Assessing Carcinogenic Potency of Untested Nitrosamines

MultiCASE Inc., USA

info@multicase.com

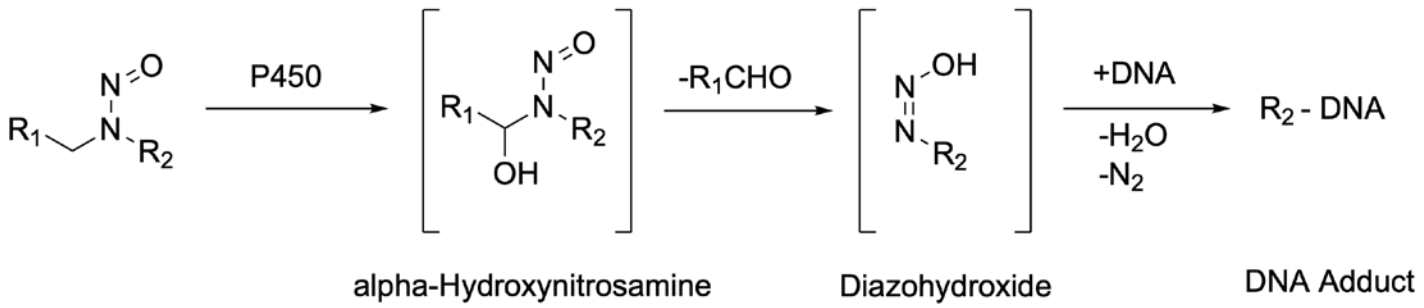
Why?

- “Some nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time.” What to Know and Do About Possible Nitrosamines in Your Medication, US FDA
- Medications, recalled due to the excessive levels of nitrosoamine impurities

- Zantac
- Nizatidine
- Metformin
- Chantix
- Valsartan
- Losartan
- Irbesartan
- Propranolol

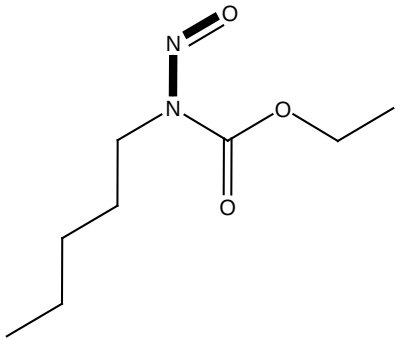
Metabolism of Nitrosamines

- Nitrosamines need metabolic activation to exert their DNA reactive toxic effects.
- The first enzymatic step is α-hydroxylation.
- It is the rate limiting step.



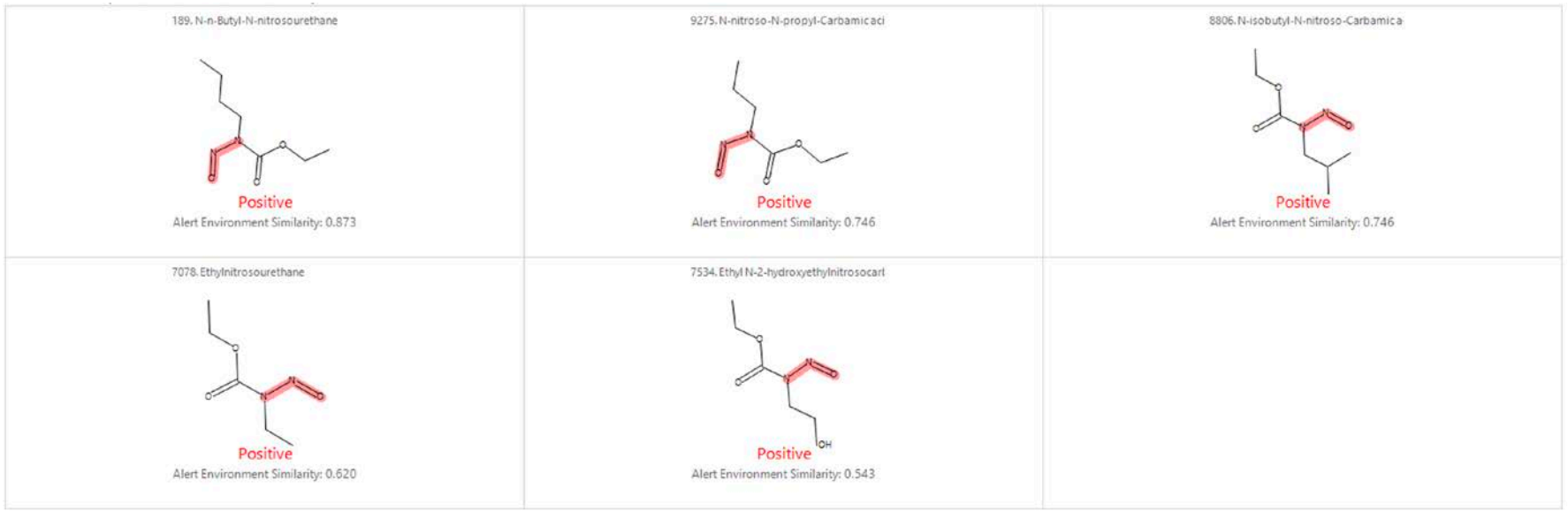
What is available already

- MultiCASE QSAR system, **CASE Ultra**, contains comprehensive Bacterial Mutagenicity and Carcinogenicity data for Nitrosamines.
- Various tools are already available to search this data to get relevant analogs to aid read across.
- Current Bacterial Mutagenicity and Carcinogenicity databases: 463 Nitrosamines with Bacterial Mutagenicity Data, 121 with TD50 data (CPDB, NTP)



Query Nitrosamine

Identified Analogs



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

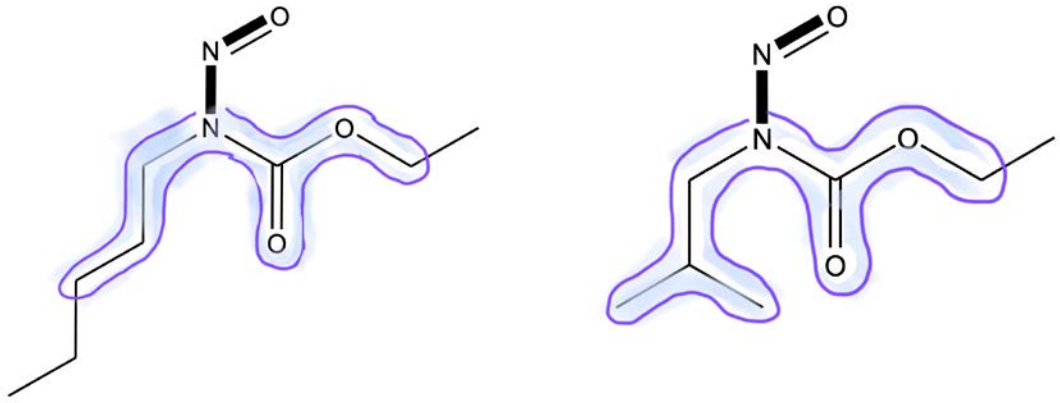
Computing similarity between structural environments of mutagenicity alerts

Suman K. Chakravarti* and Roustem D. Saiakhov

MultiCASE Inc., 23811 Chagrin Blvd, Suite 305, Beachwood, OH 44122, USA

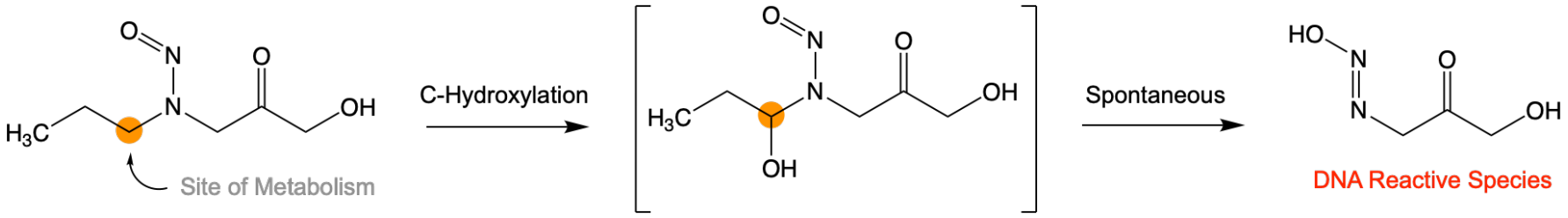
*To whom correspondence should be addressed. Tel: +1-216-831-3740; Fax: +1-216-831-3742; Email: chakravarti@multicase.com

Received 19 June 2018; Revised 16 August 2018; Editorial decision 13 September 2018; Accepted 29 September 2018.

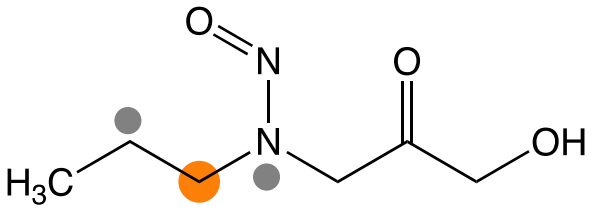


Using Structural Environment for Computing Reactivity of the Site of Metabolism

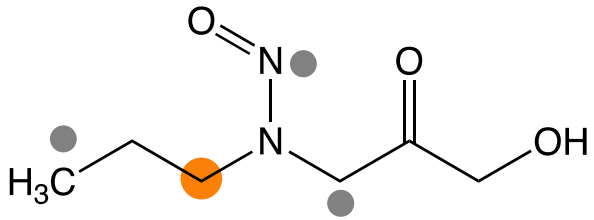
1. Metabolic transformation (predicted by *META Ultra* software)



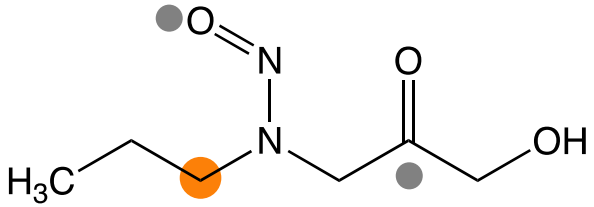
2. Structural environment used in get the above prediction



Atoms at 1-bond distance
(CH_2, N_{sp3})



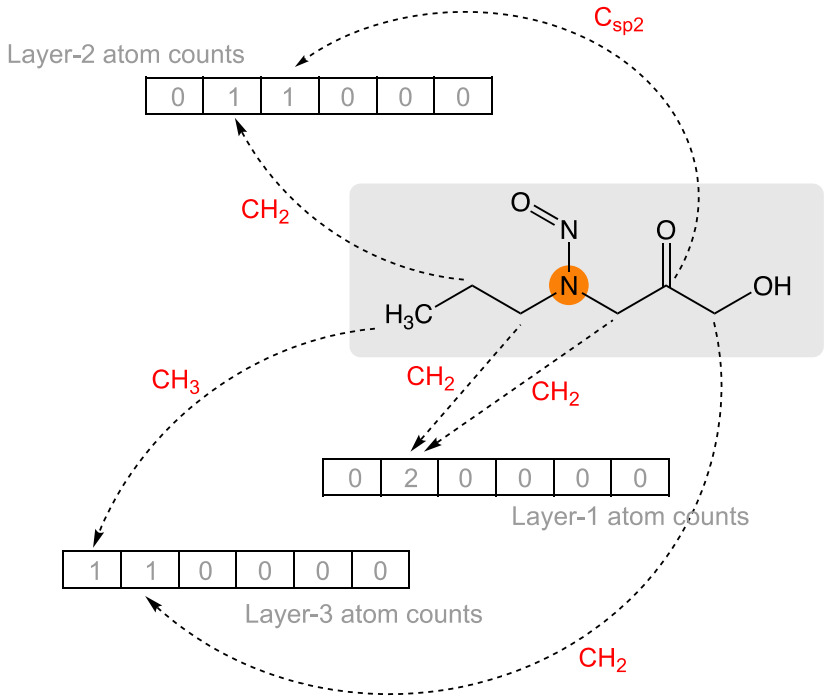
Atoms at 2-bond distance
(CH_3, N_{sp2}, CH_2)



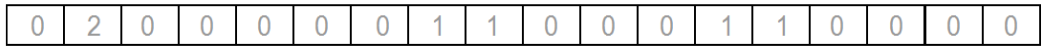
Atoms at 3-bond distance
(=O, C_{sp2})

Encoding Structural Environment as a Fingerprint

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



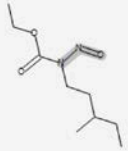
Concatenate FPs from various layers



Fingerprint with encoded information on structural environment around N-N=O group

QSAR Flex for Advanced Analog Search

- Contains better algorithm for analog search for Nitrosamines.
- Combines predictive and database search methods.
- Includes physicochemical property calculations.

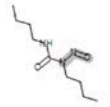
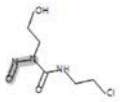
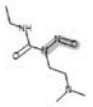
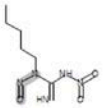
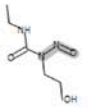


N_Nitroso new

Query #1: NO NAME

Evaluation Outcome -> 2222.792 (TD50, mg/kg bw)

Closest analogs, based on the similarity of structural environment around the alert

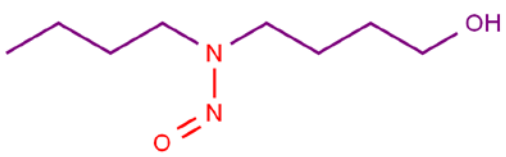
	Chemical ID	Chemical	Alert Env. Similarity	Whole Structure Similarity	Name	TD50 (mg/kg/day)	Mol. Wt.	LogP	Water Solubility (gm/L)
☑	90		0.814	0.429	*Nitrosoamylurethan*	0.339*	188.227	2.654	0.746
☑	70		0.814	0.195	*1,3-dibutyl-1-nitrosourea*	2.250*	201.270	2.840	0.483
☑	138		0.800	0.212	*1-Nitroso-1-(2-hydroxyethyl)-...*	0.152*	195.606	0.284	25.338
☑	17		0.780	0.215	*Dimethylaminoethylnitrosoeth...*	0.704*	188.231	0.653	66.426
☑	11		0.780	0.154	*N-PENTYL-N'-NITRO-N-NITR...*	10000.000*	203.202	1.644	0.517
☑	137		0.770	0.228	*N'-ethyl-N-(2-hydroxyethyl)-...*	0.477*	161.161	0.101	43.911

External validation of QSAR Flex N-Nitrosoamine carcinogenicity model

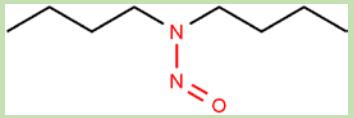
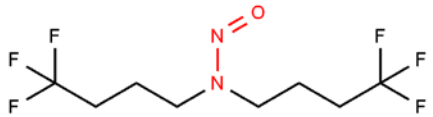
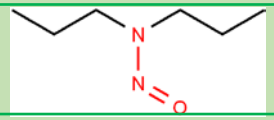
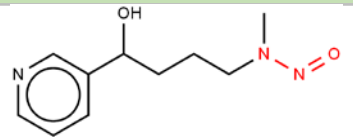
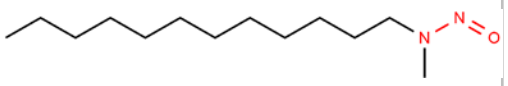
- 20 randomly selected N-Nitrosoamines with the experimental TD50 were selected for the validation
- Upon the expert review the suitable analogs were found for 19 query compounds (95% coverage)
- TD50 values for the query compounds were estimated as a most conservative value of TD50 for the available analogs
- This approached 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

Case study 1

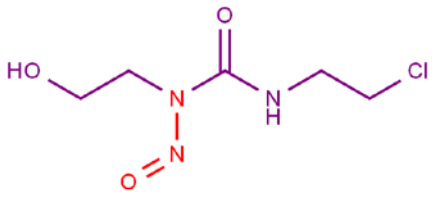


Query: N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE
CAS: 3817-11-6, **MW:** 174.244
LogP: 1.328
Water Solubility: 17.977 gm/L

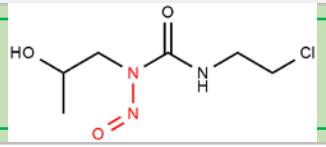
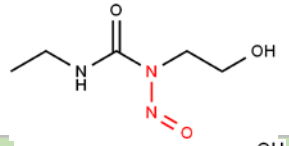
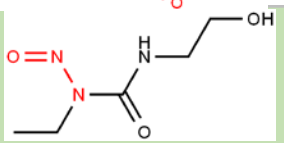
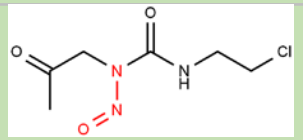
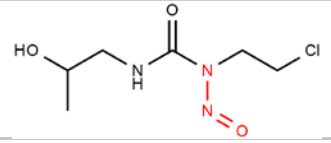
Analog	Local Similarity	Global Similarity	MW	CPDB TD_{50} mg/kg	LHASA TD_{50} mg/kg	LogP	Water Solubility gm/L
	0.800	0.808	158.245	0.691*	-	2.630*	1.270*
	0.800	0.500	266.185	0.748*	-	2.724	0.551
	0.600	0.667	130.191	0.186*	-	1.360*	13.001*
	0.550	0.281	209.249	0.103*	-	0.265	443.230
	0.500	0.645	228.380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

Case study 2

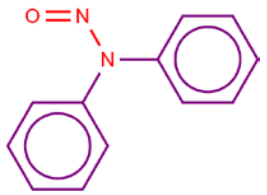


Query: 1-Nitroso-1-(2-hydroxyethyl)-3-(2-chloroethyl)urea
CAS: 96806-34-7, **MW:** 195.606
LogP: 0.090
Water Solubility: 27.796 gm/L

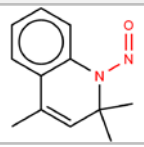
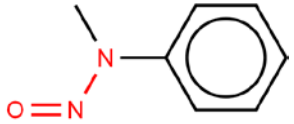
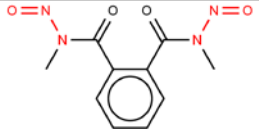
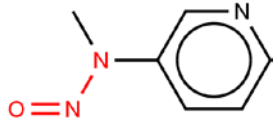
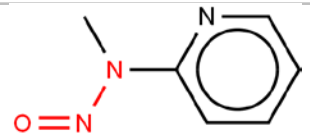
Analog	Local Similarity	Global Similarity	MW	CPDB TD_{50} mg/kg	LHASA TD_{50} mg/kg	LogP	Water Solubility gm/L
	0.950	0.655	209.633	0.873*	0.871*	0.504	12.147
	0.800	0.804	161.161	0.562*	0.477*	-0.156	52.526
	0.700	0.729	161.161	0.522*	0.347*	-0.156	52.526
	0.700	0.660	207.617	0.338*	-	0.597	7.876
	0.667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

Case study 3

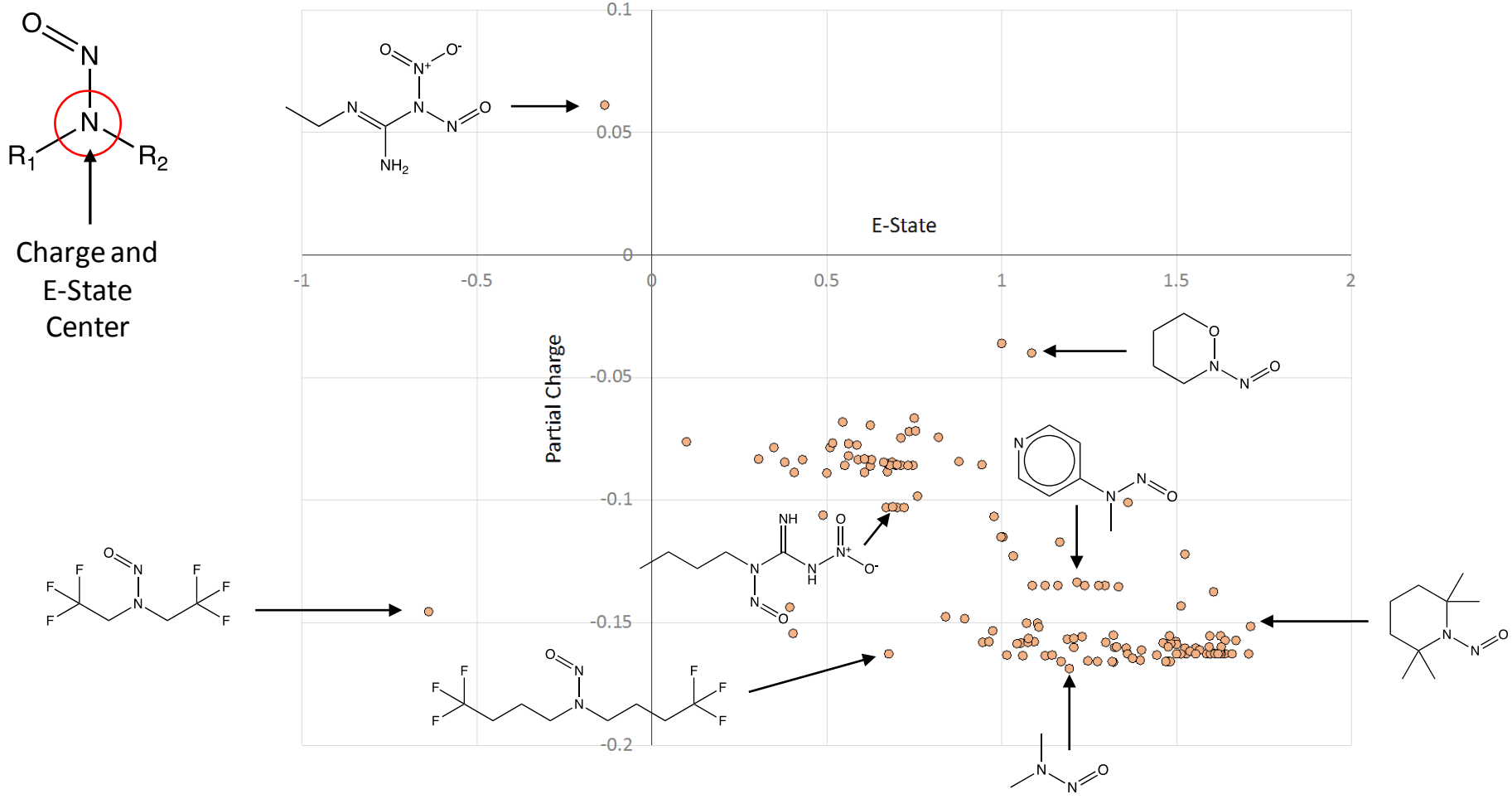


Query: N-NITROSODIPHENYLAMINE
CAS: 86-30-6, **MW:** 198.225
LogP: 3.130
Water Solubility: 0.035 gm/L

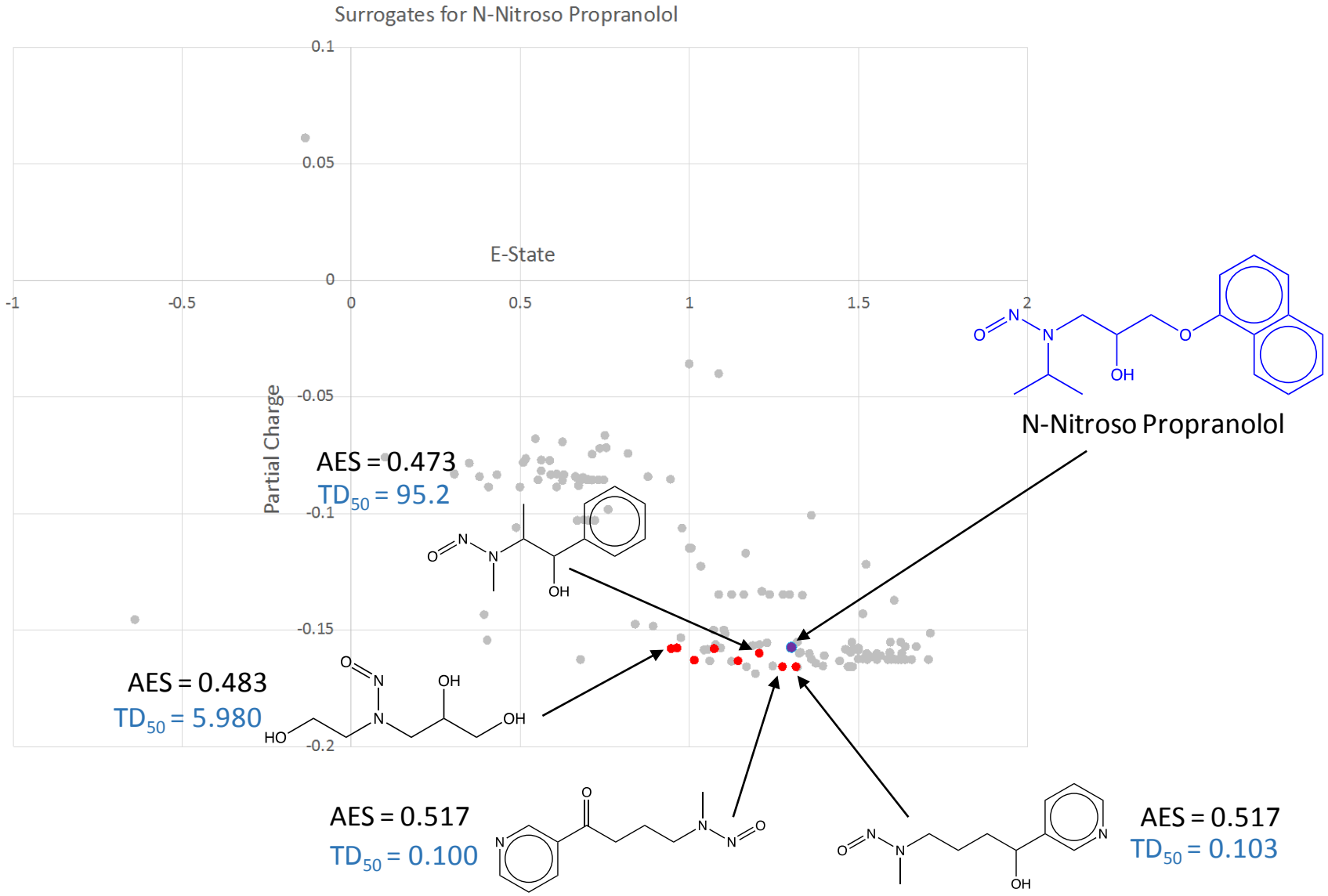
Analog	Local Similarity	Global Similarity	MW	CPDB TD_{50} mg/kg	LHASA TD_{50} mg/kg	LogP	Water Solubility gm/L
	0.475	0.313	202.257	3.830*	-	3.126	0.072
	0.469	0.733	136.154	0.142*	0.106*	1.501	3.682
	0.469	0.250	250.214	10000.000*	-	0.949	2.211
	0.422	0.525	137.142	6.090*	-	0.359	63.853
	0.422	0.455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



Summary

We are using our comprehensive databases, advanced analog search algorithms, and novel software tools to improve carcinogenicity risk assessment capabilities for Nitrosamines.

Dr Suman Chakravarti, Dr Roustem Saiakhov

MultiCASE Inc., USA

info@multicase.com