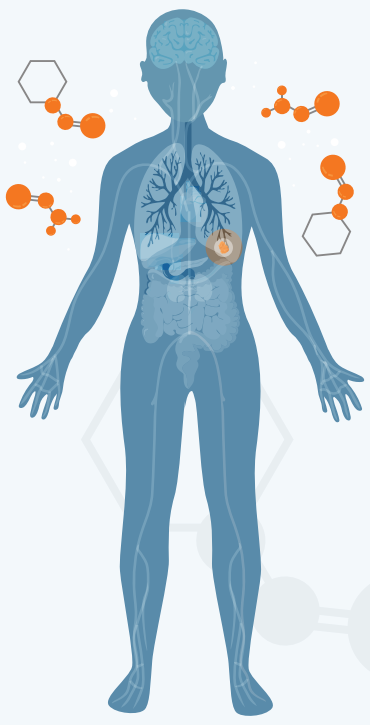
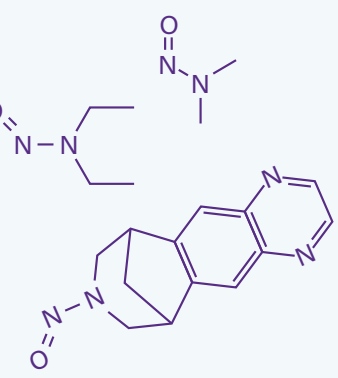
# N-Nitrosamines Analysis An Overview



## What are N-nitrosamines?

**N-nitrosamines** (nitrosamines) are mutagenic impurities that can **increase cancer risk** for those exposed to them for extended periods. The pharmaceutical industry faces significant challenges in controlling nitrosamines and exceeded acceptable intake limits has led to product recalls and withdrawals. Analytical testing is an essential aspect of nitrosamine control. Companies involved in synthesizing active pharmaceutical ingredients (APIs) and the manufacture of final drug product must have the analytical capabilities to identify and monitor nitrosamine impurities to **well below regulatory limits**, where necessary, based on risk assessment.


## Formation of Nitrosamines



Nitrosamines can form during many stages of method development, manufacturing, and storage. Sources include materials, reagents, solvents, catalysts, intermediates, and packaging. Recent years have seen an increased focus on the formation of **NDSRIs (Nitrosamine Drug Substance Related Impurities)**, as well as the low mass nitrosamines such as NDMA. Many APIs in marketed medicines are thought to be susceptible to forming NDSRIs, which poses a significant challenge for control, analysis, and regulation across a wide range of acceptable intake thresholds.

## Nitrosamine Detection and Analysis

### Method Development

LC-MS/MS is the preferred method for nitrosamine quantification due to the sensitivity, selectivity, and robustness it allows. Developing a sensitive assay for nitrosamines in the presence of API or drug product is challenging and influenced by factors like mobile phase quality and sample preparation. Optimized methods for **sensitivity, selectivity, and robustness** are crucial for successful validation, reliable performance, and future method transfer.


### Sample Preparation

Nitrosamines have diverse physicochemical properties, necessitating **comprehensive sample preparation**. Simple extraction methods are commonly sufficient, but liquid-liquid and solid phase extraction can enhance selectivity and sensitivity in complex matrices if needed. **Automated sample preparation techniques** can minimize analytical errors, improve assay reproducibility, and enhance precision.

### Chromatographic Selection

Selecting suitable chromatography and column chemistry is crucial for nitrosamine method development. A high quality separation method will chromatographically resolve the API peak from trace nitrosamines to minimize suppression effects. Using a divert valve to direct the API peak to waste, away from MS, is beneficial. **Customized methodologies are usually needed** for optimized separation in different drug substances and products.

### Optimized Sensitivity for API or Final Drug Product

**Tandem Quadrupole Mass Spectrometry** is preferred for detecting trace levels of nitrosamines in API or drug products. It is accessible and offers benefits like tailored ionization flexibility. APCI is favored for low-mass nitrosamines, while electrospray ionization usually suits larger NDSRI impurities. MRM ensures high **sensitivity and selectivity**. Full assay validation is necessary before submitting data to regulatory authorities.

### Nitrosamines & Beyond

Evolving regulatory requirements for nitrosamines drive the need for advanced analytical testing supported by end-to-end solutions. Implementing high-performance technologies and adaptable workflows that support methods surpassing regulatory thresholds will ensure a **future-proofed** lab environment for nitrosamine control and beyond.

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