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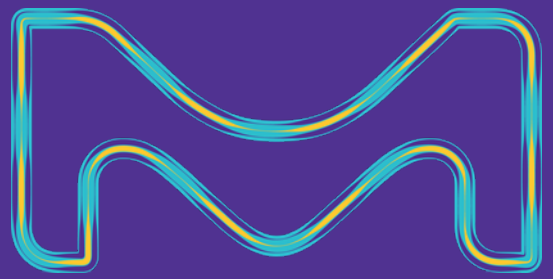
Nitrosamine risk from Atmospheric NO_x and solvent recovery

Dr. Joerg Schlingemann, Merck Healthcare KGaA

FDA 2026 GDUFA Public Workshop
FDA White Oak Campus, Silver Spring | JUN 8-9, 2026



EMD SERONO

Disclaimer

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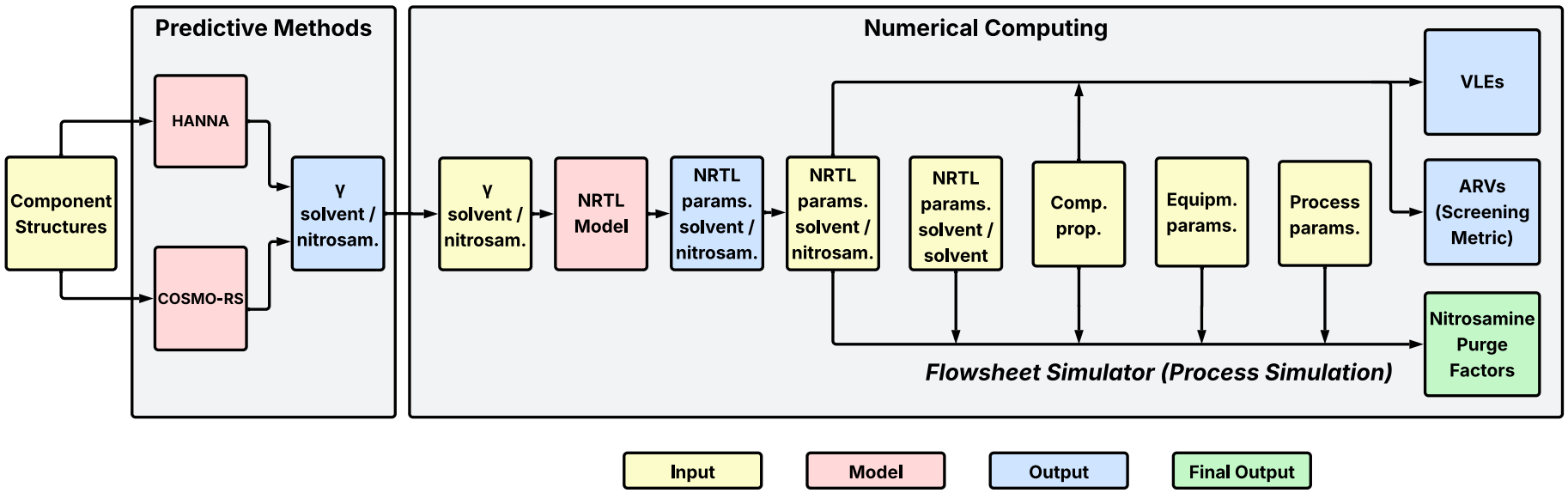
01

Solvent recovery

Research paper

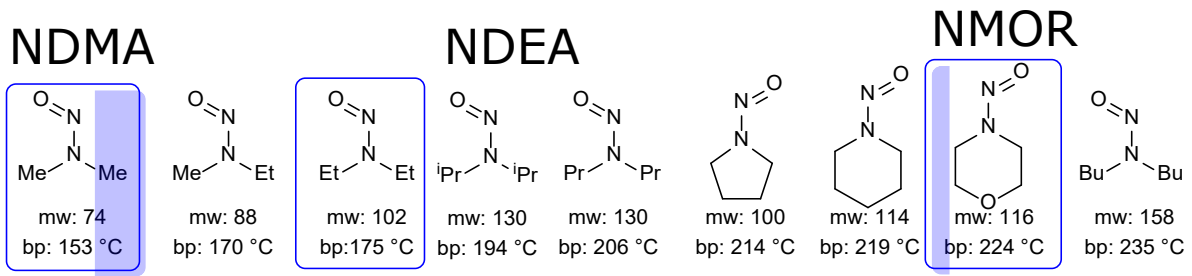
Theoretical and Experimental Assessment of Nitrosamine Risk in Industrial Solvent Recovery *

https://doi.org/10.1021/acssuschemeng.6c02602



3 model nitrosamines with 32 common solvents

Case study: Acetonitrile



*

The FDA, EMA and WHO list recovered solvents among the root causes of nitrosamine impurities.

Background: Vapor-liquid equilibria (VLE) and relative volatility of ethanol and water

Ideal mixtures follow Raoult's law

$p_i = p^*_i \, x_i$

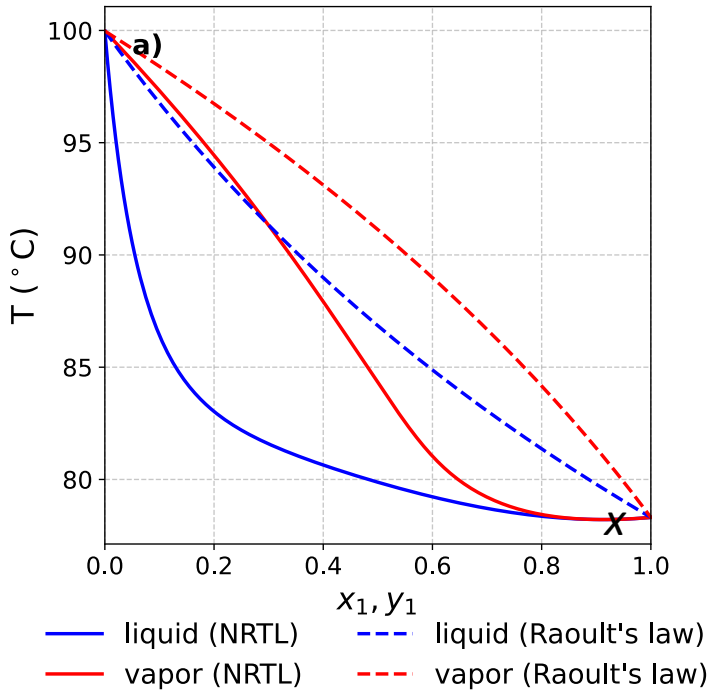
x_i = *Liquid phase mole fraction of compound i*
p^*_i = *Partial pressure of pure compound i*
p_i = *Partial pressure of component i in the mixture*

Real mixtures often deviate from ideal behavior

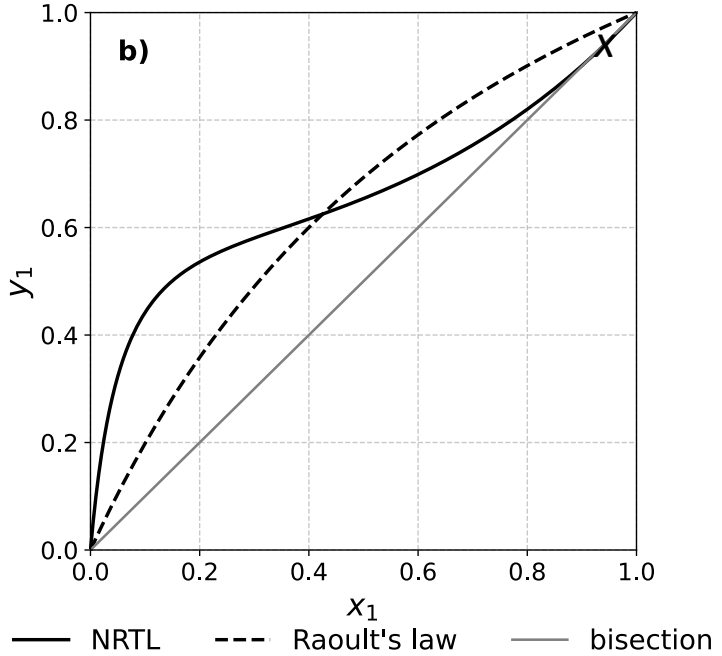
$p_i = p^*_i \, x_i \, \gamma_i$

γ_i = *Activity coefficient for given pressure, temperature and composition*

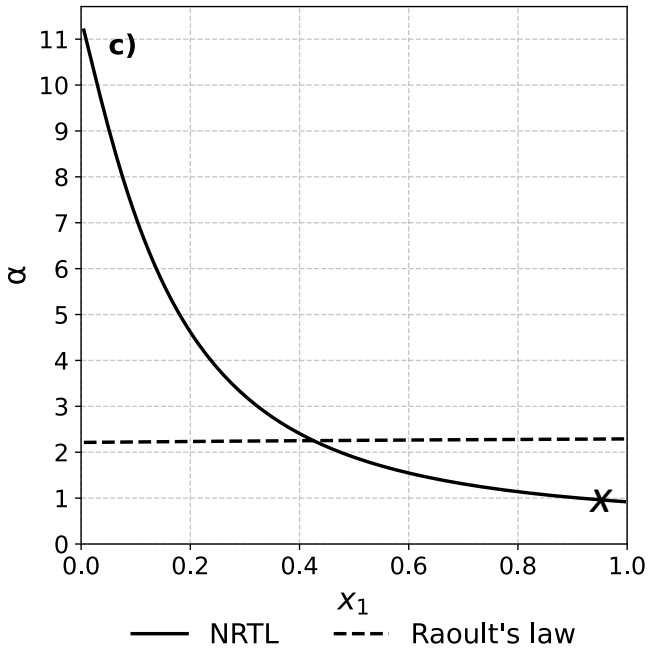
Txy-diagram



xy-diagram



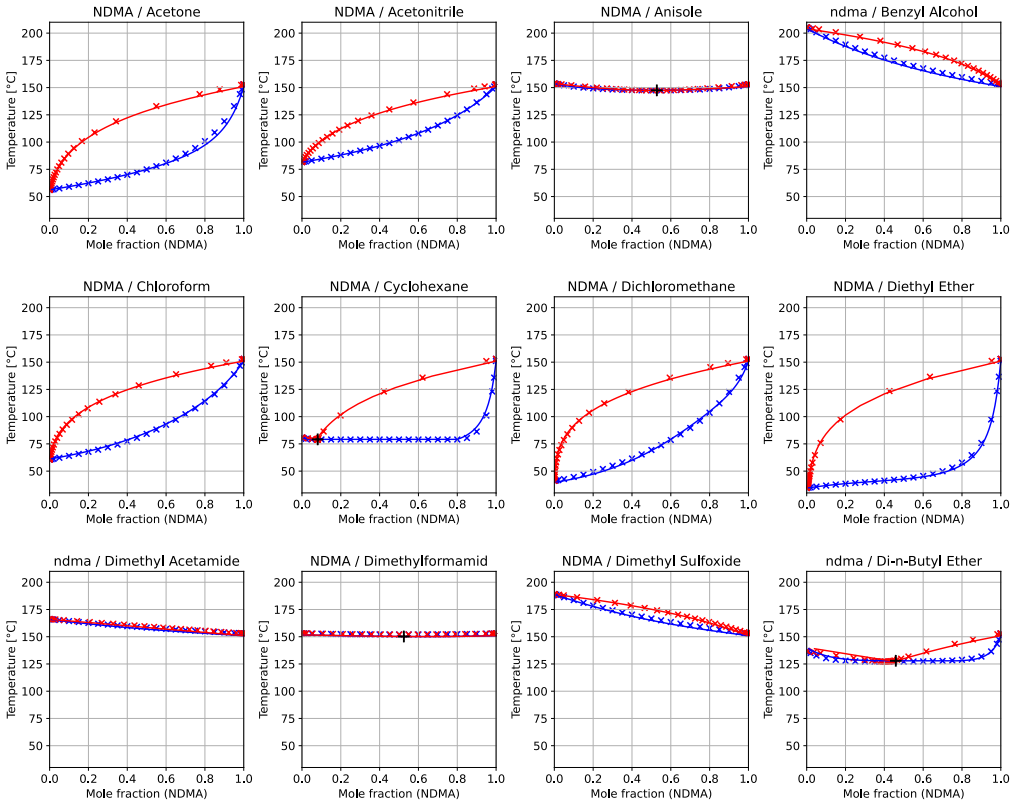
Relative volatility



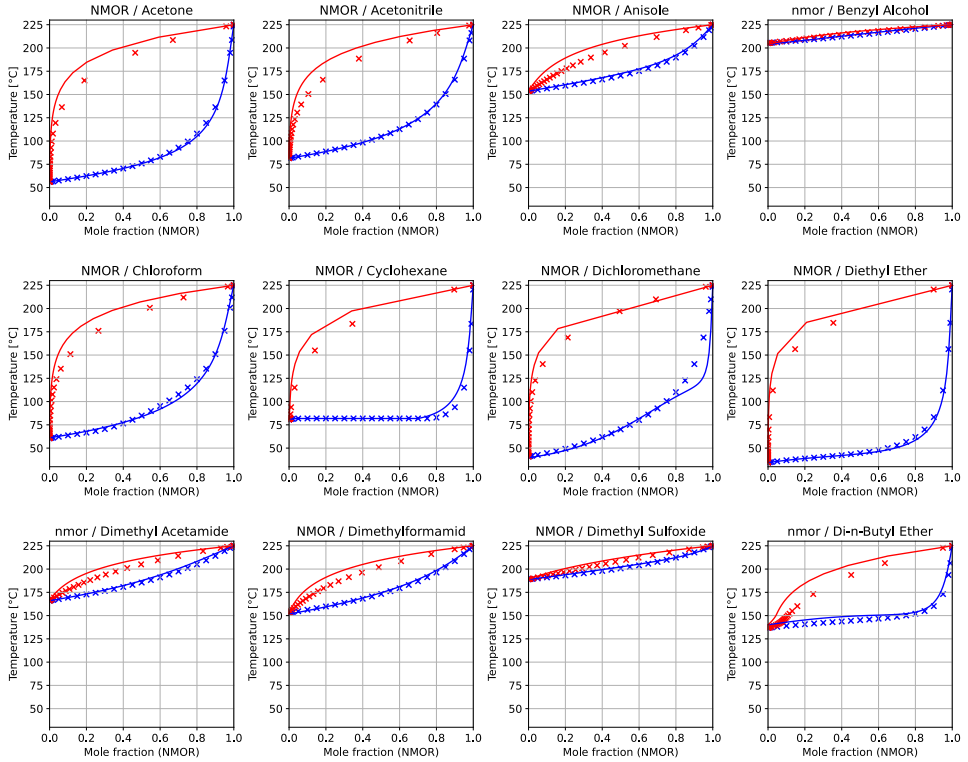
x: Azeotrope at 96.5 % EtOH

Exemplary VLEs determined with COSMOtherm

NDMA

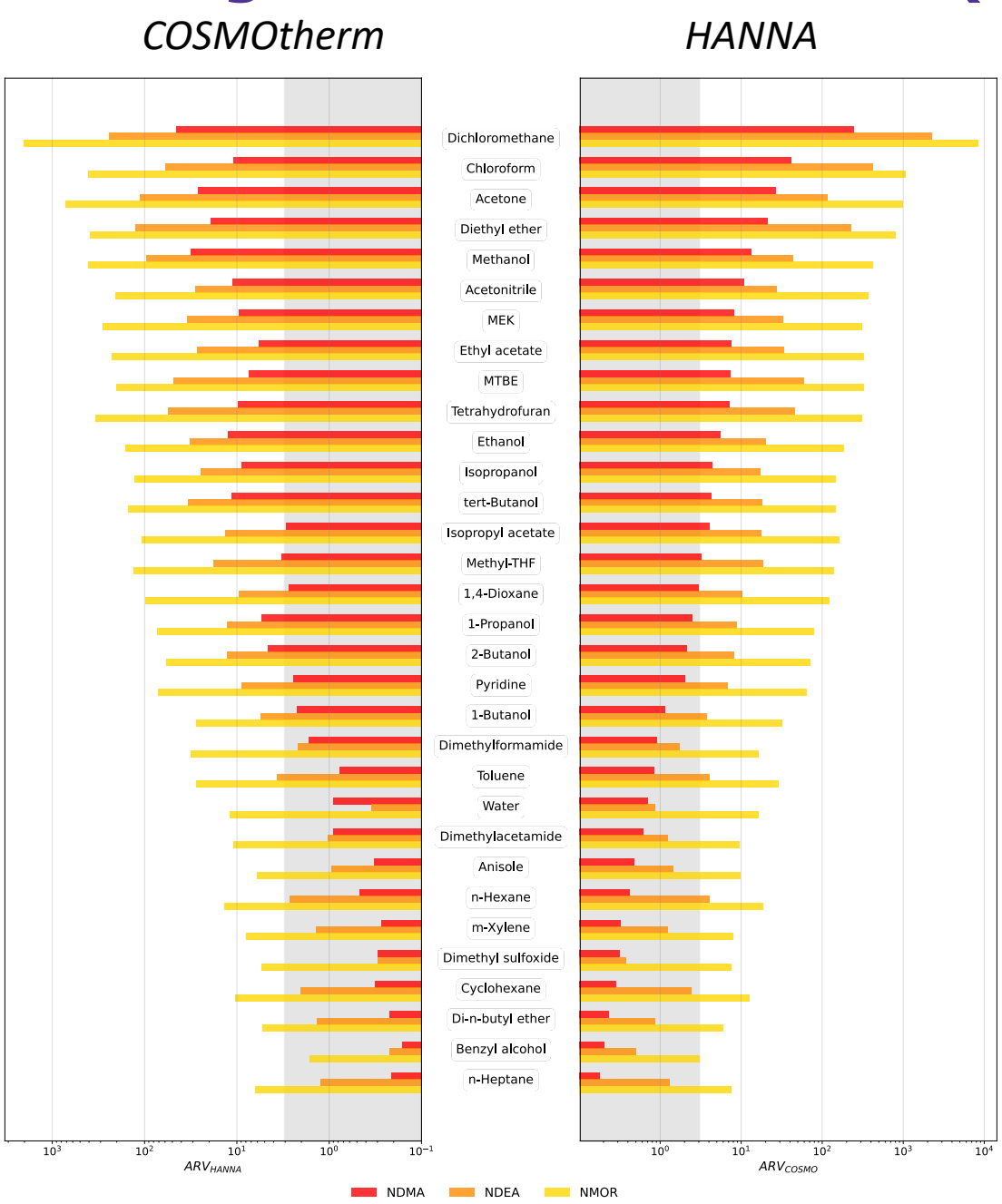


NMOR



Selected VLEs were experimentally validated

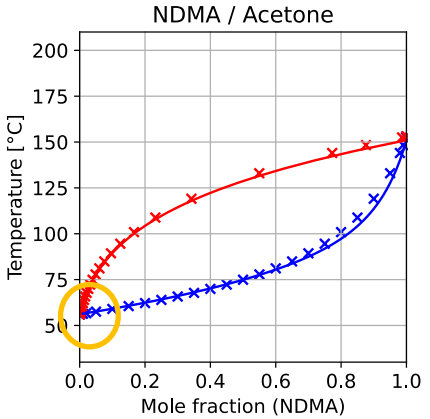
Average relative volatilities (ARVs)



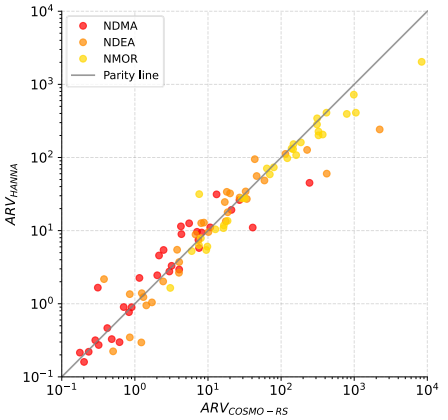
The ease of separation can be expressed quantitively as the relative volatility α of two components i and j

$$\alpha_{ij} = \frac{y_i/x_i}{y_j/x_j}$$

x_i = *Liquid phase mole fraction of compound i*
y_i = *Vapor phase mole fraction of compound i*
x_j = *Liquid phase mole fraction of compound j*
y_j = *Vapor phase mole fraction of compound j*

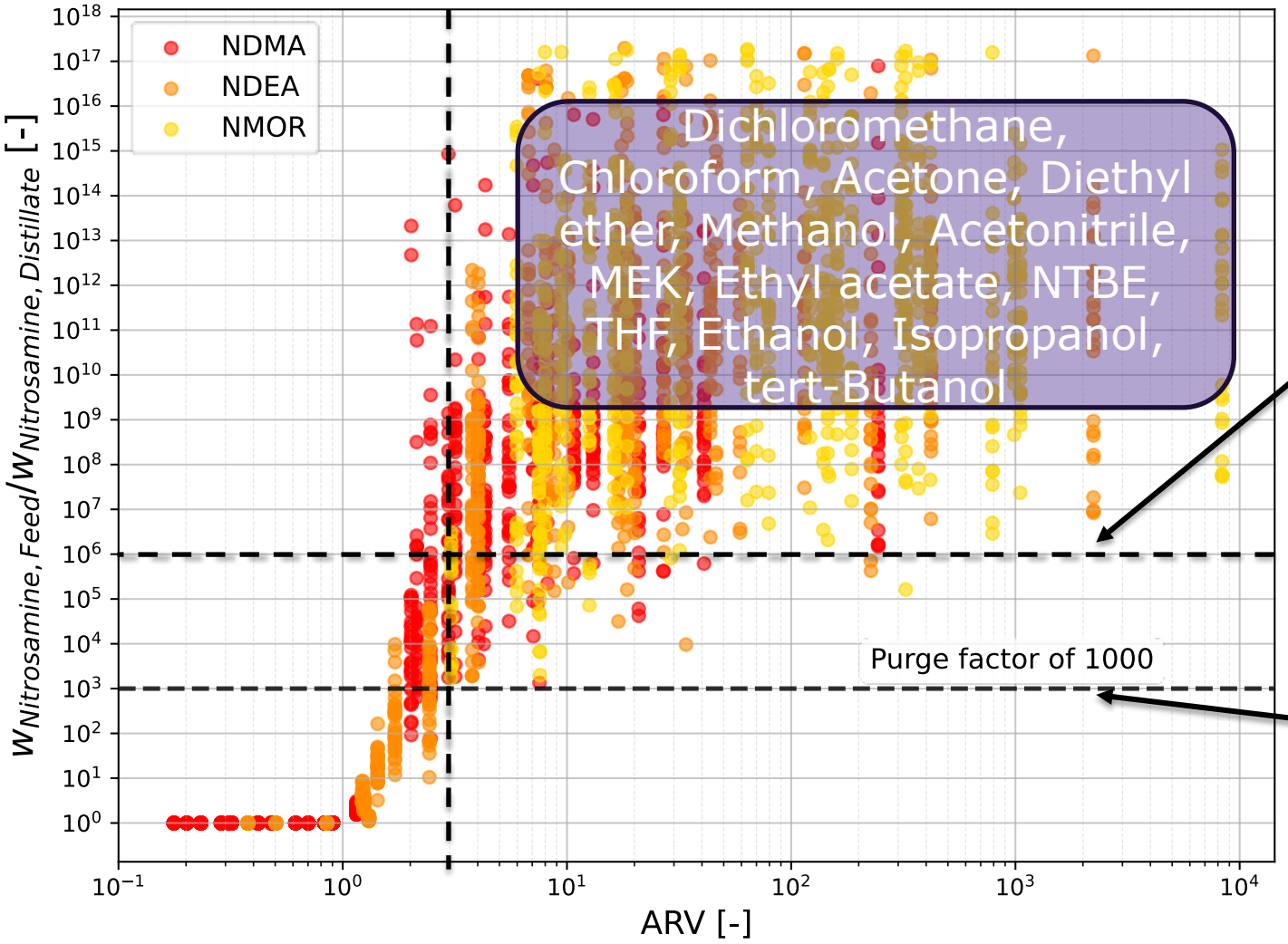


ARVs are calculated across a nitrosamine concentration range of 0-1000 ppm



Excellent agreement between ARVs calculated using two orthogonal methods

An ARV ≥ 3 ensures a nitrosamine purge factor of ≥1000



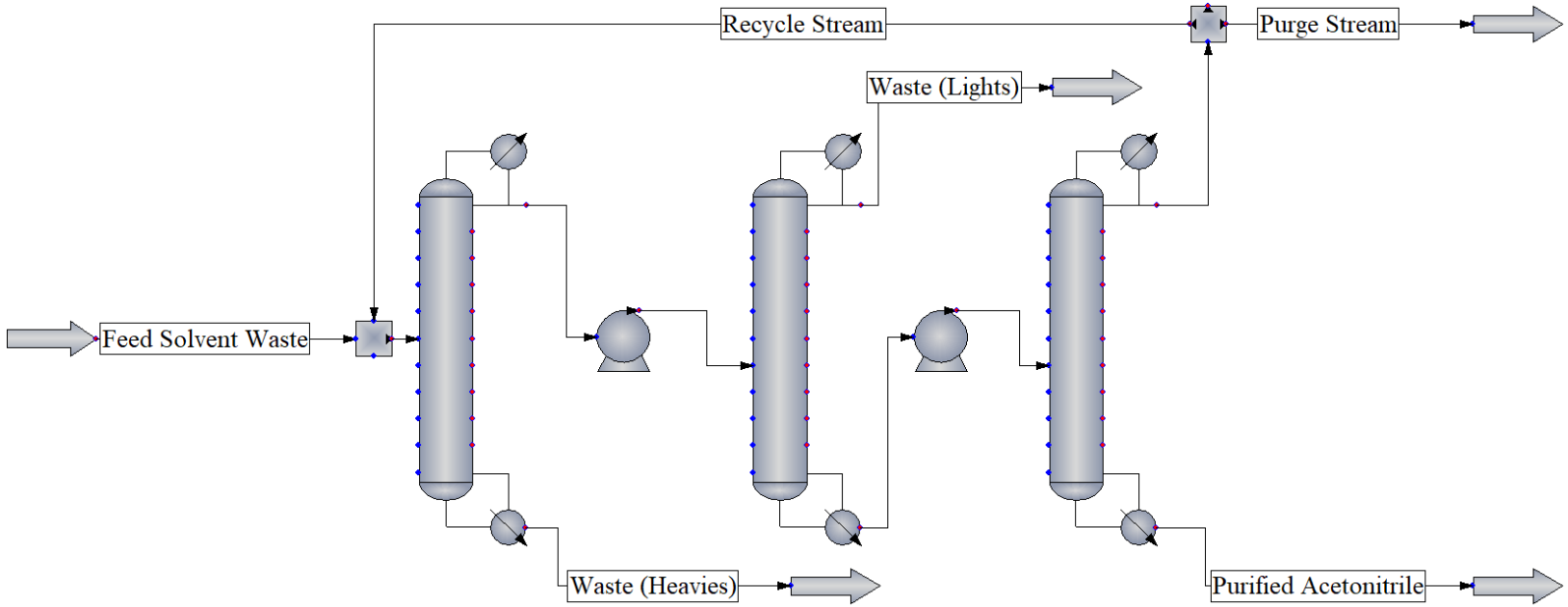
94.3% of simulated processes achieved purge factors ≥10^6 when ARV ≥ 3

100% of simulated processes achieved purge factors ≥10^3 when ARV ≥ 3

Distillations (more specifically: rectifications) were simulated with process parameters altered within common ranges by Montecarlo simulation

Case study: Acetonitrile Regeneration from Oligonucleotide Production Waste Streams

- **Meadhra et al. describe a distillation-based process recovering 85% of acetonitrile from oligonucleotide production waste streams**



- **In silico modeling predicted ≥10^6-fold reduction of NDMA, NDEA, and NMOR from an initial concentration of 100 ppm**
- **Experimental validation confirmed >200,000-fold NDMA reduction (limited by method LoD)**

Conclusions

- Solvent recovery can reduce the carbon footprint of API manufacturing by up to 40–50%
- ARV ≥ 3 correlates with purge factors >1000 (Monte Carlo simulation); most processes achieve >10^6
- Key industrial solvents (e.g., methanol, ethanol, IPA, acetonitrile) exhibit ARVs >3 vs NDMA
- Removal of higher-boiling nitrosamines and NDSRIs is generally not technically challenging
- ARV is a useful screening tool; detailed process modeling recommended for critical cases
- Case study: Acetonitrile regeneration from oligonucleotide waste: complete nitrosamine removal confirmed in silico and in vitro
- Blanket classification of recovered solvents as a nitrosamine risk is not scientifically justified.
- Science-based, process-specific risk assessment enables safe and sustainable solvent recovery
- Robust quality oversight remains essential to minimize cross-contamination and ensure compliance

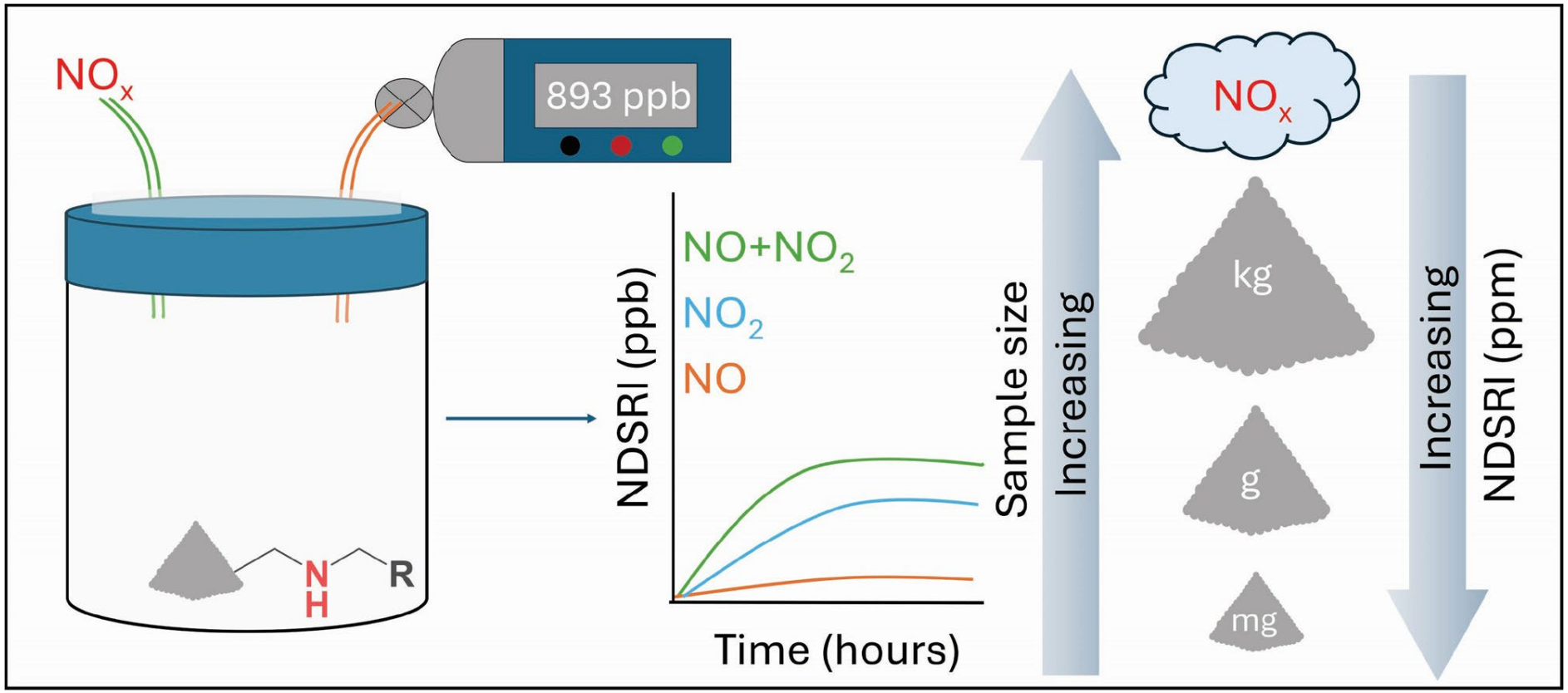
02

NO_x

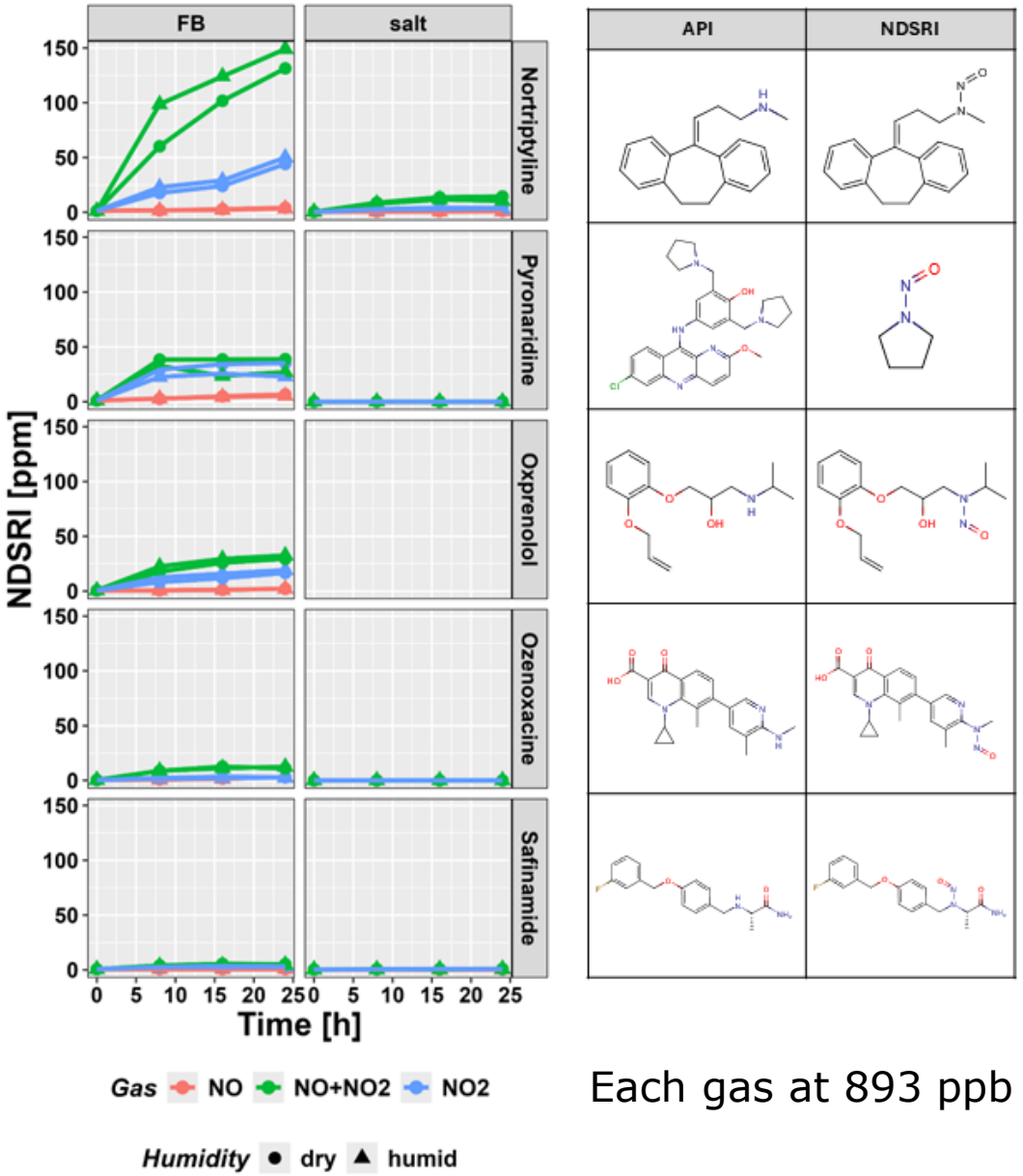
Research paper

Something in the air–Unveiling the role of atmospheric nitrogen oxides in nitrosamine formation from amine-containing APIs: Mechanistic insights and risk assessment

https://doi.org/10.1016/j.xphs.2026.104296

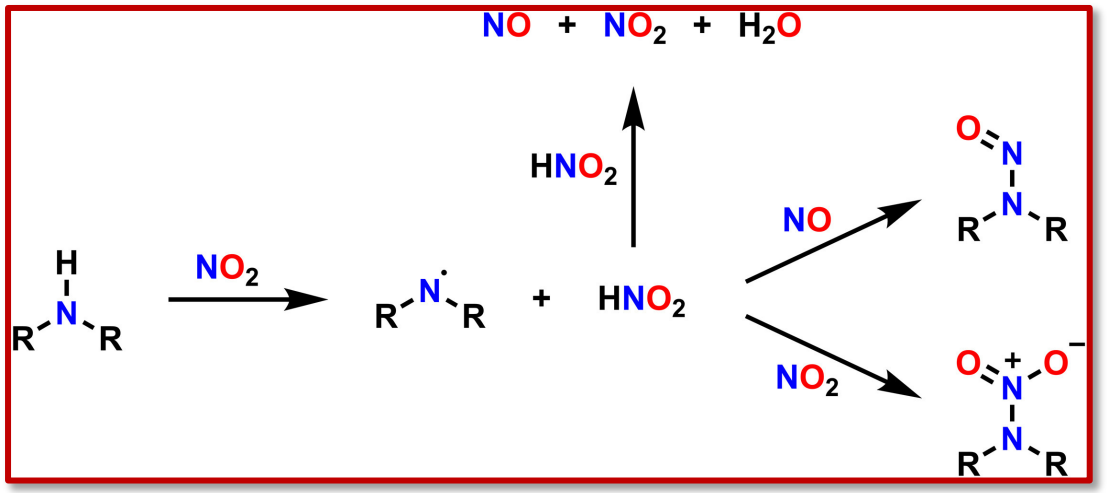


Behaviour of the model APIs

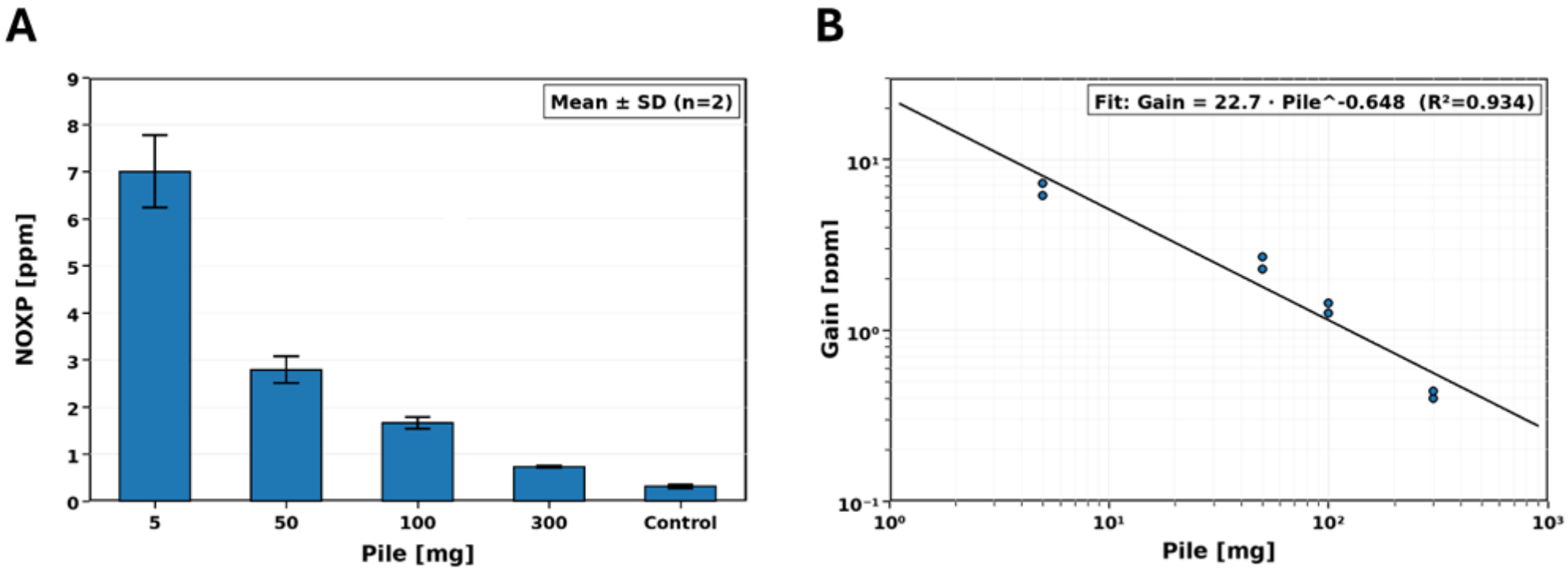


Each gas at 893 ppb

- Free base forms are significantly more reactive than corresponding salts
- Reactivity differences span up to three orders of magnitude
- NO alone does not induce nitrosation
- No significant difference observed between dry and humid condition
- Mechanism likely involves hydrogen abstraction at the gas–solid interface

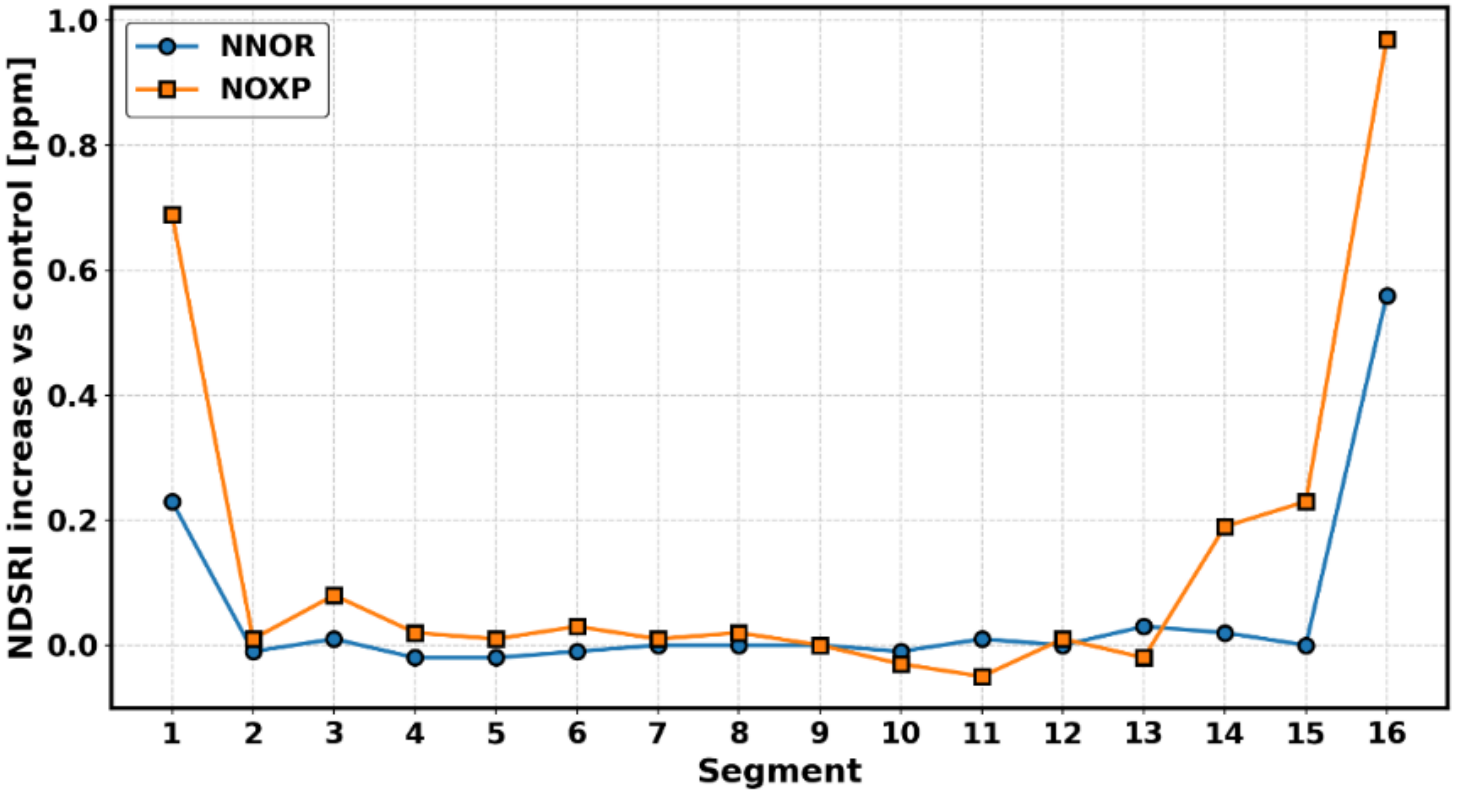


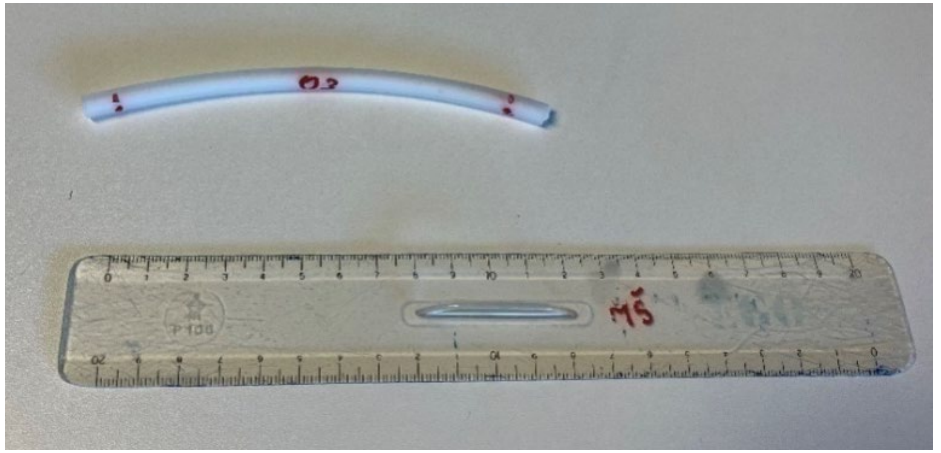
10 days open vial incubation of Oxprenolol free base: smaller samples accumulate more NDSRI



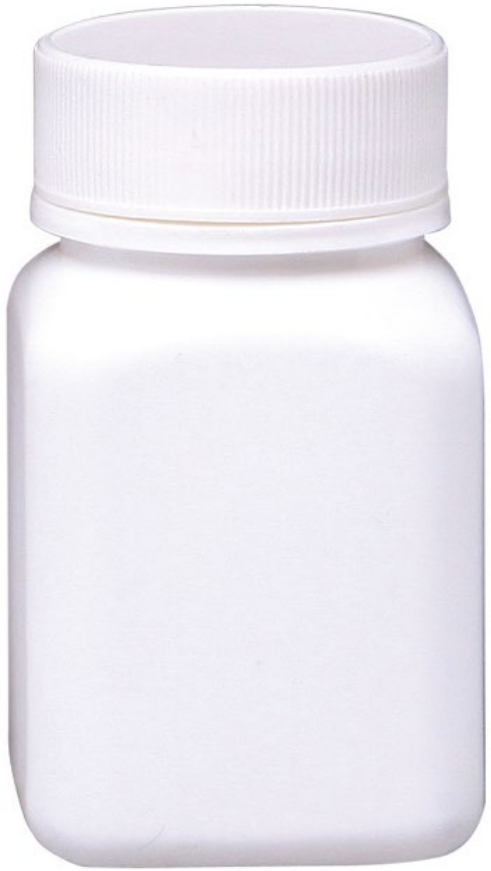
According to this model, the average NDSRI level in a 200 kg API drum would be 9.5 x 10^{-5} ppm after 10 days and 9.5 ppb after 1000 days of open storage.

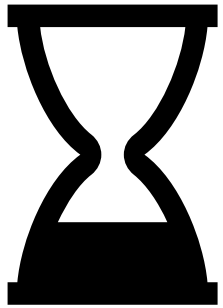
12 days incubation of NOR FB and OXP FB in a plastic tube: NDSRIs were only detected in the outermost segments





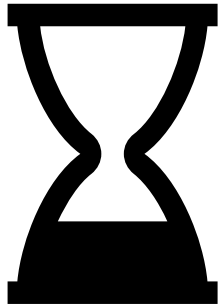
Protective performance of HDPE tablet bottles





2 weeks

Short-term protection demonstrated



longterm

Not yet investigated

Repeated opening

Not yet investigated

Other packaging materials

Low risk: large API quantities with limited NOx permeation

Alu/Alu blisters are likely impermeable to NOx. Plastic blisters may permit NOx permeation upon long-term storage.
Not yet investigated

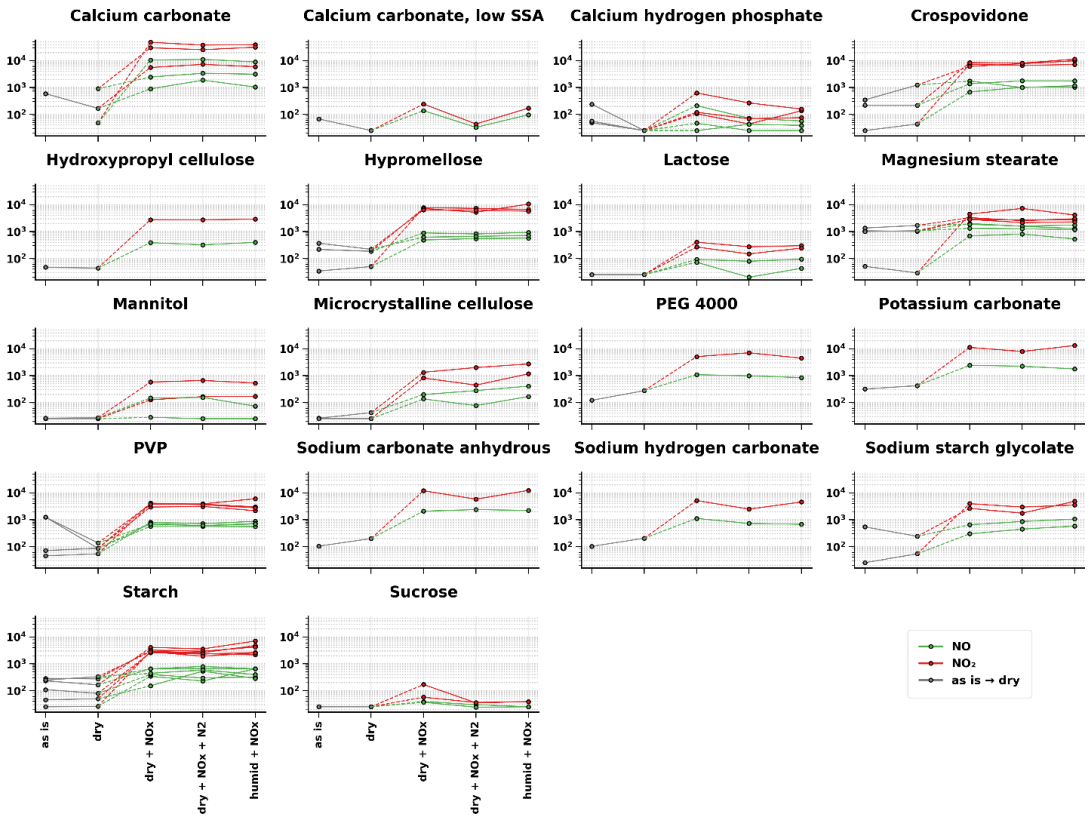
Pill cases are not air tight, but exposure >1 week is unlikely
Not yet investigated

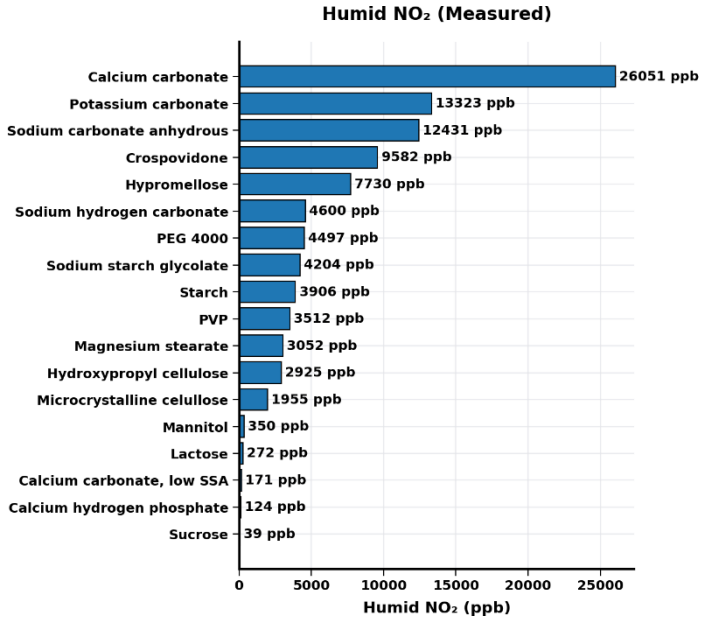
Summary & Conclusions

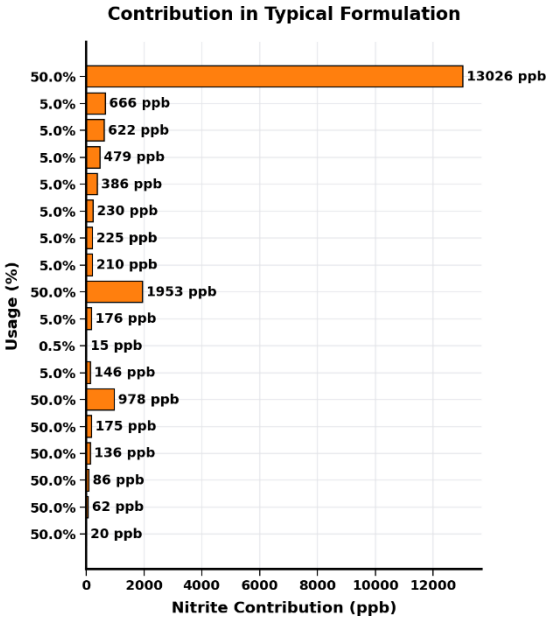
- Atmospheric NOx can nitrosate susceptible APIs
- Free base forms are significantly more reactive than salts
- Small exposed samples (e.g., in analytical/stability studies) represent a higher risk
- Bulk storage presents minimal risk due to NOx depletion effects
- Forced-air operations (fluid-bed drying, jet milling) may may increase risk for high-MDD APIs forming potent NDSRIs
- Nitrosation likely occurs either in a thin surface solution layer or at the gas–solid interface
- HDPE bottles provide short-term protection; long-term performance and other packaging systems remains to be investigated

Thunderclap Newman - Something In The Air - YouTube

One more thing…







- **24 h incubation with 893 ppb NOx**
- **Different excipients exhibit markedly different capacities to convert NOx species to nitrite and to retain them**
- **Data provided by Rok Grahek (Sandoz)**

Acknowledgements

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Paula Tomlin (Astra Zeneca)

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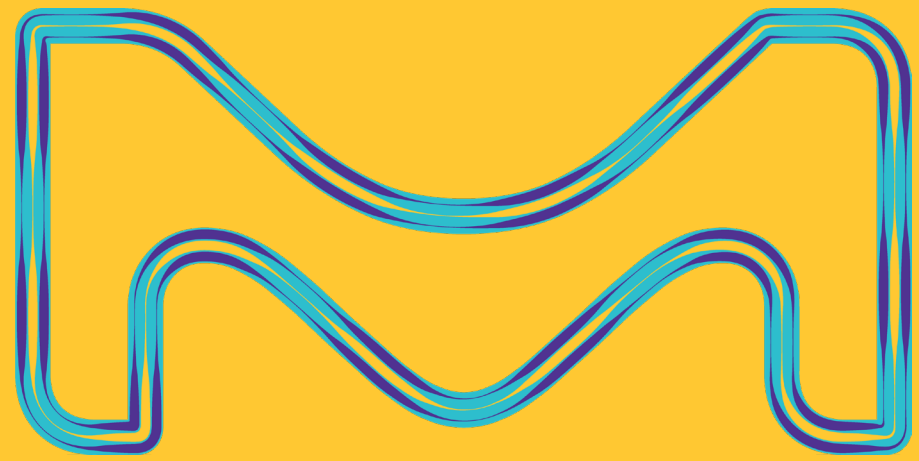
THANK YOU !!!



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Backup

Regulatory Context

- Current regulations support the recovery and reuse of solvents: GMP and ICH Q7 and the draft revision of the EMA "Guideline on the chemistry of active substances" (EMA/321776/2024):
  - Repurification and re-use procedures should be controlled and monitored
  - Repurified materials should meet specifications suitable for their intended uses
  - Companies should clearly indicate where recovered solvents are introduced into the process
  - Impact of the use of recovered materials should be considered in the overall risk assessment and discussion regarding impurities.

- Given the concerns over nitrosamine contamination, certain limitations have been established.
  - Per the draft revision of the EMA "Guideline on the chemistry of active substances" (EMA/321776/2024):
    - Recovered solvents should be used only in the same or an earlier step of the same process.
    - Use of recovered solvents should be avoided in the final manufacturing step unless otherwise justified
  - Per the WHO Good Practice Considerations for the Prevention and Control of Nitrosamines, Annex 2 particular risk if
    - solvents are mixed from different processes
    - not properly purified
    - recovered off-site without adequate oversight and quality monitoring

Scientific Background

- **Solvent recycling is commonly performed via distillation/rectification, where volatility differences allow separation because vapor and liquid compositions differ**

- **Ideal mixtures follow Raoult's law (NOT APPLICABLE FOR ACCURATE PREDICTIONS !!)**

$$p_i = p^*_i \, x_i$$

x_i = *Liquid phase mole fraction of compound i*
p^*_i = *Partial pressure of pure compound i*
p_i = *Partial pressure of component i in the mixture*

- **Real mixtures often deviate from ideal behavior; Activity coefficients (γ_i) correct for non-idealities**

$$p_i = p^*_i \, x_i \, \gamma_i$$

γ_i = *Activity coefficient for given pressure, temperature and composition*

- **Activity coefficients are a function of temperature, pressure and composition**
  In the absence of experimental data, they can be estimated with software tools (e.g. COSMOtherm)

- **The ease of separation can be expressed quantitively as the relative volatility α of two components i and j**

$$\alpha_{ij} = \frac{y_i / x_i}{y_j / x_j}$$

x_i = *Liquid phase mole fraction of compound i*
y_i = *Vapor phase mole fraction of compound i*
x_j = *Liquid phase mole fraction of compound j*
y_j = *Vapor phase mole fraction of compound j*

Insights from the Montecarlo simulation

Assumption: ARV nitrosamine vs solvent to be recovered NLT 3, recovered solvent purity is x

- Recovered solvent contains:
  - **(100 – x)% purged solvent**, nitrosamine concentration reduced **1000-fold**
  - **x% "other components"** (residues, azeotropes, non-volatiles) where **no purge occurs**
- Initial nitrosamine levels: **1, 10, 100, 1000 ppm**
- 10% bleed-through to API

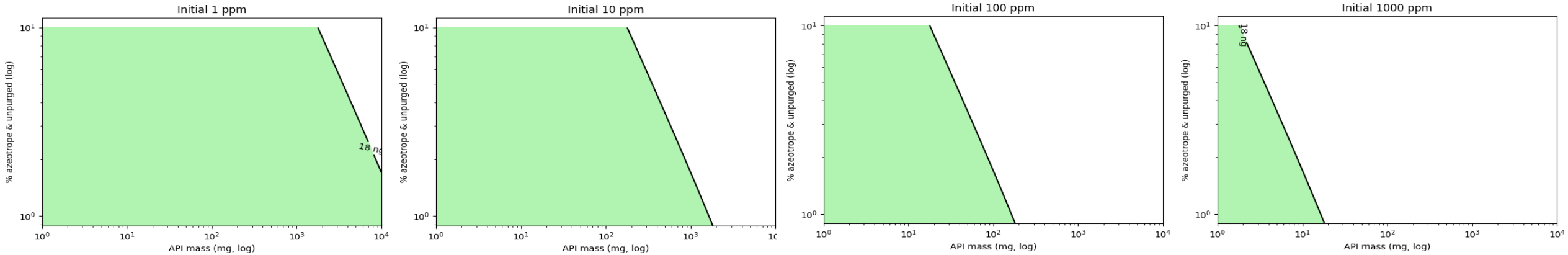
This yields the effective nitrosamine concentration in solvent as:

$$C_{\text{rec}}(x) = (1 - x)\frac{C_0}{1000} + x\,C_0$$

where x is the fraction of unpurged material (0–10%).

Nitrosamine per mg API:

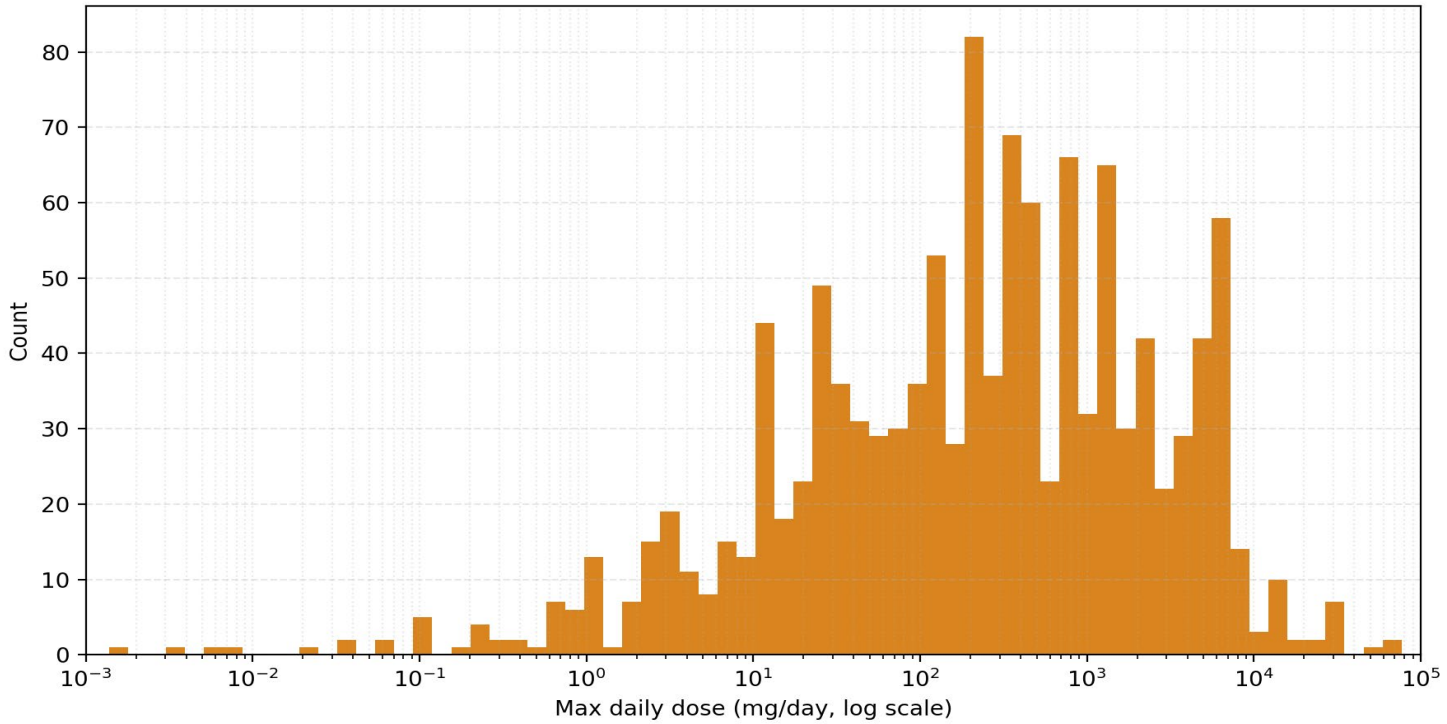
$$\text{NA}_{\text{API}} = 0.1 \cdot C_{\text{rec}}$$



Estimation of favourable distillation outcomes

Another Montecarlo simulation

Assumptions:
ARV nitrosamine vs solvent to be recovered NLT 3
95% of cases % azeotrope / non purged will be <0,5% (purity of recovered solvent NLT 99.5 %)
Distribution of maximum daily doses based on FDA database



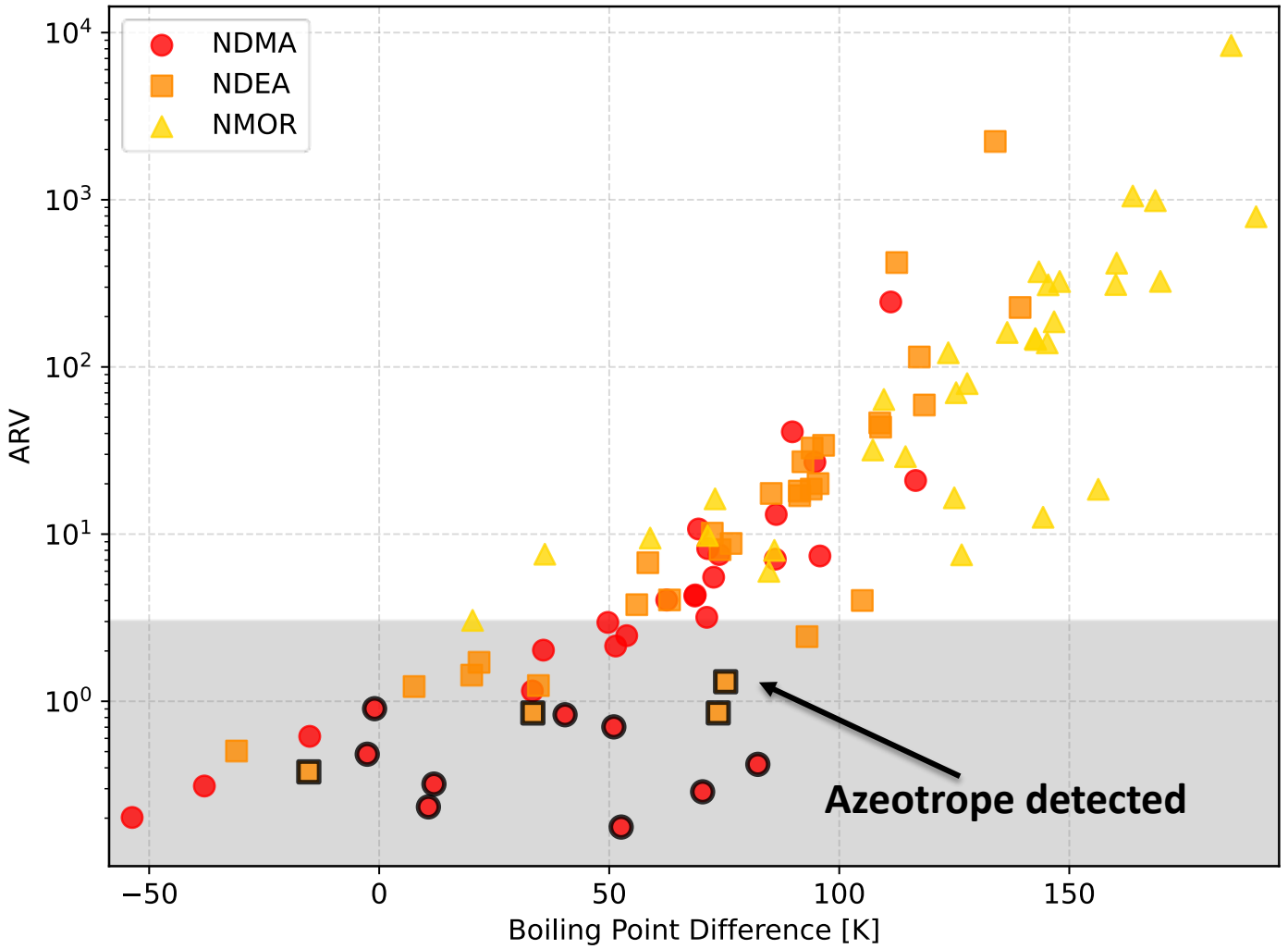
AID 1195 - DSSTox (FDAMDD) FDA Maximum (Recommended) Daily Dose Database - PubChem

Outcome (for worst case purge factor 1000)

Initial nitrosamine C_0 (ppm)	Probability API ≤ 18 ng
1 ppm	99.25 %
10 ppm	89.98 %
100 ppm	61.36 %
1000 ppm	28.31 %

For organic processes with no identified nitrosamine risk, 100 ppm NA in the solvent to be recovered is a conservative assumption. The risk that applicable solvents (ARV NLT 3) carry relevant amounts of NA after recovery is minimal

ARVs correlate with the boiling point difference between solvent and nitrosamine



- ARVs correlate with boiling point difference
- Higher ARVs reduce probability for azeotropes
- No azeotropes above ARV 3
- NDMA (lowest boiling nitrosamine) is the wors-case purification challenge

ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

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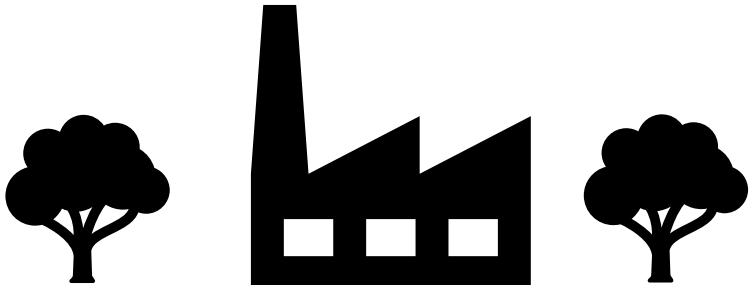
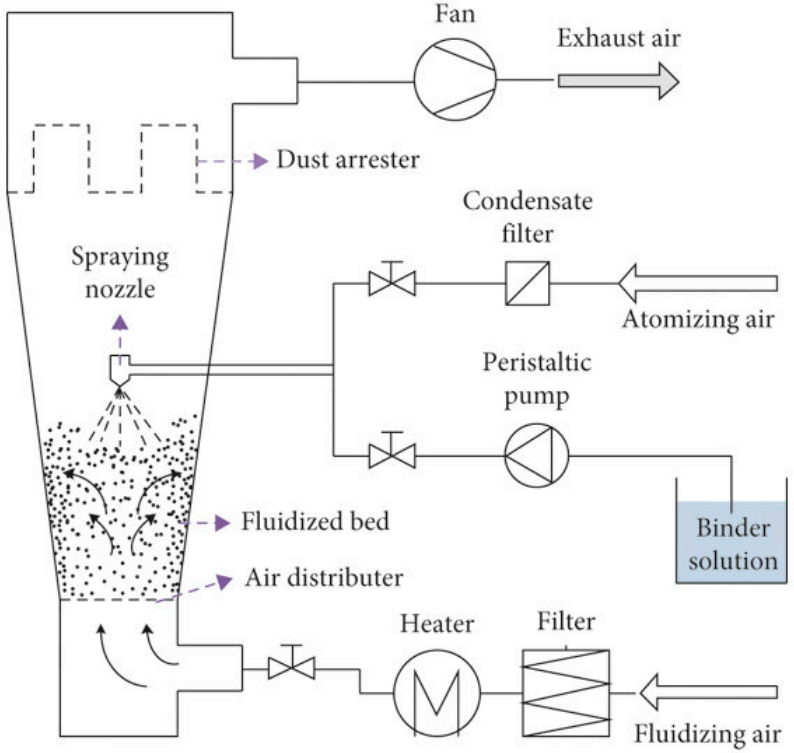
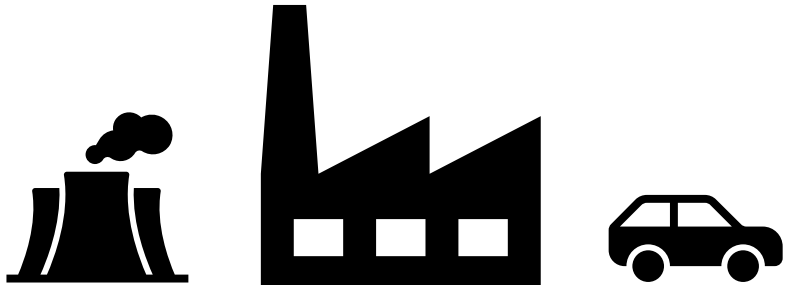
Article

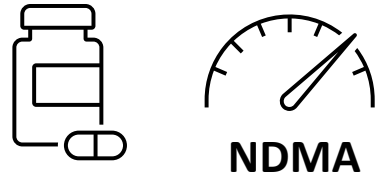
N-Nitrosodimethylamine Formation in Metformin Drug Products by the Reaction of Dimethylamine and Atmospheric NO_2

Shohei Fukuda, Kanako Kondo, Shoji Fukumoto,* Norimichi Takenaka, Osamu Uchikawa, and Itsuro Yoshida

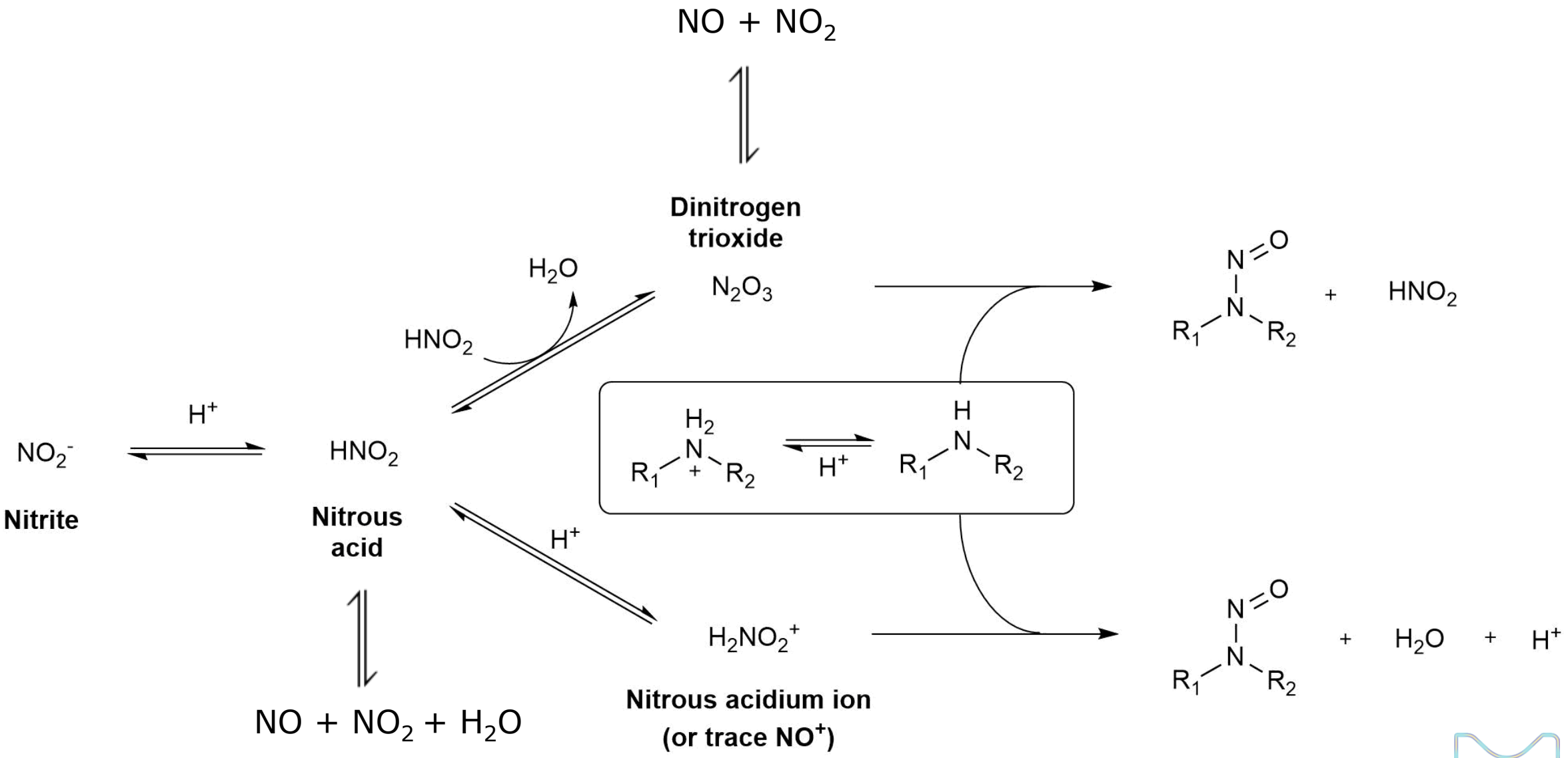






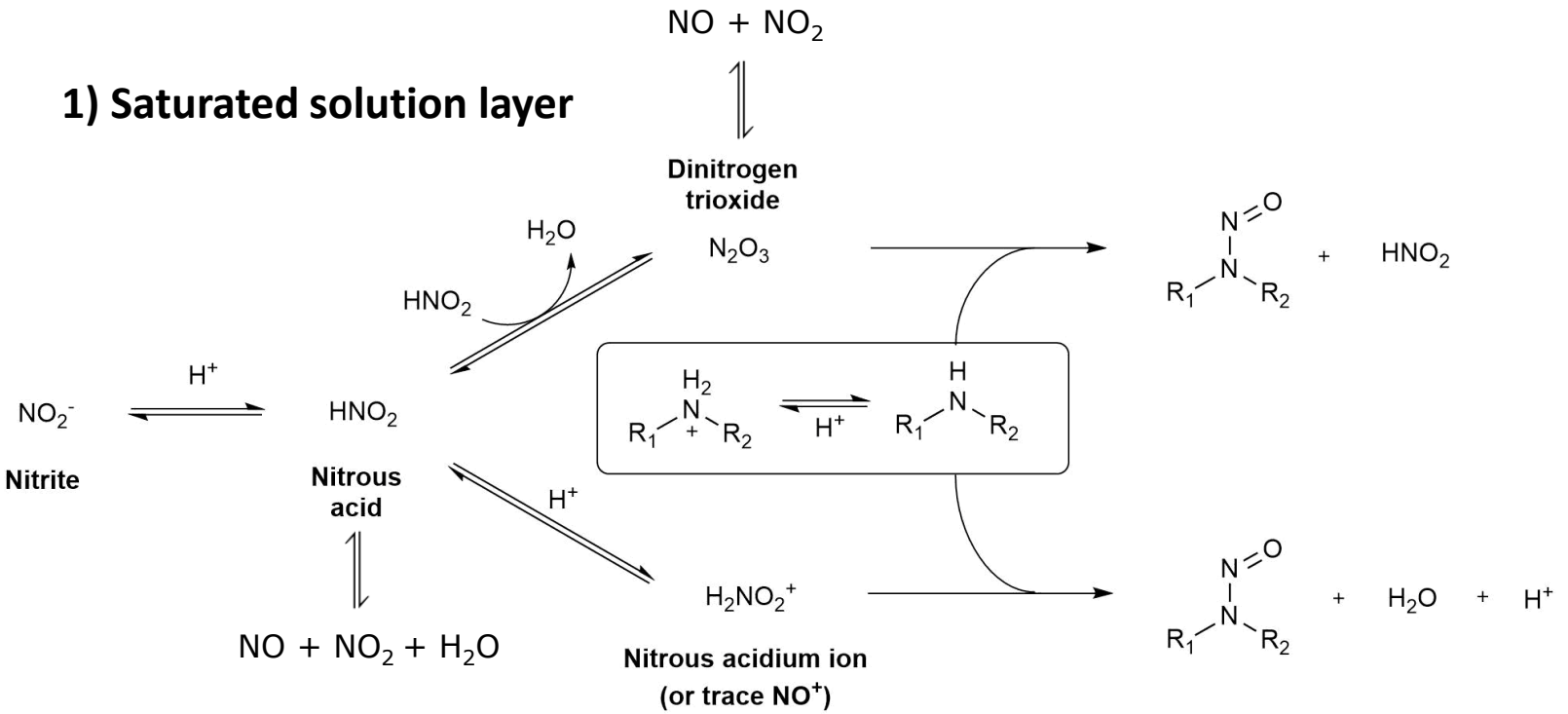


Nitrosation of a secondary amine

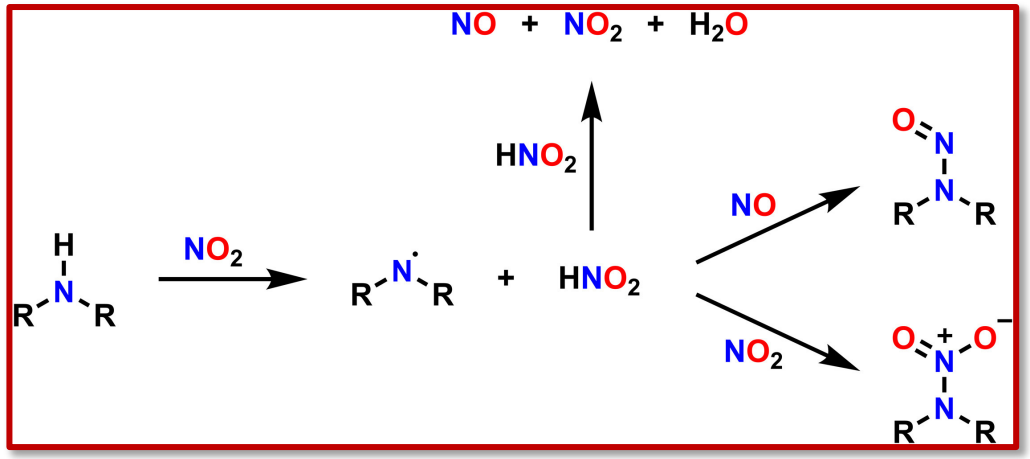


Nitrosation of a secondary amine: two potential pathways

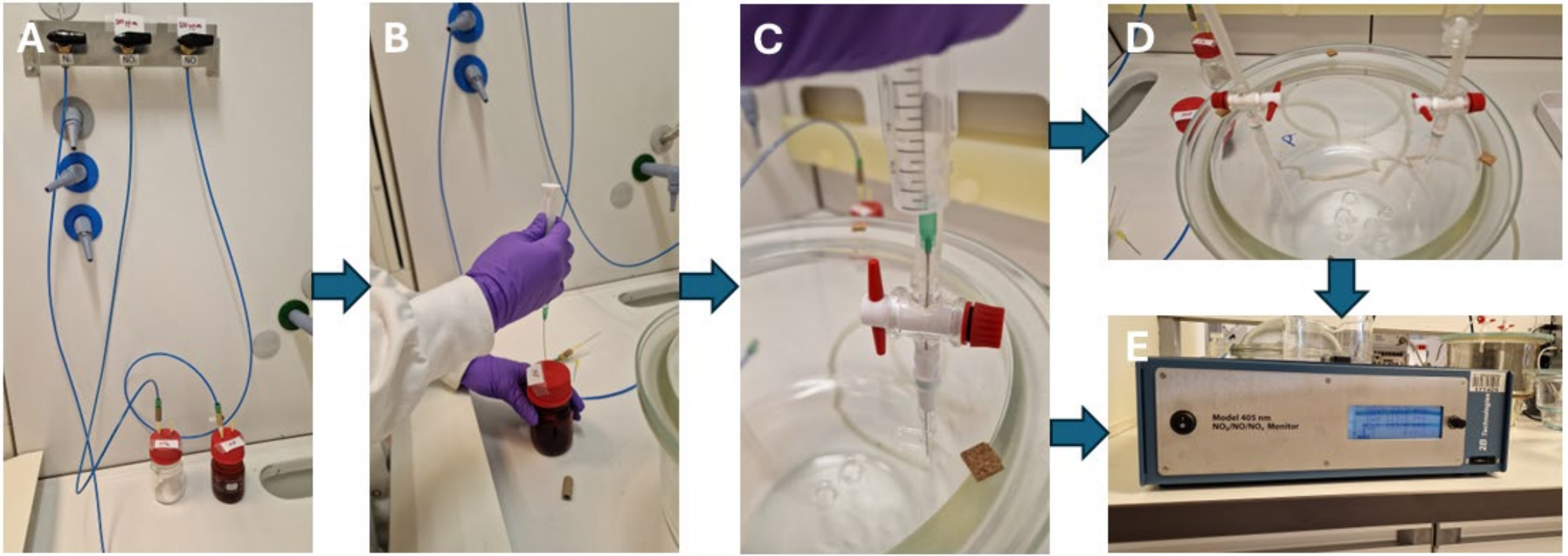
1) Saturated solution layer



2) At gas/solid interface



Workflow for controlled incubation in a glass chamber

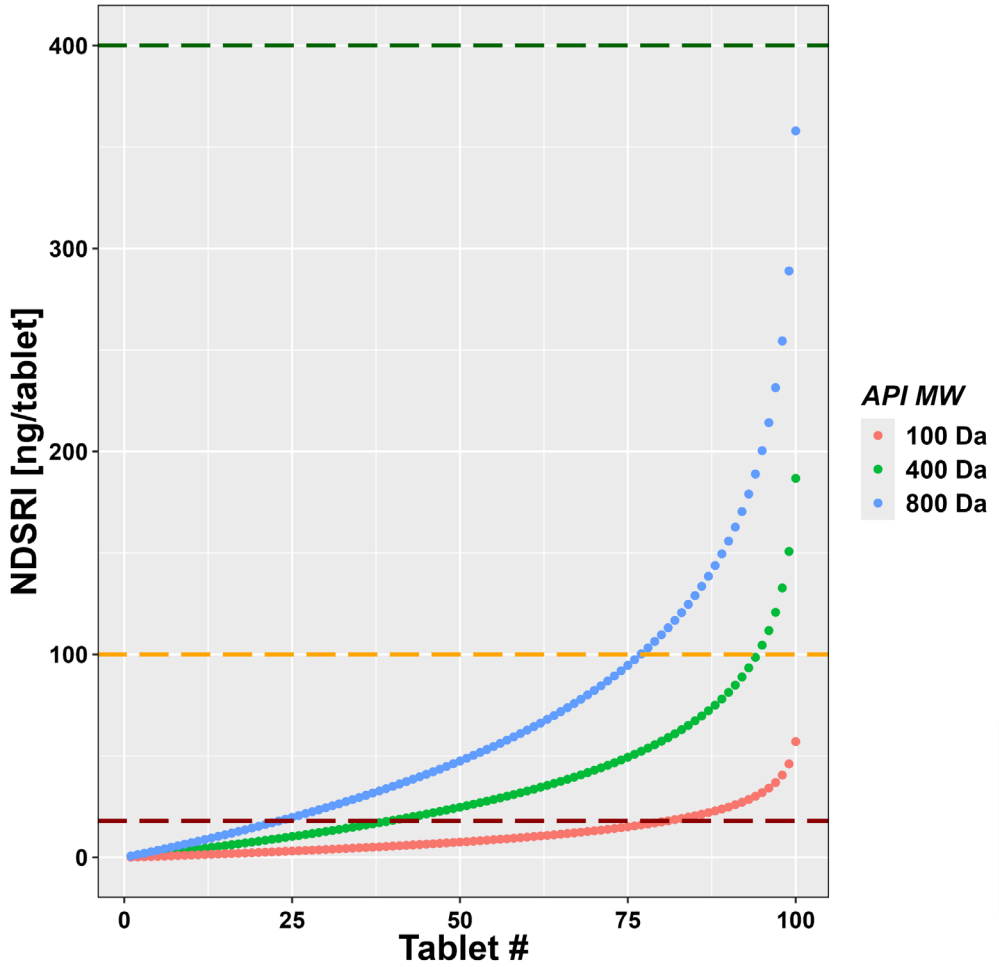


Impact of packaging material

	^{15}N-nitrosonortriptyline	^{14}N-nitrosonortriptyline
Non exposed Nortriptyline HCL tabs	n.d.	6.4 ppm
Nortriptyline HCL tabs 24 h under N_2 (NC)	n.d.	6.4 ppm
Exposed Nortriptyline HCL tabs (24 h 500 ppb $^{15}NO_x$) (PC)	148 ppm*	14.9 ppm*
Nortriptyline HCL tabs 14 days in plastic can under 500 ppb $^{15}NO_x$	n.d.	6.6 ppm
Nortriptyline HCL tabs in glass vial capped with PVDC foil (24 h)	n.d.*	9.3 ppm*

** Separate experiment performed later*

Potential impact of repeated opening (worst-case simulation)



Assumptions:

100 mL headspace

100 tablets

NO_2 at 20.1 ppb (Darmstadt avg.)

100 % conversion

BUT: the highest NOx concersion observed in our controlled incubation experiment was 1.2 %