Nitrosamines In Excipients

Understanding risk & how we manage it

Traces of nitrites in certain excipients can, in the presence of amines and under certain conditions, form nitrosamines (carcinogens). How does Lactalis Ingredients Pharma take proactive measures to ensure the safety of its pharmaceutical-grade lactose?

Nitrosamines formation cycle

Key Chemical Differences

Nitrosamines

a reaction product of nitrites and amines under acidic pH conditions, heat, or humidity

Nitrites

are nitrosating agents (that may be present in natural excipients)

Nitrates

Nitrates can also be considered a secondary concern due to their potential conversion into nitrites through reduction.

Where Do Nitrosamines in Excipients Come From?

- **Potential presence of nitrites** in ingredients of natural origin/raw materials
- **Water / agricultural practices / processing conditions** : heating, packaging, solvent recycling
- **Variability** depending on chemistry, batch, and supplier; process water is generally of little concern

Vulnerable amines:
Secondary or tertiary amine

A nitrosating agent

Appropriate conditions (elevated temperatures, acidic conditions, liquid phase / moisture)

Nitrosamines

How is estimated the potential for nitrosamine formation?

Vulnerable Amine: Secondary amine salts are typically more reactive, tertiary amines are less reactives

The risk of nitrosamines depends on several factors related to the product and its manufacturing process.

Product Information
- Product information (API content, tablet weight, daily dose) influences the patient's potential exposure.

Potential Nitrosamine
- The characteristics of nitrosamines (acceptable dose, molecular weight) allow for an assessment of the overall risk level.

Nitrosamines Risk

Nitrite Content
- Nitrite levels, which may originate from excipients, suppliers, or analytical testing, play a key role in nitrosamine formation.

Conversion Rate
- The conversion rate depends on the functional groups and the processes used during manufacturing.

Critical points & regulations

N-nitrosamines are a class of organic compounds, some of which are recognized as potentially carcinogenic

In July 2018, the European Medicines Agency (EMA) announced **the recall of several valsartan-containing products due to contamination with NDMA (N-nitrosodimethylamine).**
Following this incident, regulatory authorities **required pharmaceutical manufacturers to evaluate the risk of the presence or formation of N-nitrosamines** in medicinal products already on the market.

EMA
Oversees risk management in Europe and implements action plans

FDA
Sets thresholds and requires manufacturers to conduct inspections

ICH M7 (R2)
Global harmonization of controls

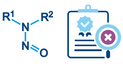
Impact: Enhanced analysis & supply chain transparency

Detection – Recent Methods

Method	Key advantage	Sensibility
Automated Total Nitrosamines Analyser (ATNA)	Rapid global screening of total nitrosamines (result in minutes)	+
High-resolution LC-MS/MS + Quantitative Structure-Retention Relationship (QSRR)	Accuracy & Prediction	++
Ion Chromatography + UV Spectroscopy (IC-UV)	Higher sensitivity, lower LOD for nitrite quantification	+++

Lactalis Ingredients Pharma Commitments

Selection of raw materials with low nitrite levels.



Process optimization: we do not use nitrite and nitrate salts, nor any other nitrosating agents.

Supplier transparency: as a supplier of pharmaceutical excipient we have completed the **Standardized IPEC (2023) questionnaire**

The **risk** of nitrosamines in pharmaceutical lactose is **generally low**, but **not zero** if vulnerable amines are present and certain conditions are met.

Collaboration between drug manufacturer and excipient supplier is key

Integrated supply chain

Thanks to Lactalis position as the **1st** world's largest cheese producer

We have direct access to a significant internal supply of whey.

Certifications for the pharmaceutical lactose manufacturing facility in Retiers

ISO 9001

EXCIPACT

Safety at the heart of your formulations

LOW NITRITES ≤ 0.1 ppm

Low nitrites

At Lactalis Ingredients Pharma, we offer a range of lactose monohydrate with a **guaranteed nitrite content ≤ 0.1 ppm,** to support the pharmaceutical industry in addressing the growing challenges associated with **nitrosamines**.

Nitrite testing is performed on **every batch** produced, and the **detailed value** are included **on each CoA.**

Conclusion

The potential presence of N-nitrosamines remains a major concern for the pharmaceutical industry and requires a comprehensive risk assessment at the finished drug product level. Although the contribution from excipients is generally low, it must be taken into account when vulnerable amines and nitrites are present. As a committed supplier, **Lactalis Ingredients Pharma offers pharmaceutical-grade lactose with controlled nitrite levels (≤ 0.1 ppm), backed by systematic analytical testing and high transparency. This approach enables us to effectively support manufacturers in their risk assessments. The control of nitrosamines relies on close and continuous collaboration throughout the supply chain.**

Let's talk about the safety of your formulations
Contact our experts | Request a sample
lactalisingredients.pharma@fr.lactalis.com

Others Sources

- Nitrosamine Contamination in Pharmaceutical Excipients: Risks & Prevention – 2025 – Lactalis Ingredients Pharma
- Nitrosamines – 2023 – Mérieux NutriSciences
- Nitrosamines : alerte de l'EFSA sur des aliments à risques – 2023 – Eurofins France

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