Nitrosamine impurities in medicines

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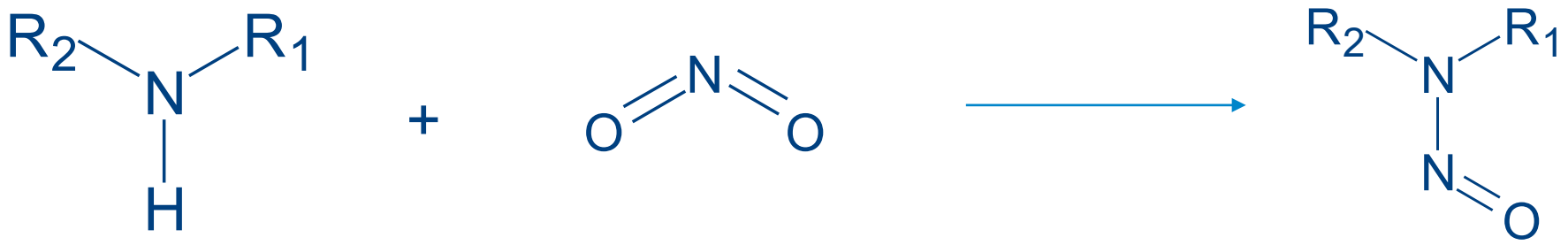
ARCS 2024

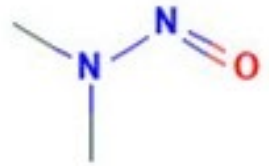
Nitrosamine formation from nitrite and amines



- Secondary amines like DMA react with nitrosating agents [e.g. NO^+ or N_2O_3 to form nitrite (NO_2^-)] in acidic conditions to afford *N*-nitroso compounds e.g. NDMA and water.
- Tertiary amines are less reactive than secondary amines.
- Nitrosamines are mutagenic and carcinogenic.

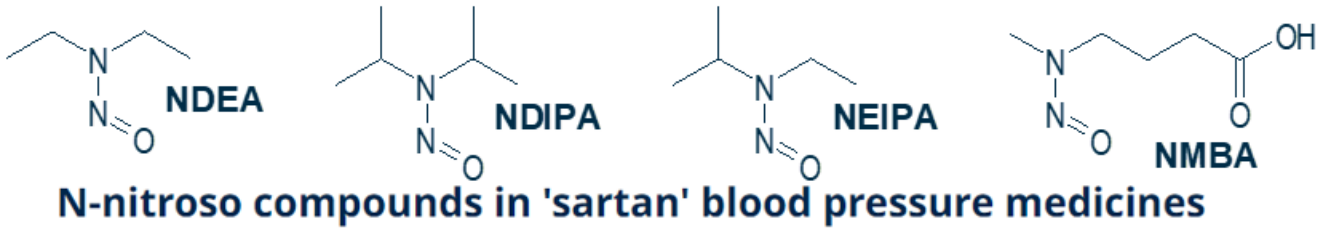
6 Years since emergence in sartan hypertension medicines

Valsartan 2018



- Mid 2018 – Zhejiang Huahai (China) first reported that *N*-nitrosodimethylamine (NDMA) present at unacceptable/harmful levels.
  - Triggered EDQM CEP suspension and international recalls (e.g. EU and US).
  - Investigation determined likely forms during tetrazole ring formation.
    - DMF used as a solvent degrades to dimethylamine (DMA), reacts with a nitrosating agent, nitrite (NO_2^-), converted in solution to nitrous acid (HNO_2) during quenching of azide.

- Not an isolated incident, additional nitrosamine impurities found in valsartan medicines and other medicines of the sartan family of products → daily medication taken by hundreds of millions of people.



N-nitroso compounds in 'sartan' blood pressure medicines

- Not just from API synthesis giving simple dialkyl nitrosamines, the API, when it is a secondary amine, can form complex nitrosamine drug substance-related impurities (NDSRIs). Some tertiary amines form NDSRIs by other pathways.

TGA participation in international activity on nitrosamines

- Nitrosamine International Strategic Group (NISG) meetings – every 3 months
  - Anvisa, EMA, US FDA, EDQM, Health Canada, HSA, MHLW/PMDA, Swissmedic, TGA
    - TGA representative is AS SEB.
- Nitrosamine International Technical Working Group (NITWG) meetings – monthly, occasionally more often
  - Safety and Quality groups
    - TGA has representatives on both.
- Bilateral meetings - *ad hoc.*

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

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HSA Health Sciences Authority

Health Canada Santé Canada

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Nitrosamines guideline

EUROPEAN MEDICINES AGENCY
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CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

15 January 2024
EMA/409815/2020 Rev.20

Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products

Nitrosamines guideline – regularly changes

- Changes in interim limits for existing products for chronic use
- Guidance on appropriate toxicological data to support acceptable limits
- Additional guidance on control strategies for products containing more than one nitrosamine impurity
- The class-specific TTC is no longer the default limit
- Interim limits

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21. What is the approach to control the presence of nitrosamines until a substance specific AI is established? (new)

Q&A 10 provides guidance on the calculation of the limit when a new nitrosamine is identified. If *N*-nitrosamines are identified without sufficient carcinogenicity data to derive a substance-specific limit for lifetime exposure as recommended in ICH M7(R1) guideline, and the class specific TTC for nitrosamines of 18 ng/day is not used for controlling the levels of the nitrosamine in the finished product, an AI agreed by the Non-clinical Working Party (NcWP) and adopted by the CHMP is required to decide on control options for the nitrosamine in the finished product.

To protect public health, to inform decisions on required market actions while ensuring at the same time availability of medicines while a formal AI is established, a temporary AI (t-AI) of 178 ng/day (total nitrosamines) can be adopted by the relevant authorities for marketed medicines identified to contain one or more nitrosamines exceeding the TTC of 18ng/day. This t-AI has been derived using

Revision History

Rev.	Summary of changes made	Date
0	Replace obsolete Q&A published in 2019 to support the initial "call for review" with a new version reflecting the main principles agreed as part of the Article 5(3) referral which concluded in July 2020.	03rd August 2020
1	Update to Q&A 3 in order to clarify products in scope of the call for review. Update to Q&A 4 in order to add the link to the outcome of the referral under article 3 of Directive 2001/83/EC for ranitidine.	29th January 2021
	for N-nitrosamines.	
17	Amendment of Q&A 22 on approach to control presence of N-nitrosamine exceeding the AI while CAPAs are being implemented to extend the scope to authorised products for chronic use and clarify the applicable limits and exemptions. Amendment of Q&A 20 and Q&A 21 on approach to control presence of nitrosamine while the AI is being established to clarify that as the AIs can be established with the new carcinogenic category approach (CPCA) the approach for a universal temporary AI (t-AI) while a formal AI is established is no longer considered necessary.	28th July 2023
18	Update of Q&A 3 to highlighting the responsibilities of MAH(s) to control, report and mitigate the detection of Nitrosamine impurities throughout the product life-cycle, by using the established procedure.	2nd October 2023

Sponsor and manufacturer obligations

- Published on the TGA website with requirements for category 1 registration applications
  - Information also for consumers and health professionals

- Required to inform TGA in writing as soon as they become aware.
  - Includes sponsors and manufacturers of medicines and biological medicines.

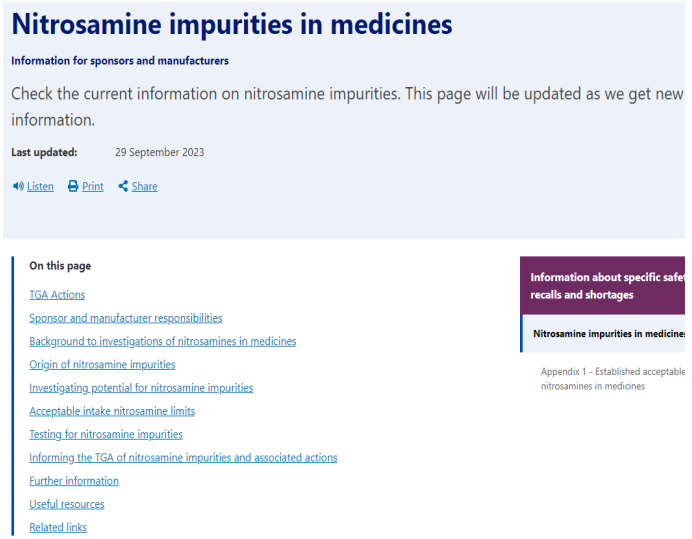
- Be familiar with the known and plausible causes of nitrosamine impurities in their products.

- Take active steps to determine whether their medicines are at risk of containing nitrosamine impurities.

- Ensure they have access to relevant information regarding potential formation and presence of nitrosamine impurities, as well as the potential for cross-contamination.

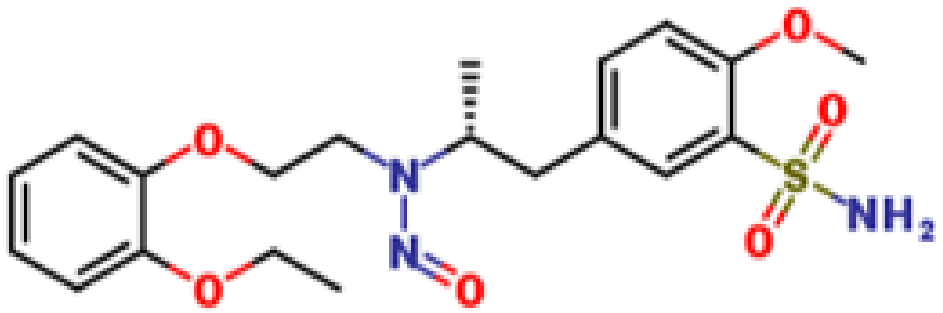
Regulatory requirements

- First published 2021, most recent update September 2023 at on the TGA website
- Sponsors to review supply chains and medicines for the possibility of nitrosamine formation and root cause.
- Many confirmed and possible root causes of contamination have been identified (in the EMA's Q&A document).
    - Includes synthetic conditions, carry-over/contamination with nitrosating agents (including nitrites) and amines/amides, contaminated recycled materials, packaging and degradation.
- If the potential for nitrosamine is identified, the Sponsor should test for the nitrosamine.
- If detected in medicines, corrective and preventative actions (CAPAs) are required to mitigate/minimise the formation of these impurities.
    - Nitrosamine levels should be kept as low as possible (ALARP principles) and below the AI for that nitrosamine.

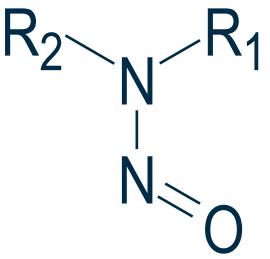


Nitrosamine drug substance related impurity (NDSRI)

- *N*-Nitroso of the active.
- Generally, no available carcinogenicity data to derive an AI.
- How do we set a safety limit when we have no data?



The standard TTC does not apply to nitrosamines

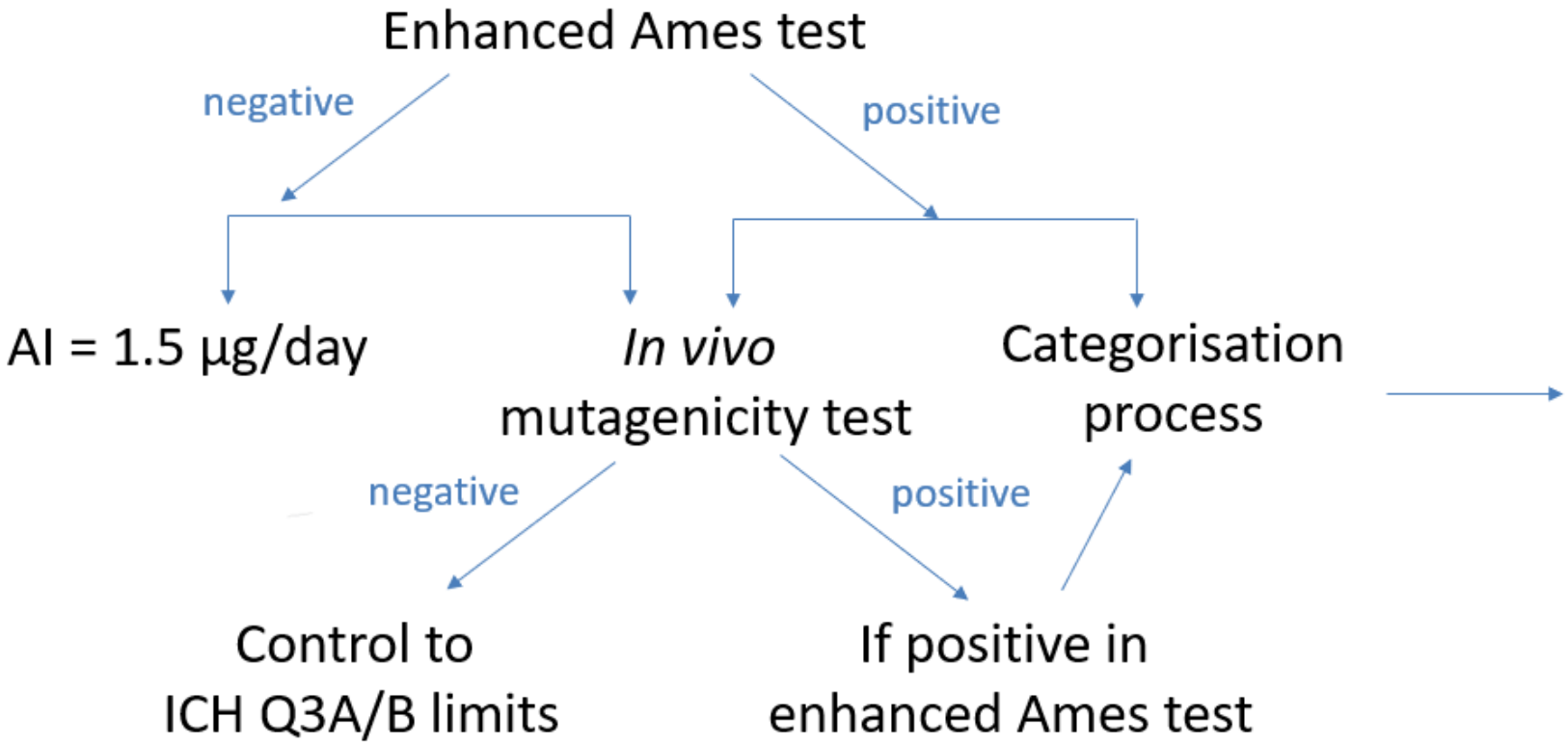


- For substances for which we have no safety data, we have a default limit: the threshold of toxicological concern (TTC)
  - a concept that refers to a level of exposure to a chemical for which there is a theoretical at most 1 in 100,000 cancer risk for mutagenic compounds and should be protective for other toxicity effects.

- ICH M7 is the international guideline on assessment and control of mutagenic impurities in pharmaceuticals to limit potential carcinogenic risk
  - specifies the TTC as 1.5 µg/day.
  - Some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk → “cohort of concern”.

- *N*-nitrosamines are a part of the “cohort of concern” → the standard TTC does not apply
  - What limit do we apply to nitrosamines?

Recently adopted approach to setting Acceptable Intake (AI)

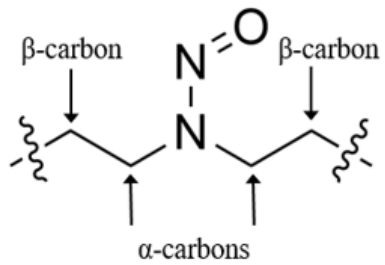


- If no '*Enhanced Ames test*' (EAT) can use '*Carcinogenic Potency Categorization Approach*' (CPCA)

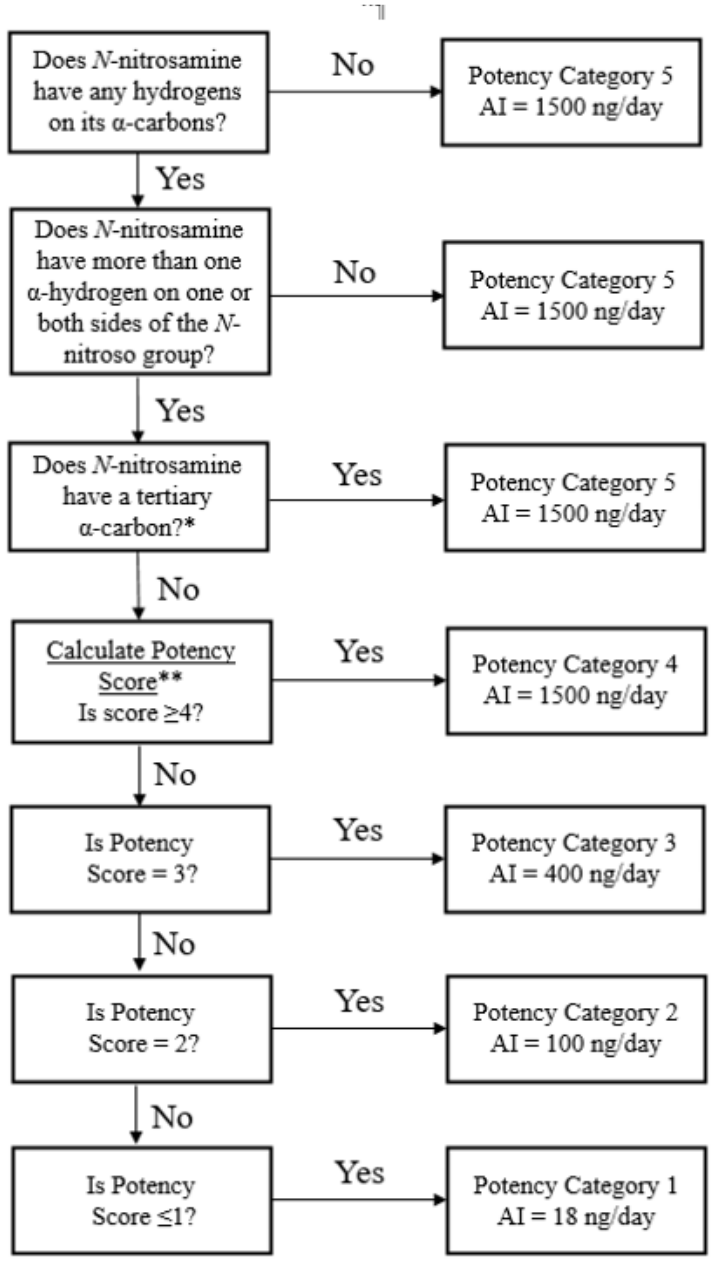
Nitrosamine AI limits by '*Carcinogenic Potency Categorization Approach*' (CPCA)

- CPCA was developed to establish an AI limit based on chemical structure determining an estimated potency.
- Carcinogenic potency of nitrosamine estimated based on structural features (alpha carbons, deactivating features, activating features) and assigned to 1 of 5 categories based on potency score.

Potency category	AI (ng/day)
1	18
2	100
3	400
4	1500
5	1500



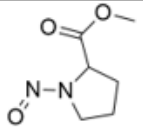
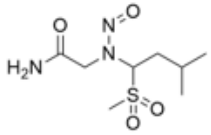
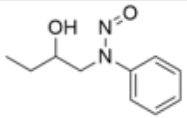
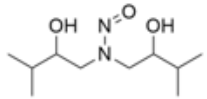
CPCA categories



*A tertiary α-carbon is defined as an α-carbon atom in an sp^3 hybridization state, bonded to three other carbon atoms.

Potency Score = α-**Hydrogen Score** + **Deactivating Feature Score** (sum all scores for features present in the *N*-nitrosamine) + **Activating Feature Score** (sum all scores for features present in the *N*-nitrosamine)

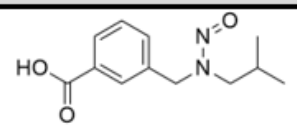
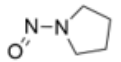
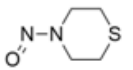
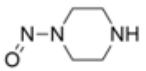
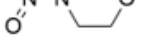
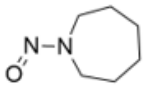
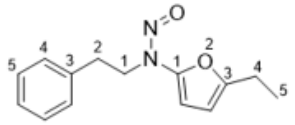
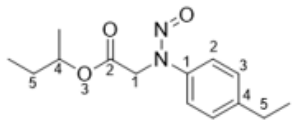
Deactivating feature score

Electron-withdrawing group** bonded to α-carbon on only one side of *N*-nitroso group (cyclic or acyclic)		+1
Electron-withdrawing groups** bonded to α-carbons on both sides of *N*-nitroso group (cyclic or acyclic)		+2
Hydroxyl group bonded to β-carbon on only one side of *N*-nitroso group (cyclic or acyclic)		+1
Hydroxyl group bonded to β-carbon on both sides of *N*-nitroso group (cyclic or acyclic)		+2

*Excludes examples where *N*-nitroso group is in a pyrrolidine ring, a 6-membered ring containing at least one sulfur atom or a morpholine ring (all counted separately).

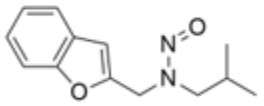
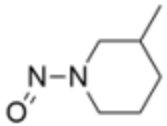
**Excludes carboxylic acid and aryl (counted separately), and ketone (conflicting data). Additional electron withdrawing group examples are limited to those described in Cross KP and Ponting DJ, 2021, Developing Structure-Activity Relationships for *N*-Nitrosamine Activity, Comput Toxicol. 20:100186, where they are referred to as "β-carbon electron withdrawing groups."

Table 3. List of deactivating features and associated scores. To calculate Deactivating Feature Score, sum the individual scores for all listed features present in the *N*-nitrosamine structure. Each deactivating feature row in the table may only be counted once. For *N*-nitrosamines where the *N*-nitroso group is within more than one ring, the feature score for only the smallest matching ring should be applied. Examples are intended to be illustrative only and are not intended to be exhaustive.

Deactivating Feature	Example	Individual Deactivating Feature Score
Carboxylic acid group anywhere on molecule		+3
N-nitroso group in a pyrrolidine ring		+3
N-nitroso group in a 6-membered ring containing at least one sulfur atom		+3
N-nitroso group in a 5- or 6-membered ring*		+2
N-nitroso group in a morpholine ring		+1
N-nitroso group in a 7-membered ring		+1
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.	 	+1

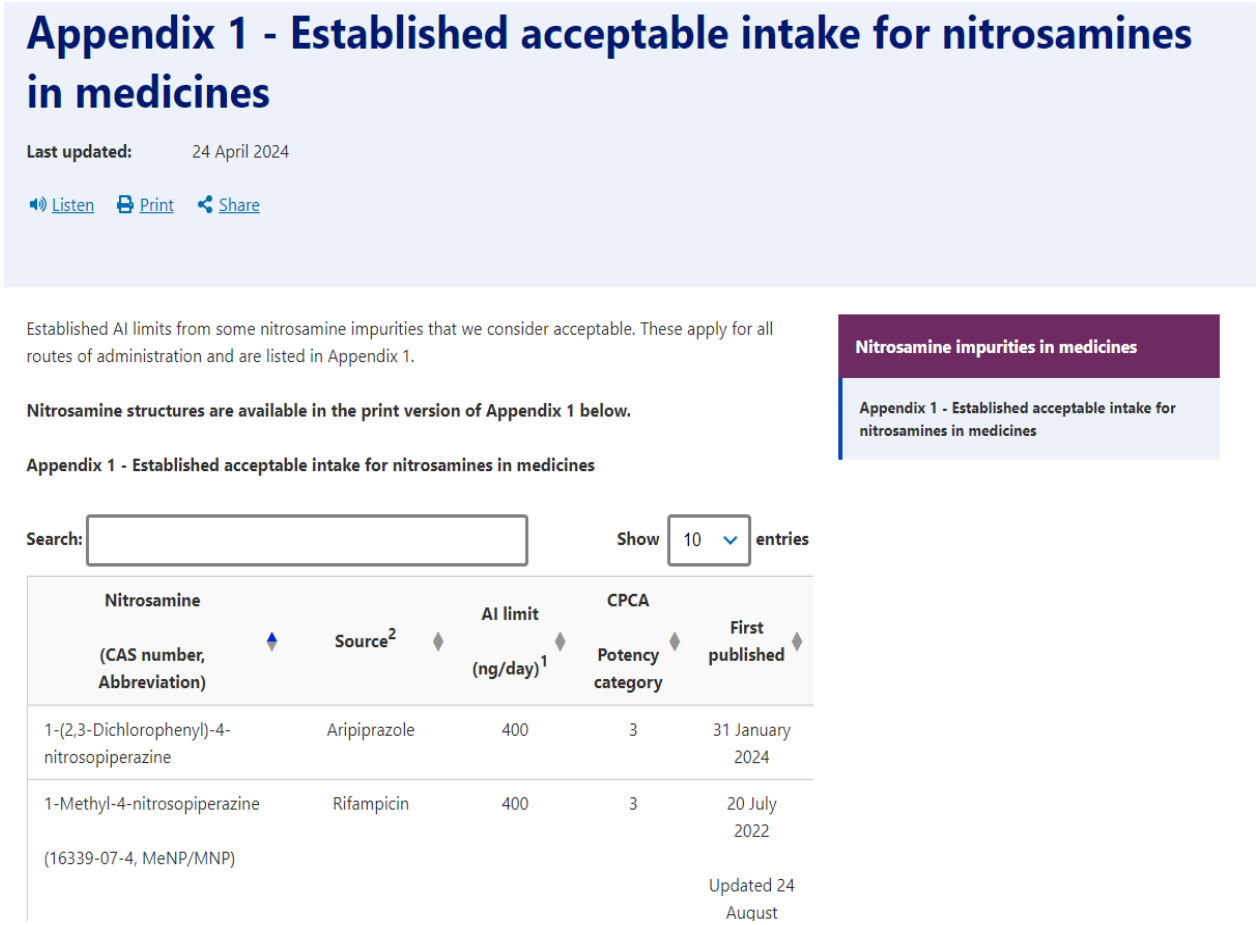
Activating feature score

Table 4. List of activating features and associated scores. To calculate Activating Feature Score, sum the individual scores for all listed features present in the *N*-nitrosamine structure. Each activating feature row in the table may only be counted once. Examples are intended to be illustrative only and are not intended to be exhaustive.

Activating Feature	Example	Individual Activating Feature Score
Aryl group bonded to α-carbon (i.e., benzylic or pseudo-benzylic substituent on *N*-nitroso group)		-1
Methyl group bonded to β-carbon (cyclic or acyclic)		-1

Published AI values

- Available in EMA's Q&A document
- We generally align; however, there are minor differences. Details in Appendix 1 on the TGA website. Most recent searchable list update was 26 April 2024 including a downloadable pdf with structures for the nitrosamine.
- >150 nitrosamines have been considered.



Appendix 1 - Established acceptable intake for nitrosamines in medicines

Last updated: 24 April 2024

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Established AI limits from some nitrosamine impurities that we consider acceptable. These apply for all routes of administration and are listed in Appendix 1.

Nitrosamine structures are available in the print version of Appendix 1 below.

Appendix 1 - Established acceptable intake for nitrosamines in medicines

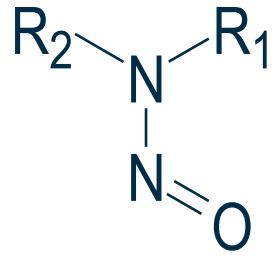
Nitrosamine impurities in medicines

Appendix 1 - Established acceptable intake for nitrosamines in medicines

Search: Show 10 entries

Nitrosamine (CAS number, Abbreviation)	Source[2]	AI limit (ng/day)[1]	CPCA Potency category	First published
1-(2,3-Dichlorophenyl)-4-nitrosopiperazine	Aripiprazole	400	3	31 January 2024
1-Methyl-4-nitrosopiperazine (16339-07-4, MeNP/MNP)	Rifampicin	400	3	20 July 2022 Updated 24 August

AI setting should be easy now… BUT…



Recent case study: Nitrosamine A

- AI of **100 ng/day** published on TGA website that was established by read-across.
- Sponsor A proposes the AI be adjusted to **163.3 ng/day** to account for differences in molecular weight between surrogate and NDSRI.
- Sponsor B proposes AI of **537 ng/day** based on read-across (using different surrogates) and quantum mechanical modelling.
- Sponsor C proposes AI of **5000 ng/day** based on *in vivo* mutagenicity assay and benchmark dose approach.
- Using the CPCA structural prediction process, the AI would be **18 ng/day**.

Post-market regulatory actions

- The presence of a nitrosamine impurity above the acceptable limit indicates that the safety and quality of the medicine may be unacceptable.
  - EMA's Q&A document: regulators may consider interim limit for up to 3 years from date of publishing the AI while CAPAs are implemented. Must not exceed 1.5 µg/day unless toxicological data supports a higher limit.
    - ➢ Not applicable to new/ ongoing regulatory applications.
    - ➢ CAPA implementation is expected to be expedited.

22. What is the approach to control presence of N-nitrosamine exceeding the AI during CAPA implementation?

In accordance with the regulatory steps taken by authorities following the identification of an *N*-nitrosamine exceeding the AI and outlined in Q&A20, the less-than lifetime (LTL) concept or the use of interim limits may be considered by the lead authority and NCAs on a temporary basis in order to inform market actions and at the same time ensure availability of medicines. MAHs are expected to establish and implement corrective and preventive actions (CAPAs) in authorised medicines without any delays in order to ensure patients safety and product quality. Nevertheless, it is recognised that implementation of CAPAs may require some time before the MAH is able to mitigate the presence of the identified *N*-nitrosamine below the established AI. Therefore, in order to avoid unnecessary risk of supply disruptions, a harmonised approach promoting the establishment of interim limits in a streamlined way is agreed. The approach is applicable to all authorised products that have:

- CAPA implementation timeline of up to 3 years from the establishment and publication of the AI (nevertheless MAHs are expected to expedite CAPAs implementation).

Treatment duration	Up to 12 months	>12 months
Interim limit	13.3 x AI*	6.7xAI*

*In any case the limit should not exceed 1.5 µg/day unless the established AI (Table 1, Q&A10) is > 1.5 µg/day or the nitrosamine concerns a category 5 according to CPCA or the nitrosamine is shown to be negative in an enhanced Ames test (EAT).

The approach is not applicable to the below instances where other approaches may be considered on a case-by-case basis in consultation with the appropriate regulatory authority:

- CAPA implementation exceeding 3 years from the establishment and publication of the AI;
- New/ongoing regulatory applications.

The above interim limits are based on the LTL approach outlined in the ICH M7 guideline, using the two most conservative adjustment factors (6.7 and 13.3 x AI). The application of these adjustment factors would not be expected to exceed a theoretical excess cancer risk of 1 in 100,000 during the period of CAPA implementation.

The approach is intended to be evaluated by the lead authority during the assessment of the case and is expected to be communicated by the lead authority to the concerned MAH as part of assessment conclusions. In terms of retrospective application, where more restrictive interim limits were previously agreed for some products as part of case assessment, upon request from the MAH, the lead authority can re-assess interim limits taking into consideration this approach to control presence of N-nitrosamine exceeding the AI during CAPA implementation.

MAHs are expected to ensure that the implementation of adequate controls for the detected nitrosamines is done as a matter of priority. During the use of the interim limit, monitoring measures may be evaluated by the lead authority as required. However, it is not the expectation that MAHs include these interim limits in specifications via variation.

Post-market regulatory actions

- Options: medicine recalls, suspending medicines, placing conditions on product registration and/or actions related to product manufacture.
    - The TGA considers the impact on medicine availability.
- Requires liaison across multiple sections and branches (PCR/VS, Tox, MQB, Labs, OTC-COMB, MSS, AEMDS, Recalls, MO advice, Advice from experts).

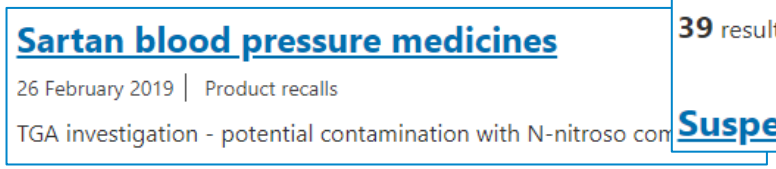
- Actions are considered on a case-by-case basis, particularly for critical medicines.
    - Recalls are published on the System for Australian recall actions database.
    - Safety advisories are published on the website.
    - Medicine shortages are published on the Medicine shortage reports database.

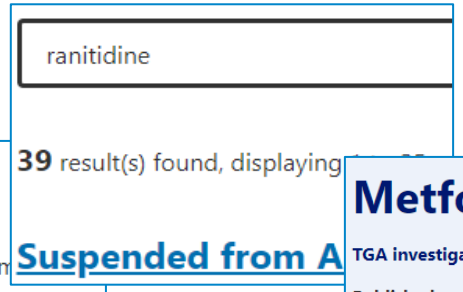
Medicine criticality criteria

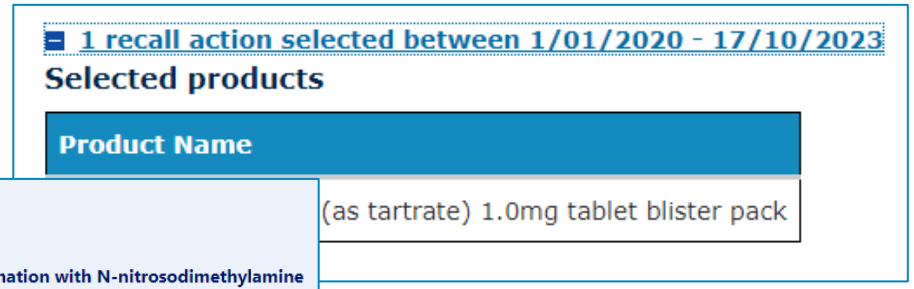
- The Medicine Shortages Section (MSS) considers the risk that informs action prioritisation.

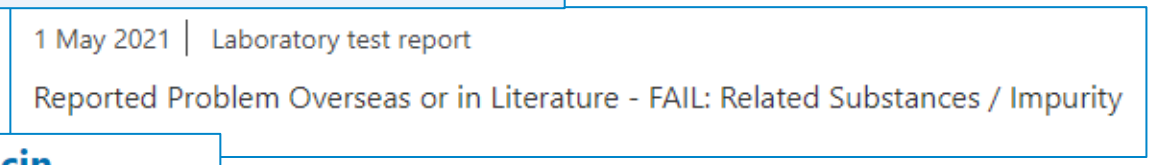
- Risk examples:
  - Indications
  - High dose
  - Chronic duration of use
  - Vulnerable populations
  - e.g. antimicrobial agent, antidote/treatment for poisoning, emergency/critical care use, anticoagulant, vaccine, obstetric, antivenom, chronic use, hypertensives, diabetes, contraceptives, other.

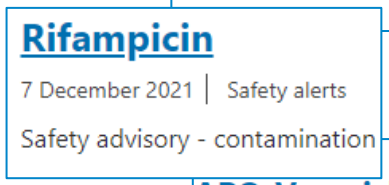
TGA actions









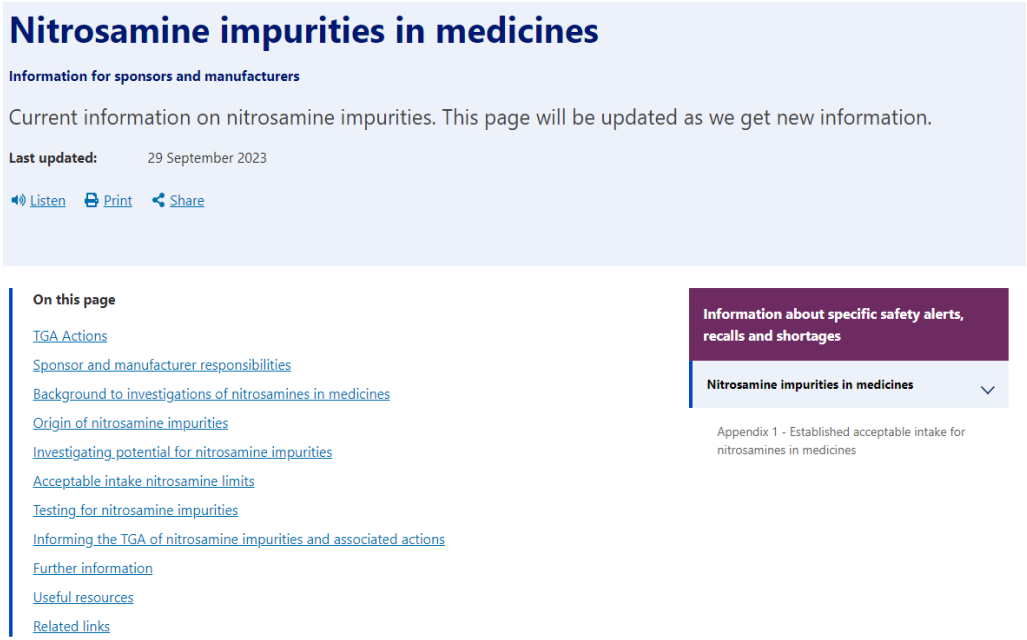


- Regulatory actions have included:
  - product suspensions
  - recalls
  - public safety communications
  - compliance investigation activities
  - requests for sponsors to provide information
  - product testing
  - imposing conditions of registration such as CAPAs and reporting
  - requirements for sponsors to monitor, investigate and address nitrosamine impurities levels in medicines including proposed medicines.

- Some medicines remain available despite ongoing issues, as they are deemed critical for vulnerable populations, while others have been suspended or withdrawn from registration.

So, what is in the pipeline?

- In 2022, 360 drug substances and/or drug products may have nitrosamine impurities.
  - 63 drug substances and/or drug products have been confirmed for the presence of nitrosamine.
  - ~ 200 drug substances and/or drug products have potential of nitrosamine presence.
- In 2023 NITWG members revised this figure to possibly > 6000 products affected.
  - A recent review by Teasdale reports conservatively that that 20 - 25% of all medicines are impacted.



Nitrosamine impurities in medicines

Information for sponsors and manufacturers

Current information on nitrosamine impurities. This page will be updated as we get new information.

Last updated: 29 September 2023

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On this page

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Sponsor and manufacturer responsibilities
Background to investigations of nitrosamines in medicines
Origin of nitrosamine impurities
Investigating potential for nitrosamine impurities
Acceptable intake nitrosamine limits
Testing for nitrosamine impurities
Informing the TGA of nitrosamine impurities and associated actions
Further information
Useful resources
Related links

Information about specific safety alerts, recalls and shortages

Nitrosamine impurities in medicines

Appendix 1 - Established acceptable intake for nitrosamines in medicines

Further information: TGA website

Email TGA Nitrosamines: Nitrosamines@health.gov.au

Website and link references	
EMA Nitrosamines Q&A guideline	https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders-applicants-chmp-opinion-article-53-regulation-ec-no-726-2004-referral-nitrosamine-impurities-human-medicinal-products_en.pdf
Information for sponsors and manufacturers	https://www.tga.gov.au/how-we-regulate/monitoring-safety-and-shortages/industry-information-about-specific-safety-alerts-recalls-and-shortages/nitrosamine-impurities-medicines
Requirements for Category 1 applications	https://www.tga.gov.au/news/news/nitrosamine-risk-assessment-category-1-prescription-medicine-registration-applications
Safety alerts	https://www.tga.gov.au/safety-information
Information for consumers and health professionals	https://www.tga.gov.au/alert/nitrosamine-impurities
ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk guideline	https://www.ema.europa.eu/en/ich-m7-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential-carcinogenic-risk-scientific-guideline
Appendix 1 – Established AIs	https://www.tga.gov.au/how-we-regulate/monitoring-safety-and-shortages/industry-information-about-specific-safety-alerts-recalls-and-shortages/nitrosamine-impurities-medicines/appendix-1-established-acceptable-intake-nitrosamines-medicines
Recent review	Andrew Teasdale, Reflections on the Impact of Nitrosamine Drug Substance Related Impurities *Org. Process Res. Dev.* 2023, 27(10): 1685–1686, October 20, 2023 https://doi.org/10.1021/acs.oprd.3c00286
System for Australian Recall Actions database	https://www.tga.gov.au/how-we-regulate/monitoring-safety-and-shortages/manage-recall/system-australian-recall-actions-sara-database
Medicine Shortage Reports database	https://apps.tga.gov.au/prod/MSI/search

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