Mission Impact

Nitrosamine Impurities: Beyond a Compendial Standard - Learnings from USP's Nitrosamines Exchange Community

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200 usp The standard of trust

1 Development of a Standard

Components that Enable Impactful Standards

Aligned with

Public health and patient safety priorities

Developed by

Independent experts
Industry and Volunteers

Practical for

- Users of the standard
- Enforcers of the standard

Adapted & Improved

In response to public health challenges

The journey of a potential standard is not a straight path and does not always end in “the monograph”

Engagement and collaboration are essential

Identifying
- Workshops
- Roundtables
- User forums
- 1:1 engagements with community members

Congealing
- Research
- Collaborations

Refining
- PF
- Open Forums

Implementation Support

Start here

Or here

Or here

Or here

Or here

Incubating
- Workshops
- Roundtables

Distilling
- EP
- Stimuli or journal articles
- White papers
- Collaborations

Final Feedback
- PF
- EC

Beyond Compendial Solutions

Nitrosamine Quick Evolution

Timeline

26 Jun — **NDMA in ZH Valsartan** *Rapid Alert Network*

Jul — Recalls of valsartan

Taiwan FDA — **NDMA in ZT Valsartan**

OMLC in Germany — **NDEA in ZH Valsartan**

20 Sep — **NDEA in HL Losartan**; Article 31 Extend the scope to review all sartans with tetrazole ring

Oct — Recall expanded to other sartans

NDEA in Irbesartan

Dec — **NDIPA in valsartan**

Jan — **NDMA in Pioglitazone**

2 May — **NMBA in HL Losartan**; Sartans End Article 31

Sept — **NDMA** Found in Ranitidine medicines

July — **NMPA in Valsartan**

Nov — Nitrosamine found in Nizatidine

12 Sep — Ranitidine Article 31 triggered

Oct19 — FDA issue warning letters due cGMP violations

Apr — Suspension of ranitidine medicines in the EU

24 Jun — Lessons Learnt Nitrosamines in Sartans

1 Apr — Ranitidine Market Withdrawal

16 Apr — Recalls of Nizatidine

Jul — Release of USP nitrsoamine standards NDMA, NDEA, NDIPA NDBA, NEIPA, NMBA

1 Sep — **NDMA** in metformin products

1 Sep — FDA issues guidance "Control of N-Nitrosamine Impurities in Huma Drugs"

1 Sep — USP <1469>

2021 — Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products

nitrosamine drug substance related impurities (NDSRIs)

2022

N-Nitroso-irbesartan

N-Nitroso-Desloratadine

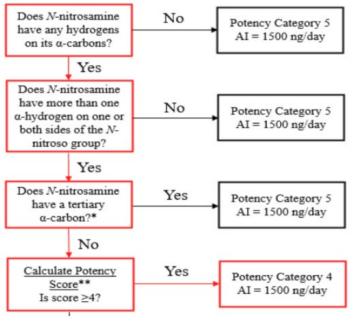
N-Nitroso-Folic Acid

N-Nitroso-Quinapril

N-Nitroso-Orphenadrine

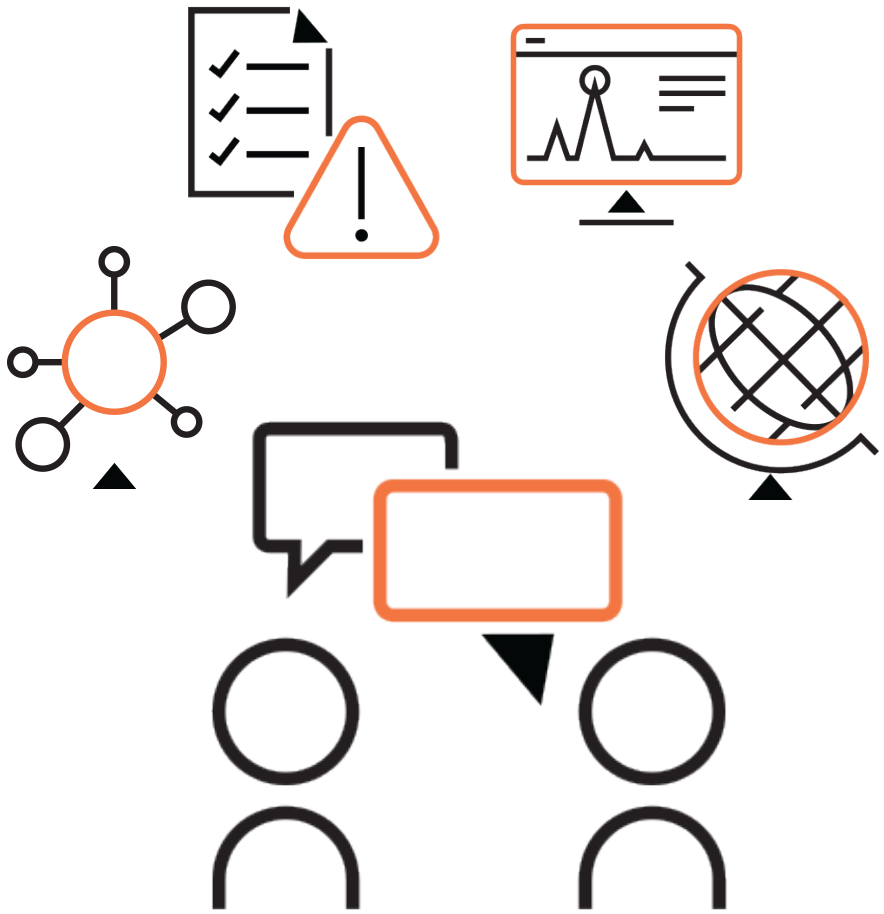
N-Nitroso-Propranolol

July — **CPCA**



2 — 2019 — 2020 — 2021 — 2022 — 2023

USP Knowledge Hub



- Unleashing the **power of online communities**
- Increase and **accelerate early scientific knowledge** exchange in select topics
- Strong **sense of community and belonging**, despite not operating in physical space
- *Democratization and inclusion of knowledge*
- Hosted by USP, BUT defined by the members
- A new tool in USP's ecosystem of engagement approaches

Join http://nitrosamines.usp.org

Knowledge Hub: Is & Is NOT

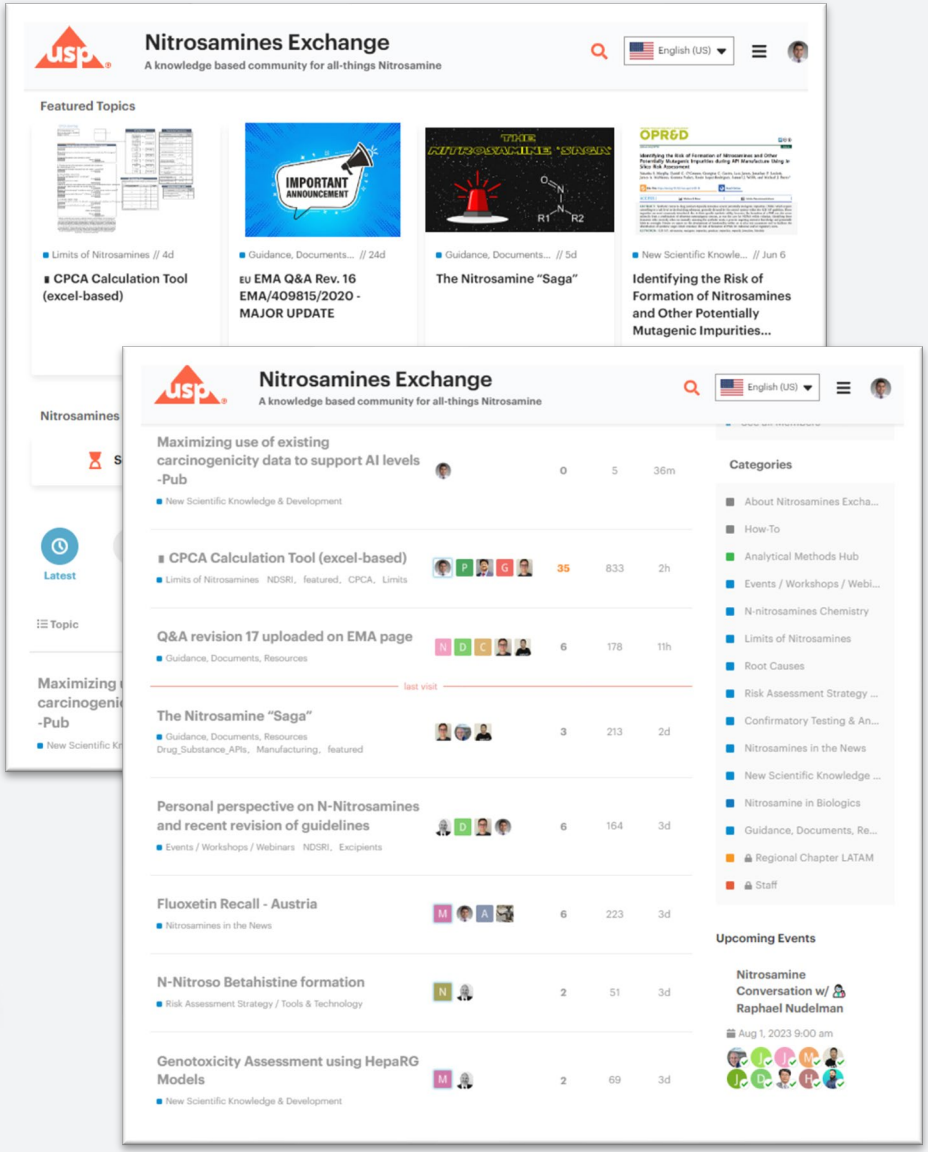
- ***It is*** supporting USP's efforts to increase early connectivity and engagement with *SMEs*
- ***It is*** a monitored community platform for scientific knowledge exchange on all-things nitrosamine
- ***It is*** a forum to incubate, learn and share knowledge/resources with a global community

- ***It is not*** focused on USP General Chapter <1469> *Nitrosamine Impurities*
- ***It is not*** a substitute for public comment in PF or compendial processes
- ***It is not*** a venue to influence or change policy

Nitrosamines Exchange

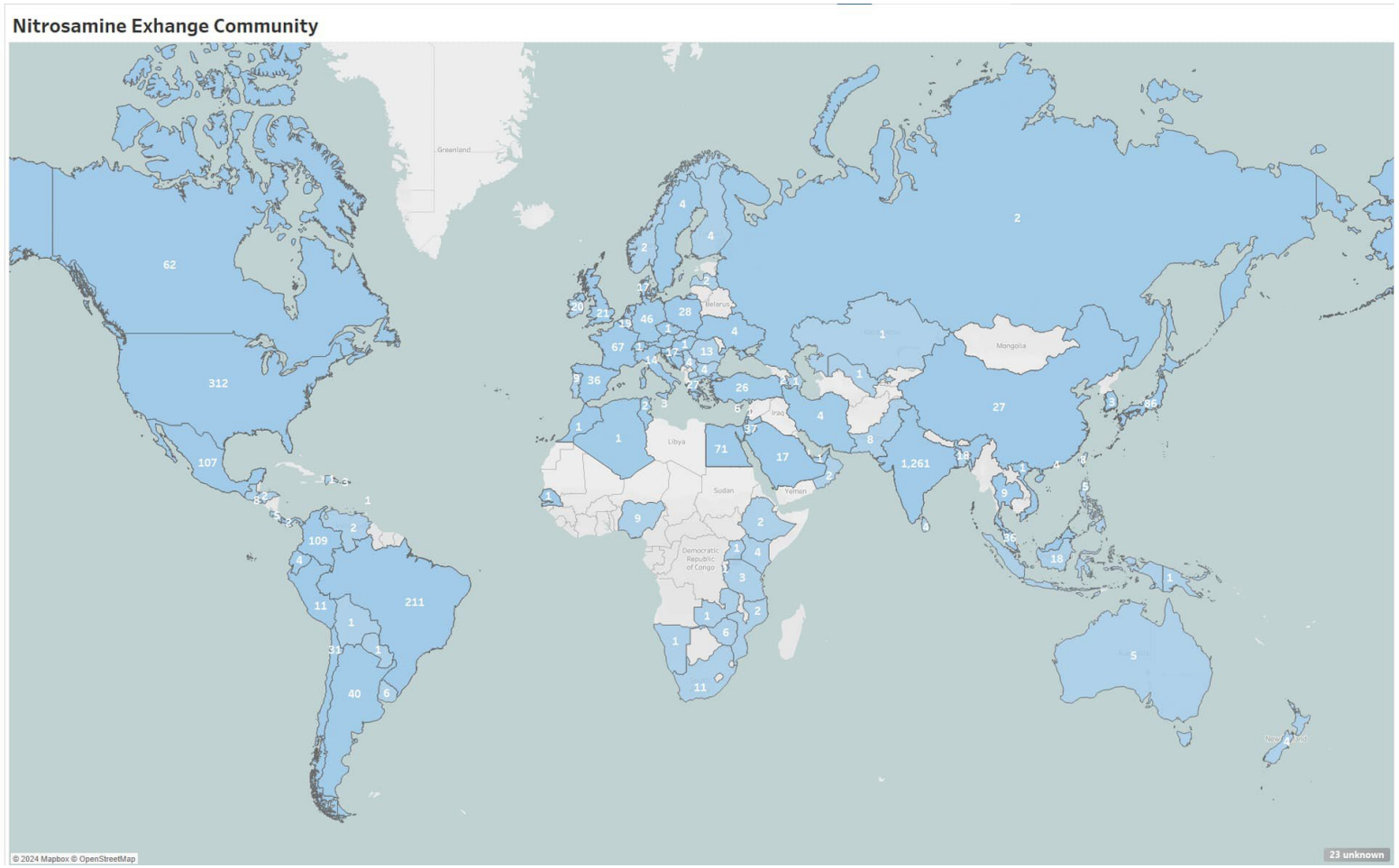
An online knowledge-based community on all-things nitrosamines

- 4600+ members, 80+ countries
- Ability to translate text between 22 languages



Join http://nitrosamines.usp.org

Nitrosamines Exchange today



- 4,600+ Members
- 89,000 page views/month
- 100+ user-to-user weekly interactions

USP Nitrosamines Analytical Hub

www.nitrosamines.usp.org

FDA-published testing method to provide an option for regulators and industry to detect NDMA impurities

The links below are to FDA-published testing methods to provide an option for regulators and industry to detect nitrosamine impurities in metformin drug substances and drug products. These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

- LC-HRMS method: an LC-MS method for the detection of NDMA in metformin drug substance and drug products.
- LC-ESI-HRMS method: an LC-HRMS method for the measurement of amounts of eight nitrosamine impurities in metformin drug substance and drug products

Nitrosamine testing activities of the OMCL Network

Methods for determination of nitrosamine drug substance-related impurities (NDSRIs) and intermediate-related contaminants

Methods for determination of nitrosamines in sartans

Methods for determination of nitrosamines in ranitidine

Methods for determination of nitrosamines in metformin

Method for determination of genotoxic substances in sartans as AZBT (azidomethyl biphenyl tetrazole) or AZBC (azidomethyl biphenyl carbonitrile)

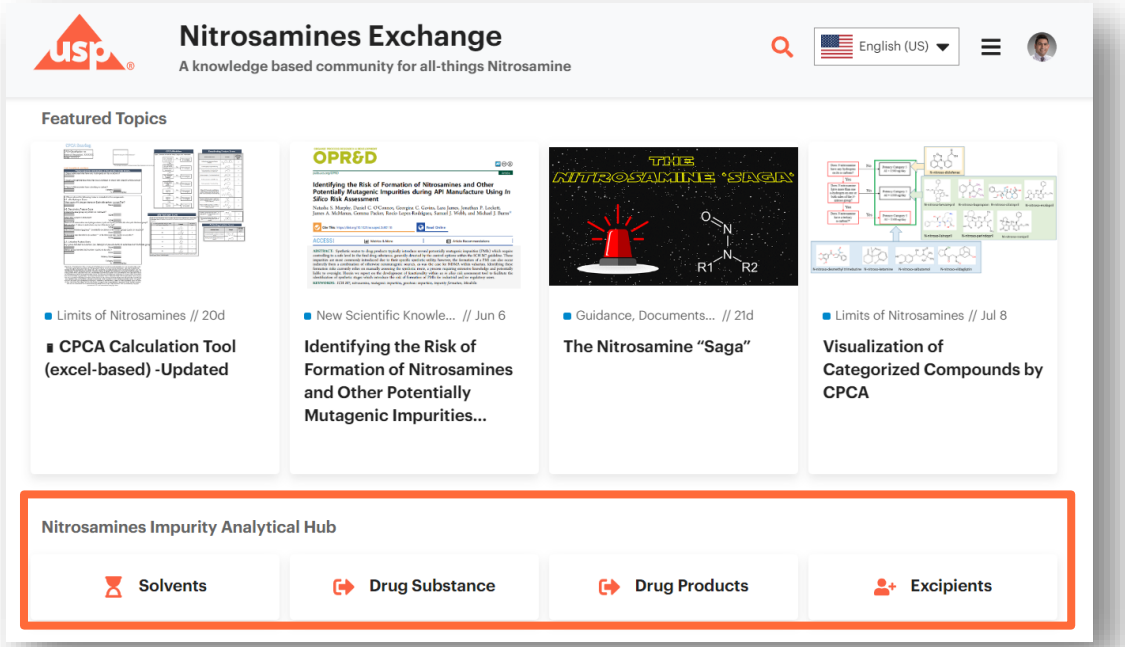
SEE ALSO

EDQM 31/05/2022 STRASBOURG, FRANCE

OMCLs participate in international regulatory collaboration on the analysis of nitrosamines in metformin-containing medicines

> N-nitrosamine contamination in brief

- Public **online repository** containing **non-compendial** analytical procedures (analytical notes) for the testing of nitrosamine impurities and related substances.
- USP's scientists curate these analytical procedures through **internal development/validation** or through scientific review of non-compendial donations. They are **NOT** compendial standards.



Analytical Peer-to-Peer Support

Testig method for nitroso Ciprofloxacin

Confirmatory Testing & Analytical Challenges NDSRI

This is the first time Rubenlalu has posted — let's welcome them to our community!

R [redacted] Sep '23

We have been working trying to analyze N-nitroso Ciprofloxacin. This impurity has a very poor solubility and the only way we have found to perform testing is dissolving it with NaOH 1N. But we face a lot of reproducibility problems and loss of sensibility in HPLC/MS (triple quad). Have anyone found a more friendly solving media?

[redacted] Oct '23

Yeah I have experience with this Nitrosamine earlier, please dissolve 5 mg in 200 ml acetonitrile and need to sonicate until it dissolves (might takes 15 to 20 minutes).

O [redacted] Nov '23

We recently had a case of analysing N-Nitroso-Ofloxacin (structural similar) and our approach was the following:

HPLC-MS (gradient)
Mobile phase A: 0.2% formic acid in water
Mobile phase B: 0.2% formic acid in acetonitrile
Solvent mixture: 0.2% Formic acid aqueous solution/Methyl alcohol (80:20)

Yosukemino Nitrosamine Exchange Ambassador 11d

I found a literature about Ciprofloxacin analysis.

Synthesis and Trace-Level Quantification of Mutagenic and Cohort-of-Concern Ciprofloxacin Nitroso Drug Substance-Related Impurities (NDSRIs) and Other Nitroso Impurities Using UPLC-ESI-MS/MS—Method Optimization Using I-Optimal Mixture Design

https://pubs.acs.org/doi/10.1021/acsomega.3c05170 18

lucas10mauriz Nitrosamine Exchange Ambassador Oct '23

@Rubenlalu, the addition of NaOH increases solubility; however, when dealing with analytes like N-nitroso ciprofloxacin, it hinders the ionization process and, consequently, sensitivity. In other words, do not use NaOH.

To address this issue, I recommend initially dissolving the N-nitroso ciprofloxacin in water. Ultrasonication (20 to 30 min., approx.) can aid in achieving a homogeneous solution. Subsequently, the addition of an organic solvent (methanol or acetonitrile), may be considered based on the requirements of the mobile phase and the MS ionization process. My suggestion: 50:50 (aqueous:organic).

Peer-to-peer Support
Sharing best practices

Identify Emerging Challenges

A new root cause? NOx

New Scientific Knowledge & Development

[redacted] 1 Nov '23

To be honest, I had never considered the geographical location of the factory as a root cause, but I'll let you all read...

N-Nitrosodimethylamine Formation in Metformin Drug Products by the Reaction of Dimethylamine and Atmospheric NO2 | Organic Process Research & Development (acs.org) 118

4 Reply

Nitrosamines evaluation in transdermal patches

Risk Assessment Strategy / Tools & Technology featured

A [redacted] 4 27d

Hi all,

Recently, it got to our attention that several NDSRIs indicated in EMA Appendix 1 theoretically could be in transdermal formulations (i.e., Rotigotine, Lidocaine, Methylphenidate etc.). with NDSRIs in Category 1, 2, 3 or more. Under EMA/409815/2020 there is no difference between route of administration unless you provide data.

Nitrosamines from polybags to finished product

Root Causes Packaging

H [redacted] 27d

HI,

I want to discuss about nitrosamines from Polybags. Can Nitrates/amines will be available in poly bags and transfer to API/Finished product during the storage. I have asked couple of vendors for the declaration, but they cannot arrange for it.
So, do we need to consider the risk from polybags also?

Thank you...

Duplex Sequencing - Future of mutagenicity assessment

Risk Assessment Strategy / Tools & Technology

Naiffer_Host Community Host Jul '23

With so much discussion around Limits and AI calculations, I want to debate for a moment to share information about 'Duplex Sequencing'. After the recent safety discussion at the Hesi/FDA meeting, I went down a rabbit hole to understand some of the proposed assays and testing that can be used to evaluate the safety or mutagenicity potential in Nitrosamines Impurities.

New paper - Use of molar, instead of weight-based, safety limits

New Scientific Knowledge & Development

[redacted] Nitrosamine Exchange Ambassador Oct '23

I've said a few times on here and in talks "watch this space" for more evidence for the use of molar limits for nitrosamines - the paper is now out!

https://doi.org/10.1016/j.yrtph.2023.105505 297

This should be particularly relevant for scaling read-across analogues, often far larger molecules than the compounds they are read-across from...

Regulatory guidelines (revisions)

www.nitrosamines.usp.org

Most active posts in the community

After the publication of Regulatory guidelines updates, community members are using the community to discuss the changes, considerations, impact and clarify cases where the framework can be challenging

EMA Q&A Rev. 16 EMA/409815/2020 - MAJOR UPDATE

Guidance, Documents, Resources
Drug_Substance_APIs, NDSRI, featured

FDA - Recommended Acceptable Intake Limits for NDSRIs Guidance for Industry

Guidance, Documents, Resources

Health Canada updated the guidance and Appendix 1(March 15, 2024)

Limits of Nitrosamines NDSRI

TGA (Australia) Updates Published Acceptable Intakes

Limits of Nitrosamines

Medicines: MAH' submission of Nitrosamine risk evaluation, risk assessment and confirmatory testing

Guidance, Documents, Resources Regulation

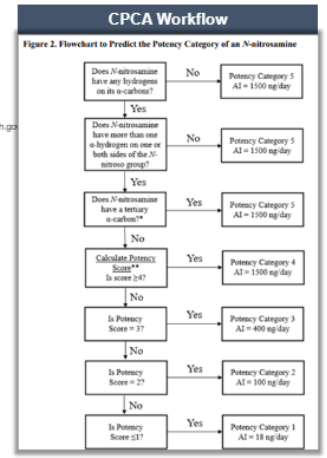
Korea Drug Review Briefing session on Nitrosamines

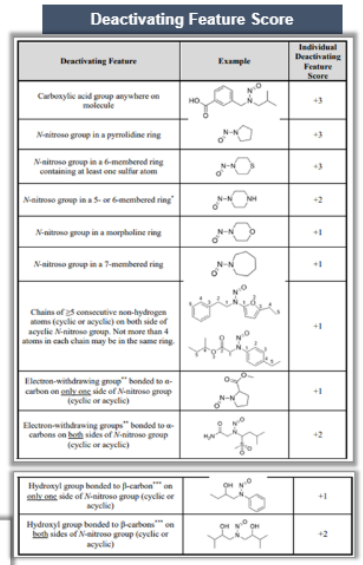
Guidance, Documents, Resources

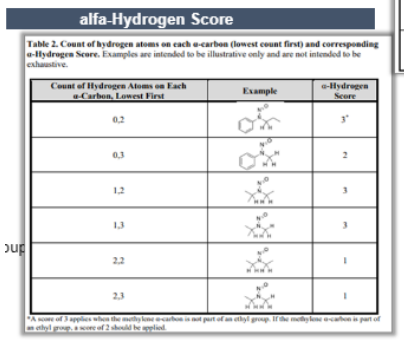
Swiss Medic Guidelines

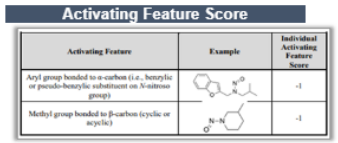
Guidance, Documents, Resources NDSRI

Carcinogenic potency categorization approach (CPCA) framework









lucas10mauriz
Lucas Maciel Mauriz Marques
Nitrosaminas LATAM

2

Yosukemino
Yosuke Mino
Nitrosamine Exchange Ambass...

15,000+

1,000+

2 weeks

Collaboration
Incubation

CPCA Scoring

CPCA Classification ver.
Name of the product: XXXXXXX
Writer: YYYYYY

Paste the structure of the compound *

* For chemical information and draw structure (https://pubchem.ncbi

Credit: Yosuke Mino & Lucas Mauriz

Please input the information of the product in the boxes.

1.Does N-Nitrosamine have any hydrogens on its α-carbons?

2.Does N-Nitrosamine have more than one α-hydrogen on one or both sides of N-nitroso group?

3.Does N-Nitrosamine have a tertiary α-carbon?

Category:
AI = ng/day

4. Please check the following features included in the compounds.
4-1. alfa-Hydrogen Score
What count of Hydrogen Atoms on Each alfa-carbon, Lowest First?
Score:

4-2. Deactivating Feature Score
Carboxylic acid group anywhere on molecule?
Score:
What ring system is included?
Score:
Chains of ≥5 consecutive non-hydrogen atoms (cyclic or acyclic) on both side of acyclic N-nitroso group?
Not more than 4 atoms in each chain may be in the same ring?
Score:
Electron-withdrawing group** bonded to α-carbon of N-nitroso group (cyclic or acyclic)?
Score:
Hydroxyl group bonded to β-carbon*** of N-nitroso group (cyclic or acyclic)?
Score:

4-3. Activating Feature Score
Aryl group bonded to α-carbon (i.e., benzylic or pseudo-benzylic substituent on N-nitroso gro
Score:
Methyl group bonded to β-carbon (cyclic or acyclic)?
Score:

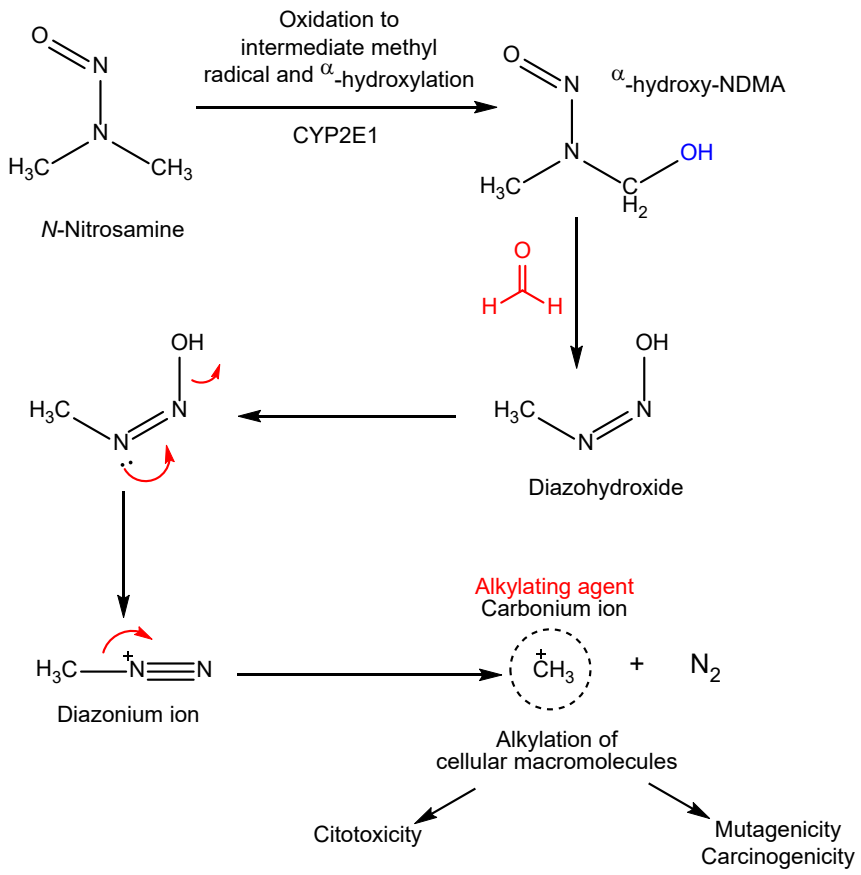
Potency Score:

Category:
AI = ng/day

3

Voices of Nitrosamines Exchange

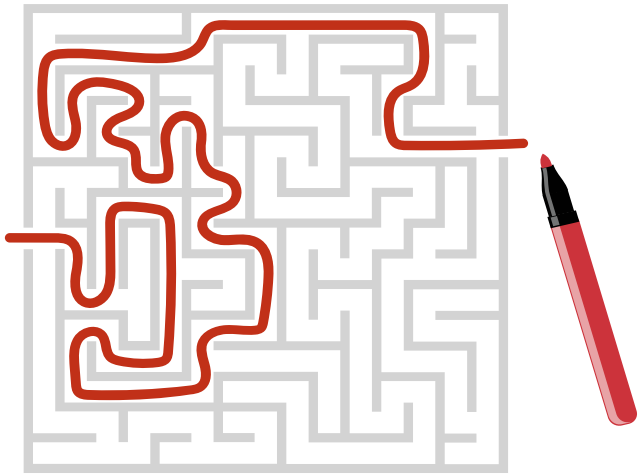
Understanding Safety …



Metabolic Studies	DNA adducts	Comet Assay	Gene-Mutation
Formation of Alkane-diazonium	Alkylation of DNA	DNA Repair	Duplex Sequencing

- Develop Additional Understanding
- Public Knowledge Sharing
- Evidence Generation for Standardization and Adoption

Understanding “Acceptable Intakes > Limits”

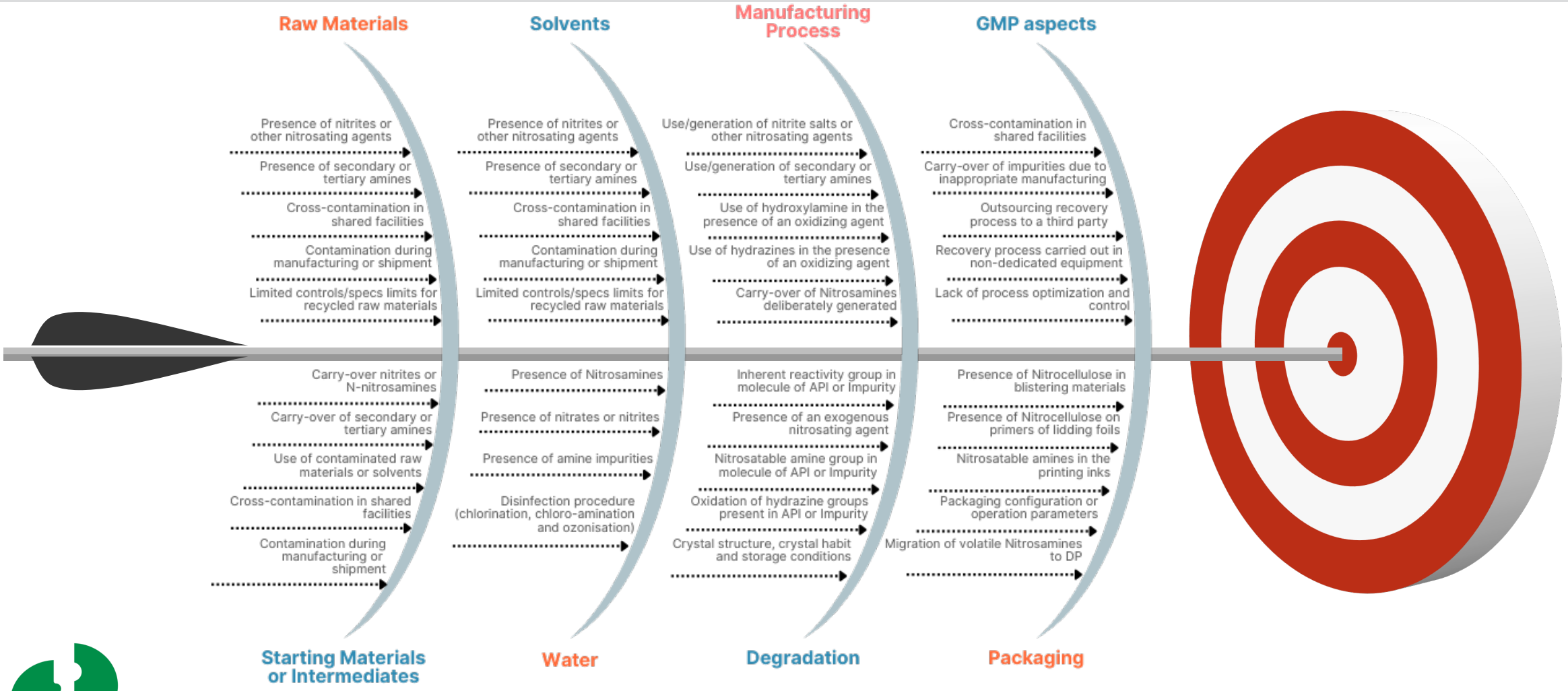


Default Limit: 26.5 ng/day → CPCA Framework

AMES → Enhanced-AMES

- Increase awareness and understanding of prediction tools that harvest Nitrosamines knowledge (Ex: reactivity & formation of impurities, toxicological assessment, Read-Across, QSAR models, etc.)
- Broadening adoption of in-silico tools through education, collaboration and experience sharing

Understanding ‘Assess the Risk’

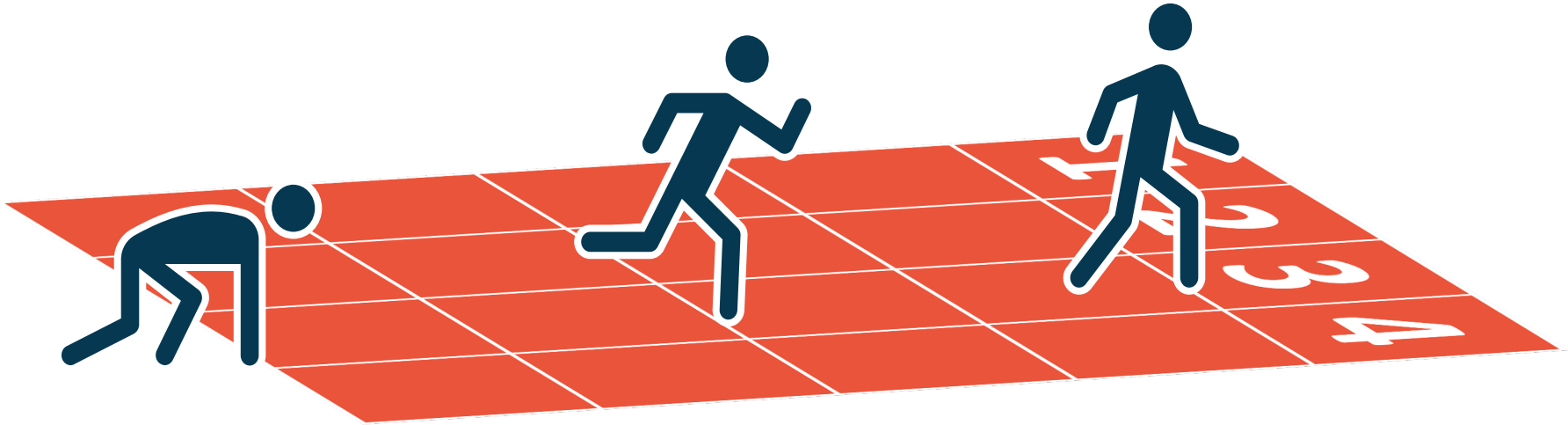


Development of Nitrosamine Impurities Risk Assessment toolkits anchored in best practices and shared knowledge

Addressing Analytical Challenges

Understanding Future Challenges

- Gather Knowledge on Nitrosation beyond ‘Nitrites in Excipients’
- Understanding and awareness of Nitroso-X beyond Nitrosamines
- Role of compendial tools to facilitate nitrosamines impurities control and/or mitigation



Scavenger as mitigation strategy

- Building mechanistic knowledge of scavenger agents (Mitigation & Prevention)
- Bridging Scavengers Permeability & Absorption

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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Bumetanide as a Model NDSRI Substrate: *N*-nitrosobumetanide Impurity Formation and its Inhibition in Bumetanide Tablets

Diaa Shakleya[a,*], Bethel Asmelash[b], Alaadin Alayoubi[a], Nicolas Abrigo[a], Adil Mohammad[a], Jiang Wang[a], Jinhui Zhang[a], Jingyue Yang[a], Tim Andres Marzan[a], David Li[a], Maha Shaklah[a], Fahd M. Alsharif[a], Saaniya Desai[a], Patrick J. Faustino[a], Muhammad Ashraf[a], Thomas O'Connor[a], Matthew Vera[b], Andre Raw[b], Vilayat A. Sayeed[b], David Keire[a]

[a] Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Office of Testing and Research, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA
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Caffeic acid
Ferulic acid
Nitrite

ABSTRACT

Nitrosamine compounds are classified as potential human carcinogens, the origin of these impurities can be broadly classified in two categories, nitrosamine impurity found in drug products that are not associated with the Active Pharmaceutical Ingredient (API), such as N-nitrosodimethylamine (NDMA) or nitrosamine impurities associated with the API, such as nitrosamine drug substance-related impurities (NDSRIs). The mechanistic pathway for the formation of these two classes of impurities can be different and the approach to mitigate the risk should be tailored to address the specific concern. In the last couple of years number of NDSRIs have been reported for different drug products. Though, not the only contributing factor for the formation of NDSIRs, it is widely accepted that the presence of residual a nitrites/nitrates in the components used in the manufacturing of the drug products can be the primary contributor to the formation of NDSRIs. Approaches to mitigate the formation of NDSRIs in drug products include the use of antioxidants or pH modifiers in the formulation. The primary objective of this work was to evaluate the role of different inhibitors (antioxidants) and pH modifiers in tablet formulations prepared in-house using bumetanide (BMT) as a model drug to mitigate the formation of *N*-nitrosobumetanide (NBMT). A multi-factor study design was created, and several bumetanide formulations were prepared by wet granulation with and without sodium nitrite spike (100 ppm) and different antioxidants (ascorbic acid, ferulic acid or caffeic acid) at three concentrations (0.1%, 0.5% or 1% of the total tablet weight). Formulations with acidic and basic pH were also prepared using 0.1 N hydrochloric acid and 0.1 N sodium bicarbonate, respectively. The formulations were subjected to different storage (temperature and humidity) conditions over 6 months and stability data was collected. The rank order of *N*-nitrosobumetanide inhibition was highest with alkaline pH formulations, followed by formulations with ascorbic acid, caffeic acid or ferulic acid present. In summary, we hypothesize that maintaining a basic pH or the addition of an antioxidant in the drug product can mitigate the conversion of nitrite to nitrosating agent and thus reduce the formation of bumetanide nitrosamines.

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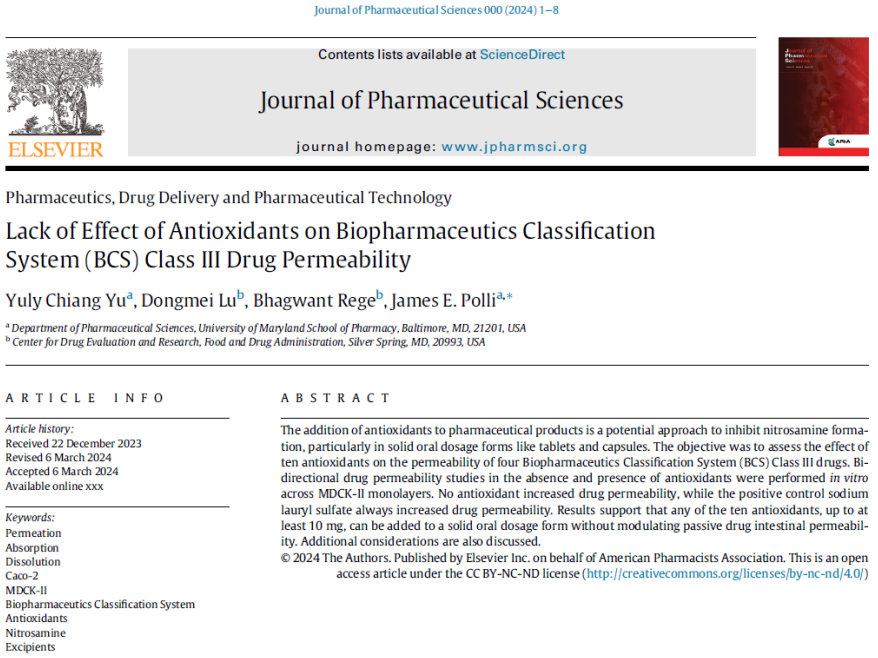
J Pharm Sci. 2023 Jun 24; https://doi.org/10.1016/j.xphs.2023.06.013



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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Lack of Effect of Antioxidants on Biopharmaceutics Classification System (BCS) Class III Drug Permeability

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Biopharmaceutics Classification System
Antioxidants
Nitrosamine
Excipients

ABSTRACT

The addition of antioxidants to pharmaceutical products is a potential approach to inhibit nitrosamine formation, particularly in solid oral dosage forms like tablets and capsules. The objective was to assess the effect of ten antioxidants on the permeability of four Biopharmaceutics Classification System (BCS) Class III drugs. Bi-directional drug permeability studies in the absence and presence of antioxidants were performed *in vitro* across MDCK-II monolayers. No antioxidant increased drug permeability, while the positive control sodium lauryl sulfate always increased drug permeability. Results support that any of the ten antioxidants, up to at least 10 mg, can be added to a solid oral dosage form without modulating passive drug intestinal permeability. Additional considerations are also discussed.

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200 usp
The standard of trust