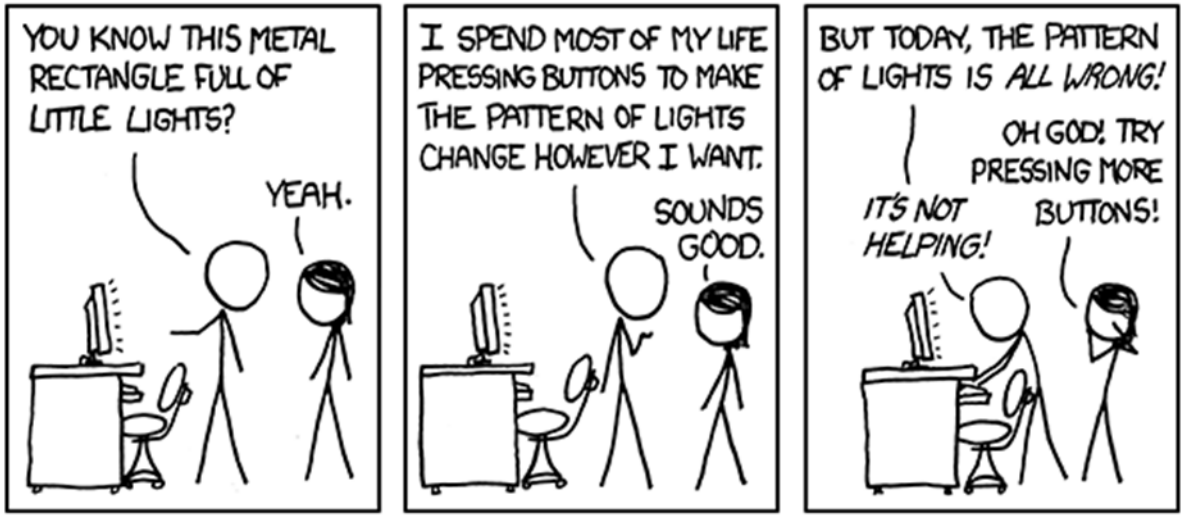

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Approaches to Kinetics & Impact on Modelling compared with Monitoring

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Overview

- Aim of FOCUS Kinetics was to produce a scientific description of degradation behaviour based on available data
  - with the intention of generating degradation rates that can be used in environmental risk assessment

- Over-conservative analysis can lead to endpoints that have little relationship to the data
  - and can generate extreme risk assessments

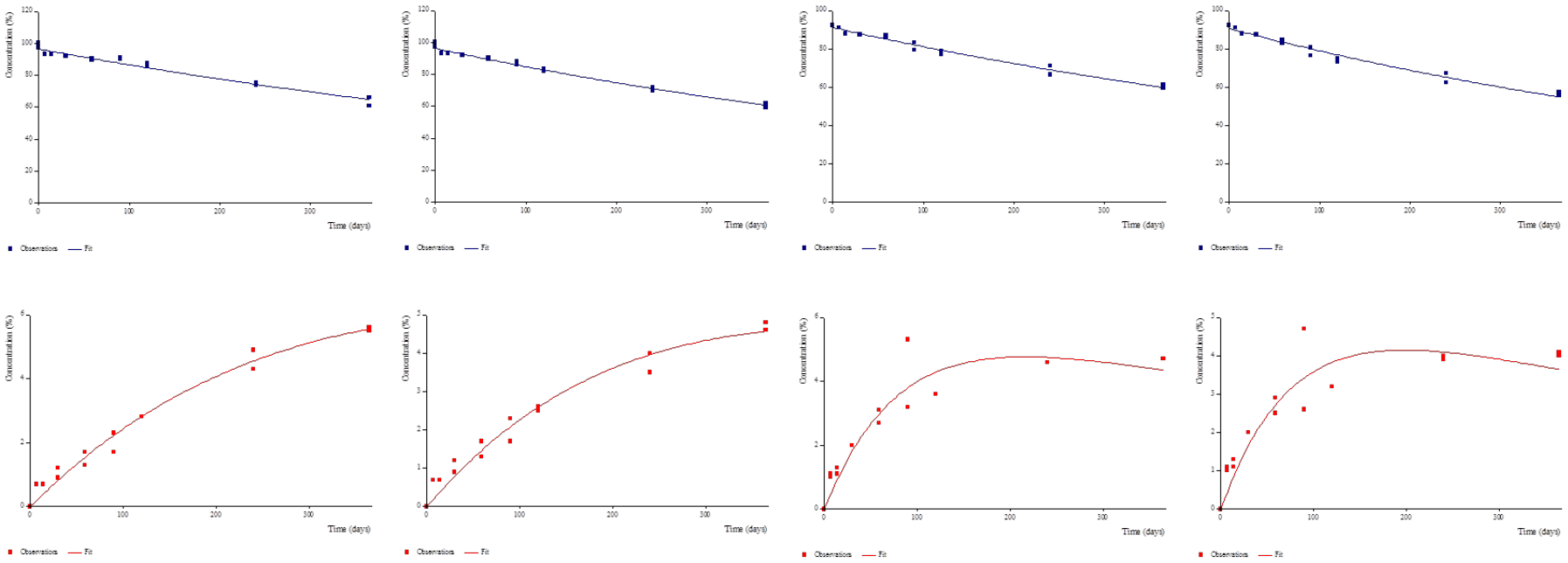
- Key points:
  - Use of data from harsh extractions
  - Use of $DegT_{50}$ = 1000d and ffm = 1 defaults
  - Weight of evidence

Harsh Extractions

- Harsh extractions are used in rate of degradation studies to reduce the levels of un-extracted material remaining after mild extractions
  - Often only used at the later time-points, when the levels become significant
- By definition, these residues are not easily extracted by standard procedures
- There is no evidence that these un-extracted residues are available for leaching

- Inclusion of mass balance from harsh extractions at later time-points
  - Introduces a bias towards bi-phasic degradation
  - Is not relevant for a leaching assessment
  - Affects assessment of metabolites, both formation fraction and $DegT_{50}$ can increase

Harsh Extractions - examples



	1 Harsh	1 Standard	2 Harsh	2 Standard
Parent $DegT_{50}$	96.5 days	96.3 days	91.1 days	90.6 days
Metabolite $DegT_{50}$	274 days	206 days	57.7 days	55.3 days
Metabolite ffm	0.28	0.23	0.7	0.55

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Use of default $DegT_{50}$ = 1000d & ffm = 1

- *If there is a clear overestimation of observed metabolite residues using the default assumptions of formation fraction of 1 and DT50 of 1000 days, alternative -but conservative- estimates should be allowed that better describe the observed patterns. The worst-case nature of the selected estimates for the study of interest should always be discussed in detail, and compared to available information from other studies for weight of evidence.* p153

- Many times fitted estimates are rejected because the levels are increasing at the end of the study
  - Perception that this must lead to uncertainty
    - But depends on the parent degradation
  - Accepting defaults does not lead to a better risk assessment
  - Metabolites further down the pathway are impacted by inaccurate estimates for precursors

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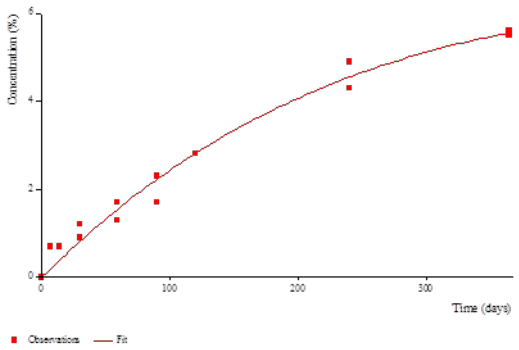
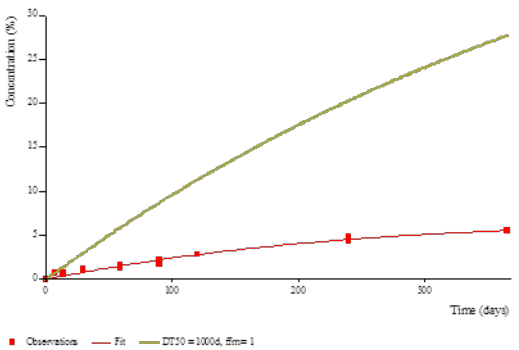
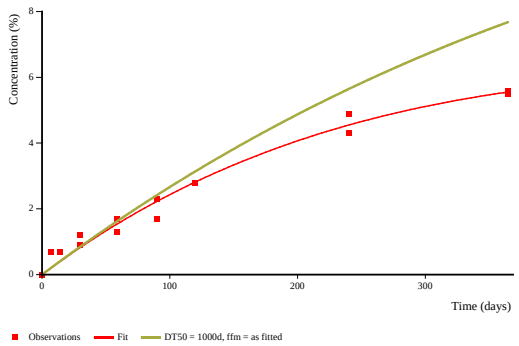
Use of default $DegT_{50}$ = 1000d & ffm = 1



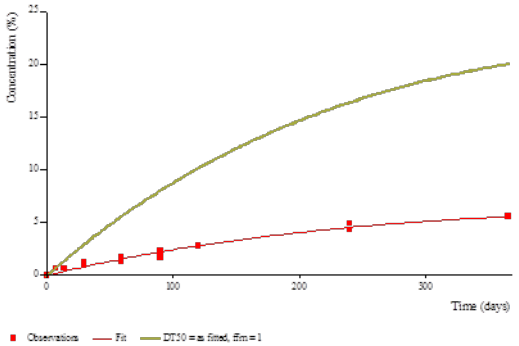
Fitted $DegT_{50}$=274d, ffm=0.28



$DegT_{50}$=1000d, ffm=1



$DegT_{50}$=1000d, fitted ffm



Fitted $DegT_{50}$, ffm=1

- In this case:
  - The combination of defaults gives an extreme over-estimation of the data
  - ffm=1 clearly over-estimates of the data
  - $DegT_{50}$=1000d is conservative in combination with the fitted ffm

- *The formation fraction parameter should be constrained between 0 and 1, or, if several metabolites are formed at once from the same substance, the sum of the formation fractions should be constrained to 1.* p143

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Weight of Evidence

- Many references to weight of evidence in FOCUS Kinetics
  - p94, p130, p150, p153, p159, p163-4, p170

- In particular:
  - *However, on a case-by-case basis, the metabolite endpoints may still be considered acceptable even though one or more of the indices are not met, as long as the endpoint value can be considered conservative, or can be justified based on weight of evidence from other studies.* p163/4
  - *Any assumption about the formation fraction must be realistic, considering the chemical or biological reactions and physico-chemical processes involved and should be justified accordingly, ideally based on supporting data or weight of evidence.* p170

Weight of Evidence example

- 5 test systems with same soil
  - 4 give reliable estimates: 390d, 190d, 99d, 147d
  - Geomean = 181d
  - 1 is unreliable and assigned default 1000d
  - Geomean = 255d

Impact on Modelling PEC_{GW}

- Use of the conservative choices discussed above leads, in some cases, to extreme over-estimates of PEC_{GW}

- This can be particularly true for metabolites
  - Combining worst-case ffm and worst-case $DegT_{50}$ gives unrealistic estimates of predicted exposure
  - This can lead to unnecessary toxicology studies to demonstrate non-relevance

Impact on PEC_{GW} example I

- Impact of conservative choices on $DegT_{50}$ across 12 soils
  - $DegT_{50}$ = 30d
  - $DegT_{50}$ = 70d

- A large scale monitoring program sampling shallow groundwater:
  - 3% of samples > 0.05 µg/L
  - 80th percentile residue = 0.003 µg/L

DT50 (days)	30	70
Chateaudun	0.004	1.166
Hamburg	0.039	2.932
Kremsmunster	0.018	2.013
Okehampton	0.050	3.312
Piacenza	0.028	2.377
Porto	0.005	1.096
Sevilla	< 0.001	0.010
Thiva	0.001	0.412

Impact on PEC_{GW} example II

- Metabolite choices determined, from 10 soils:
  - Including default 1000d & ffm=1
    - $DegT_{50}$ = 250d, ffm = 0.2
  - Good evidence from the data for:
    - $DegT_{50}$ = 250d, ffm = 0.02
    - $DegT_{50}$ = 50d, ffm = 0.2
- In long term monitoring, most detects < 10ug/L
  - Use of default values gives extreme leaching risk assessment

PEC_{GW} calculated by PEARL

DT50 (days) ffm	250 0.2	250 0.02	50 0.2
Chateaudun	104	10	31
Hamburg	135	13	58
Kremsmunster	74	7.5	29
Okehampton	64	6.0	29
Piacenza	94	9.5	23
Porto	44	4.5	15
Sevilla	105	10	8.9
Thiva	175	17	25

Summary

- FOCUS Kinetics includes a number of statements about the choice of metabolite endpoints which are often forgotten or neglected
  - *However, on a case-by-case basis, the metabolite endpoints may still be considered acceptable even though one or more of the indices are not met, as long as the endpoint value can be considered conservative, or can be justified based on weight of evidence from other studies.* p163/4
  - *Any assumption about the formation fraction must be realistic, considering the chemical or biological reactions and physico-chemical processes involved and should be justified accordingly, ideally based on supporting data or weight of evidence.* P170
- Using harsh extraction data, default values and ignoring weight of evidence can lead to endpoints which do not match the data
- The use of such endpoints in calculating PEC_{GW} can lead to extreme assessments which bear little resemblance to reality

Thank you for your attention!

- Discussion points:
  - Is it appropriate to include residues from harsh extraction, if they are only measured at later time-points?
  - Should unreliable fits be included for metabolites by using defaults?
    - where there is already additional reliable data?
  - What does weight of evidence mean?