

## Q&A with Ardena Experts

# Nitrosamine Risk Assessment According to ICH M7

**Karel Aelvoet, Ph.D.**  
Principal CMC Manager  
**Joost Steverlynck, Ph.D.**  
CMC Writer  
**Bram Ach, Ph.D.**  
CMC Writer

***What are nitrosamines, and why are they a concern in pharmaceuticals?***

Nitrosamines are chemical compounds classified as probable human carcinogens based on animal studies. They are concerning in pharmaceuticals due to their potential to cause cancer upon long-term exposure, even at trace levels. Regulatory agencies require thorough risk assessment and control to minimize patient exposure.

***What is ICH M7, and how does it relate to nitrosamine risk assessment?***

ICH M7 provides guidance on the assessment and control of DNA-reactive impurities in pharmaceuticals to limit potential carcinogenic risk. While primarily focused on mutagenic impurities, its principles are applied to nitrosamines due to their DNA-reactive nature.

Nitrosamines are included in the “cohort of concern” in ICH M7, referring to chemical classes with exceptionally high carcinogenic potency, where the general Threshold of Toxicological Concern (TTC) of 1.5 µg/day is not protective enough. The ICH M7 framework emphasizes a risk-based approach for identification, control, and acceptable limits for these impurities.

***How does the risk assessment process for nitrosamines under ICH M7 work?***

The risk assessment process involves several steps:

1. Identification: Evaluate potential sources of nitrosamines, including raw materials, reagents, solvents, intermediates, manufacturing processes, storage, and packaging.
2. Evaluation: Determine the likelihood of nitrosamine formation or contamination based on process knowledge and experimental data.
3. Control: Implement appropriate controls if the presence of nitrosamines is identified or expected. This may include modifying processes, changing materials, or enhancing analytical monitoring.
4. Qualification: For any detected nitrosamines, assess their safety based on established acceptable intake limits.

***How are analytical methods used in nitrosamine risk assessment?***

Analytical methods such as GC-MS, LC-MS, and NMR are employed to detect and quantify nitrosamines. Methods must be sensitive, specific, and validated for the intended purpose. Their development is essential for confirming the presence and levels of nitrosamines in pharmaceuticals.

***What control strategies are recommended under ICH M7 for nitrosamines?***

Control strategies include:

- Process modifications to eliminate or reduce nitrosamine formation.
- Specification of raw materials to limit nitrosamine precursors.
- Theoretical purge calculations on potential risk compounds based on process description (e.g., Teasdale approach) and experimental data.
- Analytical testing where necessary.
- Setting limits based on the acceptable daily intake (ADI) of identified nitrosamines.

***What should manufacturers do if nitrosamines are detected above acceptable limits?***

If nitrosamines are detected above acceptable limits, manufacturers must:

- Implement corrective actions to reduce or eliminate nitrosamines.
- Perform risk-benefit assessments if immediate control is not possible.
- Communicate findings to regulatory authorities as required.

***How should changes in manufacturing processes be evaluated for nitrosamine risks?***

Any change in manufacturing processes, raw materials, or suppliers must be re-evaluated for potential nitrosamine formation. Risk assessments should be updated accordingly, and analytical testing may be necessary to verify control.

***Are there any exceptions to the application of ICH M7 for nitrosamine risk assessments?***

While ICH M7 applies broadly, exemptions may apply when nitrosamines are unavoidable but present at levels considered negligible based on risk assessment. These cases require proper justification and regulatory acceptance.

Examples include palliative care and the treatment of advanced cancer patients, where a higher acceptable intake of mutagenic impurities may be appropriate since the risk of hypothetical future cancer is outweighed by the immediate therapeutic benefit.

***What documentation is expected for nitrosamine risk assessment according to ICH M7?***

Manufacturers should document:

- A complete process description used to identify potential risks.
- Comprehensive risk assessments covering potential sources of nitrosamines.
- Analytical test results, including method validation reports.
- Control measures implemented to mitigate risk.
- Justifications for any deviations from established limits or requirements.

***What is the Carcinogenic Potency Categorization Approach (CPCA)?***

The CPCA is a framework developed to classify N-nitrosamine impurities into categories based on their predicted carcinogenic potency. It supports risk assessment when experimental carcinogenicity data are not available.

The CPCA groups nitrosamines into five categories (1–5), based on structural features and read-across from available carcinogenicity studies:

- Category 1: AI ~ 18 ng/day
- Category 2: AI ~ 26.5 ng/day
- Category 3: AI ~ 150 ng/day
- Category 4: AI ~ 1500 ng/day
- Category 5: AI ~ TTC default (1500 ng/day) unless otherwise justified

**How does CPCA relate to ICH M7?**

While ICH M7 establishes general principles for mutagenic impurities, it does not provide potency-based limits for nitrosamines. CPCA fills this gap by offering a nitrosamine-specific categorization framework aligned with ICH M7 principles.

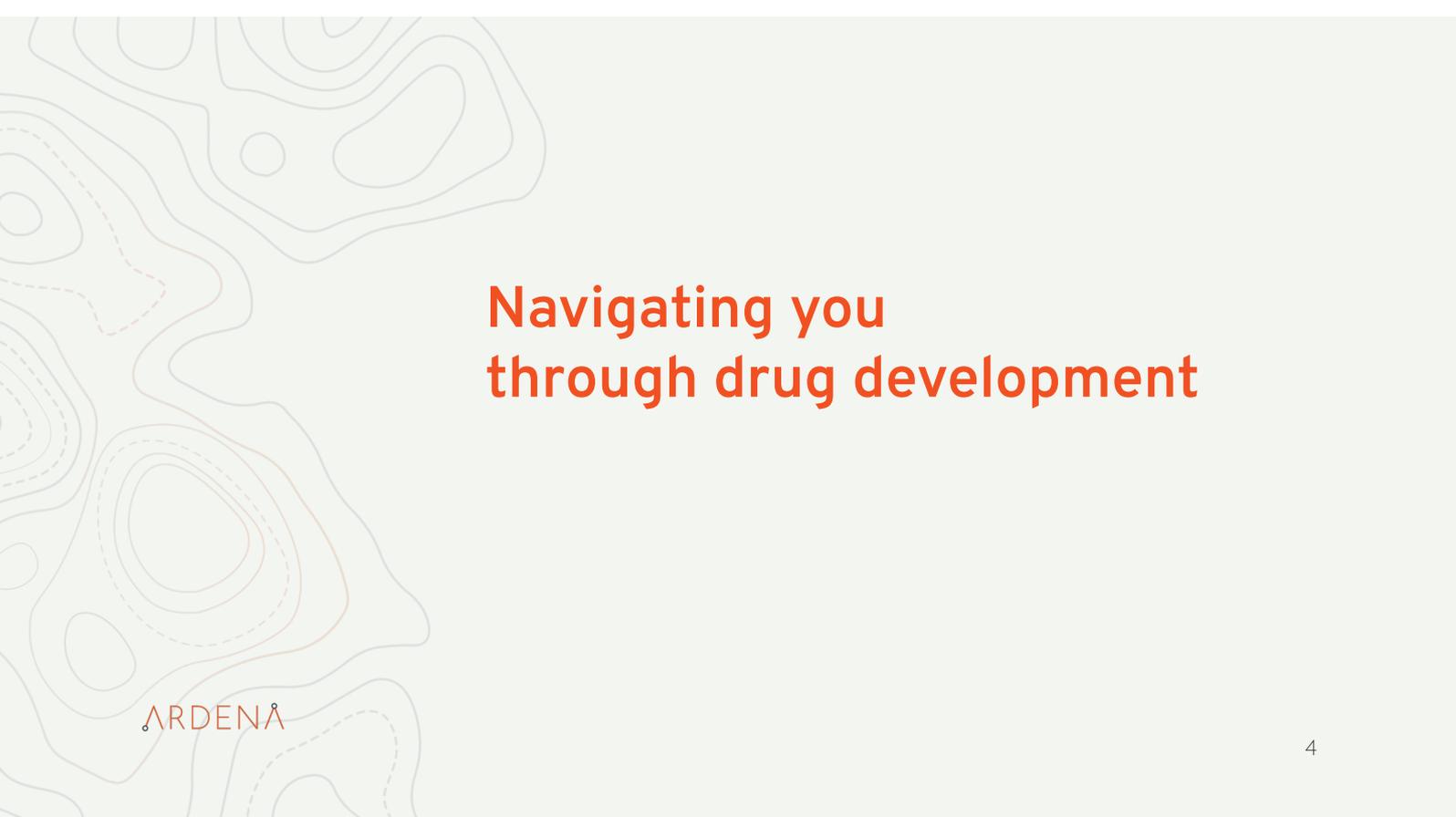
**Who accepts CPCA categorization?**

Both EMA and FDA recognize CPCA as an acceptable approach for deriving AI limits when data are lacking. Other health authorities (e.g., Health Canada, PMDA) may also accept it if adequately justified.

**What are some commonly referenced acceptable intake (AI) limits for nitrosamines?**

While CPCA provides a general framework, compound-specific limits based on toxicological data are also established. Examples include:

- 96 ng/day for N-Nitrosodimethylamine (NDMA), a common risk associated with the use of dimethylformamide (DMF) as a solvent.
- 26.5 ng/day for N-Nitrosodiethylamine (NDEA), a common risk associated with the use of triethylamine during synthesis.

A decorative background on the bottom half of the page featuring a topographic map with contour lines in shades of blue and orange.

**Navigating you  
through drug development**