Nitrosamine Risk Assessment in Type II DMFs Supporting GDUFA Applications

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FDA Disclaimer

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

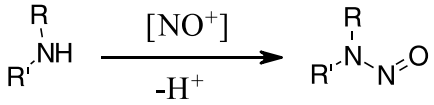

Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Learning Objectives

- Formation of nitrosamines
- Nitrosamines in drug products and FDA guidances
- Potential root causes of nitrosamines in API
- Nitrosamine risk factors in API
- Recommendations to API manufacturers
- Approaches for determining Acceptable Intake (AI) limits
- Nitrosamine control strategies
- Summary

Formation of Nitrosamines

Nitrosation of secondary amines under acidic conditions



Nitrosating agent (NO^+)	Structure	Nitrosating agent (NO^+)	Structure
Nitrite salt	MNO_2 (M = Metal)	Nitrogen dioxide	NO_2
Nitrate salt	MNO_3 (M = Metal)	Dinitrogen tetroxide	N_2O_4
Nitrous acid	HNO_2	Nitrous anhydride	N_2O_3
Nitric acid	HNO_3 (contains N_2O_4)	Alkyl nitrite	R-ONO
Nitrosyl halide	X-NO (X = halides)	Nitro compound	R-NO_2 (R = alkyl)

- Tertiary amine may undergo dealkylation to form secondary amine which may undergo nitrosation
- Amide solvent may decompose to secondary amine which may undergo nitrosation

Cohort of Concern (CoC)

- Nitrosamines are included in a group of high potency mutagenic carcinogens referred to as cohort of concern (CoC) compounds in ICH M7(R2). They are regulated more tightly than typical mutagenic impurities because of their high carcinogenic potency.

ICH M7(R2), 2023.
https://database.ich.org/sites/default/files/ICH_M7%28R2%29_Guideline_Step4_2023_0216_0.pdf

Small Molecule Nitrosamines in Drug Products

- June 2018 – FDA informed of the presence of *N*-Nitrosodimethylamine (NDMA)
- Sep 2018 – *N*-Nitrosodiethylamine (NDEA) detected in a previously recalled Valsartan
- Oct 2018 – Certain Irbesartan products voluntarily recalled due to NDEA
- Nov 2018 – Certain Losartan products voluntarily recalled due to NDEA
- Mar 2019 – *N*-Nitroso-*N*-methyl-4-aminobutyric acid (NMBA) detected in Losartan
- Dec 2019 – NDMA detected in some Metformin products
- Jan 2020 – Certain Nizatidine products voluntarily recalled due to NDMA
- Apr 2020 – FDA requested withdrawal of all Ranitidine products from U.S. market

Link: https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

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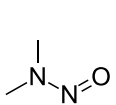
- **Feb 2021 FDA published "Control of Nitrosamine Impurities in Human Drugs" guidance**

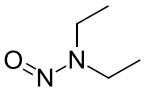
Recommended Control Limits for Certain Nitrosamine Impurities in Human Drugs

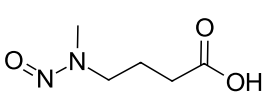
Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

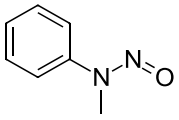
[1] The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA,NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure. Appendix B includes a description of the AI derivation for NDMA, which is an example of how FDA applied ICH M7(R1) to set a limit.

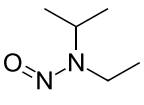
[2] The conversion of AI limit into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

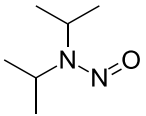

NDMA


NDEA


NMBA


NMPA


NIPEA


NDIPA

FDA, 2021. FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs (available at https://www.fda.gov/media/141720/download)

Nitrosamine Drug Substance-Related Impurities (NDSRIs) in Drug products

- Recently, FDA has received additional reports of certain types of nitrosamine impurities that formed in several drug products. These nitrosamine drug substance-related impurities (NDSRIs) are a class of nitrosamines sharing structural similarity to the API. FDA identified this issue in a public statement on November 18, 2021.

  Link: https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities

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- **Aug 2023 - FDA published "Recommended Acceptable Intake Limits (RAIL guidance) for NDSRIs"**

  Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related

RAIL Guidance for NDSRIs

NDSRI Potency category	Recommended AI (ng/day)
1	26.5
2	100
3	400
4	1500
5	1500

Link to the RAIL Guidance for NDSRIs:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related

FDA guidance webpage provides additional information on AI limits

- **Table 1:** Searchable list of 264 hypothetical NDSRIs, potency categories and associated recommended AI limit
- **Table 2:** List of NDSRIs for which FDA has identified an AI limit based on compound-specific data or read-across
- Webpage will be updated periodically

Root Cause of Nitrosamine in API

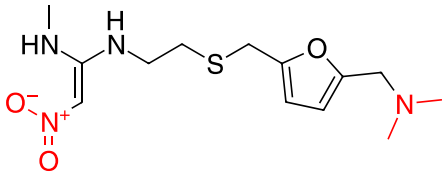
- Intrinsic Properties of API
- Process Related
- Quality of Raw Materials

1. FDA, 2021. FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs (available at https://www.fda.gov/media/141720/download)

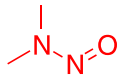
2. Journal of Pharmaceutical Sciences 2023, 112, 1166

Root Cause of Nitrosamine in API - Intrinsic Properties of API

- A nitro group and a secondary or tertiary amine are both structural components of the same molecule (e.g., ranitidine)



Ranitidine

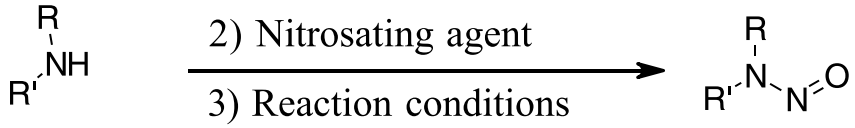


NDMA

  - ➢ Intermolecular degradation of API without the requirement for any exogenous nitrite

Org. Process Res. Dev. 2020, 24, 2915

Root Cause of Nitrosamine in API - Process Related



1) Nitrosable amine

Nitrosamine

In the most common pathway to formation of nitrosamines, three factors are required:

1. Presence of a nitrosatable amine
2. Presence of a nitrosating agent
3. Conditions conducive to *N*-nitrosamine formation

Root Cause of Nitrosamine in API - Process Related

1. Presence of a nitrosatable amine

- Amine functional groups are very common on API molecules
- Tertiary and secondary amines are common bases used in synthesis
- Amide solvents are common and can significantly degrade under high temperature to form secondary amines (e.g., Dimethyl formamide)

Root Cause of Nitrosamine in API - Process Related

2. Presence of a nitrosating agent

2a. Nitrosating Agents:

- Can be intentionally added as a nitrite salt or as nitrous acid
- Can be an impurity in another reagent such as nitric acid or sodium azide

2b. Alkyl nitrites:

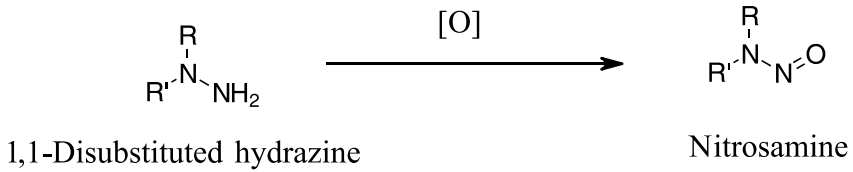
- May be added intentionally
- May be an impurity from rearrangement of nitroalkane (prevalence is unknown)

3. Conditions conducive to nitrosamine formation

- Acidic conditions facilitated nitrosating reactions

Root Cause of Nitrosamine in API - Process Related

- **Oxidation of 1,1-disubstituted hydrazines to nitrosamines** (Ref: Environ. Mol. Mutagen. 1991, 17, 59)



1,1-Disubstituted hydrazine Nitrosamine

- **Nitrite formation by oxidation of hydroxylamine or nitrite release from nitro-aromatic precursors (e.g. by fluoro de-nitration)**
- **Fluid bed drying**
  - Exposure of API to nitrogen oxides (NOx) in large volumes of air poses nitrosamine risk (Ref: Org. Process Res. Dev. 2023, 27, 2123)
- **Use of activated charcoal**
  - Use of charcoal in the final stage in the presence of secondary amine poses nitrosamine risk (Ref: Environ. Sci. Technol. 2011, 45, 8368)

Root Cause of Nitrosamine in API - Process Related

- **Poor operation/design of process steps**
  - Poorly performed aqueous/organic separation, inadequate washing during isolation of a solid
  - Purification steps are inadequate to purge nitrosamine to below acceptable limit
- **Cross contamination in multi-purpose facilities**
  - Impurities formed from one process were found in an API made by a different process due to improper cleaning between batches

Root Cause of Nitrosamines in API - Quality of Raw Materials

- **Use of raw materials containing impurities**
  - Amine and nitrosamine impurities were found in fresh solvents (e.g., toluene, methanol, methylene chloride, formalin, formic acid)
  - Use of disinfected water (chlorination, chloro-amination, ozonisation)
  - Nitrite impurities found in sodium azide, water, sodium carbonate, sodium bicarbonate and sodium hydroxide
- **Recycled materials such as solvents, reagents and catalysts**
  - Use of recovered reagents or solvents are confirmed sources of nitrosamines

Small Molecule Nitrosamine Risk Factors in API

Risk factors for small molecule nitrosamine formation

- Use of 2º or 3º amine bases or 3º amide solvents and nitrosating agents are deliberately added to the process or present as significant impurities in other materials, especially if the precursors are in the same or adjacent steps.
- 1,1-Disubstituted hydrazines or their imines are present in the process.

NDSRI Risk Factors in API

Risk factors for NDSRI formation

- The starting material, intermediate, related substances or API have a 2º or 3º amine functional group and nitrosating agents are deliberately added to the process or present as significant impurities in other materials, especially if the precursors are in the same or adjacent steps.
- The process use fluid bed drying or jet milling and the API or counterion contain 2º amine.
- Activated carbon is used in the purification of the crude or final API and the API or counterion contain 2º amine.

Recommendations to API Manufacturers

- Look at the API synthetic route holistically
- Audit starting material and intermediate vendors, understand the risk coming from purchased materials
- If a risk of nitrosamine impurities is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods
- If nitrosamines are detected-
  - Perform root cause analysis
  - Implement changes to manufacturing process to prevent/reduce nitrosamines
  - Add controls where necessary for nitrosamines which are present
- Report changes implemented to FDA

Approaches for Determining AI limit of NDSRIs

- Check whether the AI limit appears on the FDA website (Table 1 and Table 2)†
- If AI limit cannot be found in the above tables, determine AI limit using CPCA (Carcinogenic Potency Categorization Approach) recommended in RAIL (Recommended Acceptable Intake Limits) guidance for NDSRIs‡
- RAIL guidance provides applicants with options if they are unable to meet their CPCA-based AI limit:
  - Read-across from a surrogate
  - Compound-specific toxicology data
- Alternate approaches mentioned above may be used for *N*-nitroso compounds that are out of scope of the CPCA (e.g., *N*-nitrosamides)

† Link to Table 1 and Table 2: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related#predicted

‡ Link to RAIL guidance for NDSRIs: https://www.fda.gov/media/170794/download

Nitrosamine Control Strategies

- **ICH M7 options can be use as control strategies with appropriate supporting data and justification.**

- **Multiple nitrosamines are controlled in the specification:**
  - If more than one nitrosamine impurity [NDSRI(s) and/or small molecule nitrosamine(s)] is controlled in the DS specification, and the total level of nitrosamines exceeds the recommended AI limit for the most potent nitrosamine based on the maximum daily dose, the manufacturer should contact the Agency.

Challenge Question #1

Fluid bed drying or jet milling in the API manufacturing process has potential to form NDSRI when API contains:

A. Primary amine
B. Secondary amine
C. Tertiary amine
D. Amide

Challenge Question #2

Which of the following nitroso compound is out of scope of CPCA (Carcinogenic Potency Categorization Approach)?

A. *N*-Nitrosamines

B. *N*-Nitrosamides

C. *N*-Nitrosoguanidines

D. *N*-Nitrosoureas

E. All the above except A

Summary

- Nitrosamine formation may be a risk in API
- Process understanding is essential to mitigate the risk
- Build quality into the process to minimize/eliminate nitrosamine formation
- Always take a holistic approach when assessing risk
- Use CDER-OPQ-Inquiries@fda.hhs.gov for questions related to nitrosamine in API