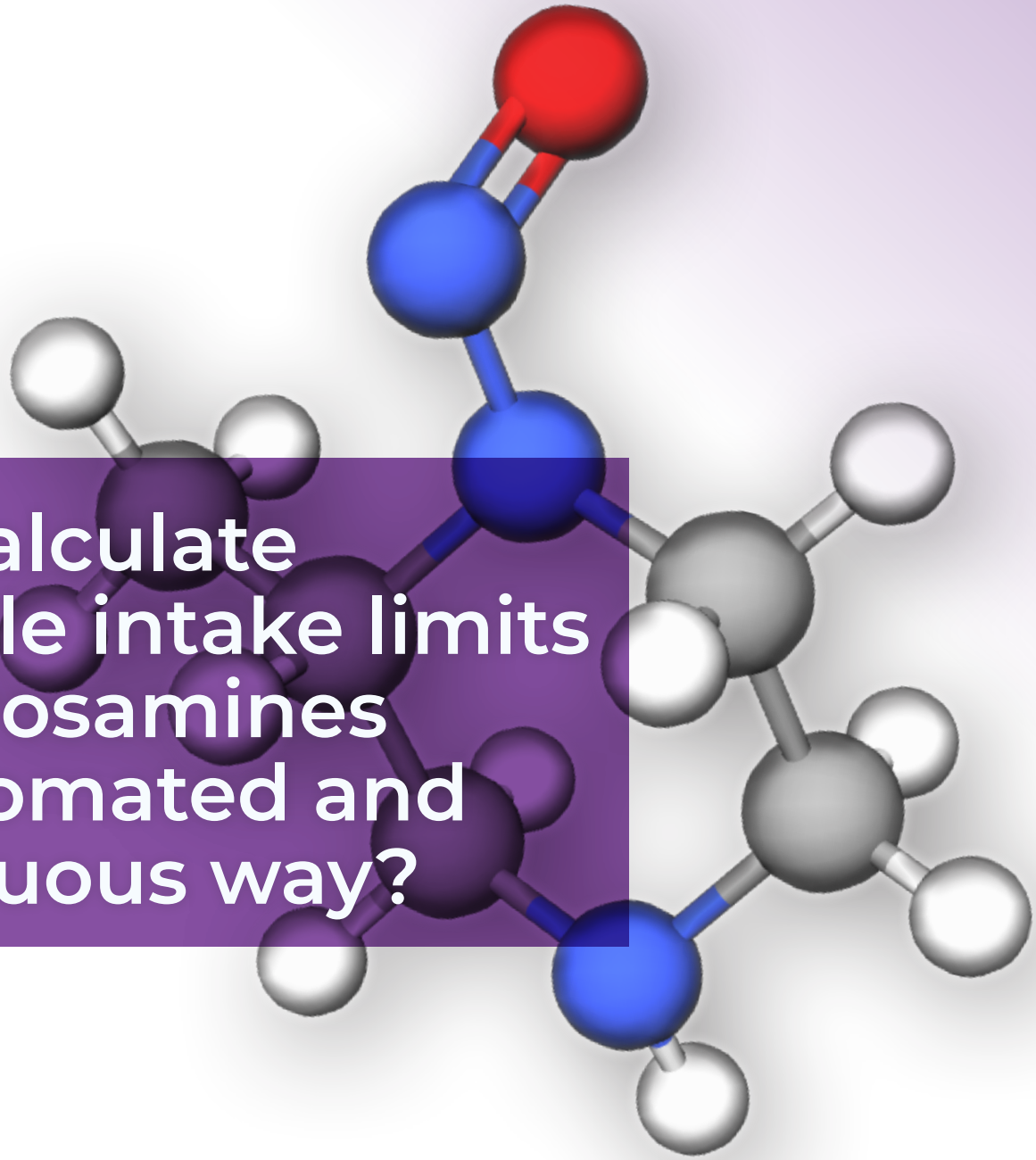
Nitro-Next™

Automatized Carcinogenicity Potency Scorer



How to calculate acceptable intake limits for N-Nitrosamines in an automated and unambiguous way?

Altox

ALTERNATIVE TOXICOLOGY

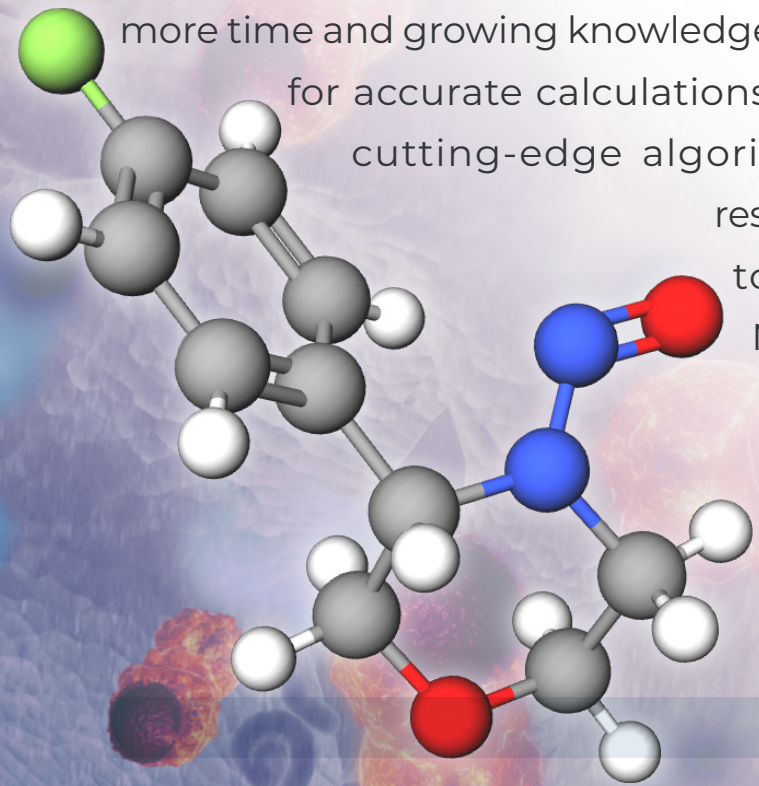
Setting safe limits for N-Nitrosamines with Nitro-Next

In the ever-evolving landscape of N-nitrosamines, Altox proudly unveils Nitro-Next, a pioneering software designed specifically for automated Carcinogenic Potency Categorization Approach (CPCA)-based calculations for N-Nitrosamines.

Following the adoption of the CPCA by EMA and FDA guidelines, Altox's innovation core, in collaboration with leading regulatory, chemistry, toxicology, and chemoinformatics experts, developed Nitro-Next.

Representing a significant advancement in toxicology and providing reports in a few seconds, Nitro-Next stands as the premier solution for analysts or expert toxicologists seeking accuracy, high efficiency in N-nitrosamine assessments and updated data regarding deactivating/activating features for compliant reports with EMA and FDA guidelines, as well as Anvisa's RDC 677/2022 and Guide 50/2021.

Nitro-Next emerges as a crucial tool amidst growing concerns over human errors in handicraft assessments, particularly, when more time and growing knowledge about new fragments is required for accurate calculations. With its intuitive interface and cutting-edge algorithms, the software empowers researchers, analysts and toxicologists to swiftly identify and quantify N-nitrosamines with unparalleled accuracy.



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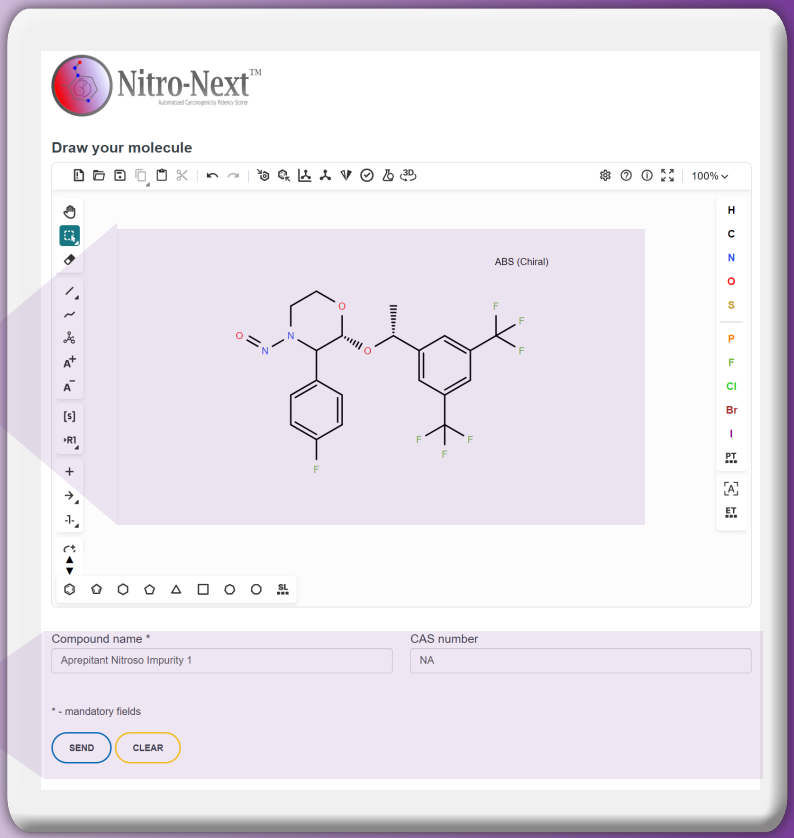
In compliance with EMA, FDA and Anvisa's RDC 677/2022 and Guide 50/2021, the software performs an *in silico* analysis to identify structural features related to the carcinogenic potency of N-Nitrosamines, enabling automated unambiguous safe limit setting for these molecules.

Draw your molecule or insert the structure using the SMILES code.

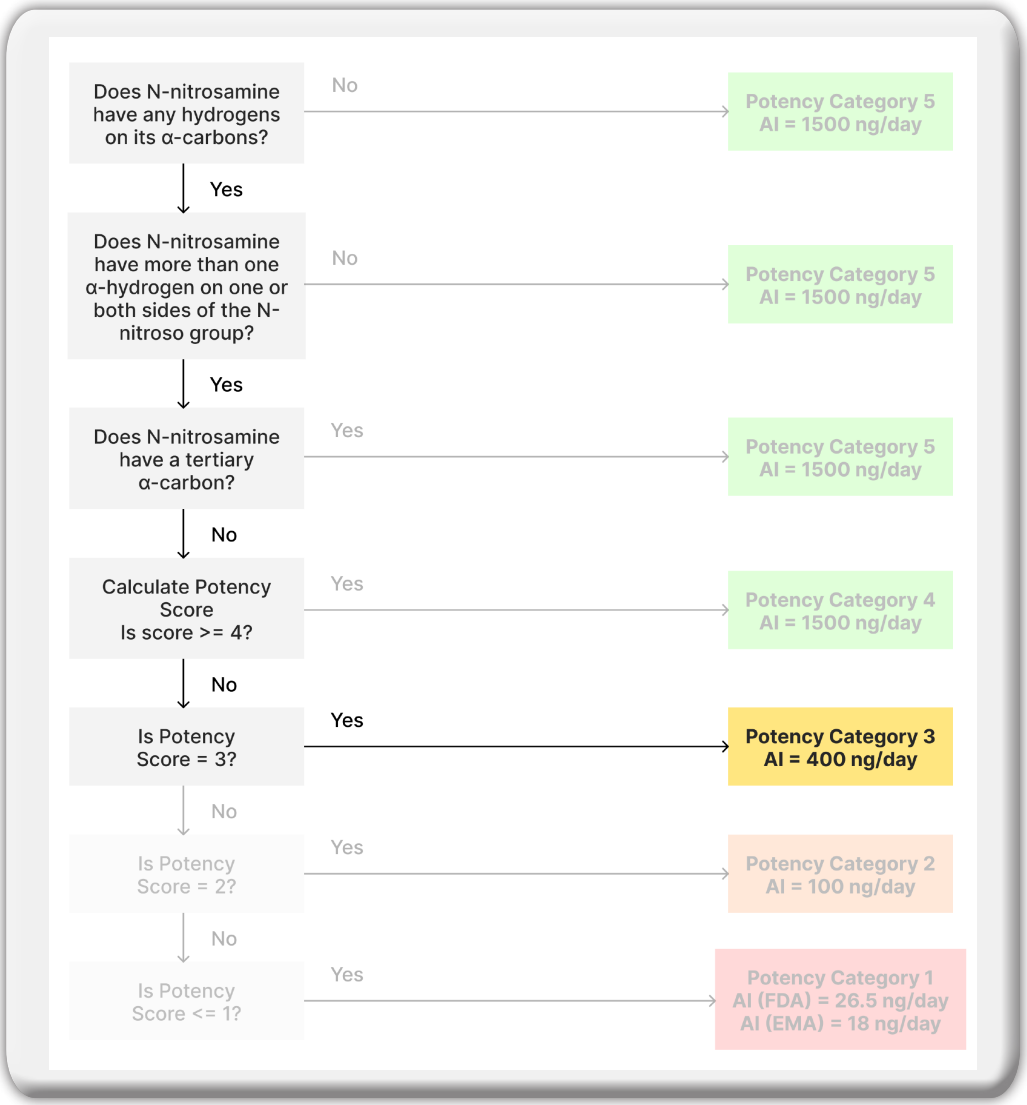
Insert the compoud name (mandatory) and CAS number (optional).

Then press the "SEND" button to start the analysis and generate the report.



1 Determination of carcinogenic potency category and acceptable intake limit

Nitro-Next algorithm analyzes N-Nitrosamine structures following the EMA/FDA CPCA flowchart:



The software accurately determine both potency category and acceptable intake limit for structures within CPCA applicability domain. If a N-Nitrosamine is outside the CPCA scope, the software generates a user report presenting this information.

2 Potency Score Calculation

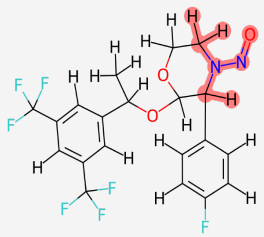
When potency score calculation is needed to determine potency category and derive the acceptable intake limit, Nitro-Next provides detailed information with visual representations for better comprehension of results.

This includes details regarding the scoring for α-hydrogen count and deactivating/activating features of the N-Nitrosamine (when applicable).

a

Scoring according to α-hydrogen count

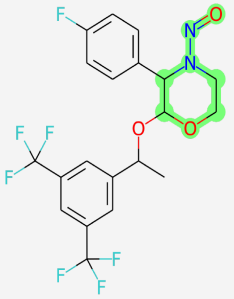
Nitro-Next identifies and counts a-hydrogens according to CPCA for appropriate score attribution. The resulting score is also presented:

Count of α-Hydrogens	Score	Feature
1,2	3	

b

Scoring according to Deactivating Features

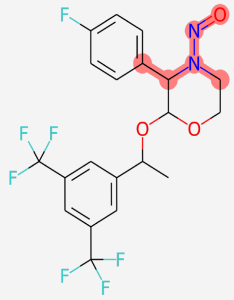
Deactivating features are identified, described, and attributed a score according to CPCA. The corresponding group is then highlighted green in the N-Nitrosamine structure:

Deactivating Feature	Score	Feature
N-nitroso group in a morpholine ring	1	

c

Scoring according to Activating Features

The software additionally identifies and highlights activating features that may be present in N-Nitrosamines (red), assigning the appropriate score based on the groups identified:

Activating Feature	Score	Feature
Aryl group bonded to α-carbon (i.e., benzylic or pseudo-benzylic substituent on N-nitroso group)	-1	

3 Final Result

The potency score calculation is demonstrated in detail and the resulting score defines the acceptable intake limit for the N-Nitrosamine under evaluation.

Potency Score = α-Hydrogen Score + Deactivating Feature Score + Activating Feature Score

Type	Score	Subtotal
α-Hydrogen Score	3	3
Deactivating Feature Score	1	1
Activating Feature Score	-1	-1

Potency Score = 3 + 1 – 1 = 3

Potency Score	Potency Category (AI Limit)
3	1 2 3 4 5 Potency Category 3 (400 ng/day)

4 Expert Review for attenuating or activating fragments

If applicable, Nitro-Next performs the exclusive **Matched Molecular Pair (MMP)** analysis that can be used in Expert Review for attenuating or activating fragments.

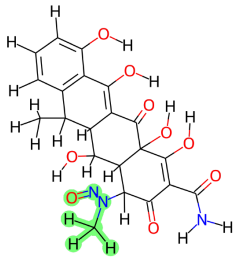
The underlying principle of MMP analysis involves comparing two molecules (L and R) and simulating a transformation in the R portion. The associated property changes are expressed as “Ratio” and “Difference/Variation” of TD50 values or toxicological outcomes:

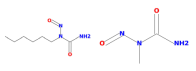
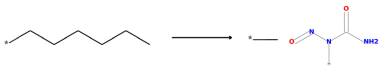
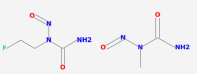
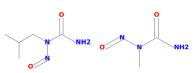
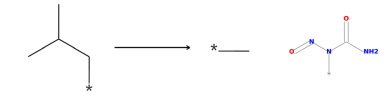
a

MMP analysis 1 - Variation in TD50 values

Molecular matched pair (MMP) analysis 1 – Variation in TD50 values

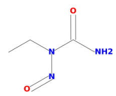
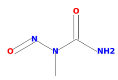
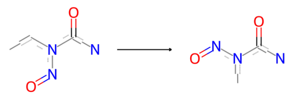
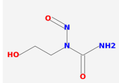
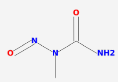
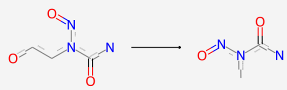
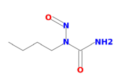
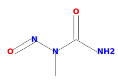
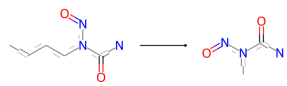
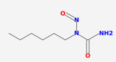
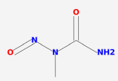
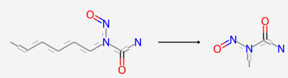
Fragment 1



Molecule L	Molecule R	Transformation	Context	Ratio	TD50 L	TD50 R	Difference / Variation
Most Similar							
				0.18	0.513	0.0927	-0.4203
				0.74	0.125	0.0927	-0.0323
				0.02	4.73	0.0927	-4.6373

b

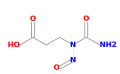
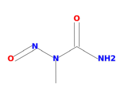
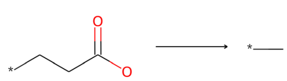
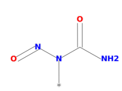
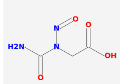
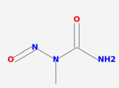
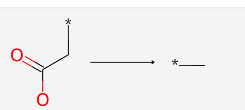
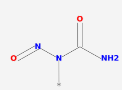
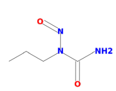
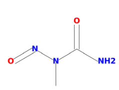
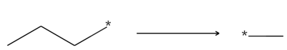
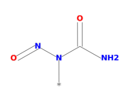
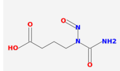
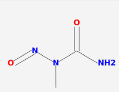
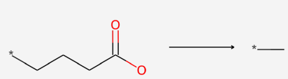
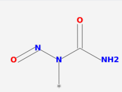
MMP analysis 2 – Variation in carcinogenic output

Molecule L	Molecule R	Transformation	Context	Result L	Result R	Difference / Variation
Most Similar						
				1	1	0
				1	1	0
				1	1	0
				1	1	0

Molecular matched pair (MMP) analysis 2 – Variation in carcinogenic output

c

MMP analysis 3 – Variation in mutagenic response

Molecule L	Molecule R	Transformation	Context	Result L	Result R	Difference / Variation
Most Similar						
				1	1	0
				0	1	1
				1	1	0
				1	1	0

Molecular matched pair (MMP) analysis 3 – Variation in mutagenic response

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