Nitrosamine Safety Assessment in Generic Drugs: A Pharm/Tox Perspective

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Nitrosamine Safety Assessment

- Overview
- Common pitfalls
- Summary and recommendations

Nitrosamine Safety Assessment Overview

- Small molecule nitrosamines and complex nitrosamines (NDSRIs)
- Potent rodent carcinogens, probable human carcinogens
- Metabolic activation necessary for downstream effects
- Belong to cohort of concern (CoC) in ICH M7
  - Require tighter control limits than typical mutagenic impurities (<1.5 mcg/day)
  - Apply compound-specific AI limits to limit nitrosamine cancer risk

NDSRIs: nitrosamine drug substance-related impurities
ICH: International Council for Harmonization
AI: Acceptable Intake

FDA Nitrosamine Safety Assessment

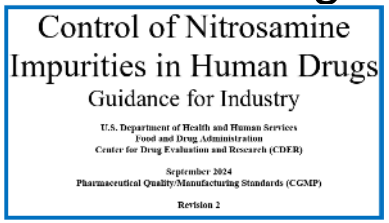
- Recommendations are based on science
  - FDA, in partnership with HESI, has actively contributed to advancing nitrosamine science
- Multidisciplinary group of experts across FDA support nitrosamine-related decisions and guidance
  - National Center for Toxicological Research
  - Nitrosamine safety team coordinates within CDER Pharm/Tox and engages CDER Quality, compliance, drug shortage staff, regulatory policy experts for enhanced coordination
- FDA participates international harmonization efforts for nitrosamine impurities

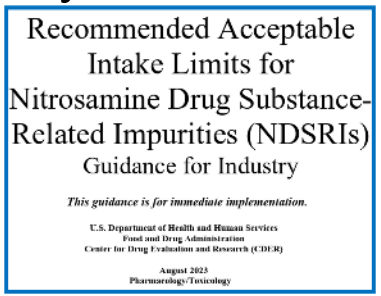
HESI: Health and Environmental Sciences Institute

Nitrosamine Safety Assessment Overview

FDA Recommendation

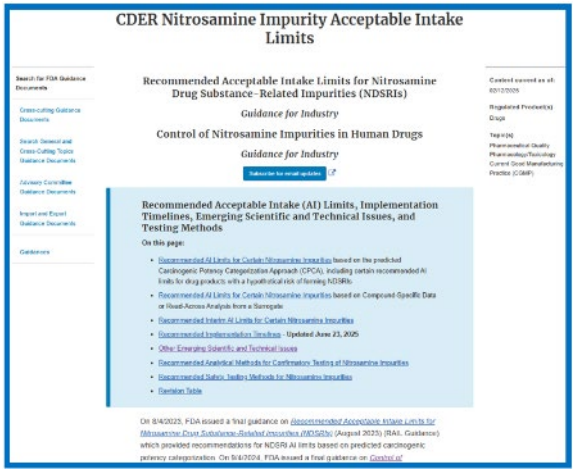
- Follow FDA guidances for nitrosamine impurities
- Recommended methods for setting AI limits
  - Carcinogenic Potency Categorization Approach (CPCA)
  - AI limit based on compound-specific data
  - Read-across from a surrogate with robust carcinogenicity data
- FDA guidance
  - Quality guidance (2024)
  - Safety guidance ("RAIL" Guidance, 2023)
  - Nitrosamine Webpage: CDER Nitrosamine Impurity AI Limits


Control of Nitrosamine Impurities in Human Drugs
Guidance for Industry
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 2024
Pharmaceutical Quality/Manufacturing Standards (CGMP)
Revision 2


Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)
Guidance for Industry
This guidance is for immediate implementation.
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2023
Pharmacology/Toxicology

FDA Recommendation
Nitrosamine Webpage

- Provides updated guidance
- List of recommended AI limits and interim limits for certain nitrosamine impurities
- Recommendations on analytical methods and safety testing methods
- Guidance on emerging issues
- Implementation timelines



FDA Recommendation
"RAIL" Guidance

- Use the CPCA framework to establish an AI for NDSRI
  - CPCA-based AI as starting point, in absence of toxicity data
- Approaches to justify alternate AI limit
  - AI ≤1500 ng/day: (-) enhanced Ames test (EAT), in vitro mammalian mutation, in vitro metabolism data
  - AI > 1500 ng/day: additional (-) in vivo mutagenicity (transgenic rodent assay)
  - Read-across (RaX) to surrogate: structurally relevant nitrosamine, robust carcinogenicity data
- (-) in vivo mutagenicity ≠ ICH Q3A/Q3B qualification threshold

Nitrosamine Safety Assessment Common Pitfalls

- Inadequate EAT to assess mutagenicity
- Alternate AI limit solely based on negative EAT
- Inappropriate surrogate to establish AI limit

Common Pitfalls
Inadequate EAT

- Inadequate dose selection of test article, low top dose
- Selected solvent concentration interfering with metabolic activation
- Lack proper nitrosamine positive controls
- Insufficient metabolic activation condition

Common Pitfalls

Alternate Limit Based on Negative EAT only

- FDA recommends additional studies
  - In vitro mammalian mutation assay
  - In vitro metabolism study focusing on α-hydroxylation
- Support alternative AI ≤ 1500 ng/day

Common Pitfalls

Inappropriate Surrogate for RaX

- Structure consideration:
  - *N*-nitroso alert in the same chemical environments
  - Degree of substitution
  - Steric bulk
  - Electronic influences
  - Metabolic activation potential and resulting metabolites stability/reactivity
  - Overall molecular weight (MW)
- Data consideration
  - Surrogate should have robust carcinogenicity data

Additional Pitfalls

- Applying approaches that are currently being investigated for their applicability
  - MW or less-than-lifetime (LTL) adjustment
  - AI limit based on in vivo mutagenicity data
    - A positive mutagenicity signal warrants a CPCA-based AI limit
- Using general toxicity study to justify alternate AI
  - Mutagenicity evaluation is critical
  - Recommend transgenic rodent gene mutation assay (OECD 488)

Additional Pitfalls (continued)

- Controlling at ICH Q3A/Q3B qualification threshold for non mutagenic nitrosamine
  - FDA considers outcomes of compound-specific assessment and batch testing
- Citing other regulators' AI recommendation without supporting data or right of reference
- Controlling nitrosamine at level observed in RLD
- Considering interim AI limit as final product control limit

Nitrosamine Safety Assessment Summary and Recommendations

- Follow FDA nitrosamine guidances
- Use CPCA-based AI limits in the absence of compound-specific data
- Monitor FDA nitrosamine webpage for updates
- OGD Pharm/Tox collaborates on nitrosamine science, assessment, and harmonization
- Reach out to OGD for questions (e.g., Controlled Correspondence)

Resources

- FDA Guidance for Industry Control of Nitrosamine Impurities in Human Drugs (Revision 2) September 2024; https://www.fda.gov/media/141720/download
- FDA Guidance for Industry Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs), August 2023; https://www.fda.gov/media/170794/download
- CDER Webpage, CDER Nitrosamine Impurity Acceptable Intake Limits; Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs); Control of Nitrosamine Impurities in Human Drugs, Content current as of 06/30/2025; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related
- Guidance for industry M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (July 2023); https://www.fda.gov/media/170461/download
- Guidance for industry Good ANDA Submission Practices (January 2022); https://www.fda.gov/media/110689/download
- Guidance for industry Controlled Correspondence Related to Generic Drug Development (March 2024); https://www.fda.gov/media/164111/download
- HESI nitrosamine research; https://hesiglobal.org/gttc-nitrosamines/