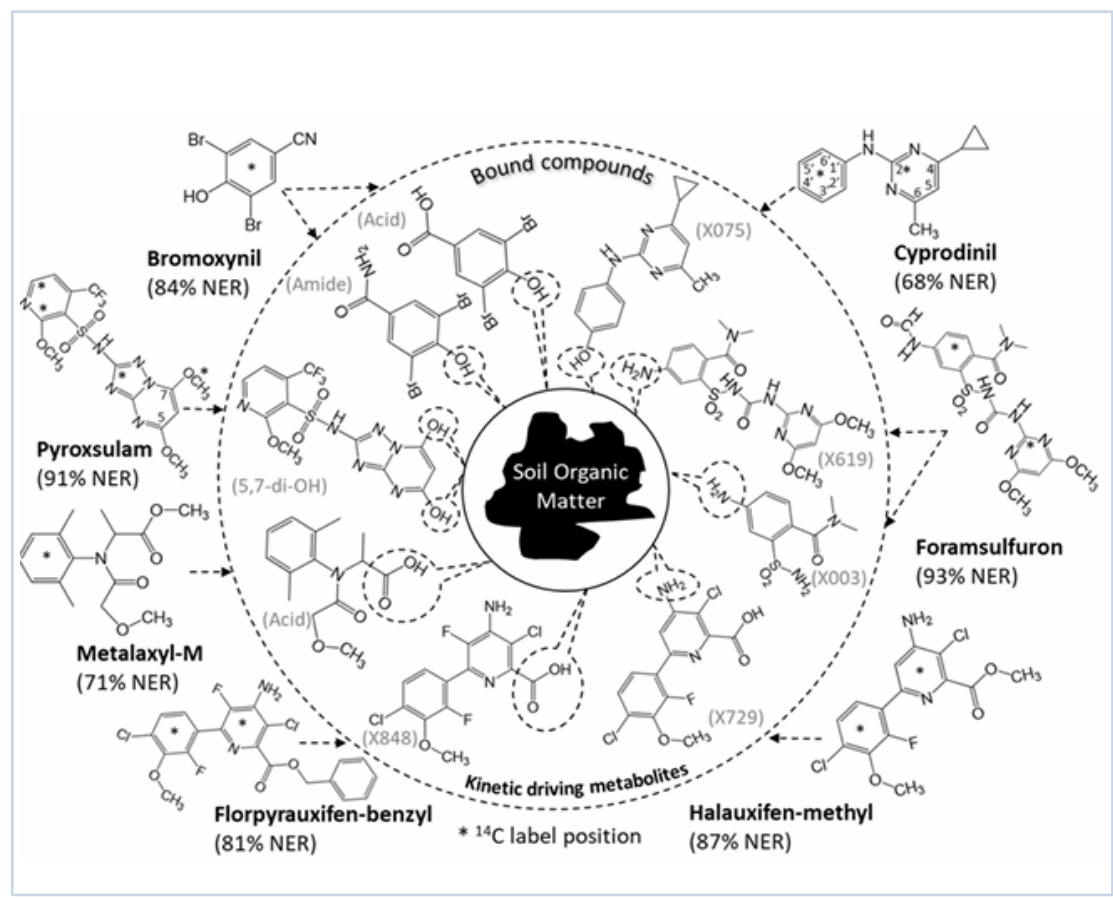




From NER Formation to Risk Assessment: A Four-Pool Kinetic Tool for Regulatory Evaluation

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INTRODUCTION

Regulatory background

Non-extractable residues (NERs) can represent a substantial fraction of applied radioactivity in soil degradation studies (OECD 307) and water/sediment degradation studies (OECD 308). Regulatory guidance increasingly requires consideration of NERs in persistence assessments (e.g. in PMT classification, ECHA 2024) and total residue concept (EPA 2014). However, NERs are often treated conservatively because it is unknown whether they are derived from the parent compound, metabolites, or biogenic residues. This limits persistence evaluation and ecotoxicological risk assessment of environmental relevance.

Objectives

- Develop a user-friendly kinetic analysis tool based on a four-pool (parent compound, metabolites, NERs and CO₂) framework (Huang et al. 2024, Huang et al. 2026)
- Identify compounds that kinetically drive NER formation
- Support more mechanistic interpretation of NERs in persistence and risk assessment

MATERIALS & METHODS

A dedicated analysis tool was developed based on the four-pool kinetic framework (Huang et al. 2024, Huang et al. 2026).

Benefits and workflow of the tool

- ✓ Applies one 4-pool framework to both OECD 307 and OECD 308 studies.
- ✓ Uses existing regulatory residue datasets; no additional experiments are required.
- ✓ Distinguishes parent-driven from metabolite-driven NER formation.
- ✓ Links NER formation to degradation pathways and kinetics.

Key Assumptions and applicability

- ✓ The 4-pool model assumes a sequential degradation pathway. When a metabolite is identified as the NER-driving compound, contribution from precursor metabolites cannot be ruled out. Therefore, except for first-generation metabolites, both parent- and metabolite-dosed studies should be evaluated where available.
- ✓ For OECD 308 studies, Rp (parent) or Rm (metabolite) must be derived through additional water/sediment kinetic modeling. Rp or Rm is the ratio between transfer from water to sediment and degradation in the water phase. The ratio should be $\gg 1$, indicating that transfer to sediment is much faster than degradation in water - a prerequisite for sediment NER formation.

RESULTS & DISCUSSIONS

Case study 1: OECD 307 soil degradation (Figure 1). The parent→NER model did not adequately describe NER formation. In contrast, the metabolite→NER model resolved the metabolite pool into kinetic fractions, with the M1 profile matching the Stage 1 metabolite profile. This indicates that NER formation was driven by the Stage 1 metabolite. A subsequent soil kinetic pathway fit was conducted with CAKE (2026), including NER formation from the identified metabolite pool.

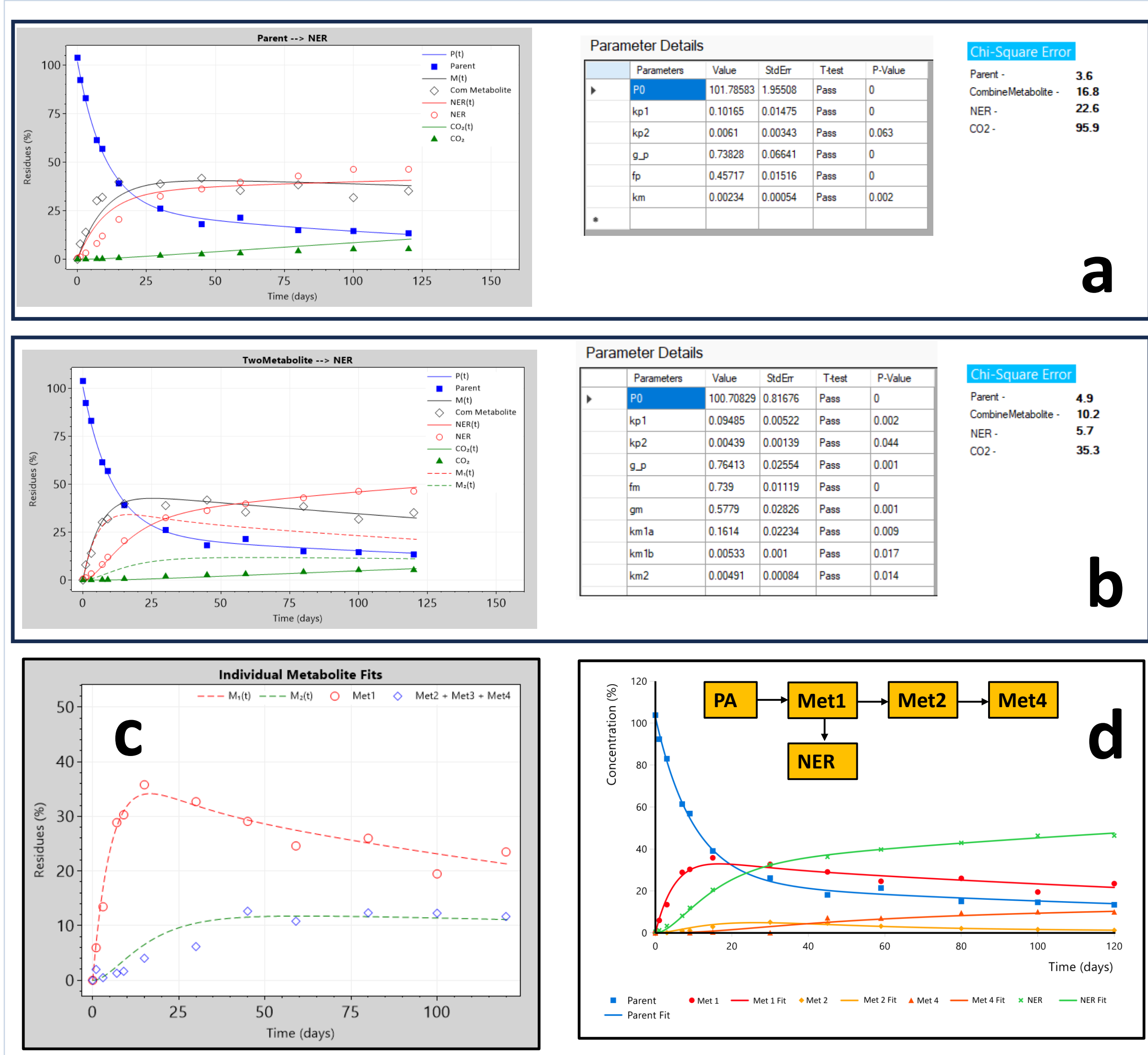


Figure 1. 4-Pool kinetic analysis and kinetic pathway fit for an aerobic soil degradation (OECD 307) study
a: “Parent → NER” 4-Pool kinetic fit b: “Metabolite → NER” 4-Pool kinetic fit
c: Matching of individual metabolite profiles with the resolved M1/M2 pool
d: Soil kinetic pathway fit (with CAKE) including NER formation

Case study 2: OECD 308 water/sediment degradation (Figure 2). The 4-pool analysis indicated that NER formation was associated with metabolite formation rather than direct parent binding. Additional water/sediment kinetic modelling with gmKin (Ranke, 2017) was used to evaluate candidate metabolites in water and sediment phases. Rm values were derived for Met1 and Met3. Met3 showed Rm > 100, while Met1 showed Rm < 1, indicating that Met3 reached the sediment much faster than it degraded in the water phase. Therefore, Met3 is the most likely metabolite driving sediment NER formation.

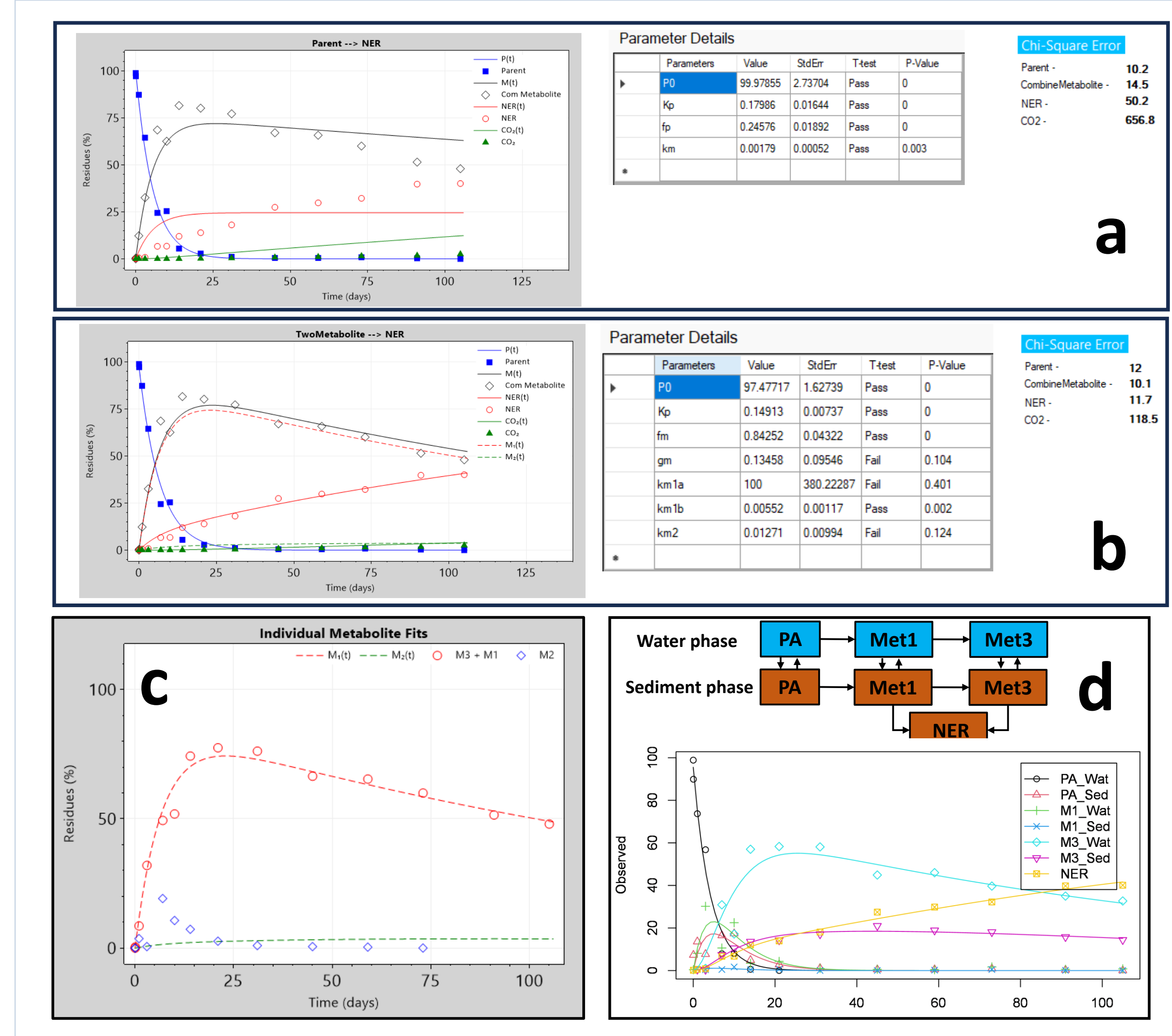


Figure 2. 4-Pool kinetic analysis and kinetic model fit for a water/sediment degradation (OECD 308) study
a: “Parent → NER” 4-Pool kinetic fit b: “Metabolite → NER” 4-Pool kinetic fit
c: Matching of individual metabolite profiles with the resolved M1/M2 pool
d: Water/sediment kinetic pathway fit (with gmkin) at Level M-II

CONCLUSIONS

- Improved understanding of NER formation remains an active area of research within regulatory environmental fate assessment.
- The 4-pool kinetic tool provides a scientifically sound, data-driven approach to identify compounds driving NER formation.
- A unified framework can be applied to both OECD 307 soil and OECD 308 water/sediment studies using existing regulatory residue data.
- The tool links NER formation to degradation pathways and kinetics, supporting mechanistic interpretation of NERs.
- The approach supports more transparent, robust, and more realistic interpretation of persistence and total residues.

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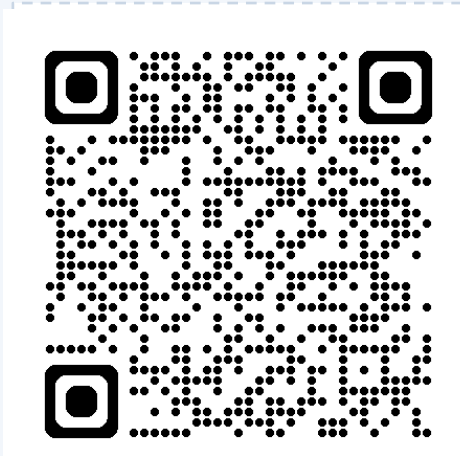
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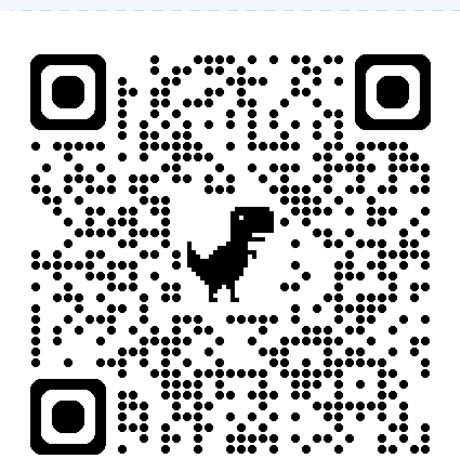
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Scan for full paper Huang et al. (2024)



Scan for full paper Huang et al. (2026)