

Nitrosamine Risk Assessment

Write the three-step nitrosamine report: risk evaluation, confirmatory testing, and changes and control. Acceptable intakes come from published values or the CPCA potency category.

WRITES

3.2.S.3.2

3.2.P.5.5

Report

PRODUCT TYPE

Small molecule

GUIDANCE IT FOLLOWS

FDA Control of Nitrosamine Impurities in Human Drugs (Rev. 2, 2024) and Recommended AI Limits for NDSRIs (2023); ICH M7(R2); ICH Q2(R2)

TIME TO LEARN

About 20 minutes with the example

Open the tool at <https://app.cmcfy.com/app/nitrosamine-assessment.html>. This guide is also online at <https://cmcfy.com/guides/nitrosamine-assessment.html>

1. What this module does

You tick the risk factors that apply, and enter each nitrosamine with its root cause and either a published acceptable intake (AI) or the CPCA inputs: α -hydrogen counts on each side, deactivating and activating feature scores, and whether there is a tertiary α -carbon.

The tool works out the CPCA category and AI, converts the AI to a limit at your maximum daily dose, and checks each result, the sum across nitrosamines, the LOQ, the batches and the control strategy.

What you get

- A Word or PDF report: Nitrosamine risk assessment (steps 1 to 3).

2. Before you start

Have these ready. You can still start with the example data and replace it piece by piece.

- The maximum daily dose of the drug substance.

- The structure of each nitrosamine (for the CPCA) or its published AI.
- Confirmatory test results, the LOQ and the batches tested.

Your data stays on your computer. The bar under the title counts every network request the page makes; it stays at 0 because your data never leaves your computer. [Download offline copy](#) saves a single file that opens from your own computer with all network access blocked, for air-gapped PCs.

3. Step by step with the example

Open the tool at app.cmcfy.com/app/nitrosamine-assessment.html. The example is loaded when the page opens, so every panel already has realistic data. Follow the steps to see how it works, then replace the example with your own data.

1 Describe the product

Enter the product, the maximum daily dose and the regulations. In the EU the category 1 AI is 18 ng/day; in the US it is 26.5 ng/day.

The screenshot shows the 'Nitrosamine Risk Assessment' tool interface. At the top, there's a navigation bar with 'CMCfy', 'Nitrosamine Risk Assessment', and links for 'Projects', 'All modules', 'Training', and 'Security'. Below this, a status bar indicates 'Runs entirely on this device', 'Training guide', and 'Protocol builder'. The main content area is titled 'PROJECTS' and includes instructions: 'Keep this work in a project, with version history and your company logo on every report.' It also has buttons for 'Choose projects folder' and 'Keep in this browser'. A section below shows three status indicators: 'Network requests since load: 0' (Counted live by your browser. Your data never leaves this device.), 'Works offline' (Everything the tool needs is inside this page.), and 'Locked offline copy' (Save a single file that opens from your own computer with all network access blocked.). Below these are tabs for '3.2.S.3.2', '3.2.P.5.5', and 'Report'. A 'Save project' button is visible. The main text area contains instructions: 'Write the nitrosamine risk assessment report: step 1 risk evaluation, step 2 confirmatory testing and step 3 changes and control. The tool works out the acceptable intake from a published value or the CPCA potency category, converts it to a limit at your maximum daily dose, and checks each result, the total, the method sensitivity and the control strategy.' It also provides guidance: 'Guidance: FDA Control of Nitrosamine Impurities in Human Drugs (Rev. 2, 2024) and Recommended AI Limits for NDSRIs (2023) / EMA Questions and answers on nitrosamine impurities (EMA/409815/2020) with Appendix 1 (AI list) and Appendix 2 (CPCA); ICH M7(R2); ICH Q2(R2)'. The '1 · PRODUCT' section has input fields for 'Product' (CMX-201 tablets 20 mg (CMX-201 hydrochloride)), 'Regulations' (Both US and EU), 'Maximum daily dose of the drug substance (mg/day)' (40), 'Report number' (NA-RA-012), and 'Product stage' (Marketed or in an applica...). The 'RESULT' section shows '3 nitrosamines · all within the AI' and details: '3 risk factors. N-nitroso-CMX-201: AI 100 ng/day (CPCA category 2), limit 2.500 ppm, 0.32 (13% of AI); NDMA: AI 96 ng/day, limit 2.400 ppm, <0.01; NDEA: AI 26.5 ng/day, limit 0.662 ppm, <0.005. Sum of fractions 0.13.' A table below shows 'RISK FACTORS' (3), 'NITROSAMINES' (3), and 'HIGHEST % OF AI' (13%). The 'MDD' is 40 mg/day. At the bottom, there's a section for 'ACCEPTABLE INTAKES AND RESULTS'.

2 Evaluate the risk

Tick each risk factor that applies and describe your evaluation.

3 Enter the nitrosamines

One row per nitrosamine. Write the α -hydrogen counts as "2;3". Leave the published AI empty to use the CPCA.

ACCEPTABLE INTAKES AND RESULTS						
Limit = AI ÷ maximum daily dose. "<" results count as 0 in the total.						
NITROSAMINE	BASIS	CPCA SCORE	CATEGORY	AI (NG/DAY)	LIMIT (PPM)	MAX FO
N-nitroso-CMX-201	CPCA	2	2	100	2.500	0.32
NDMA	published	—	—	96	2.400	<0.01
NDEA	published	—	—	26.5	0.662	<0.005

AIs, limits and results.

4 Resolve alerts and download

A result above the AI, or a total above 1, is critical. Missing tests, an LOQ that is too high, and results above 10% of the AI without a control are flagged. Then preview and download.

Preview and review before download

Review
Checked on this device: gaps in the data, gaps in the report against ICH and regional expectations, and differences from the protocol.

No open gaps

No open gaps: the data, the report and the protocol (if given) match every rule checked, or you accepted the rest. Read the review before you sign.

Compare with the protocol
Load or paste the approved protocol. Every requirement and acceptance criterion in it is looked for in the report.

Paste the protocol text here, or load the file.

Load protocol file Compare

AI review against guidance
AI reads the report, the protocol and the data against the ICH, FDA or EMA requirements for these sections, and lists gaps with the guideline it applies, protocol and data mismatches, and how to fix them. You see exactly what is sent before anything leaves this device. Results and pass/fail are not changed.

Run AI review

Nitrosamine risk assessment
CMX-201 tablets 20 mg (CMX-201 hydrochloride) · NA-RA-012 · US (FDA) and EU (EMA)

Product	CMX-201 tablets 20 mg (CMX-201 hydrochloride)
Report number	NA-RA-012
Maximum daily dose	40 mg/day
Regulations	US (FDA) and EU (EMA)

1. Step 1: risk evaluation

A nitrosamine risk evaluation was performed for CMX-201 tablets 20 mg (CMX-201 hydrochloride) covering the drug substance synthesis, starting materials, reagents and solvents, excipients, the manufacturing process, packaging and storage.

The following risk factors were identified: the drug substance, an intermediate or an impurity has a secondary or tertiary amine (NDSRI risk); nitrite may be present (excipients, water, reagents); formation on storage is possible (amine and nitrite together in the drug product).

CMX-201 has a secondary amine (acyclic, with an electron-withdrawing group on one α -carbon) that can form N-nitroso-CMX-201 (NDSRI). Nitrite is present in microcrystalline cellulose and croscarmellose sodium (0.2–1.1 ppm, supplier data). The synthesis uses no nitrite or nitrosating agents and no recovered solvents. NDMA and NDEA were considered from the dimethylamine and triethylamine used in steps 2 and 4.

Risk factor	Present
The drug substance, an intermediate or an impurity has a secondary or tertiary amine (NDSRI risk)	Yes
Excipients, process aids or degradants contain amines	No
Nitrite may be present (excipients, water, reagents)	Yes
Nitrosating agents are used or formed in the process (nitrite, nitrous acid, NOx)	No
Recovered solvents, reagents or catalysts are used	No
Starting materials or reagents come from processes with a known nitrosamine risk	No

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4. Field reference

Every input in the tool, panel by panel. Tables accept rows pasted straight from Excel, comma-separated text, or a loaded file; check the columns after loading a file. Fields marked “when it applies” appear only for the choices that need them.

1 - Product

FIELD	WHAT TO ENTER
Product	Type it in.
Regulations	Choose one: US: FDA nitrosamine guidance; EU: EMA nitrosamine Q&A; Both US and EU.
Maximum daily dose of the drug substance (mg/day)	Type a number.
Report number	Type it in.
Product stage	Choose one: Marketed or in an application; Clinical development.

2 - Step 1: risk evaluation

Tick every factor that applies to the drug substance, the drug product or the packaging.

FIELD	WHAT TO ENTER
The drug substance, an intermediate or an impurity has a secondary or tertiary amine (NDSRI risk)	Tick the box if it applies.
Excipients, process aids or degradants contain amines	Tick the box if it applies.
Nitrite may be present (excipients, water, reagents)	Tick the box if it applies.
Nitrosating agents are used or formed in the process (nitrite, nitrous acid, NO _x)	Tick the box if it applies.

FIELD	WHAT TO ENTER
Recovered solvents, reagents or catalysts are used	Tick the box if it applies.
Starting materials or reagents come from processes with a known nitrosamine risk	Tick the box if it applies.
Packaging contains nitrocellulose or amines (for example blister lidding)	Tick the box if it applies.
Formation on storage is possible (amine and nitrite together in the drug product)	Tick the box if it applies.
Evaluation of the risk factors	Type or paste text.

3 · Step 2: confirmatory testing

One row per nitrosamine. Give a published AI, or the CPCA inputs (α -hydrogen counts on each side, deactivating and activating scores, tertiary α -carbon). Results in ppm ($\mu\text{g/g}$ of drug substance).

FIELD	WHAT TO ENTER
Nitrosamines	Write results below the LOQ as "<0.01". They count as 0 in the total. A table. Columns: Nitrosamine Root cause Published AI (ng/day) α -H counts (e.g. 2;3) Tertiary α -carbon (yes/no) Deactivating score Activating score Max found (ppm) LOQ (ppm) Batches tested. Paste rows from Excel, type comma-separated rows, or press Load file (Excel, CSV, Word, PDF or a scan).
Method	Type it in.
Method validated	Tick the box if it applies.
Batches tested	Type or paste text.

4 · Step 3: changes and control

FIELD	WHAT TO ENTER
Control strategy	Choose one: No routine test: consistently below 10% of the AI; Specification test on the drug substance or drug product; Control upstream (raw material or intermediate test); Skip testing after consistent results.
Proposed specification limit for the controlled nitrosamine (ppm) <small>when it applies</small>	Type a number.
Mitigation and changes	Type or paste text.

5. Checks and alerts

Calculations and pass/fail outcomes always come from fixed rules, never from AI. The tool checks:

- CPCA category and AI for each nitrosamine.
- Each result and the sum of fractions against the AI.
- LOQ, batches, method validation and control strategy.

How to resolve alerts

- **Critical** alerts block the download and must be fixed in the data. A failing result can instead be linked to an investigation: type the investigation reference and outcome and press **Record**.
- **Major** alerts block the download until you fix them or type a justification and press **Accept justification**.
- **Minor** alerts do not block anything. They are listed in the documents so the reviewer sees them.
- Some alerts have an **Apply fix** button that makes the change for you. **Reopen** undoes a justification.

Narratives

This module writes: Step 1: risk evaluation; Step 2: confirmatory testing; Step 3: changes and control strategy. Each narrative is written by fixed rules from your data. You can edit it in the box. **Rewrite with AI** (where your plan includes AI) rewrites it in regulatory style; every number in the text is checked against your data, and a number that does not match is flagged under the box and blocks the download until you correct it. **Reset to rule-based text** brings back the original.

6. Preview, gap review and download

1. Press **Preview** next to a section, or **Preview and download all**. The document opens in a preview window, exactly as the Word file will read.
2. The left side lists the review, run on your device: **gaps in the data** (missing values, open alerts), **gaps in the report** (missing content the guidance expects, placeholders such as [site] or TBD left in the text) and, if you load the approved protocol under **Compare with the protocol**, **differences from the protocol** (requirements, criteria, batches or time points it plans that the report does not show).
3. Click a finding to jump to the place in the preview. Fix it in the tool, then preview again.
4. Optional **AI review**: a second read for contradictions, claims without data and vague wording. The report text is sent to Claude only when you press it, and only where your plan includes AI. Check every AI finding; AI can be wrong.
5. Press **Download Word (.docx)** or **Download PDF**. With several documents open, **All as Word (.zip)** and **All as PDF (.zip)** download the set. The download buttons stay disabled while a blocking alert is open; the preview still works.

Documents this module produces

SECTION	DOCUMENT
Report	Nitrosamine risk assessment

Use **Save project** to keep your work as a file on your computer, and **Open project** to continue later. **Start blank** clears every field; **Load example** brings the example back. Nothing is stored on CMCfy servers.

7. US and EU submissions

US follows the FDA nitrosamine guidance (Rev. 2, 2024) and the NDSRI AI guidance. EU follows the EMA nitrosamine Q&A (EMA/409815/2020) and its Appendix 2 (CPCA).

8. Working with other modules

- The nitrosamine section of the drug substance and product impurity profile is in the Impurity & Risk Studio.

9. Common pitfalls

- Forgetting the NDSRI from the drug substance itself.
- An LOQ too high to show results below 10% of the AI.

10. Practice exercises

Each exercise starts from the example (press [Load example](#) to reset). We run these on every update of this guide, so the result you see should match.

1. Exceed the AI

Change the N-nitroso-CMX-201 result from 0.32 to 3.1 ppm.

EXPECTED RESULT

The headline shows one nitrosamine above the AI.

Guide updated 28 October 2026 for the current version of the tool. CMCfy drafts are for review by a qualified person before use in a submission.