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Produits de transformation de la carbamazépine générés par des procédés d'oxydation - modélisation cinétique.

Jeanne Trognon, Jean-Marc Choubert et Claire Albasi

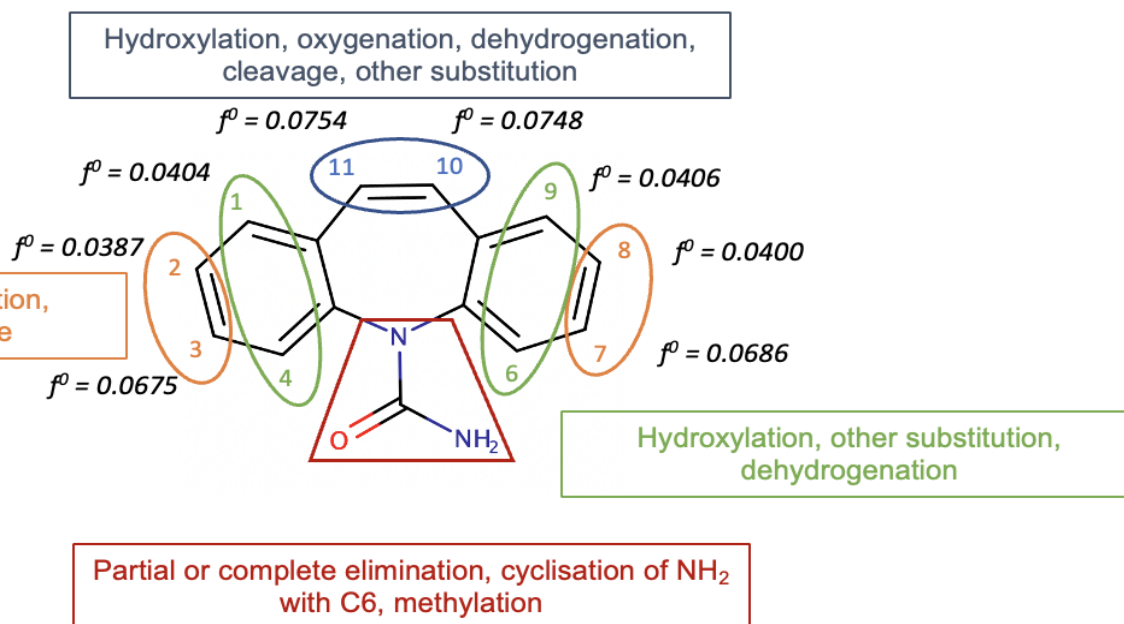
17/10/2024

ANR TRANSPRO 18-CE04-0006-01

Carbamazepine (CBZ) = anticonvulsant drug (treatment of epilepsy, bipolar disorder and trigeminal neuralgia)

- Worldwide consumption > 1000 t/year
- Poor removal (< 25%) by conventional secondary processes
- 500-1000 ng.L⁻¹ in WWTP effluents

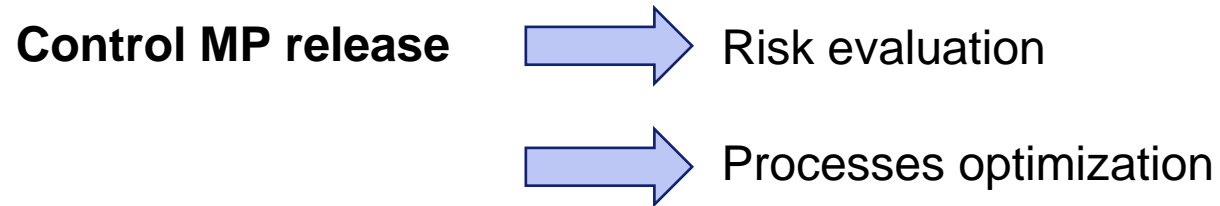
AOP : radicals attack on CBZ structure  Generation of **transformation products (TPs)**



- **Various** TPs (structures, physico-chemicals characteristics, concentrations)
- Many **unknown** about the fate and behavior of such diversity of TPs

Trognon, Albasi and Choubert, *Sci. Tot. Env.* (2024)

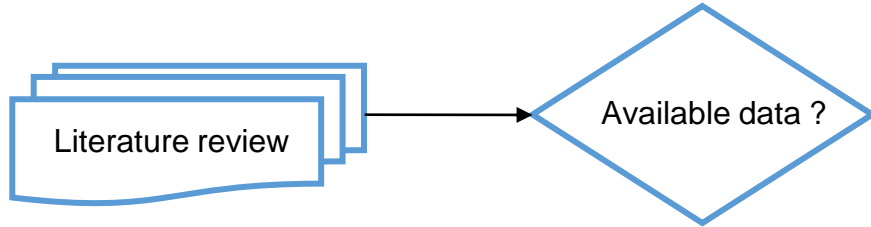
Computer-based modelling as a promising tool to predict the fate of MPs



Aims: improve the knowledge on the **nature**, **fate** and **dynamics** of CBZ and its TPs
Fill the research gap of the mechanisms occurring between CBZ removal and TPs effect

Identification and modelling of CBZ transformation pathways in various oxidation processes to improve the knowledge of TPs

Scientific approach: Development of individual models



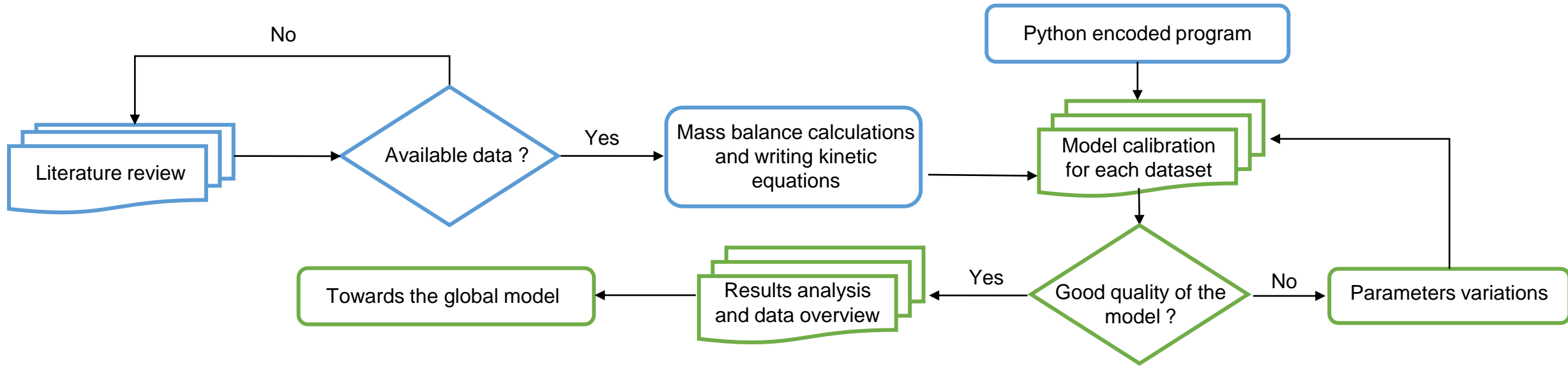
Scientific approach: Development of individual models

Source of data	Process	[CBZ] ₀ (μM)	[oxidant]	Time	Data for the TPs	Reaction scheme
Jelic et al., 2013	UV/TiO ₂	42.3	100 mg.L ⁻¹	120 min	Normalized peak area (A _{TPs} /A _{CBZ})	
Suara et al., 2022	UV/Cl	42.3	10 mg.L ⁻¹	10 min	[TPs]	
Pan et al., 2017	UV/Cl	2.1	5 mg.L ⁻¹	15 min	[TPs]	
Lu & Hu, 2019	UV/H ₂ O ₂	169	3 g.L ⁻¹	30 min	Normalized [TPs]/[CBZ] ₀	

- 3 different processes
- Diversity of operational conditions



Challenge : experimental [TPs]



$$dCBZ/dt = -k_{CBZ} * [CBZ] \quad (1)$$

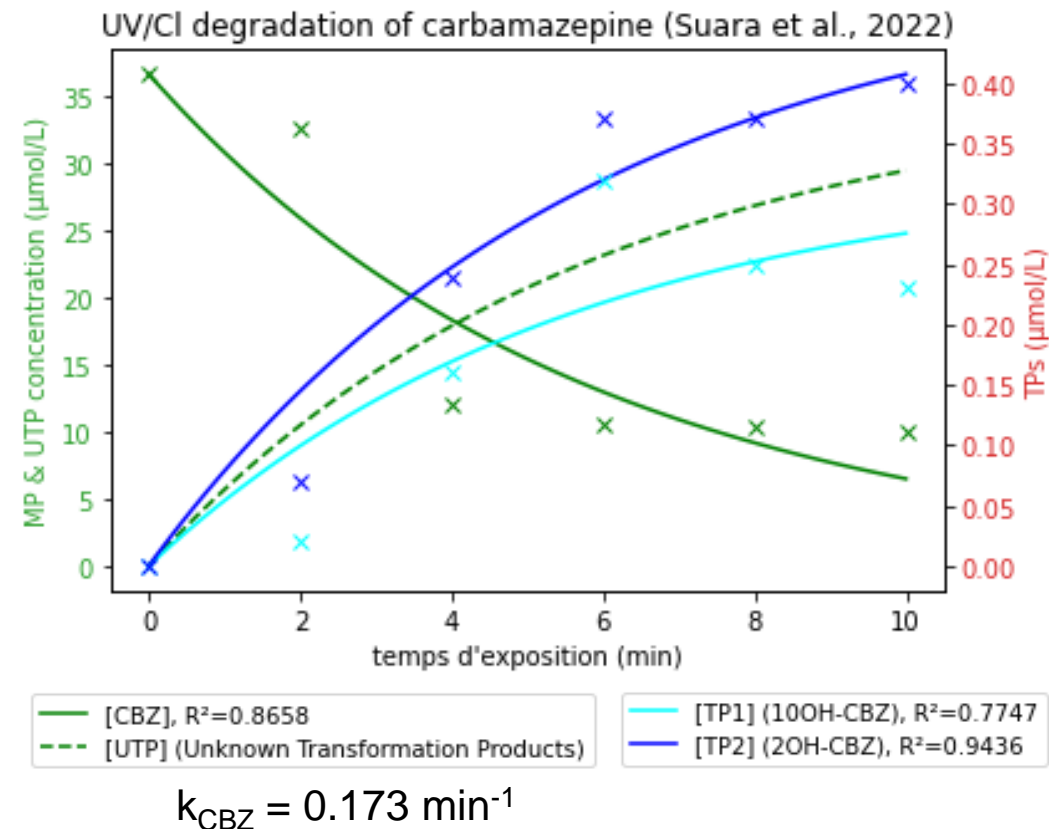
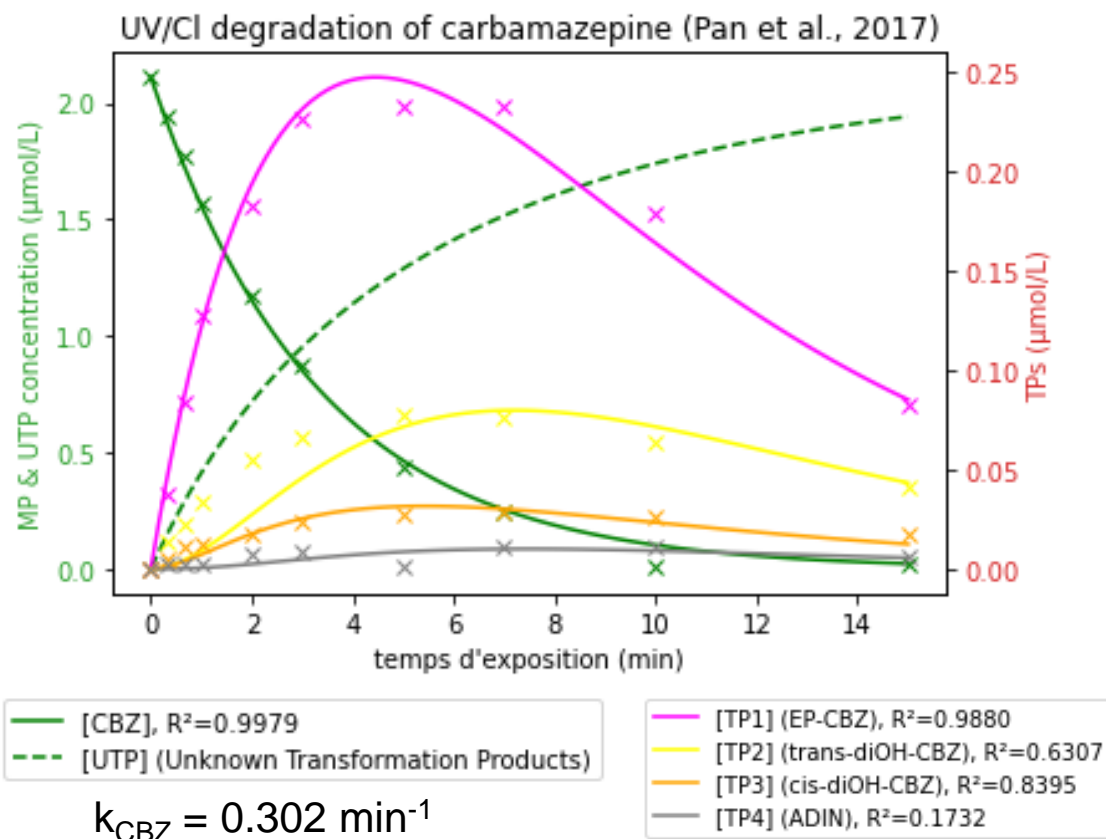
$$dTP/dt = k_{stoi TP} * k_{molécule mère} * [molécule mère] - k_{TP} * [TP] \quad (2)$$

$$dUTP/dt = |dCBZ/dt| - |\Sigma(dTP/dt)| \quad (3)$$

Paramètres du modèle :

k_{stoi} : coefficients stœchiométriques

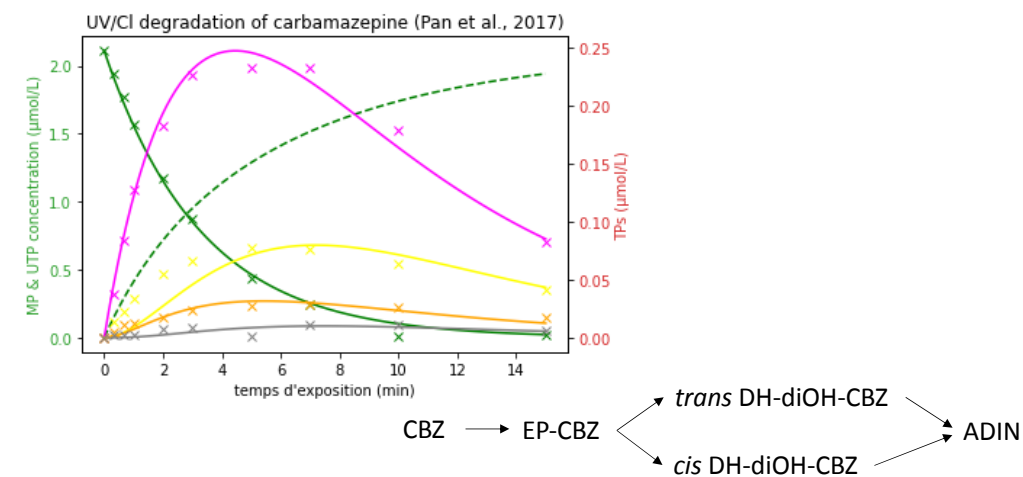
k : constantes cinétiques de dégradation



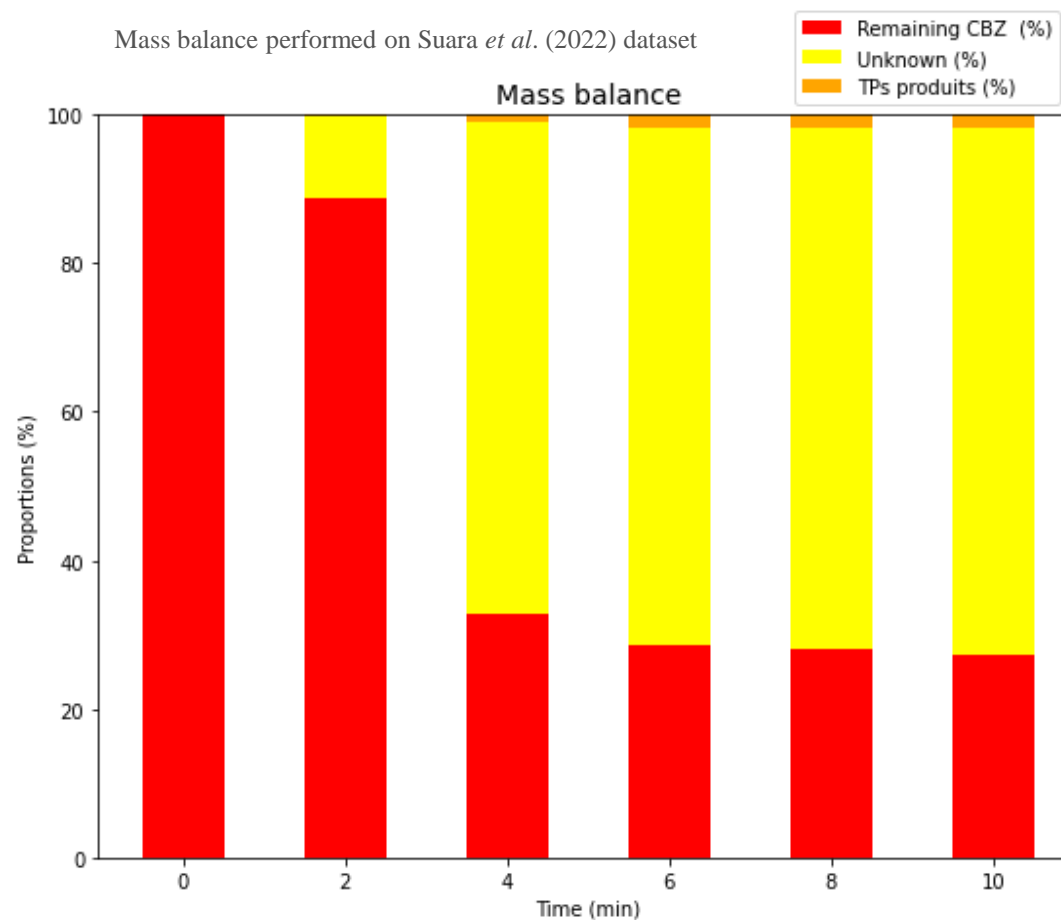
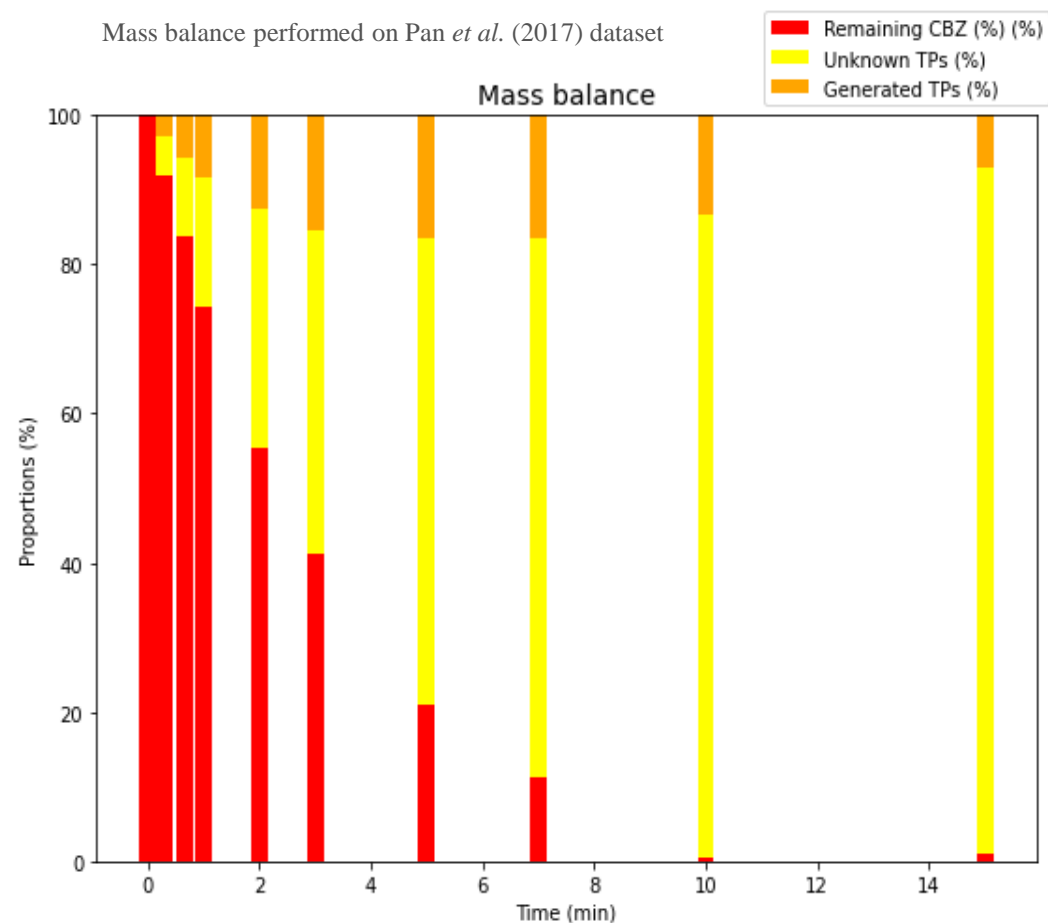
- good adequation between predicted and experimental data ($R^2 > 86\%$)
- k_{CBZ} resulting from model and k_{CBZ} originally calculated in datasets are comparable
- Pseudo-first order equation appropriate for $\frac{3}{4}$ datasets

Reference	TPs	R ² _{TPs} (%)	k _{TPs} (min ⁻¹)	k _{stoi}
Jelic et al., 2013	DH-diOH-CBZ	94.2	0.134	0.54
	2OH-CBZ	99.9	0.071	0.24
	3OH-CBZ	90.3	0.053	0.29
Suara et al., 2022	CBZ-10.11-dione	86.0	0.025	0.12
	10OH-CBZ	77.5	0.003	0.009
	2OH-CBZ	94.3	0.001	0.013
	EP-CBZ	98.8	0.161	0.24
Pan et al., 2017	trans-diOH-CBZ	63.1	0.439	1.00
	cis-diOH-CBZ	83.9	1.230	1.00
	ADIN	17.3	1.110	0.19
	EP-CBZ	18.5	1.001	0.12
Lu & Hu, 2019	9CHO-CBZ	42.8	2.060	0.05
	DH-diOH-CBZ	96.1	0.302	1.00
	2/3OH-9CHO-ADIN	85.5	0.152	0.96
	ADIN	22.9	2.312	0.32

- 11/15 TPs predicted and experimental data fit-well ($R^2 > 63\%$)
- Quality of the fit decreases for secondary and final TPs (*reaction scheme*) or lowest concentrations
- Predicted concentrations consistent with the reaction pathway



Modelling of CBZ degradation & TPs formation – mass balance

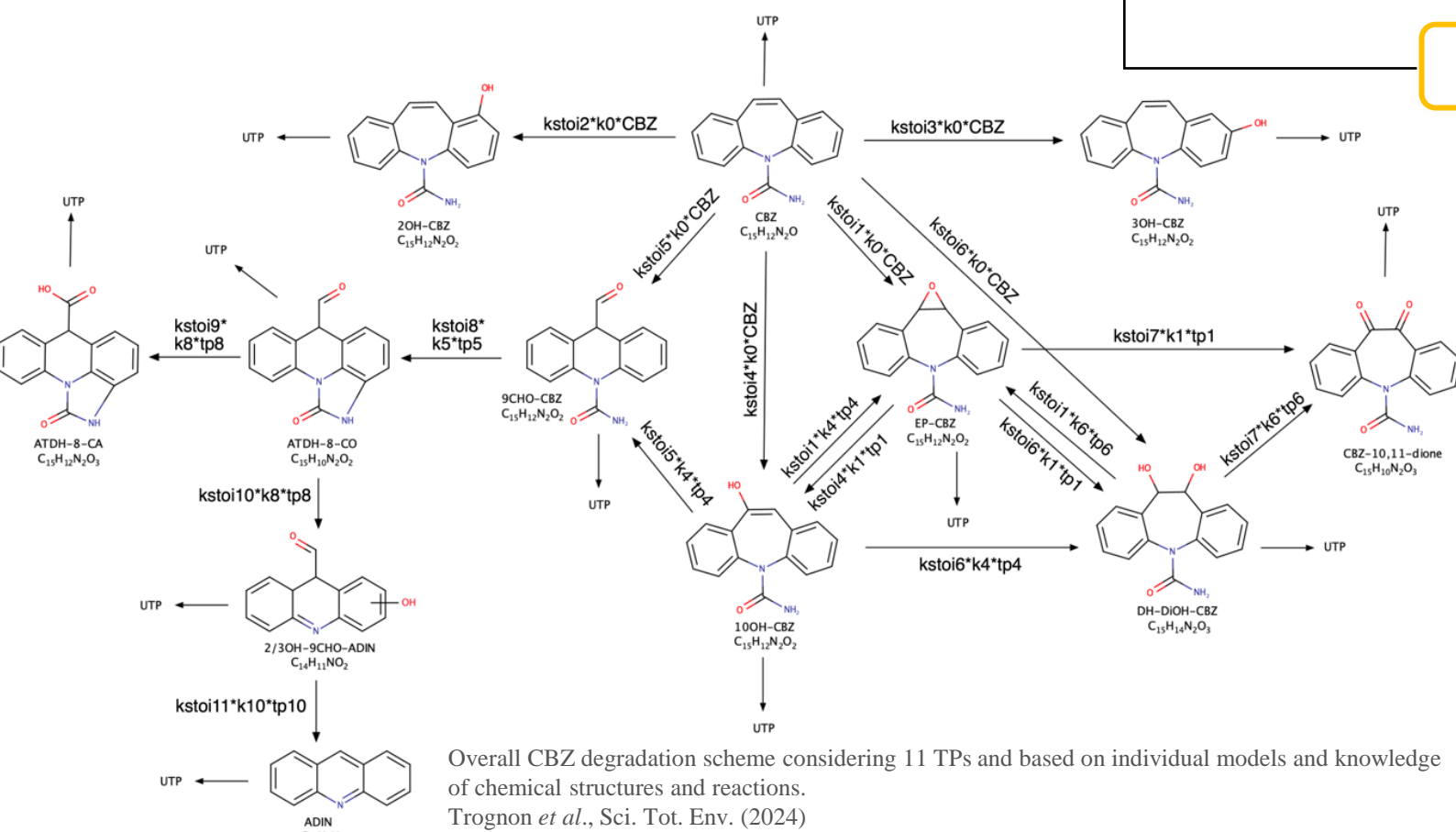
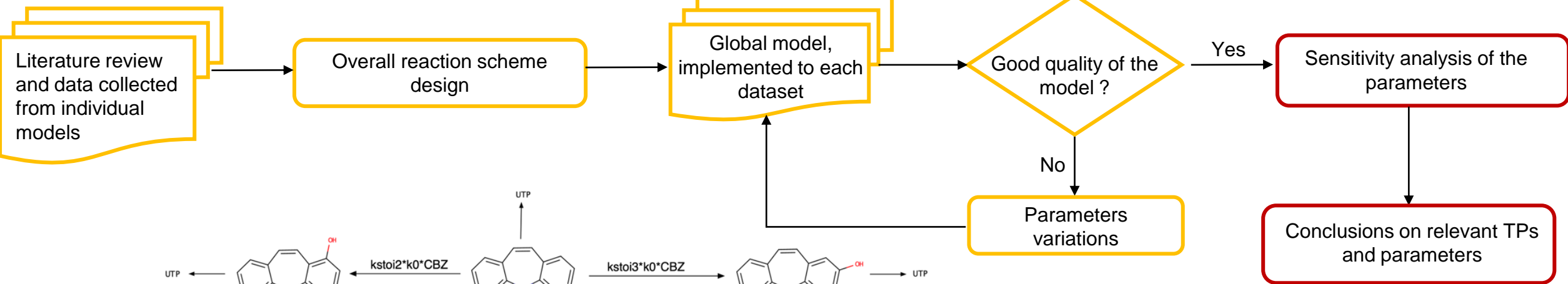


- Studied TPs represents 2 % to 17% of the transformed CBZ
- Major proportion of unknown TPs



Choice of molecules of interest
Lack of reference standards

Scientific approach: Development of a global model



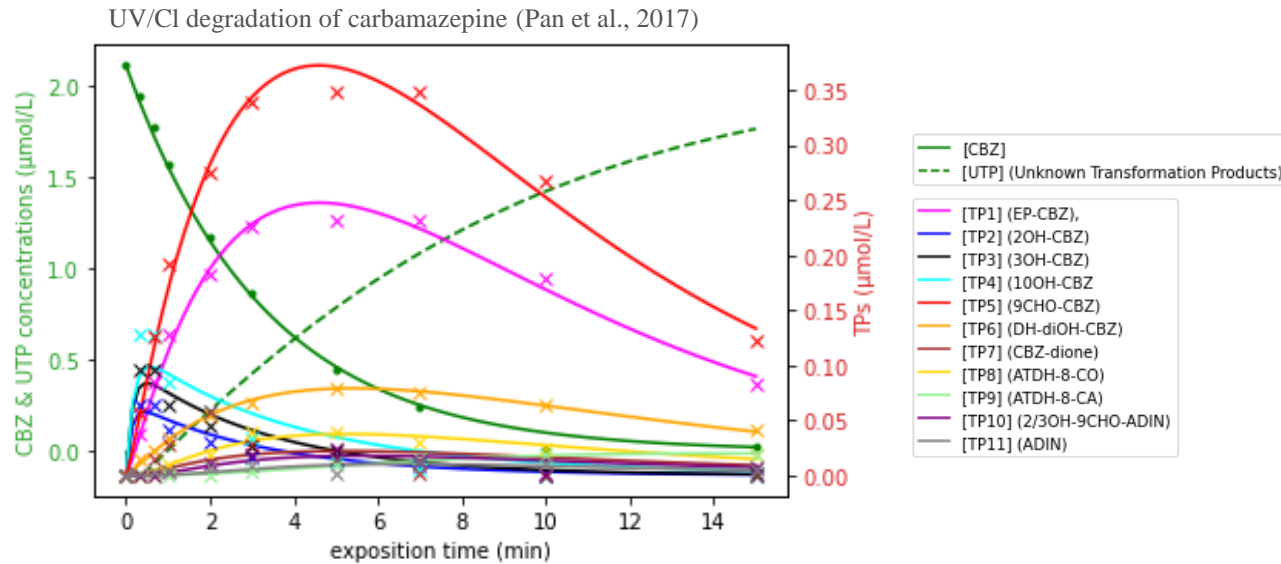
12 molécules

23 paramètres:

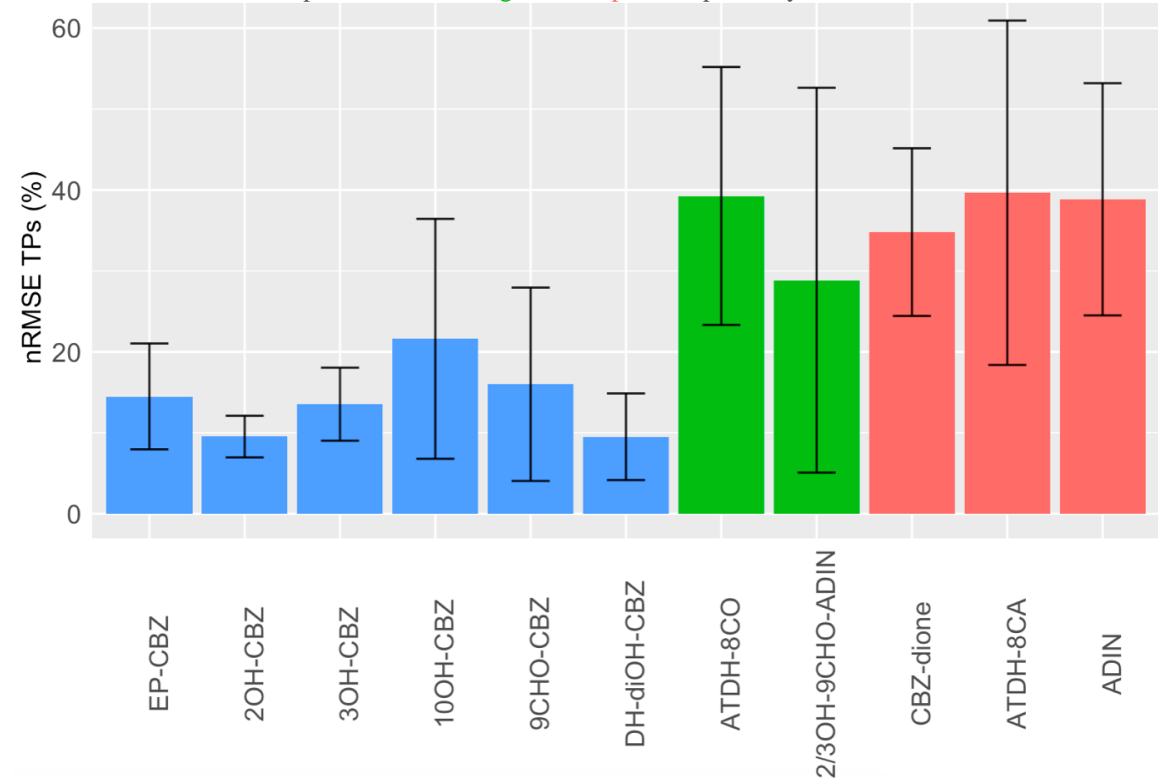
11 *kstoi*

12 *k*

Global model based on an overall reaction scheme – CBZ and TPs results



Mean nRMSE (%) of each TP, calculated using data from all four datasets. Primary, intermediate and final TPs are represented in blue, green and pink, respectively.



- Good adequation between predicted and experimental data ($R^2 > 80\%$, data not shown)
- Modelling error for primary TPs $< 22\%$; Modelling error for intermediate and final TPs $> 35\%$

Global model based on an overall reaction scheme – sensitivity analysis

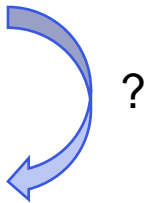
Global model = 12 molecules, 13 differential equations, 23 parameters (k_{stoi} , k)

→ Which TPs ? Which parameters ?

→ Help future calibration

TPs parameters

Quality of the
model prediction



Observing the changes in the CBZ and primary TPs prediction upon variations of their parameters

For each parameter studied, 5 different values were used:

0.1, 0.3, 0.5, 0.7 and 0.9 for k_{stoi} ,
 10^{-4} , 10^{-3} , 10^{-2} , 10^{-1} and 10^0 for k

Global model based on an overall reaction scheme – sensitivity analysis

		Global Model Quality	R ² TPs	
<i>k_{stoi}</i>	EP-CBZ	+++	++	+++ Strong influence ++ Moderated influence + Low influence - No influence
	2OH-CBZ	+++	++	
	3OH-CBZ	++	+	
	10OH-CBZ	+++	++	
	9CHO-CBZ	+++	+	
	DH-diOH-CBZ	++	+	
<i>k (min⁻¹)</i>	CBZ	+	+	
	EP-CBZ	++	++	
	2OH-CBZ	-	++	
	3OH-CBZ	-	+	
	10OH-CBZ	-	+	
	9CHO-CBZ	++	+	
	DH-diOH-CBZ	-	++	

- *k_{stoi}* have more influence on the model quality than *k*
- 4 Primary TPs appear as important for the overall quality of the model (EP-CBZ, 9CHO-CBZ, 2OH-CBZ and 10OH-CBZ)

- Development of a **model resolving ordinary differential equations** (ODEs) based on formation/degradation kinetic equations and mass balance approach
- **Overall reaction scheme**
- Promising results with **good correlation** between the model predictions and the experimental data for both CBZ and TPs and for both the individual and the global model
- **4 primary TPs** are instrumental for the quality of the predictions: EP-CBZ, 9CHO-CBZ, 2OH-CBZ and 10OH-CBZ. Future model calibrations should focus on the **stoichiometric k_{stoi} parameters**, rather than the kinetic constants k .

Outlooks:

Model **validation**

Investigation of the **UTP** fraction

Add more **parameters** in the model such as macroscopic properties of the TPs (hydrophobicity, ...)

Merci pour votre attention

Des questions ?