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Jeanne Trognon, Jean-Marc Choubert, Claire Albasi. Modélisation cinétique des produits de transformation de la carbamazépine générés par des procédés d'oxydation. 15e Congrès International du Gruttee, May 2024, Talence (Bordeaux), France. hal-04748019

**HAL Id: hal-04748019**

**<https://hal.science/hal-04748019v1>**

Submitted on 22 Oct 2024

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# Modélisation cinétique des produits de transformation de la carbamazépine générés par des procédés d'oxydation.

Jeanne Trognon, Jean-Marc Choubert et Claire Albasi

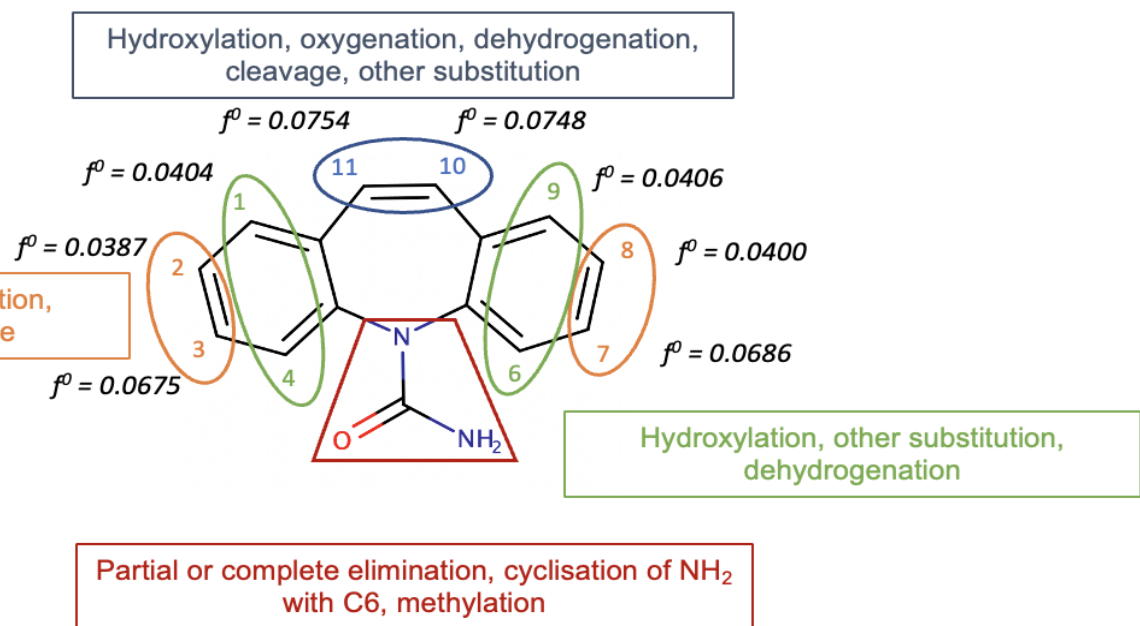
ANR TRANSPRO 18-CE04-0006-01

# Carbamazepine and water treatment

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<sup>-1</sup> in WWTP effluents

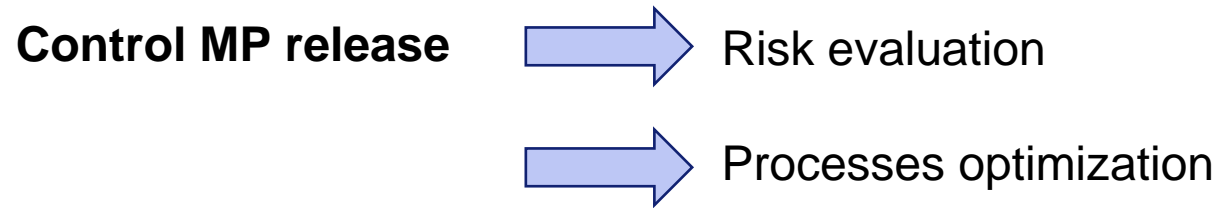
AOP : radicals attack on CBZ structure  Generation of **transformation products (TPs)**



- **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

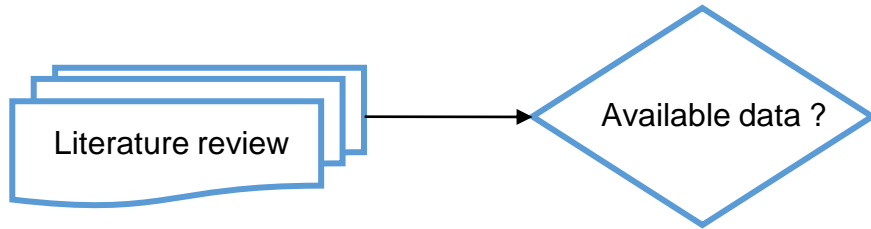


Aim: improve the knowledge on the **nature**, **fate** and **dynamics** of CBZ and its TPs

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

Fill the research gap of the mechanisms occurring between CBZ removal and TPs effect

# Scientific approach: Development of individual models



# Scientific approach: Development of individual models

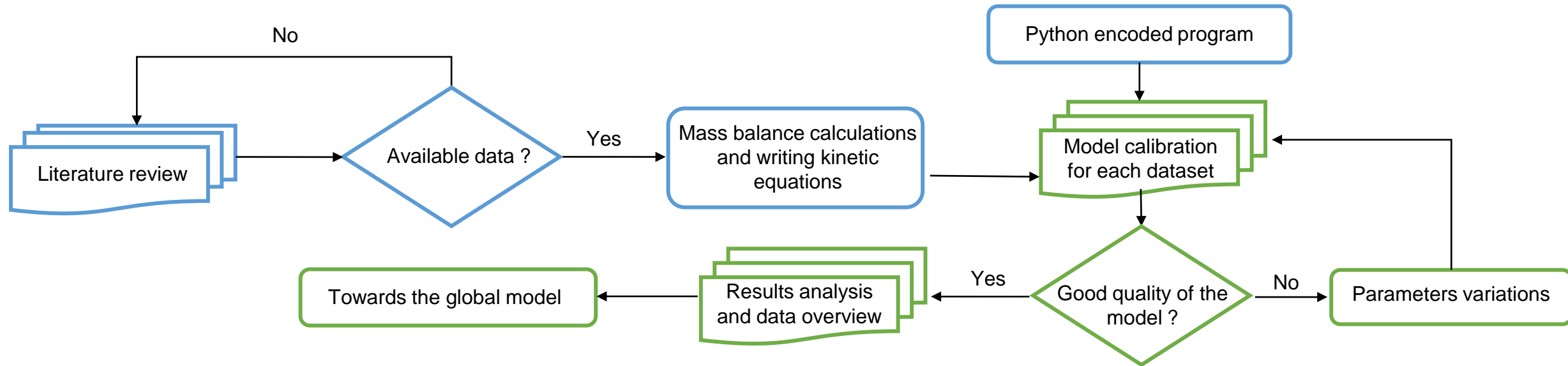
Source of data	Process	[CBZ] <sub>0</sub> (μM)	[oxidant]	Time	Data for the TPs	Reaction scheme
Jelic et al., 2013	UV/TiO <sub>2</sub>	42.3	100 mg.L <sup>-1</sup>	120 min	Normalized peak area (A <sub>TPs</sub> /A <sub>CBZ</sub> )	
Suara et al., 2022	UV/Cl	42.3	10 mg.L <sup>-1</sup>	10 min	[TPs]	
Pan et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

- 3 different processes
- Diversity of operational conditions



Challenge : experimental [TPs]

# Scientific approach: Development of individual models



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

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

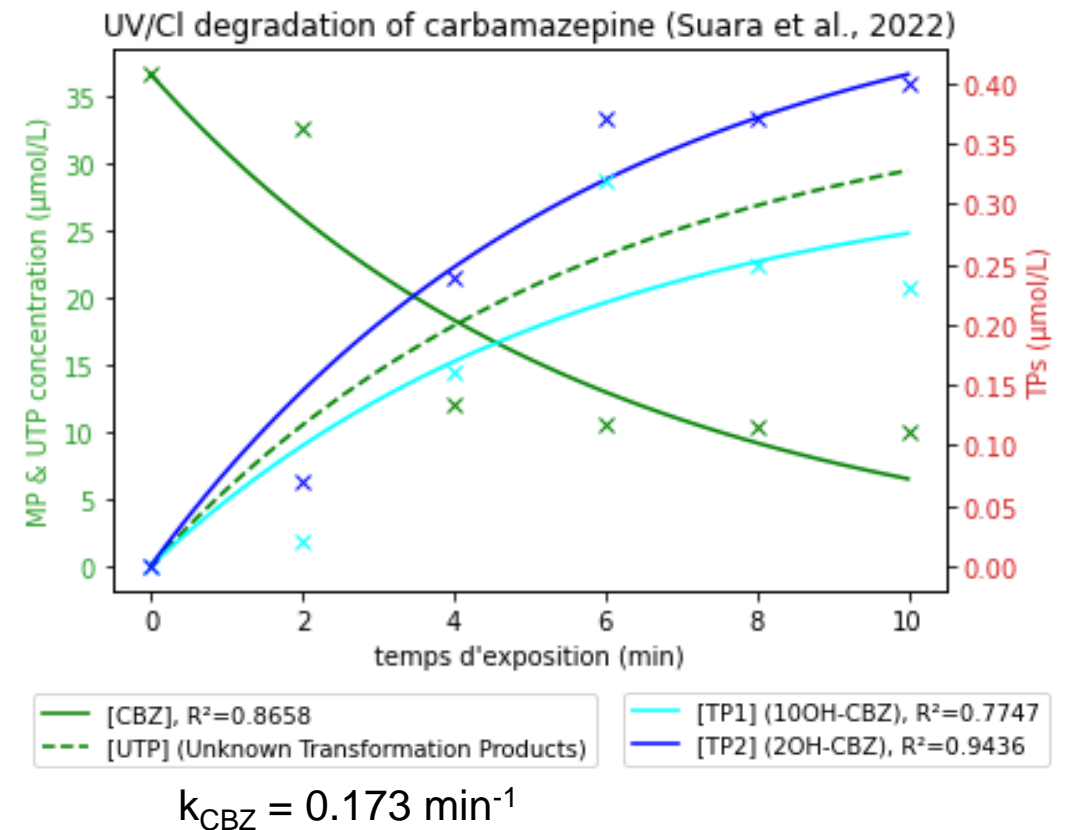
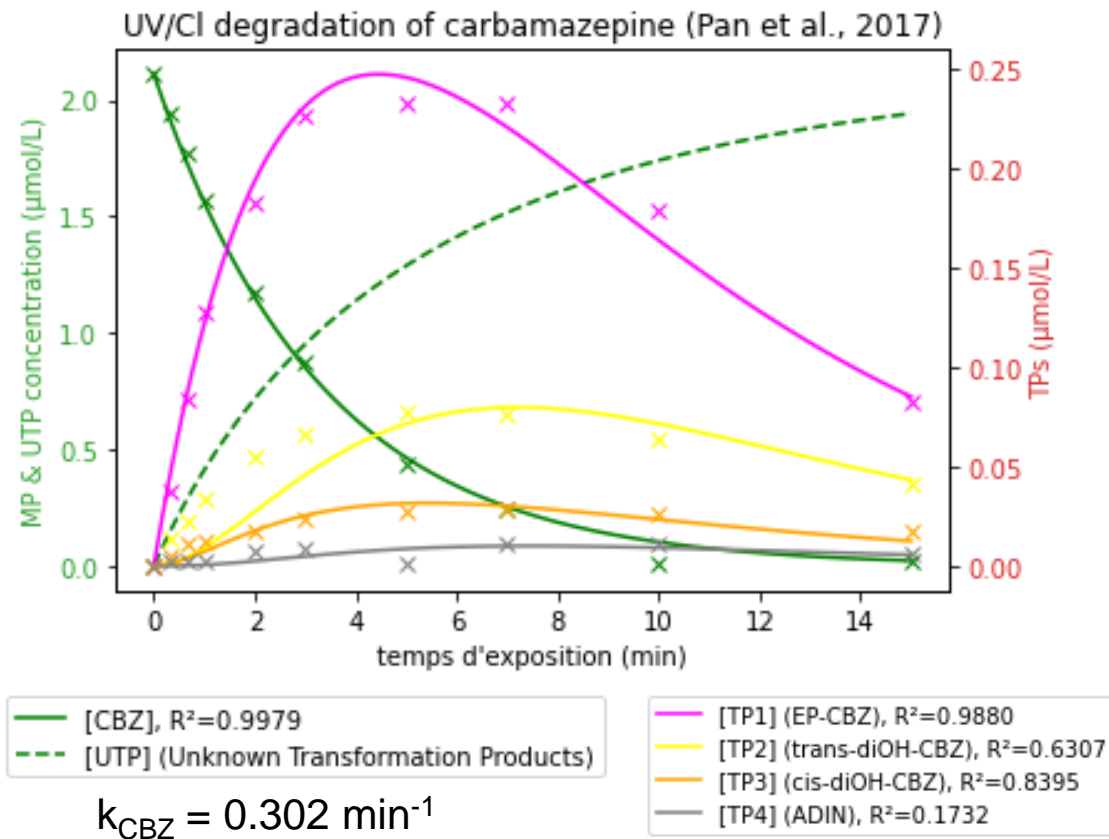
$$dUTP/dt = |dCBZ/dt| - |\Sigma(dTP/dt)| \quad (3)$$

Paramètres du modèle :

$k_{stoi}$  : coefficients stœchiométriques

$k$  : constantes cinétiques de dégradation

# Modelling of CBZ degradation



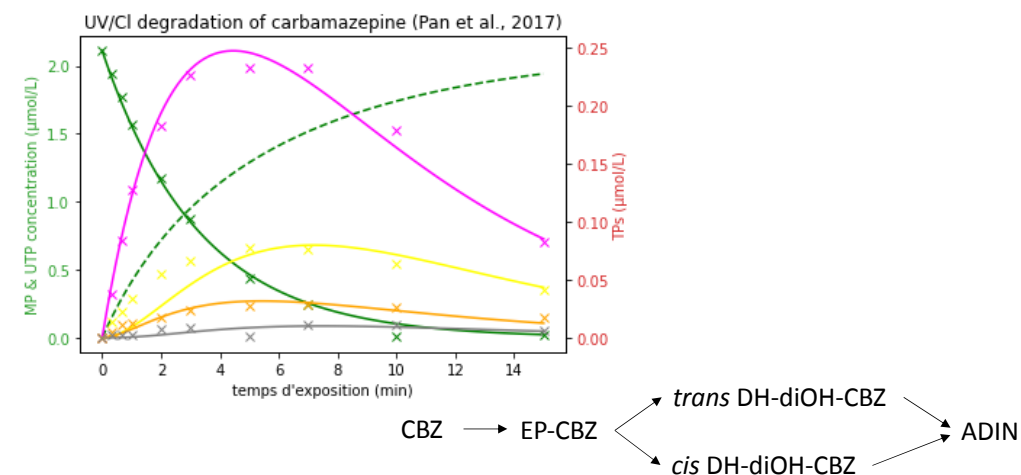
- good adequation between predicted and experimental data ( $R^2 > 86\%$ )
- $k_{\text{CBZ}}$  resulting from model and  $k_{\text{CBZ}}$  originally calculated in datasets are comparable
- Pseudo-first order equation appropriate for  $\frac{3}{4}$  datasets



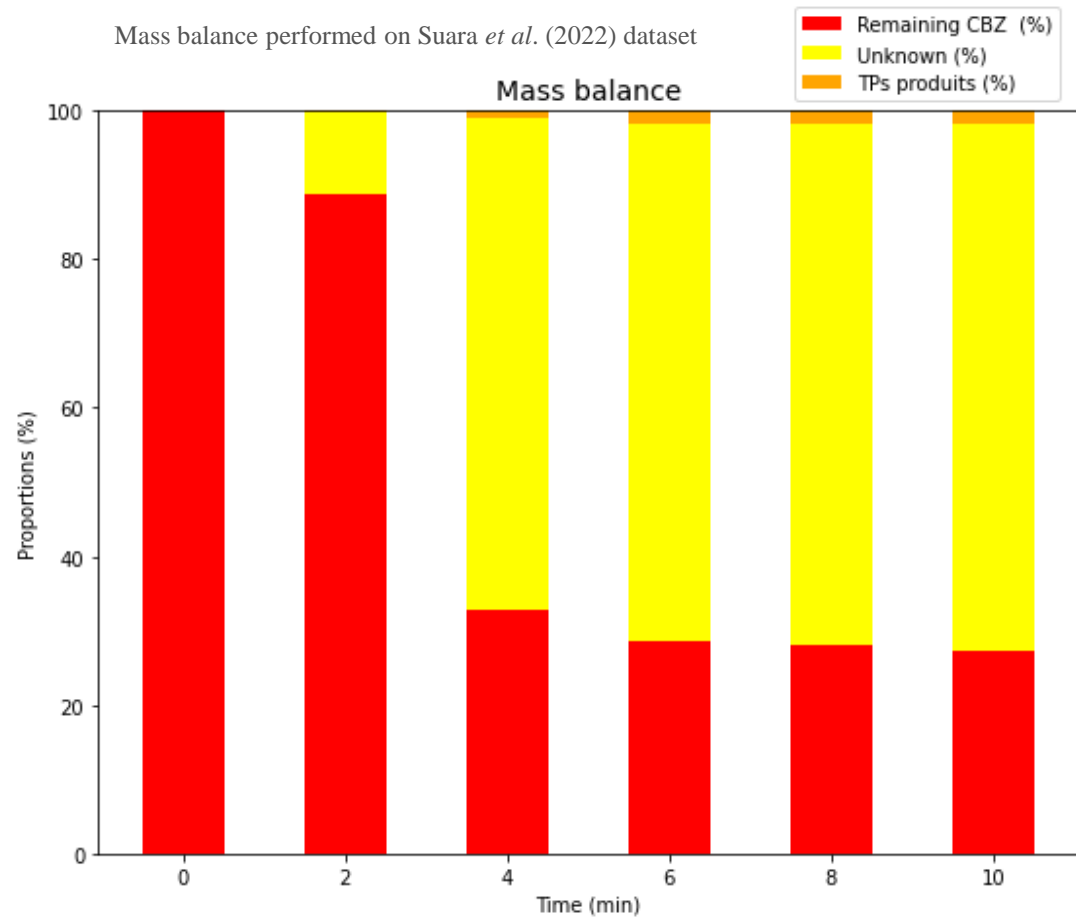
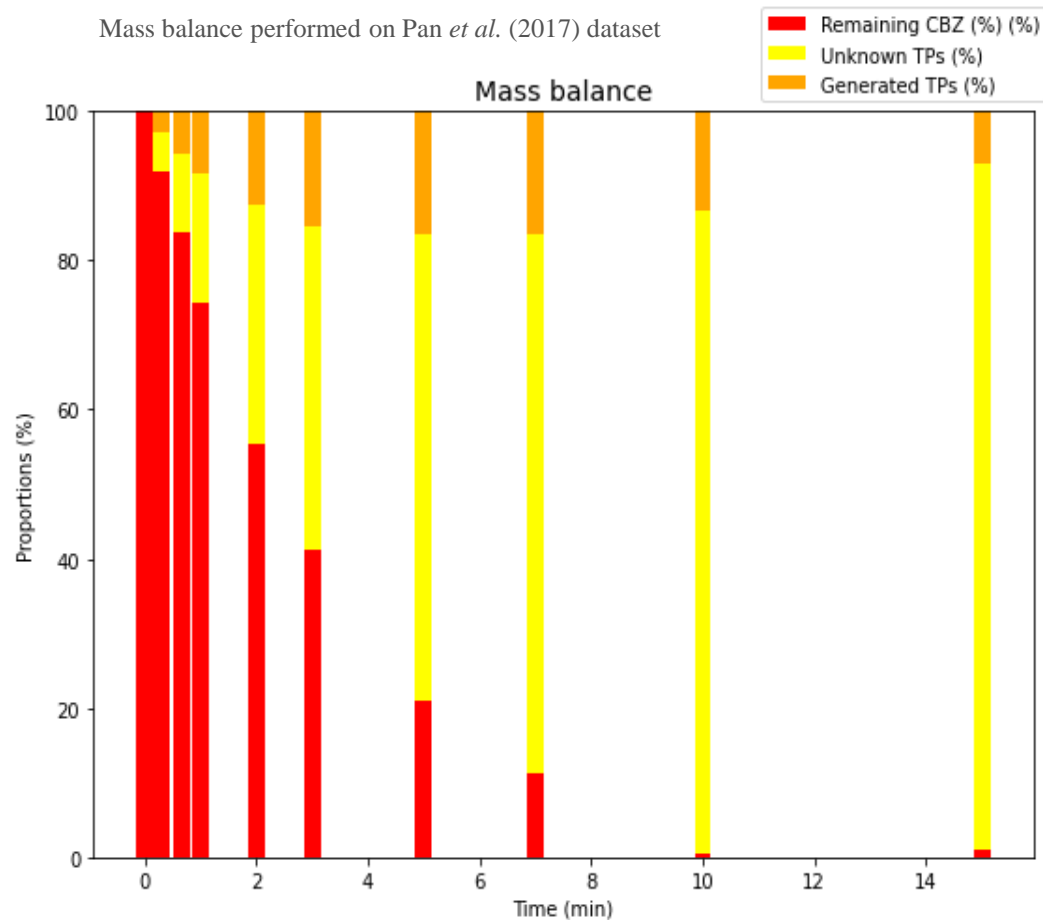
# Modelling of TPs formation/degradation

Reference	TPs	R <sup>2</sup> <sub>TPs</sub> (%)	k <sub>TPs</sub> (min <sup>-1</sup> )	k <sub>stoi</sub>
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

Literature review and data collected from individual models

Overall reaction scheme design

Global model, implemented to each dataset

Good quality of the model ?

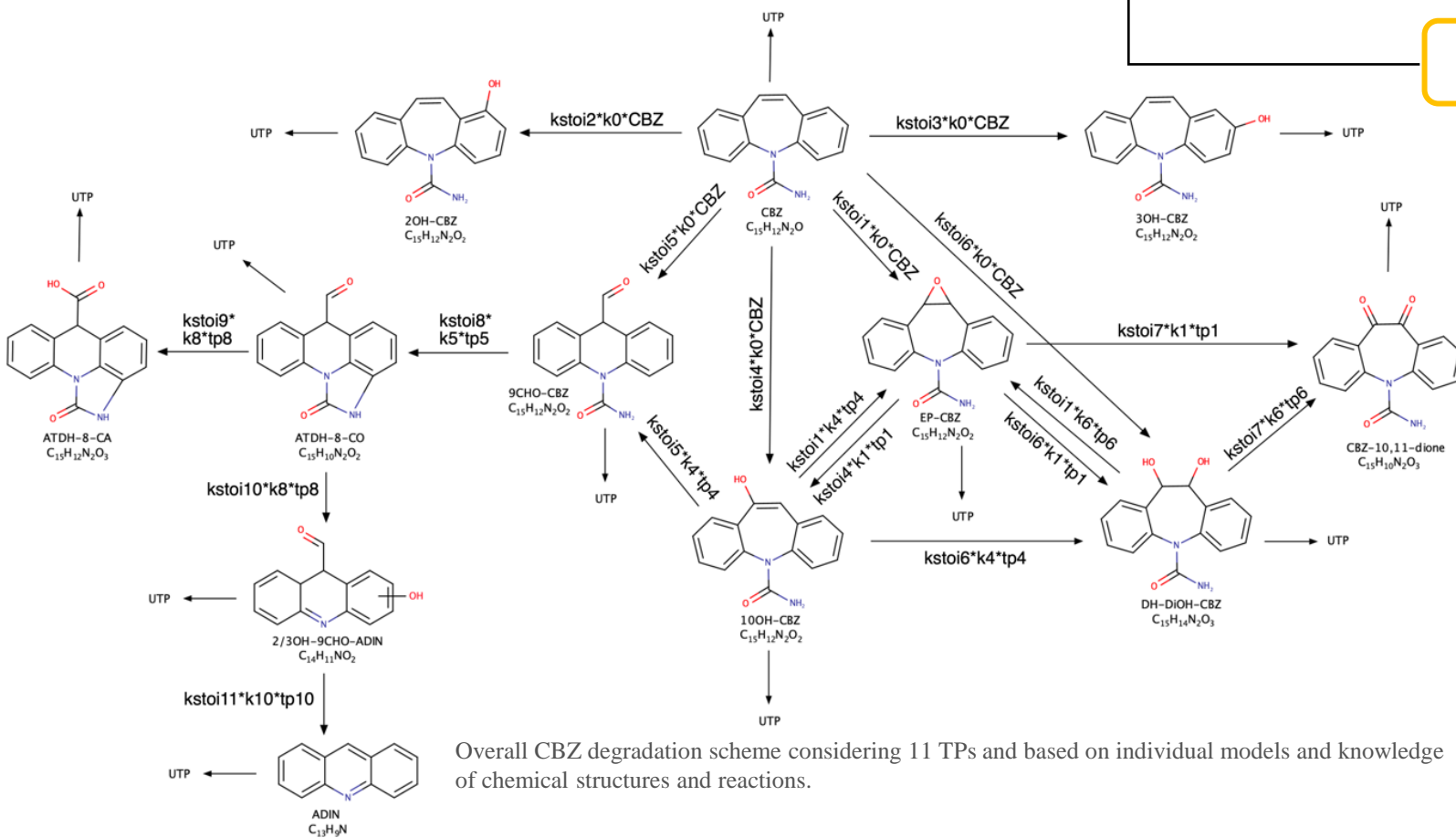
Yes

Sensitivity analysis of the parameters

No

Parameters variations

Conclusions on relevant TPs and parameters



12 molécules

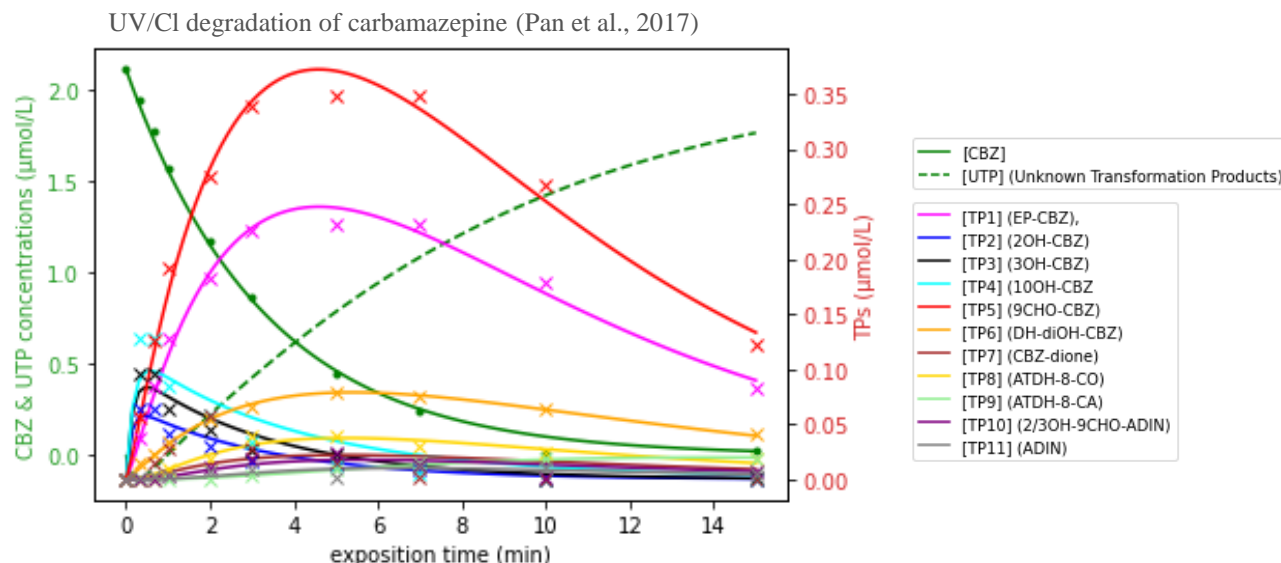
23 paramètres:

11 *kstoi*

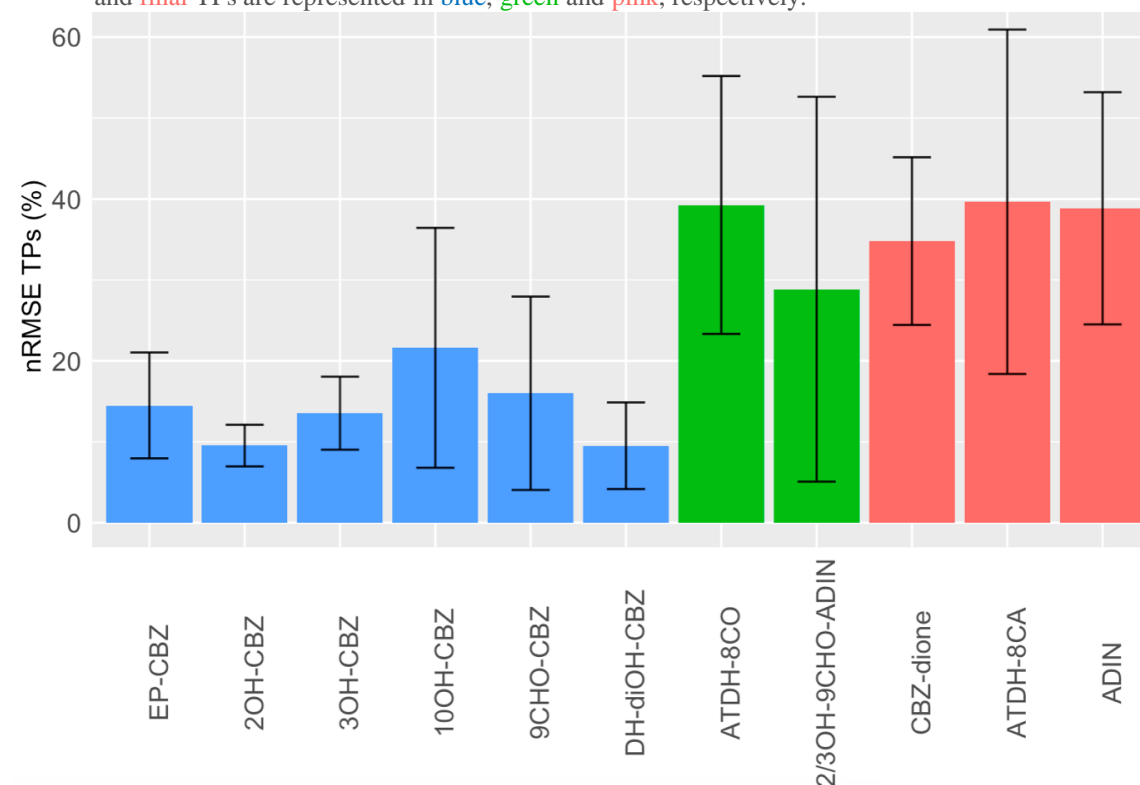
12 *k*

# Modelling of CBZ degradation & TPs formation

## 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  $> 35\%$

# Modelling of CBZ degradation & TPs formation

## Global model based on an overall reaction scheme – sensitivity analysis

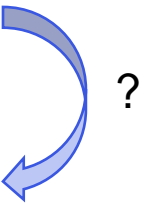
Global model = 12 molecules, 13 differential equations, 23 parameters ( $k_{stoi}$ ,  $k$ )

→ 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  $k$

# Modelling of CBZ degradation & TPs formation

## Global model based on an overall reaction scheme – sensitivity analysis

		Global Model Quality	R <sup>2</sup> TPs	
<i>k<sub>stoi</sub></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<sup>-1</sup>)</i>	CBZ	+	+	
	EP-CBZ	++	++	
	2OH-CBZ	-	++	
	3OH-CBZ	-	+	
	10OH-CBZ	-	+	
	9CHO-CBZ	++	+	
	DH-diOH-CBZ	-	++	

- *k<sub>stoi</sub>* 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)

# Conclusions & outlooks

- 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  $k_{\text{stoi}}$  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, ...)