

Eurofins Regulatory AG

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Kinetic evaluations of environmental metabolism data for agrochemicals using R

1. Eurofins Regulatory AG
2. Modelling and risk assessment of agrochemicals in the environment
3. Kinetic evaluations of environmental metabolism data
4. Outlook

Weidenweg 15, Rheinfelden (CH)

- Part of Eurofins group
- Experience in agrochemicals, biocides, pharmaceuticals and REACH
- Complete registration dossiers on EU and member state level
- Consulting and higher tier risk assessments

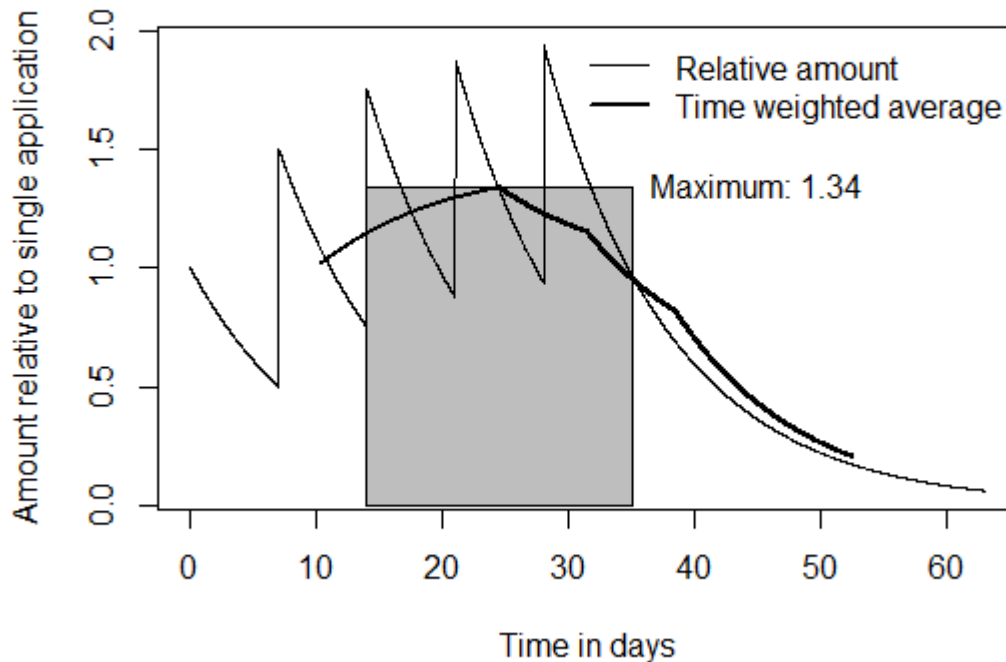
Interpret agricultural practice and environmental fate data

- Translate available information into model input
- Kinetic modelling of metabolism and degradation data

“Predict” environmental concentrations (PECs) in

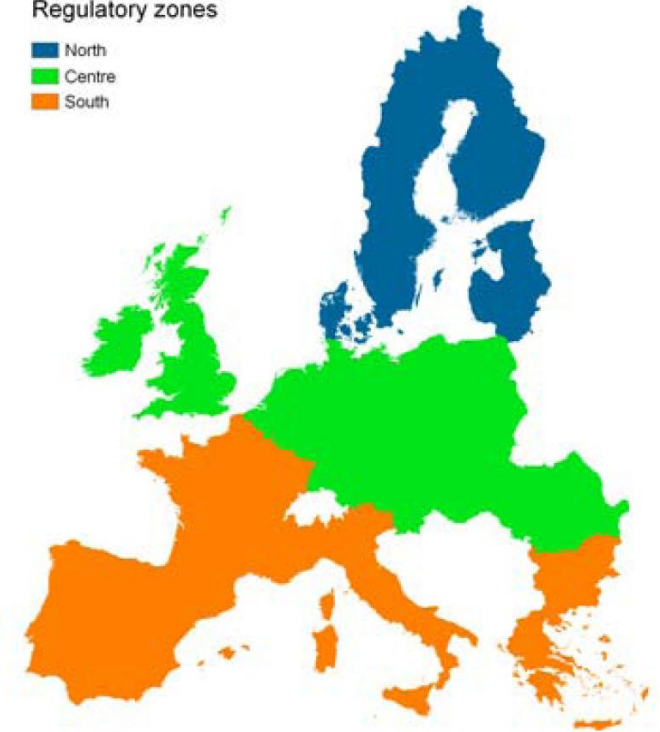
- Soil
- Groundwater
- Surface water

Basis for terrestrial risk assessments



Regulatory zones

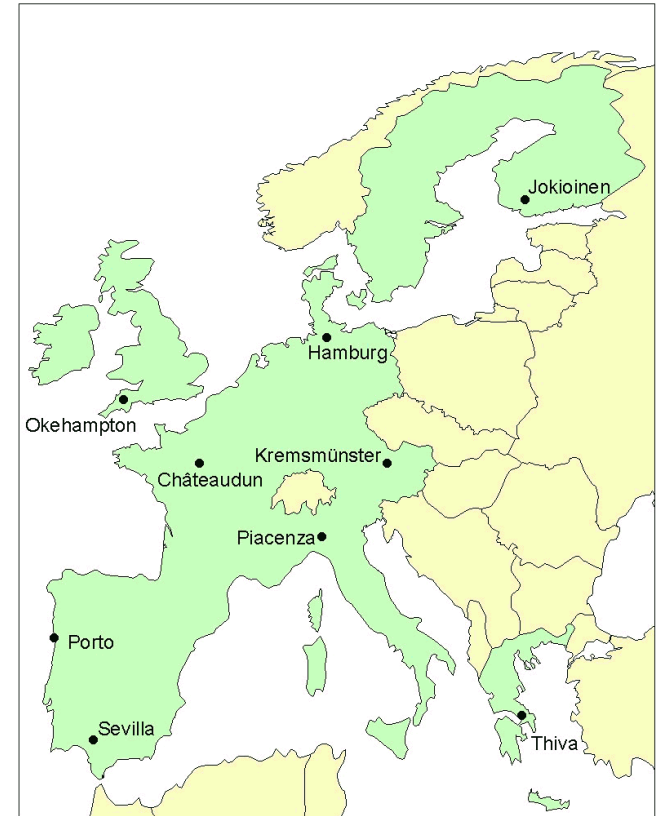
- North
- Centre
- South



PPR panel (2012) EFSA Opinion on PEC soil scenarios *EFSA Journal* 10(2) 2562

Registration if

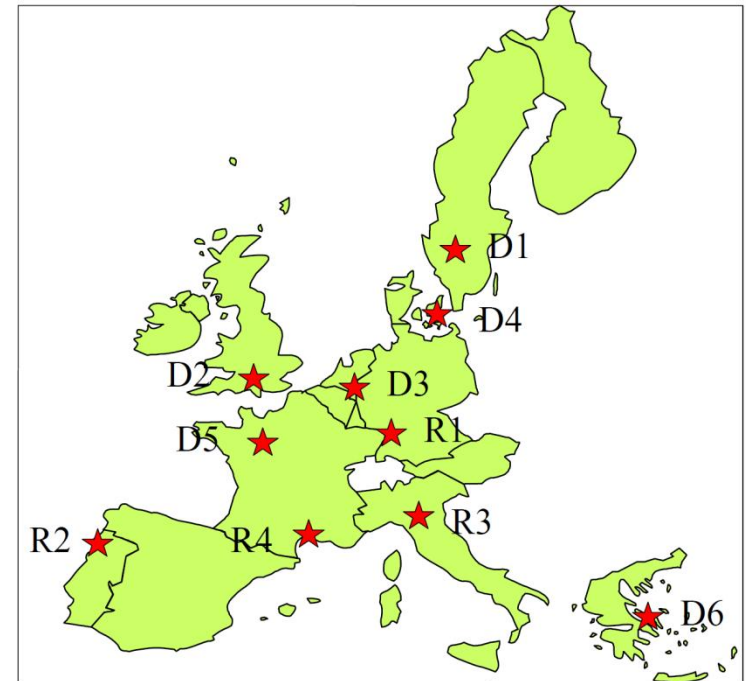
- PEC_{GW} active substance $< 0.1 \mu\text{g/L}$
- PEC_{GW} relevant metabolites $< 0.1 \mu\text{g/L}$
- PEC_{GW} non-relevant metabolites $< 0.75 \mu\text{g/L}$
- PEC_{GW} non-relevant metabolites with risk assessment $< 10 \mu\text{g/L}$



FOCUS (2009) Groundwater report 2, FOCUS (2011) Tier 1 groundwater guidance

Basis for aquatic risk assessments

- FOCUS Steps 1 to 4
- Entry via spray drift, drainage and run-off
- Concentration profiles over time
- Risk mitigation at Step 4



FOCUS (2011) Surface water scenario guidance

Status 2008

- FOCUS DegKin (Excel spreadsheet)
- KinGUI (based on Matlab runtime)
- ModelMaker

Development in R starting 2008

- kinfit
- mkin

mkin spin-offs

- KinGUII (Bayer Crop Science)
- CAKE (Tessella Software, sponsored by Syngenta)

Fitting of parent decline kinetics

- SFO, FOMC, HS, DFOP, SFORB
- Standardised report including χ^2 error level
- Plotting routines
- Validated with FOCUS example datasets in 2009

Stable release: <http://cran.r-project.org/package=kinfit>

Development versions: <http://kinfit.r-forge.r-project.org>

Fitting of multicompartment kinetics

- SFO, FOMC, HS, DFOP, SFORB for parent
- SFO and SFORB for metabolites
- Standardised report including χ^2 error level
- Plotting routines
- Validated with FOCUS example datasets
- 2011: Fitting of log-transformed rates and ilr-transformed formation fractions, model formulation with or without formation fractions
- Codebase for KinGUI and CAKE

Stable release: <http://cran.r-project.org/package=mkin>

Development versions: <http://kinfit.r-forge.r-project.org>

```
library(mkin)
LOD = 0.5
FOCUS_2006_Z = data.frame(
  t = c(0, 0.04, 0.125, 0.29, 0.54, 1, 2, 3, 4, 7, 10,
        14, 21, 42, 61, 96, 124),
  Z0 = c(100, 81.7, 70.4, 51.1, 41.2, 6.6, 4.6, 3.9, 4.6,
        4.3, 6.8, 2.9, 3.5, 5.3, 4.4, 1.2, 0.7),
  Z1 = c(0, 18.3, 29.6, 46.3, 55.1, 65.7, 39.1, 36, 15.3,
        5.6, 1.1, 1.6, 0.6, 0.5 * LOD, NA, NA, NA),
  Z2 = c(0, NA, 0.5 * LOD, 2.6, 3.8, 15.3, 37.2, 31.7,
        35.6, 14.5, 0.8, 2.1, 1.9, 0.5 * LOD, NA, NA, NA),
  Z3 = c(0, NA, NA, NA, NA, 0.5 * LOD, 9.2, 13.1, 22.3,
        28.4, 32.5, 25.2, 17.2, 4.8, 4.5, 2.8, 4.4))
FOCUS_2006_Z_mkin <- mkin_wide_to_long(FOCUS_2006_Z)
```

FOCUS (2011) Generic guidance for estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU registration, App. 7

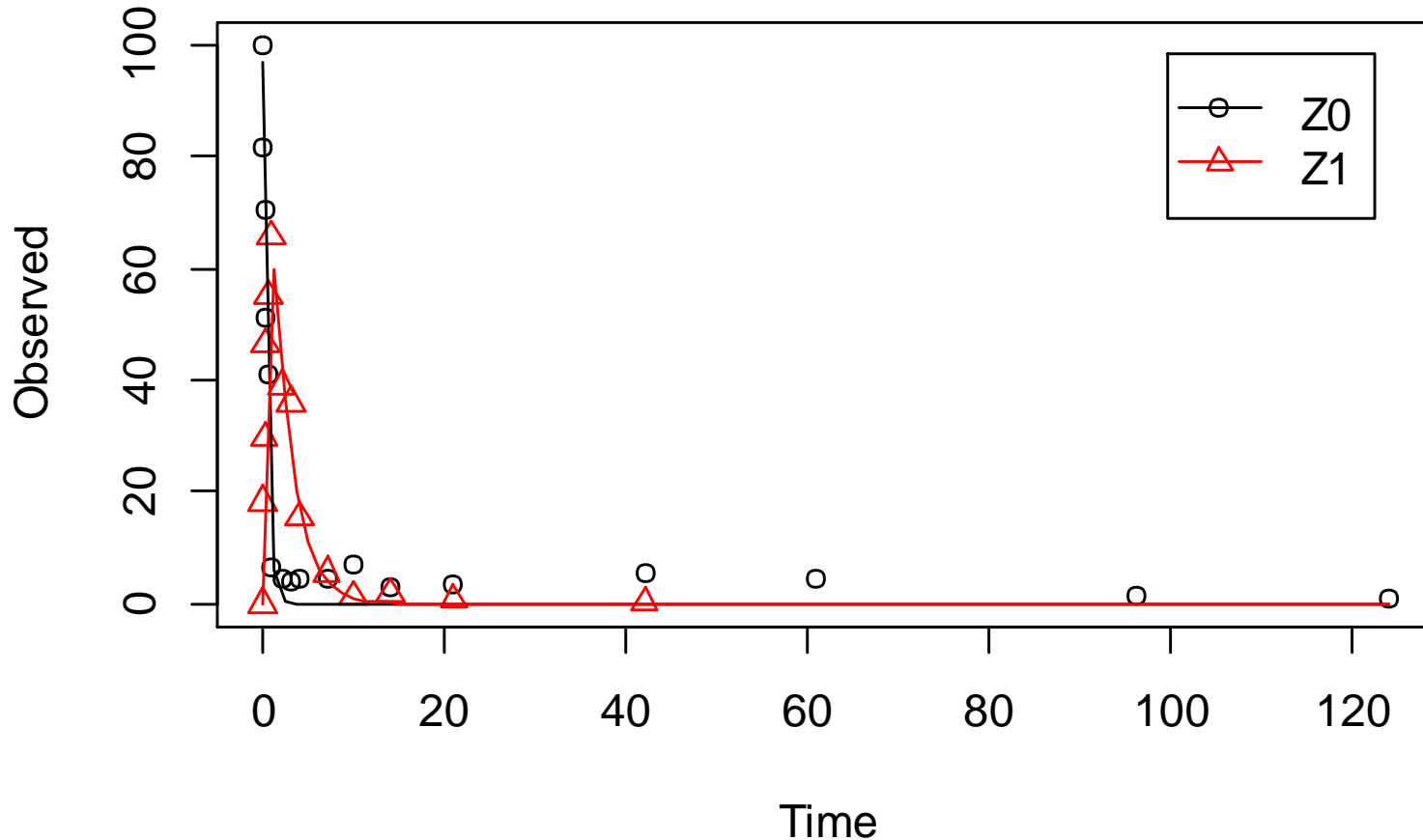
```
Z.2a <- mkinmod(Z0 = list(type = "SFO", to = "Z1"),  
              Z1 = list(type = "SFO"))
```

```
m.Z.2a <- mkinfit(Z.2a, FOCUS_2006_Z_mkin)
```

```
summary(m.Z.2a)
```

```
plot(m.Z.2a)
```

Check plot and summary



Warnmeldung:

```
In summary.mkinfit(m.Z.2a) :
```

```
Cannot estimate covariance; system is singular
```

From summary:

...

Backtransformed parameters:

	Estimate
Z0_0	97.015
k_Z0_sink	0.000
k_Z0_Z1	2.236
k_Z1_sink	0.482

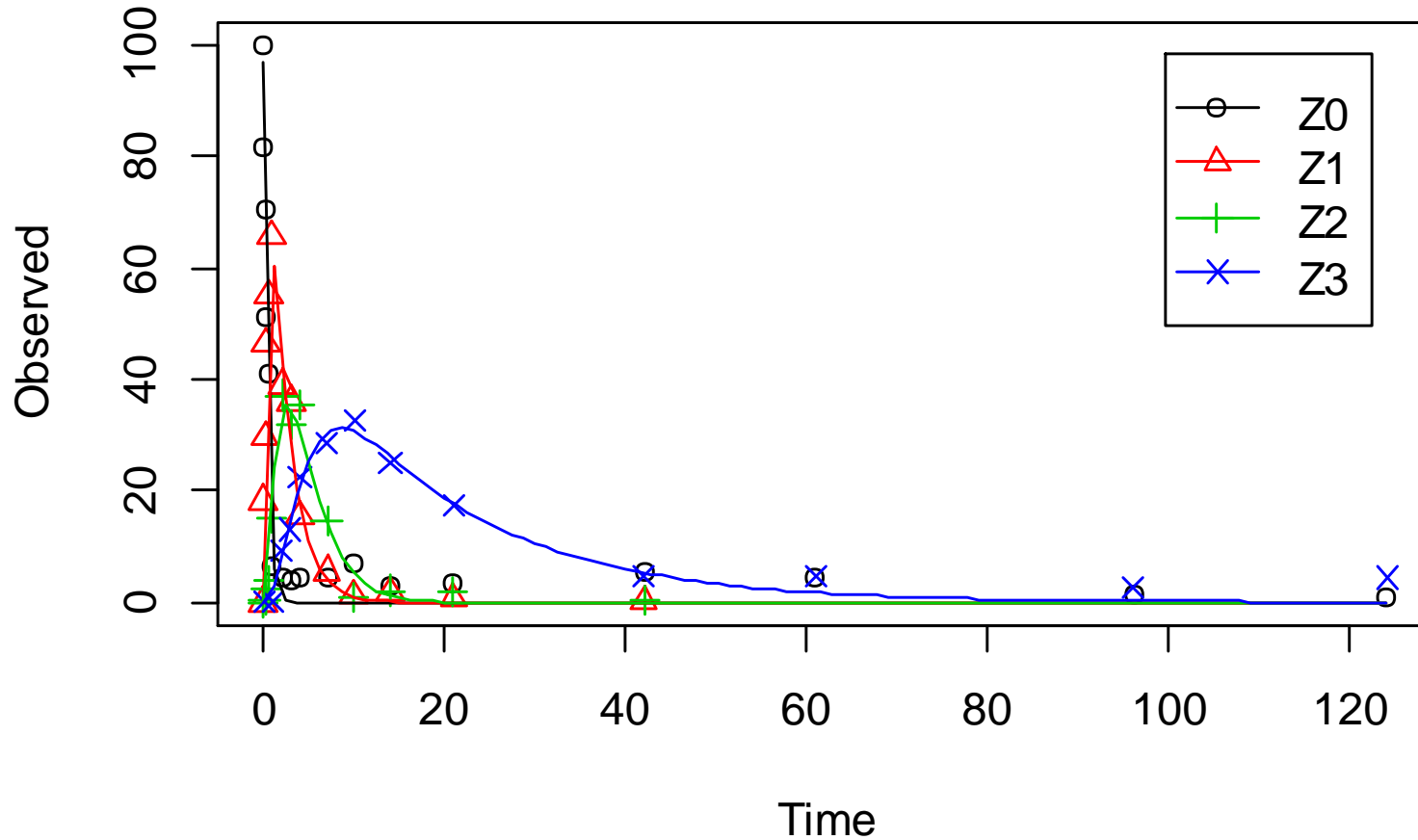
...

Refined model:

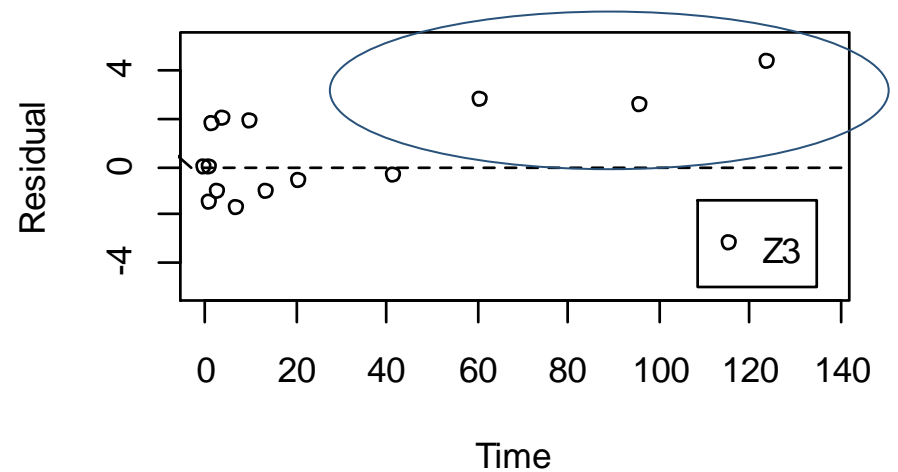
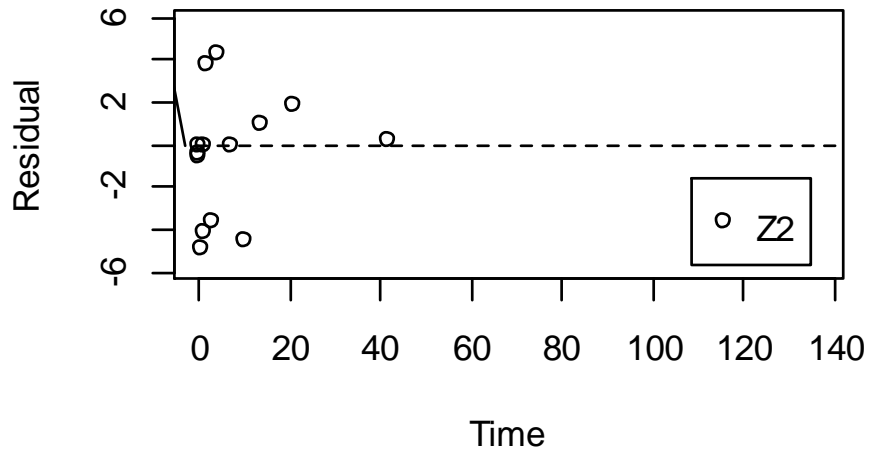
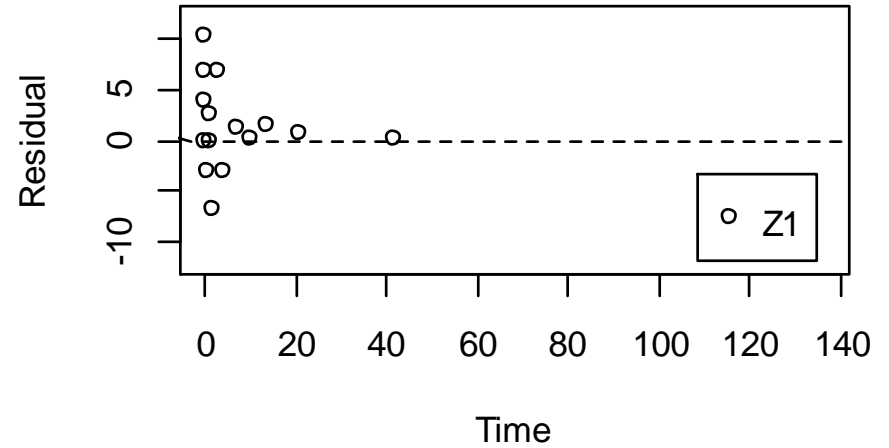
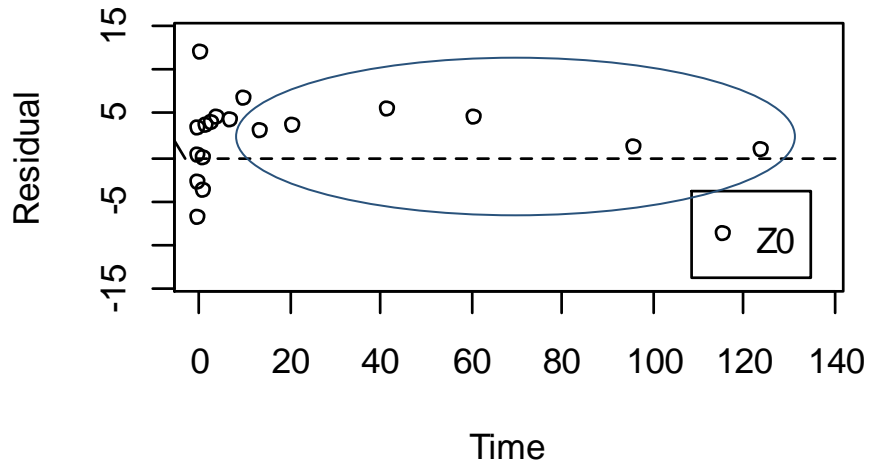
```
Z.3 <- mkinmod(Z0 = list(type = "SFO", to = "Z1",  
                        sink = FALSE),  
              Z1 = list(type = "SFO"))
```

```
Z.FOCUS <- mkinmod(  
  Z0 = list(type = "SFO", to = "Z1", sink = FALSE),  
  Z1 = list(type = "SFO", to = "Z2", sink = FALSE),  
  Z2 = list(type = "SFO", to = "Z3"),  
  Z3 = list(type = "SFO"))  
  
m.Z.FOCUS <- mkinfit(Z.FOCUS, FOCUS_2006_Z_mkin,  
  parms.ini = c(k_Z0_Z1 = 2, k_Z1_Z2 = 0.5))
```


Plot of the FOCUS proposed model



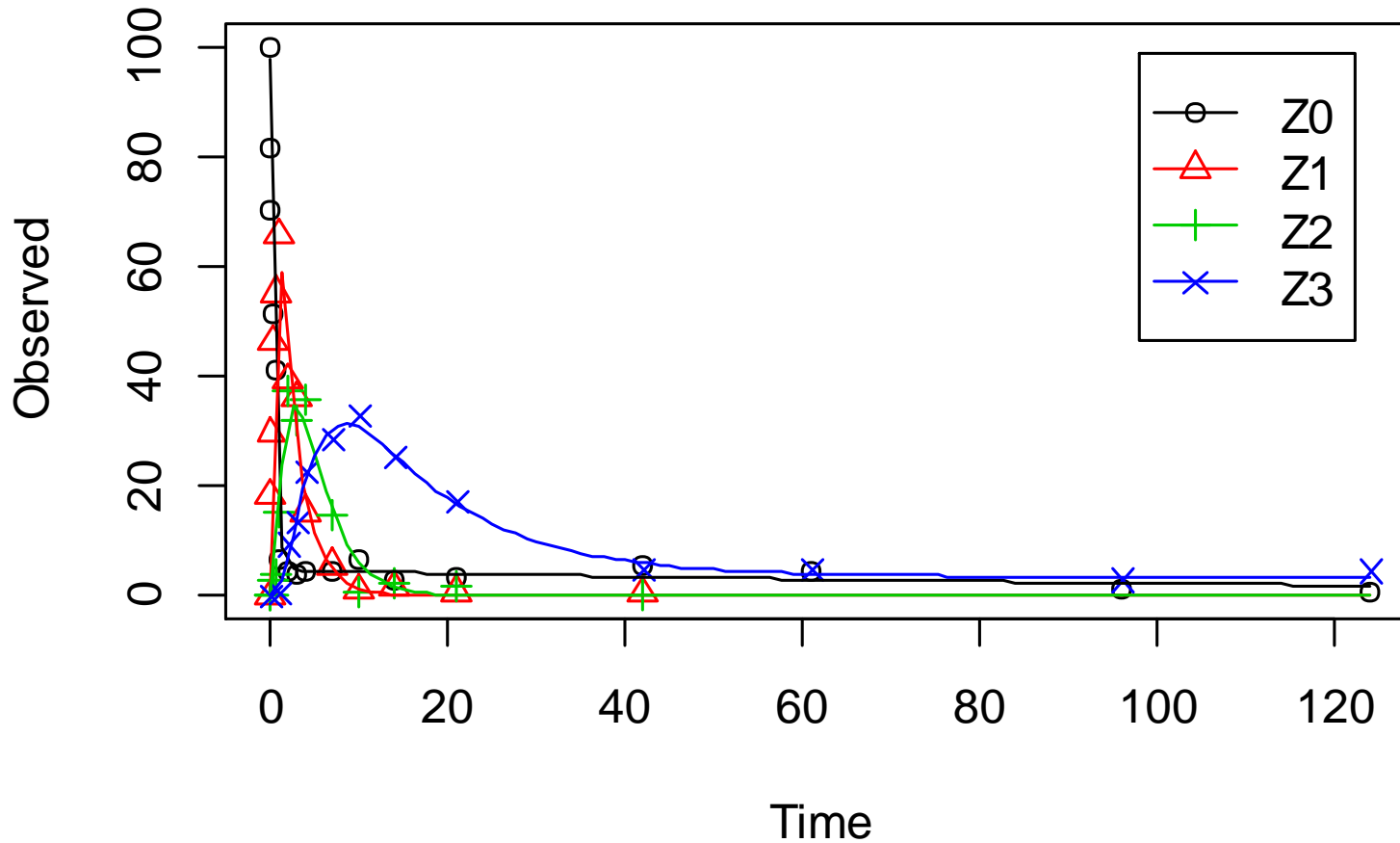
Residual plots



```
Z.mkin.5 <- mkinmod(  
  Z0 = list(type = "SFORB", to = "Z1", sink = FALSE),  
  Z1 = list(type = "SFO", to = "Z2", sink = FALSE),  
  Z2 = list(type = "SFO", to = "Z3"),  
  Z3 = list(type = "SFORB"))  
  
m.Z.mkin.5 <- mkinfit(Z.mkin.5, FOCUS_2006_Z_mkin,  
  parms.ini = c(k_Z1_Z2 = 0.2))
```

Details in: http://kinfit.r-forge.r-project.org/mkin_static/vignettes/examples.pdf

Plot of the final model



Regarding kinetic evaluations

- Further use, testing, development and advocacy of mkin
- Any help is appreciated!

Other uses of R in the field

- Fitting dose-response data using the drc package
- Automatic generation of Tables and complete Appendices in Office Documents using RDCOMClient
- Geo-referenced data
- Many day to day calculations and graphics

- RCC/Harlan team, especially Adrian Gurney for introduction to agrochemical fate modelling, Katrin Lindenberger for discussions and contributions, former line managers Barbara Minten and Andreas Wais at RCC/Harlan
- FME package by Karline Soetaert and Thomas Petzoldt
- Nonlinear regression analysis book by Douglas Bates
- René Lehmann (UBA) for isotropic logratio transformation
- R community