Assessing Carcinogenic Potency of Untested Nitrosamines.

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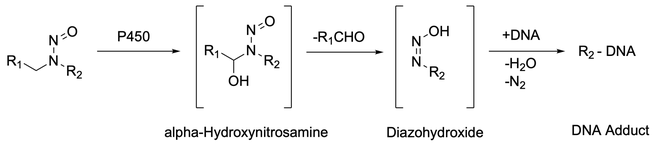
Abstract

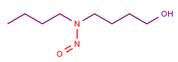
Recently N-nitrosamines (NA) became a focus of regulatory agencies and industry, as they were identified in several widely used medications as impurities. Nitroso compounds belong to the “cohort of concern chemicals” due to their high potential to cause cancer. While the data from experimental carcinogenicity studies of more than a hundred NAs are available with different degree of robustness, the most concerning drug-like NA derivatives have not been tested. We report the results of a recent study, where the carcinogenic potency of untested NAs were identified with the help of surrogate NAs. These surrogates were selected based on their local structural environment around the N-nitroso group, the potential for metabolic activation, and physicochemical properties. A new type of molecular fingerprint and similarity measure was developed and used for this purpose. These fingerprints reflect the structural information in the vicinity of the N-nitroso group. They account for the factors known to modulate carcinogenic potential, including the type of substitution at the alpha-carbon position, ring membership, and presence of bulky or electron-donating/withdrawing substituents. This approach was validated on 20 randomly selected NAs with available experimental TD50 values. TD50 values for the query were estimated as the most conservative TD50 value from suitable surrogates. Upon expert review, suitable surrogates were found for 19 query compounds (95% coverage). For 63% of the query NAs, estimated TD50 values were within 1 log unit of the experimental value. The use of this approach is illustrated in a few case studies. The potential use of E-state descriptors and partial charges as additional tools to validate the identified surrogates is also illustrated. The results support the conclusion that the combination of comprehensive databases, advanced analog search algorithms, and novel cheminformatics tools improve our carcinogenicity risk assessment ability for Nitrosamines.

Background

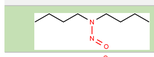
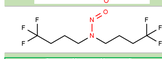
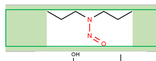
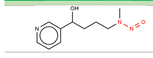
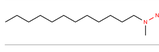
- “Some nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time.”[1]
- Medications, recalled due to the excessive levels of nitrosamine impurities: Zantac, Nizatidine, Metformin, Chantix, Valsartan, Losartan, Irbesartan, Propranolol
- In the absence of robust empirical carcinogenicity data, an acceptable intake can be calculated using TD50 values from structurally related analogs, or surrogates. There is a demand to develop a computational local similarity method to more objectively and efficiently calculate the most relevant surrogates to a data-poor NA[2]
- Nitrosamines need metabolic activation to exert their DNA reactive toxic effects.
- The first enzymatic step is α-hydroxylation. It is the rate limiting step.



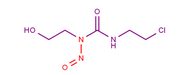
Examples



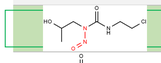
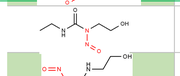
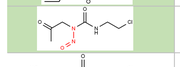
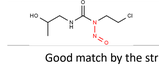
Query: N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE
CAS: 3817-11-6, **MW:** 174.244
LogP: 1.328
Water Solubility: 17.977 gm/L

Analog	Local Similarity	Global Similarity	MW	CPDB TD_{50} mg/kg	LHASA TD_{50} mg/kg	LogP	Water Solubility gm/L
	0.800	0.808	158.245	0.691*	-	2.630*	1.270*
	0.800	0.500	266.185	0.748*	-	2.724	0.551
	0.600	0.667	130.191	0.186*	-	1.360*	13.001*
	0.550	0.281	209.249	0.103*	-	0.265	443.230
	0.500	0.645	228.380	0.537*	-	5.102	0.004

Good match by the structural features, LogP and Water Solubility; The suggested TD50 for the query substance is **0.186** mg/kg/day.
The actual value for the query substance is **0.261** mg/kg/day

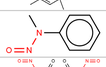
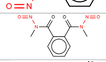
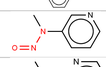
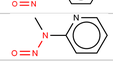


Query: 1-Nitroso-1-(2-hydroxyethyl)-3-(2-chloroethyl)urea
CAS: 96806-34-7, **MW:** 195.606
LogP: 0.090
Water Solubility: 27.796 gm/L

Analog	Local Similarity	Global Similarity	MW	CPDB TD_{50} mg/kg	LHASA TD_{50} mg/kg	LogP	Water Solubility gm/L
	0.950	0.655	209.633	0.873*	0.871*	0.504	12.147
	0.800	0.804	161.161	0.562*	0.477*	-0.156	52.526
	0.700	0.729	161.161	0.522*	0.347*	-0.156	52.526
	0.700	0.660	207.617	0.338*	-	0.597	7.876
	0.667	0.655	209.633	0.124*	-	0.504	6.687

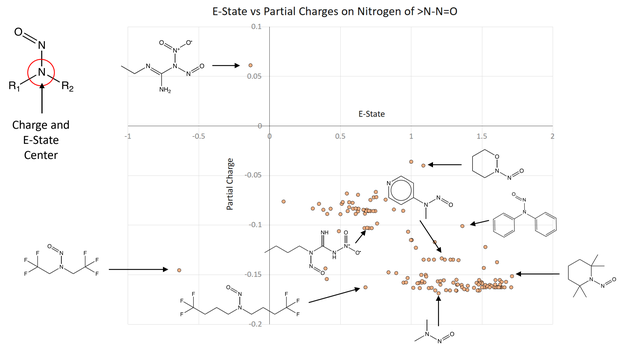
Good match by the structural features, LogP and Water Solubility; The suggested TD50 for the query substance is **0.871** mg/kg/day.
The actual value for the query substance is **0.152** mg/kg/day

Query: N-NITROSODIPHENYLAMINE
CAS: 86-30-6, **MW:** 198.225
LogP: 3.130
Water Solubility: 0.035 gm/L

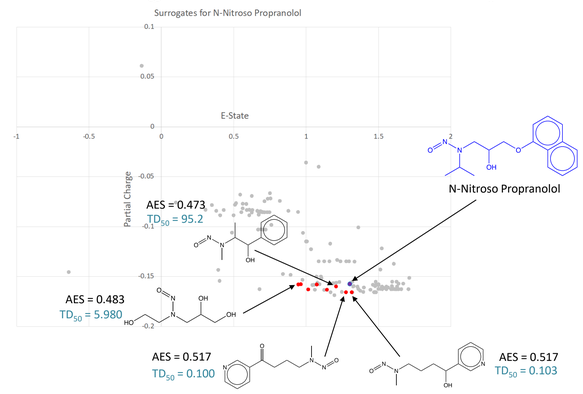
Analog	Local Similarity	Global Similarity	MW	CPDB TD_{50} mg/kg	LHASA TD_{50} mg/kg	LogP	Water Solubility gm/L
	0.475	0.313	202.257	3.830*	-	3.126	0.072
	0.469	0.733	136.154	0.142*	0.106*	1.501	3.682
	0.469	0.250	250.214	10000.000*	-	0.949	2.211
	0.422	0.525	137.142	6.090*	-	0.359	63.853
	0.422	0.455	137.142	0.214*	-	0.763	28.881

No good matches by the structural features; The suggested TD50 for the query substance cannot be generated
The actual value for the query substance is 167.000 mg/kg/day

Use E-state descriptors and partial charges to identify good surrogates



QSAR Flex Surrogates for N-Nitroso Propranolol



Performance evaluation

- 20 randomly selected N-Nitrosamines with the experimental TD50 were selected for the external validation. Upon expert review, the suitable analogs were found for 19 query compounds (95% coverage)
- TD50 values for the query compounds were estimated as a most conservative value of TD50 for the available analogs
- This approach produced the estimated values of TD50 with the following ranges of differences from the actual TD50

% of estimated TD50	Within Log units from the actual TD50
26	0.5
63	1
84	2

Approach: Alert Environment Similarity Based Analog Search

- Uses similarity of structural environment around alerts.
- Retrieves highly relevant analogs.
- Accounts for effects of substituents on metabolism of nitrosamines

Original Manuscript

Computing similarity between structural environments of mutagenicity alerts

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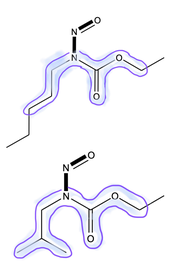
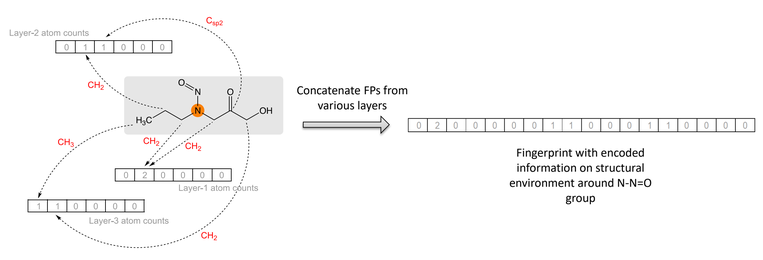


Encoding Structural Environment as a Fingerprint

- The fingerprint can be used for searching analogs that have experimental carcinogenicity data.
- Potentially useful for making decisions about the query chemical.



Conclusion

We successfully demonstrated that the novel software tool QSAR Flex, utilizing our comprehensive databases and advanced analog search algorithms, significantly improves Nitrosamines' carcinogenicity risk assessment capabilities.

References

1. US FDA “What to Know and Do About Possible Nitrosamines in Your Medication”. https://www.fda.gov/consumers/consumer-updates/
2. Naomi L. Kruhlak, Suman Chakravarti, Govindaraj Kumaran, Roustem Saiakhov. A New Structural Similarity Method to Identify Surrogate Compounds for Assessing the Carcinogenicity of Nitrosamine Impurities. Poster, SOT 2022.