TECHNICAL BULLETIN

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Lifecycle Nitrosamines Risk Assessment

Introduction

In line with European nitrosamine risk assessment requirements, EIGA Member companies have evaluated the potential presence and formation of nitrosamines in medicinal gases and associated manufacturing, storage, and distribution systems (lifecycle).

The purpose of this EIGA Technical Bulletin is to present EIGA's evaluation on this topic and to summarise the experience, scientific rationale, and risk assessment conclusions of EIGA Member companies regarding the potential risk of nitrosamine contamination in medicinal gases.

Background

Nitrosamines are chemical impurities classified as probable human carcinogens. Their unexpected detection in certain medicines in 2018 led to significant regulatory action across the Europea Union (EU). The European Medicines Agency (EMA), together with national authorities, launched a comprehensive review to assess and control the risk of nitrosamine impurities in human medicines.

The EU has established a structured, risk-based approach for managing nitrosamine impurities in medicines. This framework applies to all chemical and biological medicinal products and is harmonized with international partners such as the US FDA and Japan's PMDA.

Key Requirements

Risk Evaluation: Marketing Authorisation Holders (MAHs) and manufacturers must assess all products and manufacturing processes for the potential formation or contamination of nitrosamines. This includes evaluating raw materials, solvents, reagents, catalysts, packaging, and the entire supply chain.

Confirmatory Testing: If a risk is identified, manufacturers must conduct sensitive analytical testing using validated methods. The scope of testing covers both active pharmaceutical ingredients (APIs) and finished drug products.

Control and Reporting: If nitrosamines are detected above the permitted limits, manufacturers must immediately notify authorities, update product authorisations, and implement control strategies to mitigate the risk. Ongoing monitoring and periodic reassessment are required throughout the product lifecycle.

Risk assessments must cover all stages of API and drug product manufacturing, including the use of recovered, reagents, catalysts, and packaging materials. Root causes for nitrosamine formation include the use of nitrosating agents (such as sodium nitrite) with amines, contaminated raw materials, and cross-contamination from equipment or recovered materials. Analytical methods must be highly sensitive and validated for nitrosamine detection.

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***EUROPEAN INDUSTRIAL GASES ASSOCIATION** AISBL*
AVENUE DE L'ASTRONOMIE 30 ♦ B-1210 BRUSSELS
PHONE +32 2 217 70 98 E-mail : info@eiga.eu - www.eiga.eu

Acceptable Intake Limits

The EMA has set Acceptable Intake (AI) limits for various nitrosamines based on their carcinogenic potency. For nitrosamines not yet categorized, a provisional AI limit is established using the Carcinogenic Potency Categorization Approach (CPCA). The general principle is to ensure that the theoretical cancer risk does not exceed 1 in 100,000 over a lifetime of exposure.

EIGA Assessment

Unlike chemically synthesized active substances, medicinal gases are not produced through organic synthesis routes involving amines, nitrosating agents, solvents, catalysts or reaction intermediates that are recognized contributors to nitrosamine formation.

The manufacturing processes for medicinal gases are predominantly based on physical separation, purification, compression, distillation, liquefaction and blending operations. These process types do not provide conditions conducive to nitrosamine generation.

What does Nitrosamine formation generally require:

- secondary or tertiary amines,
- nitrosating species,
- suitable reaction conditions.

The fundamental chemical prerequisites for nitrosamine formation are not present within medicinal gas production, purification, storage and cylinder filling operations.

Additionally, no intentional use of secondary amines, tertiary amines, nitrites or other nitrosating agents occurs during medicinal gas manufacture and filling.

Based on the nitrosamines risk assessment of manufacturing processes, raw materials, equipment, storage systems and distribution practices, no credible mechanism for the formation, introduction or accumulation of nitrosamines has been identified for medicinal gases. Consequently, the risk of nitrosamine contamination is considered negligible.

The risk assessments covered the full lifecycle of:

- Nitric Oxide and nitric oxide–containing gas mixtures, (Annex A)
- Nitrous Oxide, including nitrous oxide/oxygen mixtures, (Annex B)
- Oxygen, Nitrogen and Argon produced by cryogenic air separation, including Synthetic Air (Annex C)

Across all assessed processes, the calculated residual risk scores remained within the “no / negligible risk” category, as defined by the adopted risk rating scale, with values well below the threshold requiring qualitative or quantitative confirmatory testing.

The risk analyses demonstrate that:

No intentional use of nitrosating agents or amines is present in the assessed medicinal gas manufacturing and filling processes, except for upstream raw material production steps that are subject to purification and risk-mitigating controls prior to medicinal gas use.

Where potential sources of nitrosamines are theoretically identified (e.g. trace levels in air, water, raw materials or upstream intermediates), the manufacturing processes include multiple effective mitigation steps, such as washing,

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***EUROPEAN INDUSTRIAL GASES ASSOCIATION** AISBL*
AVENUE DE L’ASTRONOMIE 30 ♦ B-1210 BRUSSELS
PHONE +32 (0)2 217 70 98 E-mail: info@eiga.eu - www.eiga.eu

drying, filtration, adsorption, freezing-out, chemical degradation and significant dilution, which substantially reduce or eliminate any residual nitrosamines.

For Nitric Oxide and Nitrous Oxide mixtures, the high dilution factors applied during final product preparation further reduce any hypothetical impurity levels to concentrations well below levels of toxicological concern.

Note: Nitric oxide itself is not a nitrosamine and does not contain a nitrosamine impurity. Furthermore, the production and blending processes used for medicinal nitric oxide do not involve amine-containing reagents required for nitrosamine formation.

For Oxygen, Nitrogen and Argon produced via air separation units, although trace nitrosamines may theoretically occur in ambient air or water no evidence exists that these compounds can survive the sequence of compression, purification, adsorption and cryogenic distillation steps used in air separation processes. Consequently, transfer into the final medicinal gas product is not considered a credible contamination pathway.

Based on the absence of credible formation pathways and the negligible theoretical risk identified, EIGA considers that routine confirmatory nitrosamine testing is not scientifically justified and would not be expected to provide meaningful additional assurance of product quality or patient safety. , unless:

- a process change is introduced that could alter the risk profile, or
- new information becomes available indicating a potential new source of nitrosamines.

This is consistent with the risk-based approach established by EU authorities for nitrosamine management in medicinal products and supports the principle that controls should be commensurate with the identified level of risk throughout the product lifecycle.

Note: To the knowledge of EIGA and its member companies, no confirmed cases of nitrosamine contamination attributable to medicinal gas manufacturing, storage, distribution or cylinder filling have been reported.

EIGA Conclusion

Based on the performed assessments, medicinal gases should be categorized as products with no identified nitrosamine risk or, where a risk categorization scheme is applied, as products presenting a negligible theoretical risk not warranting confirmatory testing.

Member companies are committed to:

- report any issue related to nitrosamines risk assessments
- process changes are evaluated for nitrosamines risk through change control,
- and periodic review is performed in line with regulatory expectations.

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