

Establishing best practice for *N*-nitrosamine read-across and surrogate selection

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A reproducible, regulator-aligned framework for confidently selecting nitrosamine read-across analogues.

The best-practice method outlined in this paper illustrates how toxicologists can:

- remove assessor subjectivity
- increase acceptance likelihood
- enable higher, science-justified acceptable intake (AI) limits for nitrosamine drug substance-related impurities (NDSRIs)

Making read-across usable in practice.

9x

Increase in AI limit using read-across vs. CPCA for *N*-nitroso-paroxetine.

Up to 1900 ng/day

100x increase in AI for *N*-nitroso-trientine via read-across compared to CPCA.

500+

potential *N*-nitroso analogues for users to access and evaluate

90%

time saved using Lhasa read-across tool Acroscopic.

Read-across is powerful, but without standardisation...

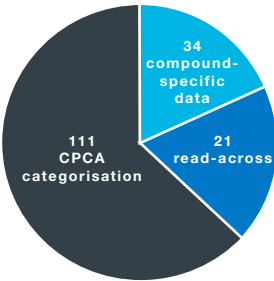


...two experts can reach two very different conclusions. This is due to factors such as subjective differences in perception of similarity or data quality.

This framework brings transparency, reproducibility and therefore confidence to nitrosamine surrogate selection.

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Most nitrosamine limits rely on default CPCA categorisation, not compound-specific evidence.



This pie-chart shows how AI limits were determined for 166 nitrosamine compounds

Regulatory guidance permits multiple approaches to determining AIs. In practice, most limits are set using CPCA categorisation, while compound specific data and read-across are applied far less frequently.

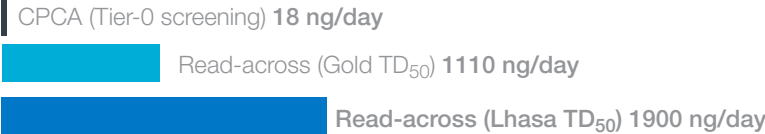
Read-across is accepted, but remains uncommon, due to it being difficult to apply consistently - underscoring the need for a robust, repeatable framework.

A best-practice framework for nitrosamine read-across.

- 1 Define the applicability domain**
Identify the structural and mechanistic features that drive nitrosamine potency. Confirm the compound fits the *N*-nitrosamine space.
- 2 Retrieve, filter and rank analogues systematically**
Apply structural filters (toxicophores, activating/deactivating groups) and rank analogues using local similarity, logP, mechanistic relevance, and global similarity metrics.
- 3 Expert review with transparent documentation**
Assess carcinogenicity data quality, evaluate uncertainty, and clearly document the rationale to support regulatory acceptance.

Best-practice read-across enables more realistic acceptable intakes.

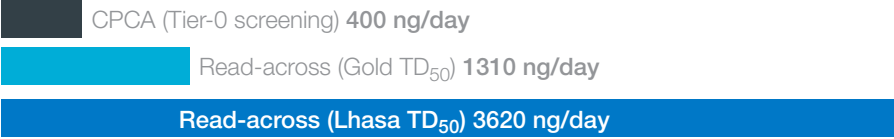
AI derived using published read-across methodology for *N*-nitroso-trientine.



For *N*-nitroso-trientine, CPCA assigns the lowest default AI despite the availability of suitable analogue data.

Applying a structured, best-practice read-across enables scientifically justified AI that is **~100x higher than the default CPCA limit**.

AI derived using published read-across methodology for *N*-nitroso-paroxetine.



When default CPCA screening is applied, *N*-nitroso-paroxetine is assigned a conservative AI based on categorisation rather than compound-specific evidence.

Applying a structured, best-practice read-across enables scientifically justified AI that is **9x higher than the default CPCA limit**.

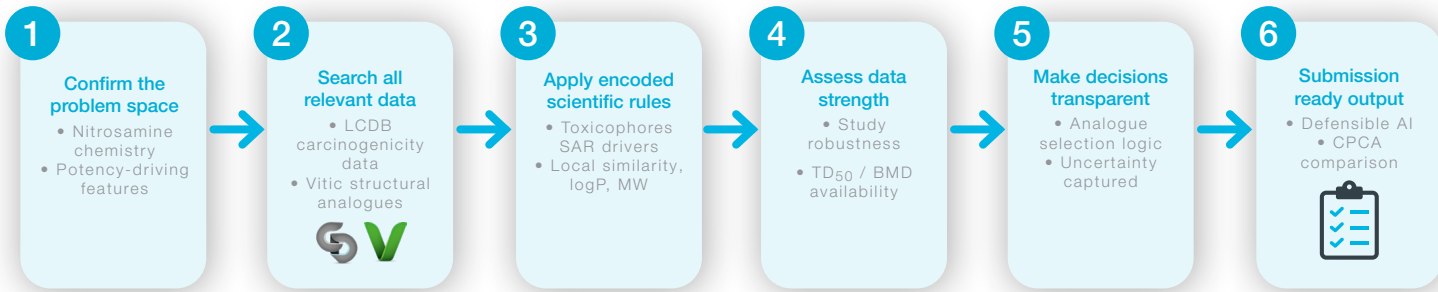
Applying a structured, best-practice read-across enables more realistic compound-specific AI limits while maintaining patient safety. This reduces unnecessary recalls and supports continued medicine supply.



Acroscopic

Using *in silico* tools for a structured approach to best practice read-across, resulting in defensible decisions.

A six-phase workflow that turns nitrosamine read-across guidance into reproducible, regulator-aligned outcomes:



Key

1. LCDB - Lhasa Carcinogenicity Database
2. SAR - structure-activity relationship
3. logP - partition coefficient
4. MW - molecular weight
5. TD₅₀ - median toxic dose
6. BMD - benchmark dose
7. AI - acceptable intake
8. CPCA - Carcinogenic potency categorisation approach

An actionable blueprint for defensible read-across.

Key steps to support transparent, reproducible, and regulator-aligned nitrosamine read-across decisions.

- ✓ Always confirm applicability domain - is the compound a nitrosamine?
- ✓ Use both structural and mechanistic similarity, not fingerprints alone.
- ✓ Filter out analogues with mismatched activating/deactivating features.
- ✓ Prioritise analogues with robust carcinogenicity data (TD₅₀/BMD).
- ✓ Document every decision for regulatory transparency.

Designed by scientists for scientists, Lhasa bridges industry and regulators to advance safer, more reliable chemical risk assessment.

This best-practice approach supports confident chemical safety decisions for the benefit of human health, reflecting the Lhasa purpose.

By enabling transparent and reproducible, read-across, Lhasa *in silico* solutions help organisations reach scientifically justified conclusions and support successful regulatory submissions without animal testing.

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