Progress in regulatory degradation kinetics
SETAC Europe 24th Annual Meeting

PD Dr. Johannes Ranke
Scientific consultant

Basel, 13 May 2014
How do you define progress?
Outline

1. The tasks of regulatory degradation kinetics
Outline

1. The tasks of regulatory degradation kinetics
2. Parameter confidence intervals
Outline

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3. Biphasic models for metabolites
Outline

1. The tasks of regulatory degradation kinetics
2. Parameter confidence intervals
3. Biphasic models for metabolites
4. Conclusions
The tasks of regulatory degradation kinetics

- Derive endpoints for fate modelling
The tasks of regulatory degradation kinetics

- Derive endpoints for fate modelling
- Provide endpoints for comparison with trigger values
The tasks of regulatory degradation kinetics

- Derive endpoints for fate modelling
- Provide endpoints for comparison with trigger values
  - Triggers for further data requirements
    (EU pesticides: FOCUS kinetics “persistence endpoints”)

Confidence intervals
Metabolite models
Conclusions
The tasks of regulatory degradation kinetics

- Derive endpoints for fate modelling
- Provide endpoints for comparison with trigger values
  - Triggers for further data requirements
    (EU pesticides: FOCUS kinetics “persistence endpoints”)
  - Triggers for persistence, P and vP
    (Regulation 1107/2009, REACH)
The tasks of regulatory degradation kinetics

- Derive endpoints for fate modelling
- Provide endpoints for comparison with trigger values
  - Triggers for further data requirements
    - (EU pesticides: FOCUS kinetics “persistence endpoints”)
  - Triggers for persistence, P and vP
    - (Regulation 1107/2009, REACH)
- Reflect endpoint uncertainty
Motivation to improve regulatory degradation kinetics

Provide the best possible foundation

- Transparency
Motivation to improve regulatory degradation kinetics

Provide the best possible foundation

- Transparency
- Scientific quality
Motivation to improve regulatory degradation kinetics

Provide the best possible foundation

- Transparency
- Scientific quality
- Technical quality
Motivation to improve regulatory degradation kinetics

Provide the best possible foundation

- Transparency
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- Collaboration
Motivation to improve regulatory degradation kinetics

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Motivation to improve regulatory degradation kinetics

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- Scientific quality ?
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Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration
Motivation to improve regulatory degradation kinetics

Provide the best possible foundation

- Transparency ✓
- Scientific quality ?
- Technical quality
- Collaboration

Model cost at call 161 : 242.2306
Model cost at call 165 : 242.2306
Model cost at call 171 : 242.2306
Model cost at call 175 : 242.2306
done successfully.

Executing test function test.SFO_solution_types ... done successfully.

--------------------- UNIT TEST SUMMARY ---------------------
RUNUNIT TEST PROTOCOL -- Fri May 9 16:30:24 2014
Number of test functions: 0
Number of errors: 0
Number of failures: 0

1 Test Suite : mkin Unit Tests - 0 test functions, 0 errors, 0 failures

www.r-project.org - focus.jrc.ec.europa.eu/dk
R CMD check mkin_0.9-27.tar.gz
Motivation to improve regulatory degradation kinetics

Provide the best possible foundation

- Transparency ✓
- Scientific quality ?
- Technical quality
- Collaboration !

Model cost at call 161 : 262.2306
Model cost at call 165 : 262.2306
Model cost at call 171 : 262.2306
Model cost at call 175 : 262.2306

done successfully.

Executing test function test.SFO_solution_types ... done successfully.

------------- UNIT TEST SUMMARY -------------

RUNIT TEST PROTOCOL --- Fri May 9 16:30:24 2014
*****************************************************************************
Number of test functions: 8
Number of errors: 0
Number of failures: 0

1 Test Suite:
  mkin Unit Tests - 8 test functions, 0 errors, 0 failures

www.r-project.org - focus.jrc.ec.europa.eu/dk
R CMD check mkin_0.9-27.tar.gz - github.com/jranke/mkin

Generic guidance for Estimating
Persistence and Degradation Kinetics from
Environmental Fate Studies on Pesticides in
EU Registration

Version: 1.0
Date: 23 November 2011
Critical areas

- t-test for parameter significance (assumes normal distribution for estimator)
- Confidence intervals for fitted parameters
- Modelling biphasic behaviour of metabolites
Elements of success

mkin was first published in May 2010, including biphasic models for metabolites since May 18. It was then used to develop

- KinGUII (Bayer Crop Science)
- CAKE (Syngenta)

by adding a graphical user interface (GUI), iteratively reweighted least squares (IRLS) and Markov Chain Monte Carlo (MCMC)
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Isometric logratio transformation (ILR) for fitting formation fractions together with René Lehmann (UBA) in 2012
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Parameter confidence intervals based on transformed parameters (2013)

Ranke and Lehmann, SETAC World 20-24 May 2012, Berlin
Elements of success

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Isometric logratio transformation (ILR) for fitting formation fractions together with René Lehmann (UBA) in 2012

Parameter confidence intervals based on transformed parameters (2013)

mkin (≥ 0.9-27) allows for fitting models with or without formation fractions, with or without parameter transformations.

Ranke and Lehmann, SETAC World 20-24 May 2012, Berlin
mkin 0.9-27 published on CRAN 10 May 2014
Soil metabolism of 2,4,5-T in the lab

McCall et al. (1981) J Agric Food Chem 29 100-107
2,4,5-T in Commerce soil in gmkin
Pathway from 2,4,5-T-phenol to sink?

Cl
Cl Cl
OH

\[
\begin{align*}
\text{Pathway from 2,4,5-T-phenol to sink?} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{OH} & \\
\end{align*}
\]

**Progress in regulatory kinetics**

**Tasks and motivation**

**Confidence intervals**

**Metabolite models**

**Conclusions**

**PD Dr. Johannes Ranke**

**Equations:**

1. \(d_{\text{T245}} = - k_{\text{T245 sink}} \cdot \text{T245} - k_{\text{T245 phenol}} \cdot \text{T245} \)
2. \(d_{\text{phenol}} = + k_{\text{T245 phenol}} \cdot \text{T245} - k_{\text{phenol sink}} \cdot \text{phenol} - k_{\text{phenol anisole}} \cdot \text{phenol} \)
3. \(d_{\text{anisole}} = + k_{\text{phenol anisole}} \cdot \text{phenol} - k_{\text{anisole sink}} \cdot \text{anisole} \)

**Method used for solution of differential equation system:**

eigen

**Weighting:**

manual

**Starting values for optimised parameters:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Type</th>
<th>Transformed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T245_0</td>
<td>100.0000</td>
<td>state</td>
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<td>k_T245_sink</td>
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</tr>
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<td>k_anisole_sink</td>
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**Fixed parameter values:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Type</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td>state</td>
</tr>
<tr>
<td>anisole_0</td>
<td>0</td>
<td>state</td>
</tr>
</tbody>
</table>

**Optimised, transformed parameters:**

| Parameter       | Estimate | Std. Error | Lower | Upper | t value | Pr(>|t|) | Pr(>|t|) |
|-----------------|----------|------------|-------|-------|---------|---------|---------|
| T245_0          | 1.039e+02 | 2.426e+01 | 58.760000 | 1.090e+02 | 4.235e-15 | 3.236e-15 |
| k_T245_sink     | 1.636e-02 | 0.133850 | -0.022350 | 0.5496e-02 | 6.591e-01 | 3.218e-01 |
| k_T245_phenol   | 2.701e-02 | 0.179650 | -0.027120 | 0.674e-02 | 1.504e+00 | 1.000e+00 |
| k_phenol_sink   | 0.306e+00 | 0.016100 | -0.590e00 | 1.095e+00 | 1.000e+00 | 5.000e-01 |
| k_phenol_anisole| 1.628e-01 | 0.019300 | -0.073100 | 0.251e+00 | 2.515e-02 | 1.075e-01 |
| k_anisole_sink  | 6.679e-03 | 0.000815 | 0.004856 | 0.601e-03 | 8.146e+00 | 1.000e+00 |

**Backtransformed parameters:**

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Upper</th>
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<tbody>
<tr>
<td>T245_0</td>
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<td>58.760000</td>
<td>1.090e+02</td>
</tr>
</tbody>
</table>

**k_phenol_sink negligible - fix to zero**
Pathway from 2,4,5-T-phenol to sink?

**Progress in regulatory kinetics**

**PD Dr. Johannes Ranke**

**Tasks and motivation**

**Confidence intervals**

**Metabolite models**

**Conclusions**

\[ \text{k}_{\text{phenol}, \text{sink}} \text{ negligible} - \text{fix to zero} \]
Pathway from 2,4,5-T-phenol to sink?

k_phenol_sink negligible - fix to zero
2,4,5-T in Commerce soil, no path to sink
2,4,5-T in Commerce soil, no path to sink
Rate parameters log transformed during fit

**Starting values for optimised parameters:**

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<td>state</td>
</tr>
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<td>0.1000</td>
<td>deparm</td>
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<tr>
<td>k_T245_phenol</td>
<td>0.1001</td>
<td>deparm</td>
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<tr>
<td>k_phenol_anisole</td>
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<td>0.1004</td>
<td>deparm</td>
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</table>

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<td>state</td>
</tr>
<tr>
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<td>0</td>
<td>deparm</td>
</tr>
</tbody>
</table>

**Optimised, transformed parameters:**

| Parameter   | Estimate | Std. Error | Lower  | Upper  | t value | Pr(>|t|) | Pr(>|t|) |
|-------------|----------|------------|--------|--------|---------|---------|---------|
| T245_0      | 103.9000 | 2.35200    | 98.930 | 108.800 | 0.160   | 1.292e-20 | 0.463e-21 |
| k_T245_sink | -4.1130  | 0.13250    | -4.350 | -3.6350 | -3.1030 | 5.648e-18 | 4.823e-18 |
| k_phenol_anisole | -0.9037 | 0.30380    | -1.544 | -0.2637 | -2.955  | 8.127e-03 | 4.063e-03 |
| k_anisole_sink | -5.0090 | 0.11150    | -5.343 | -4.7750 | -44.750 | 9.601e-21 | 4.950e-21 |

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<td>100.8000</td>
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<td>1.636e-02</td>
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<td>0.02155</td>
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<td>k_T245_phenol</td>
<td>2.701e-02</td>
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<td>k_anisole_sink</td>
<td>6.675e-03</td>
<td>0.005255</td>
<td>0.00844</td>
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</tbody>
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Proposal regarding t-test

Instead of testing rate constants for significant difference from zero:

- Use best available estimate
Proposal regarding t-test

Instead of testing rate constants for significant difference from zero:

- Use best available estimate
- Consider if it is negligibly small
2,4,5-T in Fargo soil

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<tr>
<td>k_phenol_sink</td>
<td>0</td>
<td>deparr</td>
</tr>
</tbody>
</table>

Optimised, transformed parameters:

| Parameter      | Estimate | Std. Error | Lower  | Upper  | t value | Pr(>|t|) | Pr(>|t|) |
|----------------|----------|------------|--------|--------|---------|----------|----------|
| T245_0         | 101.300  | 2.256600   | 96.810 | 106.100| 44.9100 | 9.366e-21| 4.698e-21|
| k_T245_sink    | -5.922   | 0.763330   | -7.179 | -4.671 | -7.759  | 2.638e-07| 1.319e-07|
| k_T245_phenol  | -4.030   | 0.03497    | -4.310 | -3.782 | -47.310 | 3.530e-21| 1.755e-21|
| k_phenol_anisole| -2.570   | 0.16670    | -3.390 | -1.750 | -2.221  | 15.420  | 3.354e-12| 1.697e-12|
| k_anisole_sink | -5.490   | 0.34400    | -6.219 | -4.779 | -15.980 | 1.750e-12| 8.548e-13|

Backtransformed parameters:

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<th>Upper</th>
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<tbody>
<tr>
<td>T245_0</td>
<td>1.013e+02</td>
<td>9.661e+01</td>
<td>1.051e+02</td>
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<tr>
<td>k_T245_sink</td>
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<td>1.325e-02</td>
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<tr>
<td>k_T245_phenol</td>
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<td>1.503e-02</td>
<td>2.145e-02</td>
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<tr>
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<tr>
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<td>1.591e-03</td>
<td>8.434e-03</td>
</tr>
</tbody>
</table>
2,4,5-T in Fargo soil
Model with formation fractions

Fixed parameter values:

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<tr>
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<th>type</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenol_0</td>
<td>0</td>
<td>state</td>
</tr>
<tr>
<td>anisole_0</td>
<td>0</td>
<td>state</td>
</tr>
<tr>
<td>f_phenol_to_anisole</td>
<td>1</td>
<td>deparm</td>
</tr>
</tbody>
</table>

Optimised, transformed parameters:

| parameter     | Estimate | Std. Error | Lower | Upper | t value | Pr(>|t|) | Pr(>|t|) |
|----------------|----------|------------|-------|-------|---------|---------|---------|
| T245_0         | 101.30000| 2.25600    | 96.6100| 106.100| 44.510  | 9.396e-21| 4.690e-21|
| k_T245         | -3.6610  | 0.07455    | -4.0370| -3.325 | -52.550 | 5.028e-22| 2.914e-22|
| f_T245_to_phenol | 0.6701 | 0.05263    | 0.6756 | 1.065 | 9.363   | 1.502e-08| 7.511e-09|
| k_phenol       | -2.5410  | 0.15677    | -2.7910| -2.281 | -15.429 | 3.394e-12| 1.697e-12|
| k_anisole      | -5.4850  | 0.34400    | -6.3190| -4.779 | -15.560 | 1.709e-12| 0.947e-13|

Backtransformed parameters:

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<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>T245_0</td>
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<td>96.6100</td>
<td>106.100</td>
</tr>
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<td>k_T245</td>
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<td>f_T245_to_phenol</td>
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<tr>
<td>k_anisole</td>
<td>0.00409</td>
<td>0.001591</td>
<td>8.404e-03</td>
</tr>
</tbody>
</table>
2,4,5-T in Fargo soil
Model with transformed formation fractions

We get a plausible confidence interval without doing an MCMC simulation
Parallel formation of metabolites

Confidence intervals only for single formation fractions (slide corrected after the meeting)


Optimized, transformed parameters:

| Parameter         | Estimate | Std. Error | Lower  | Upper  | t value | Pr(>|t|) | Pr(>|t|) |
|-------------------|----------|------------|--------|--------|---------|---------|---------|
| parent_0          | 93.1400  | 2.0660     | 79.9000| 106.3800| 47.3800 | 6.727e-35 |
| k_parent          | -3.1500  | 0.0571     | -3.2650| -3.0350| 5.4200  | 3.950e-03 | 5.905e-03 |
| f_parent_to_A1    | 0.4960   | 0.0395     | 0.4170 | 0.5750 | 2.1600  | 4.374e-02 | 2.117e-02 |
| f_parent_to_B1    | -0.1430  | 0.0300     | -0.2030| -0.0830| -5.5600 | 8.950e-01 | 8.950e-01 |
| f_parent_to_C1    | 0.0125   | 0.0360     | -1.0800| 1.1150 | 0.6234  | 9.815e-01 | 9.805e-01 |
| k_A1              | -3.4810  | 0.3412     | -4.1870| -2.7750| -13.1300| 3.575e-12 | 1.790e-12 |
| f_A1_to_A2        | 0.3210   | 0.0370     | 0.2470 | 0.3950 | 8.6800  | 1.015e-01 | 1.600e-01 |
| k_B1              | -0.2760  | 0.0600     | -0.3930| -0.1590| -6.2500 | 2.043e-06 | 1.021e-06 |
| k_C1              | -3.4020  | 0.4373     | -3.3080| -2.4970| -7.7760 | 6.025e-08 | 3.466e-08 |
| k_A2              | -3.5880  | 0.4320     | -3.6810| 1.4830 | -1.9830 | 1.370e-01 | 7.945e-02 |

Backtransformed parameters:

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<tr>
<th>Parameter</th>
<th>Estimate</th>
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<tr>
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</table>
Conceptual comparison of DFOP and SFORB

Both possible for metabolites, but with two extra parameters.
Alternative with one extra parameter

We could also use an Indeterminate Order Rate Equation (IORE) for metabolites

\[
\frac{dm}{dt} = ... - k_m m^n ...
\]

This is used in North America for parent compounds as an equivalent alternative to the FOMC model, with the possibility to test if \( n \) is different from unity.
Challenges for the future

- Better collaboration
Challenges for the future

- Better collaboration
- Improve error model
Challenges for the future

- Better collaboration
- Improve error model
- Evaluate related datasets in one step (mixed effect models)
Challenges for the future

- Better collaboration
- Improve error model
- Evaluate related datasets in one step (mixed effect models)
- Improve model comparisons (ANOVA, AIC)
Conclusions

- With gmkin + mkin, we now have a completely open sourced software toolset
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- Biphasic models for metabolites can conveniently be fitted
- The use of t-tests for parameter significance is questioned
- Plausible confidence intervals for rate constants and single formation fractions are easily available

(slide corrected after the meeting)
mkin
The R package mkin provides calculation routines for the analysis of chemical degradation data, including multicomartment kinetics as needed for modelling the formation and decline of transformation products, or if several compartments are involved.

Installation
You can install the latest released version from CRAN from within R:

```
install.packages("mkin")
```

If looking for the latest features, you can install directly from github, e.g. using the devtools package. Using `devtools` skips docs, multiple-architecture builds, demos, and vignettes, to make installation as fast and painless as possible.

```
require(devtools)
install_github("mkin", "jranke", quick = TRUE)
```

Background
In the regulatory evaluation of chemical substances like plant protection products (pesticides), blockies and other chemicals, degradation data play an important role. For the evaluation of pesticide degradation experiments, detailed guidance and helpful tools have been developed as detailed in 'Credits and historical remarks' below.

Usage
A very simple usage example would be

```
library("mkin")
example_data <- data.frame( 
  name = rep("parent", 6), 
  time = c(6, 1, 3, 7, 14, 28, 63, 91, 116), 
  value = c(85.1, 57.5, 29.5, 14.6, 5.7, 2.6, 4.1, 0.6) 
)
SFO <- mkinmod(parent = list(type = "SFO"))
SFO.fit <- mkinfit(SFO, example_data)
summary(SFO.fit)
plot(SFO.fit)
```

For more examples see the documentation or the package vignettes referenced from the mkin package documentation page.

Features

kinfit.r-forge.r-project.org/mkin_static