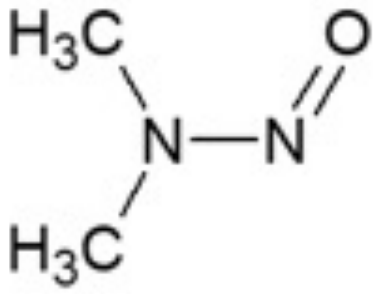
The ATNA Brochure

N-Nitrosodimethylamine
(NDMA)



NDMA, the simplest secondary amine nitrosamine

What are nitrosamines and why is impurity analysis important?

Nitrosamines are a general term used to designate a group of organic N-nitroso compounds with the chemical structure R2N– N=O. N-nitrosamines are produced by the reaction of a secondary or tertiary amine with a nitrating source such as nitric oxide, nitrites, nitrates (to a lesser extent than nitrites), dinitrogen tetroxide, or nitrous acid. These reactions maybe catalysed under acidic conditions or at elevated temperatures.

As many excipients contain nitrites/nitrates these should also be screened so that excipients with high concentration of nitrites/nitrates are not combined with amine based API's thus eliminating the risk of nitrosamine formation.

Nitrosamines are known to be carcinogens when ingested. They have been shown to cause tumours in the liver, lung, nasal cavity, oesophagus, pancreas, stomach, urinary tract, bladder, colon, kidneys, and central nervous system. Nitrosamines exist in safe, low concentrations in a wide variety of goods, including cosmetics, rubber products, tobacco products, processed meats, brewing and malting, agrochemicals, packaging and pharmaceutical drugs.

Current guidance from the US Food and Drug Administration (FDA) recommends the acceptable intake limits of 96ng/day for NDMA & NMBA and 26.5 ng/day for NDEA, NMPA, NIPEA, and NDIPA.

Nitrosamine analysis

In recent years nitrosamines have been a particular issue for the pharmaceutical industry with several high-profile product recalls. Off the back of these cases, regulatory bodies have required pharmaceutical companies to monitor their products, ingredients and processes for the potential to form nitrosamines.

Pharmaceutical companies do not have the resources to screen the ingredients and excipients for nitrites, nitrates and nitrosamines; so they tend to screen the formulated products for nitrosamines and perform risk assessments for the likelihood of nitrosamine formation during storage.

Historically this has been performed using mass spectrometry coupled to a GC or HPLC system. This has, however, proved very inefficient for pharmaceutical companies due to the sheer volume of samples and sample types, the often-complex sample preparation required, the extremely low detection limits and the potential for false positives.

Achieve regulatory limits for nitrosamine impurity analysis

Not only can nitrosamines be present in raw materials but also in active pharmaceutical ingredients (APIs), depending on the ingredients and solvents used in the manufacturing process. When present, even in small concentrations, they present a health and safety risk and are therefore a major concern for pharmaceutical manufacturers. Manufacturers need to have confidence in the accuracy of results and the instruments used to test for the formation of nitrosamines in both the raw materials and the finished product.

Ellutia has developed the ATNA system that offers a quick, reliable, sensitive, cost-effective screening method that identifies “of-risk” samples, reduces waste and costs, but increases the number and scope of testing and the safety of their products

The ATNA features:

- Provides an alternative to GC and LC-MS instruments, which can be expensive when testing for nitrosamine impurities.
- Analyse down to low ppb levels.
- Easily screen samples for nitrosamines, eliminating the need for a detailed speciated analysis.
- Screen excipients for nitrites/nitrates.
- Enable users to analyse a range of sample types.
- Increase the rate at which samples can be analysed.
- Fit into any laboratory without compromising sensitivity or selectivity when identifying nitrogen-containing compounds.
- It is a quick, reliable, sensitive, cost-effective screening method that identifies “of-risk” samples, reduces waste and costs, but increases the number and scope of testing and the safety of their products

How does the ATNA work?

1. Sample preparation

Some sample types can be added directly to the sample vial; others may require extraction into a solvent first. Once in the sample vial, the reagent can be added. The vial is then sealed and loaded into the autosampler.

2.Automated chemical reaction process

Samples are vortexed and then heated. The chemical reaction causes the NO groups from any nitrosamines, nitrites or nitrates present to be released into the headspace of the vial.

3.Headspace sampling

The samples are allowed to cool to ensure vapours from the samples or reagent have condensed. Then, a sample of the headspace, which contains the NO molecules that have been released, is injected into the detector.

4.Detection by TEA

The carrier gas sweeps the headspace to the reaction chamber of the TEA, reacting with ozone to produce NO_2 in an excited state. As the NO_2 relaxes, a photon of light is released and measured by a photomultiplier tube.

Automating Total Nitrosamine Testing

The ATNA offers a unique method for the rapid detection of nitrosamine compounds down to 1ppb NDMA. The ATNA offers a simple, accurate, and reliable test that delivers a clear pass/fail result for apparent total nitrosamine, nitrite or nitrate content (ATNC) within minutes.

Samples can be immediately cleared for release or positive samples sent for further testing by gas chromatography (GC) or liquid chromatography (LC). This allows manufacturers to meet the legal requirements of risk assessments without needing to outsource testing of raw materials or products at different stages of the manufacturing process.

If you would like to discuss the challenges you are facing, please feel free to contact us:

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Ellutia