FOCUS work group on degradation kinetics

Overview and parent kinetics

Presentation at the
3rd European Modelling Workshop
Catania, Sicily, 17-19 February 2004
Introduction

- The degradation rates of parent and metabolites are important variables in assessing environmental exposure and movement to water

- Assumptions used in calculating degradation rates can significantly affect these assessments

- Need for harmonisation
FOCUS (an organization co-sponsored by the EU and industry) established a work group to provide guidance on calculation of degradation rates of parent and metabolites

- laboratory studies
- field studies
- water sediment studies
FOCUS WORK GROUP ON DEGRADATION KINETICS

- Group of 13 scientists chaired by Jos Boesten
  - research institutes
  - regulatory agencies
  - academia
  - industry

- Six meetings starting in September 2002

- Essentially complete final report (will be submitted to the FOCUS Steering Committee in early March)
Work Group Members

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Russell Jones  Sylvia Karlsson  Ton van der Linden  Oriol Magrans Soria  Otto Richter  Guy Soulas
Types of Kinetics

Single first-order (SFO)
Time for decrease from 100% to 50% same as time for decrease from 50% to 25%
DT90 = 3.32 x DT50

Bi-phasic
Degradation initially fast, then slower
e.g. due to declining microbial activity (artefact!), increasing sorption
Gustafson and Holden (FOMC)
Hockey-stick (HS)
Bi-exponential (DFOP)
Types of kinetics

Lag-phase
Degradation initially slow, then faster
e.g. due to inappropriate storage before study (artefact!), adaptation of micro-organisms

Modified Hockey-stick model
Logistic model
Goodness of Fit

- Aim to identify statistical measure that matches expert judgement

- No single statistical measure was found to be universally valid

  ➔ Acceptability of fits are judged on the basis of a Chi\(^2\) test and visual assessment
Chi\(^2\) Test (variant)

\[
\chi^2 = \sum \frac{(C - O)^2}{(\text{err} / 100 \times \bar{O})^2}
\]

- \(C\) = calculated value
- \(O\) = observed value
- \(\bar{O}\) = mean of all observed values
- \(\text{err}\) = measurement error percentage

If \(\chi^2 > \) tabulated value then the model is not appropriate at the chosen level of significance (usually 5%)

Error unknown
→ Calculate error level at which test is passed

Model with smallest error percentage is best-fit model
Visual Inspection

- Graph of predicted and observed concentrations vs time

- Graph of residuals vs time (for kinetic models for exposure assessment, consider only the residues through the DT90)
Spreadsheet for parent SFO and FOMC

Version 1.0
Parameter optimisation for SFO kinetics with Excel Solver Add-In
Visual assessment and chi2-test
For datasets without replicates, optimisation of two parameters (M0 and k)

User input, all other cells calculated or automated
Optimise using Solver (click on grey button)

Name of dataset: Example dataset L3

<table>
<thead>
<tr>
<th>No</th>
<th>Time</th>
<th>Observed</th>
<th>Calculated</th>
<th>SFO parameters and endpoints</th>
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1000.727 Residual Sum of Squares

Chi2 Test SFO passed

1000.727 Residual Sum of Squares
8 Number of observations
2 Number of parameters
42.0 Average of observed
21.2 % Error
8.91 Scaled Error
12.632 Chi2 calculated
12.692 Chi2 Table
0.000 Chi2 calculated - Chi2 Table

Calculate % error at which test passed
Objectives for Parent Kinetic Analysis

- DT50 and DT90 values used to trigger additional studies
  - Chose best-fit model kinetics on statistical and visual analysis

- Endpoints to calculate predicted environmental concentrations in groundwater and surface water
  - Standard versions of most fate models use SFO
  - Preference for SFO when an adequate fit is obtained
  - Correction procedures if an adequate fit is not obtained
Estimating Endpoints Used as Trigger Values

- Run SFO and FOMC. If fit for SFO is better, then use SFO.

- If FOMC is better, run DFOP. Use whichever model gives the best fit (lowest error in Chi\(^2\) test).

- Assess by visual inspection whether the best fit model provides an acceptable description of the data.
Parent Endpoints for Exposure Modelling

Run SFO

SFO statistically and visually acceptable?

yes -> SFO DT50

no

Decline in study below 10% of dose?

yes

Tier 1 fate modelling based on DT50 back-calculated from DT90 for FOMC
DT50 = DT90 / 3.32
worse case approach

no

Tier 1 fate modelling based on slower degradation rate of Hockey Stick or DFOP model
worst case approach
Example A (laboratory study)
Example A (laboratory study)
Example A (laboratory study)

- **Conclusions**
  - Chi$^2$ error value for SFO is 4%
  - No systematic error apparent in residual plots
  - Well behaved data-set, very limited scatter in the measured data
  - **SFO appropriate for use in modelling**

- **Additional Information**
  - No improvement in Chi$^2$ error or residual pattern with FOMC
Example B (laboratory study)
Example B (laboratory study)
Example B (laboratory study)

Conclusions
- Chi\(^2\) error value for SFO is 15%
- No systematic error apparent in residual plots up to DT90 (~5 days), underestimation afterwards
- **SFO appropriate for use in modelling**

Additional Information
- Chi\(^2\) error value for FOMC is 7%
- No improvement in residual pattern with FOMC up to DT90
Example C (laboratory study)
Example C (laboratory study)
Example C (laboratory study)

- Conclusions-SFO
  - $\text{Chi}^2$ error value for SFO is 22%
  - SFO misses measured initial concentration
  - Residual plot indicates systematic deviation for later sampling dates in period up to DT90
  - **SFO inappropriate for use in modelling**
Example C (laboratory study)

- **Conclusions-FOMC**
  - Chi² error value for FOMC drops to 8%
  - Better description of initial concentration
  - No improvement with regard to random nature of residuals, however overall smaller absolute deviations compared to SFO
  - **Use bi-phasic kinetics approaches for modelling**
    - DT90 FOMC/3.32 or higher tier approaches
Example D (field study)
Example D (field study)
Example D (field study)

Conclusions-SFO

- Chi$$^2$$ error value for SFO is 22%
- Residuals plots indicate no systematic error of the SFO model, rather that the observed pattern is most likely due to scatter of early measurements
- SFO appropriate for use in modelling, confirm against bi-phasic kinetics
Example D (field study)

- Conclusions-FOMC
  - No improvement in $\chi^2$ error value
  - No improvement in residual pattern
Other Topics in the Report

- General data issues
  - Replicates
  - Data transformation and weighting
  - Outliers
  - Data below LOD and LOQ
  - Time zero samples
Other Topics in the Report

- Metabolites

- Water sediment studies

- Use of kinetic endpoints in regulatory assessments
  - when averages are desired, use geometric mean
    - same value when half-lives and degradation rates are averaged
    - best description of averages of entire degradation curves
Other Topics in the Report

- Discussion of statistical measures
- Normalization of field data
- Higher tier approaches if degradation is bi-phasic
- Reporting of results
- Review of software packages