Standard Operating Procedure for Using the NAFTA Guidance to Calculate Representative Half-life Values and Characterizing Pesticide Degradation[1]

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[1] This document is a modified version of a draft document provided to EPA by PMRA. Personal Communication (email subject PMRA EAD draft evaluator kinetics guidance) June 21, 2012 to Rochelle Bohaty, EPA from Greg Malis, PMRA

Contents

Acronyms and Nomenclature

EPA	Environmental Protection Agency
EFED	Environmental Fate and Effects Division
NAFTA	North American Free Trade Agreement
PMRA	Pesticide Management Regulatory Authority
PestDF	Pesticide degradation fitting tool used to calculate half-lives
SFO	Single First Order
S_{SFO}	Objective function of the SFO fit to be minimized
S_c	The critical value that defines the confidence contours
S_{IORE}	Objective function of IORE fit to be minimized
S_{DFOP}	Objective function for DFOP fit to be minimized
C_{model}	Modeled value at time corresponding to C_d
C_d	data
P	Number of parameters
t_{rep}	Representative half-life for model input
K	Rate constant of decline 1/days
k_1	Rate constant for compartment 1 in1/days
k_2	Rate constant for compartment 2 in 1/days
$t_{\frac{1}{2}}$	Half-life
DT50	The time required for the concentration to decline to half of the initial value-- natural log (2)/k
DT90	The time required for the concentration to decline to 10% of the initial value-- ln (10)/k
T_{IORE}	Representative half-life for model input for the IORE model
DFOP	Double first-order in parallel
IORE	Indeterminate order rate equation
DERs	Data Evaluation Records
TFD	Terrestrial field dissipation
LOD	Limits of Detection
LOQ	Limits of Quantification
C_0	Initial pesticide concentration at time zero
C_t	concentration at time t
FOMC	First Order Multi-Compartment
FTT	Fate Tech Teach

1   Introduction

In 2011, EPA's Environmental Fate and Effects Division (EFED) in the Office of Pesticide Programs and Canada's Pesticide Management Regulatory Authority (PMRA) formalized the NAFTA degradation kinetics project. This document provides the results of the degradation kinetics project and describes a general approach for calculating and selecting representative half-life values from soil and aquatic transformation studies for risk assessment and exposure modeling purposes. As highlighted in this NAFTA guidance[2], several tools are available to assist EFED and PMRA evaluators in conducting their individual environmental fate study reviews and risk assessments, including Excel, Sigma Plot, and the PestDF Tool[3]. **APPENDIX A** provides a step-by-step instruction manual explaining how to use the PestDF Tool to calculate half-lives based on criteria defined in the NAFTA guidance, while **APPENDIX B** is a quick reference guide for using PestDF. The NAFTA degradation guidance is under evaluation for a six-month period, after which time modifications to the process may occur.

2   Background

The rate of transformation of pesticides in the environment is commonly described using first-order kinetics, often referred to as single first-order (SFO). The first-order representation is convenient because the rate is summarized with a single parameter (the rate constant, k), and the rate of transformation is independent of the initial concentration. The half-life, $t_{1/2} = \ln(2)/k$, indicates the time required to reduce the concentration by 50% from any concentration point in time. It is an intuitive way to express the rate of decline of a first-order degradation. In contrast, the DT50 is the time required for the concentration to decline to half of the initial value. For non-first-order decay, the time to reach half the concentration from any other concentration point on the curve will be different.

EFED exposure models require first-order inputs for pesticide transformation processes even though pesticide transformations in soil and aquatic systems often do not follow a single exponential decline pattern. For this reason, the NAFTA guidance introduces a "representative half-life (t_{rep})," to estimate an SFO half-life for model input from a degradation curve that does not follow the SFO equation. The procedure takes into consideration the frequent observation that pesticides can degrade fast initially and then slowly as times passes, much more so than a first-order representation would predict. The representative half life considers both the initial and the slower portions of the decline and is not necessarily numerically similar to the value of the DT50.

PMRA developed a tool termed PestDF for calculating and selecting the representative half-life value based on the NAFTA guidance. The tool considers three transformation models: SFO, double first-order in parallel (DFOP), and indeterminate order rate equation (IORE) and a set

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[2] *Guidance for Evaluating and Calculating Degradation Kinetics in Environmental Media*, Health Canada, U.S. Environmental Protection Agency, December 21, 2011.
[3] Kennedy, I.. *PestDF a R software compatible script (filename 0.8.4.zip)*; Health Canada, U.S. Environmental Protection Agency, May 10, 2012. The file is now being identified as PestDFV1.zip.

criteria for selecting parameters. Based on the number of fitted parameters, SFO is the simplest of the three models, while DFOP is the most complex. The model descriptions are provided in **APPENDIX C**.

This document provides guidance on how to prepare data for kinetic analysis and how to report necessary kinetic parameters in Data Evaluation Records (DERs) and exposure assessments. Guidance is also provided on how to characterize rates of degradation in these documents.

3   Data Preparation

Table 1 summarizes the suggested strategy for preparing data for kinetic analysis, while the subsections below are a detailed discussion of these suggestions.

Table 1. Summary Table for Data Preparation

Issues	Comments
Minimum Number of Data Points	Five or more data points are required to fit all three standard models.
Replicates	Independent replicates[1]: use individually Analytical replicates[2]: use average
Measured Values are < LOQ and < LOD	Omit all samples < LOD (unless later samples > LOD). When a <LOD has detections later in sampling, set the value equal to the LOD. Set samples between LOD and LOQ to measured value, or 0.5 (LOQ + LOD) if the value was not reported.
Outliers	Do not remove outliers. When outliers are suspected, run kinetic models with and without the outlier to assess the influence on half-life analysis.
Time Zero Concentration	Use the measured concentration at time zero, not the estimated application rate.
1 Individual replicates are samples taken for separate test systems (*i.e.*, two different replicate experiments). 2 Analytical replicates are aliquots taken from an individual test system at the same time and extracted; or one aliquot taken from a sample at one time, extracted, and the extract run through the analytical method multiple times.	

3.1   Minimum Number of Data Points

For the use of the transformation kinetic models described here (SFO, IORE and DFOP), the number of available data points should be at least one greater than the number of estimated parameters for the equation to be mathematically solvable. The DFOP model uses four parameters and thus requires a minimum of five data points; the SFO and IORE models require fewer. Datasets with four data points will cause DFOP analysis to fail, but can still be used to determine if the SFO model is acceptable. In practice, more data points may be needed to avoid numerical problems in curve-fitting. Therefore, it is recommended that at least five data points be used for fitting all of the models.

3.2   Replicates

Samples taken from independent (separate) test systems at the same time (independent replicates) should not be averaged before conducting the data analysis. All the individual data points should be included in the curve-fitting. In contrast, analytical replicates (repeated analyses of a single sample or aliquots taken from the same test system) are not true independent replicates and should be averaged and treated as one value during the data analysis.

Data from independent experiments (*i.e.*, those conducted under the same conditions such as soil, temperature, moisture, soil incubation prior to pesticide application, *etc.*) should be combined in a single dataset. For example, data from two test systems in the same study on the same pesticide, conducted on the same soils with the same conditions and pesticide application procedure, but different radiolabels, should be combined into a single dataset unless data from the two show visibly different concentration profiles. If two such studies do show different concentration declines, then the reason for the difference should be investigated and reported.

3.3   Values Below the Limits of Detection (LOD) and Quantification (LOQ)

In laboratory studies, measurements near the end of the study may occur below the LOQ or LOD; values below LOQ occurring before the DT90 indicate an inadequate analytical method, and the study may be considered questionable. When a value is measured as less than the LOQ or LOD and is followed by detections, a default zero value should never be used. Instead, the value may be assumed to be at the LOD. The following rules for handling values <LOD or LOQ can be used:

- Omit all samples < LOD unless later samples > LOD. When a <LOD is observed with detections later in sampling, set the value equal to the LOD.
- Set samples between LOD and LOQ to the measured value, or 0.5 (LOQ + LOD) if the value was not reported.

3.4   Outliers

Data points that appear to be "outliers" should not be removed from the dataset. Analysis of the data with and without the "outlier" should be completed to investigate the impact that the "outlier" has on the dataset. Outlier examples and the corresponding kinetic analysis should be brought to the Environmental Fate Tech Team (FTT) for discussion.

3.5   Time Zero Samples

The initial pesticide concentration at time zero (C_0) in the study should be the measured value at time zero, and not the calculated initial concentration based on the mass applied. If there are measured transformation products at time zero, the total radioactive residues at time zero are used, unless there is a reason to believe these initial transformation products are impurities.

3.6 Transformation Products

The models included in the NAFTA guidance are designed for use on a single compound degrading from an initial spike. They are not for use on transformation products, which have the transient feature of a rise and fall in concentration from the formation from the parent compound and then subsequent decay.

Guidance is currently under development for modeling transformation products. For more information on modeling transformation of degradation kinetics see the white paper and minutes of the 2008 Scientific Advisory Panel discussing *Pesticides with Persistent, Bioaccumulative, and Toxic Characteristics (USEPA, 2009).*

4 Data Interpretation

4.1 Determining the Representative Half-life Value

The NAFTA degradation kinetics guidance document is used to determine the representative half-life value for modeling and is either a one- or two-step process.[4] The first step is to determine if the SFO model can be used to determine the representative value. If it cannot be used, the second step is to generate a t_{rep} value using the IORE or DFOP model. The t_{rep} (representative half-life value for modeling) for IORE is $t_{IORE,}$ while the t_{rep} for DFOP corresponds to the slow $t_{1/2}$ (*i.e.*, the half-life corresponding to the slower rate constant for DFOP). Further discussion of this topic is provided in the NAFTA final report (NAFTA, 2011). A flow chart showing the decision tree is shown in **Figure 1**.
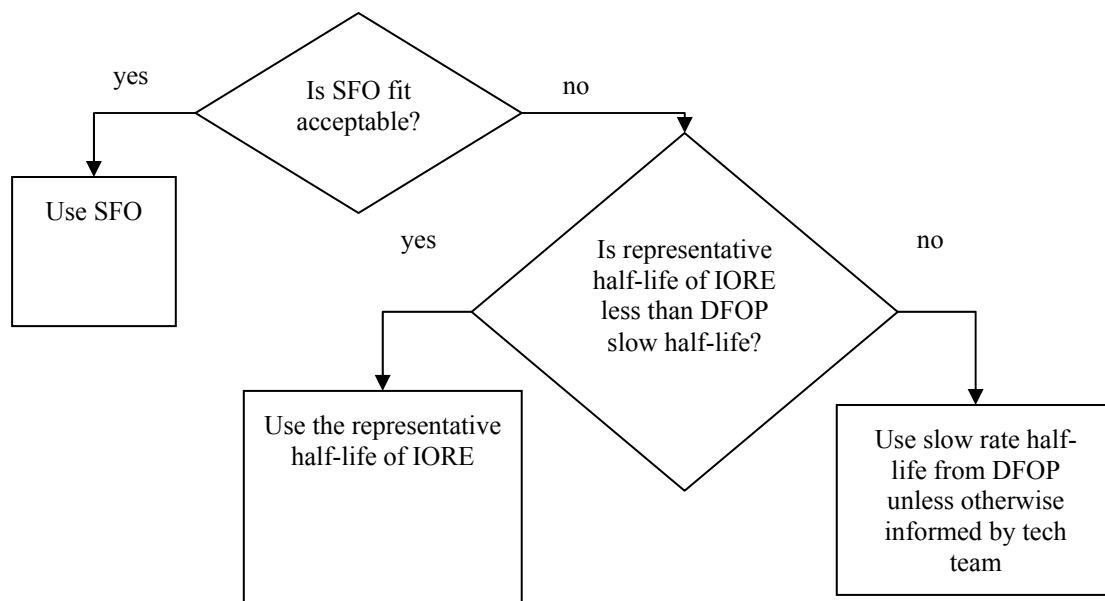

Figure 1. Flow Chart Showing the Decision Process for Determining tR

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[4] For some datasets the representative half-life value may be derived from a model that is not the best fit model. The NAFTA degradation kinetics guidance is not intended to identify a best fit model but rather to determine a representative half-life value for developing model input values.

7

As a first step, the S_{SFO} value (objective function of the SFO fit to be minimized[5]) is compared with the S_C value (critical value that defines the confidence contours based on S_{IORE}[6]). If the S_{SFO} value is smaller than the S_C value, it falls within the confidence interval for IORE parameters. In this case the SFO model is adequate, and there is no need to conduct additional analysis. The SFO half-life can be used to estimate a final model input.

When the SFO value is not adequate, the representative half-life (either t_{IORE} or the slow $t_{1/2}$ of DFOP, whichever is shorter) is used as a model input (or used to calculate the model input value). If S_{SFO} is larger than S_C, then the SFO model is not used to determine the representative model input value. The second step is conducted by selecting the smaller of the two representative half-life values from the IORE and DFOP models, t_{IORE} and the slow $t_{1/2}$.

Again, the slow rate for DFOP (slow $t_{1/2}$) and the t_{IORE} values may not reflect the DT50 for the IORE, DFOP, or SFO equations, especially for chemicals that deviate severely from first-order representation. Instead, these values are used to determine a conservative input value for modeling, which uses an SFO equation. For exposure modeling, use the selected t_{rep}, **NOT** the calculated DT50 values from IORE or DFOP.

The analysis in this guidance does not provide support for making claims that one model is better than another and should not be used to determine a best fit-model or representative half-life values in place of those recommended in the approved NAFTA kinetic guidance.

As mentioned in the introduction section of this document, the NAFTA guidance document is under evaluation for six months and may be revised after this period of time. The decision criteria presented in **Figure 1** may need to be revised if the NAFTA guidance is updated.

4.2   Characterizing the Data in the Data Evaluation Records and Risk Assessments

What you need to report depends on the type of review you are developing. For EFED reviews, report the t_{rep} (along with the model the t_{rep} is derived from *e.g.*, SFO half-life, T_{IORE}, or the value estimated based on the DFOP slow rate) with a qualitative characterization of the degradation curve. Details or values to report are included in the data evaluation record templates (USEPA, 2012). For reviews, which will be shared with others (*e.g.*, global joint reviews), additional details may need to be reported. Two different DER reporting tables are included in **APPENDIX D** as examples. An example table for reporting results in risk assessments is also available in **APPENDIX D**.

In general, risk assessors should explain the degradation kinetics in descriptive words (*e.g.*, 50% of the chemical degraded by time x, the transformation of chemical does not follow SFO kinetics) in risk assessments and DERs. The qualitative description can include any properties of the curve that can be considered important. For data which fits the SFO model well, the description can consist of a simple statement that it fits the SFO model and the SFO half-life is

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[5] S_{SFO} is the residual sum of squares for the SFO model.
[6] S_{IORE} is the residual sum of squares for the IORE model.

used in the model input estimate. For data which does not fit the SFO model, information can be gleaned from the parameters of the IORE and DFOP models. For example, the IORE *N* parameter (which is the "order" of the nth-order rate equation and is a model parameter and may not be equivalent to the reaction order[7]) indicates how far the data has deviated from an SFO curve. A value of *N*=1 is equivalent to the SFO model, and higher values of N demonstrate there is slowing of the degradation rate at later times.

To characterize metabolism and abiotic experiments, the results of the model fits (SFO, IORE, and DFOP) are compared to empirical measures of degradation. The empirical measures used are the "DT50 interval" (time interval in which concentration fell below 50% of initial concentration) and the "DT90 interval" (time interval in which concentration fell below 10% of initial concentration).

The observed DT50 and DT90 values should be compared with DT50 and DT90 values from the models included in the NAFTA guidance. Results of this comparison should be reported in a table summarizing the degradation kinetics in the DER (examples provided in **Appendix D**). If the risk assessor has concerns regarding the characterization of a given dataset, the dataset and corresponding kinetic analysis should be brought to the FTT. *Note: The NAFTA guidance is intended to provide a consistent process for selecting a representative half-life, value and while statistical methods are used in the process, it is not the intent of this guidance to select a statistically best fit model.*

4.3   Exposure Modeling

For all exposure modeling, the current model input parameter guidance should be followed.

5   Precautions and Additional Information

Occasionally a program may give unreasonable results for one or more curve fits. This may be due to the way that it performs calculations, or it may be due to the nature of the degradation data. When the results from a regressed curve appear unreasonable, the results should be brought to the FTT for discussion. Examples are discussed below.

5.1   Kinetic Analysis

5.1.1   Model Parameters

Negative k values should never be used. The DFOP model, for example, sometimes fits best with a negative slow degradation rate. In general, this indicates that degradation has slowed by the end of the study to the point where the compound is stable. A negative IORE *N* value indicates that degradation is accelerating, which in most cases indicates poor data quality. When the IORE N is less than 1, it may not be appropriate to use IORE as the model input as it predicts a DT50 that is faster than the SFO half-life. In either case, half-life values obtained from a model with negative parameters are not reported. Studies results which show a negative IORE *N* value may be brought to the FTT.

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[7] The power to which the concentration of a reactant is raised in a rate law equation.

5.1.2 Analysis Not Completed Correctly

A visual inspection of the graph should be completed in order to determine whether the model actually ran correctly. If the tool used for nonlinear regression does not complete the analysis for one or more of the models correctly, another tool may be used for the regression. When this situation occurs, consult the FTT.

5.1.3 IORE Not Fitting Well

The method for deciding whether or not the SFO model provides an adequate fit depends on a comparison with the fit from the IORE model. Occasionally, IORE itself does not fit the data and a comparison indicating SFO is close to IORE really means that both fit poorly. The IORE model usually fits poorly when the data shows a rapid initial decline followed by a slower but consistent decline. Cases such as this should be brought to the attention of the FTT.

5.2 DT50 Not Observed

During the six-month evaluation period, if a DT50 is not observed during the course of an experiment, the kinetic analysis should be brought to the FTT for consultation.

5.3 Log Transformation

In the past, half-lives were calculated using linear regression on the natural log of the concentrations measured in an experiment. The data should not be transformed as it is not part of the NAFTA guidance.

5.4 Global Review Considerations

5.4.1 Converting IORE to FOMC and FOMC to IORE

The nth-order rate equation (IORE) used by PMRA and US EPA/OPP is mathematically equivalent to the first-order multi-compartment (FOMC) model used in the EU and other jurisdictions following the FOCUS guidelines. In global joint reviews, it may be necessary to report FOMC results with IORE outputs. The equations to calculate the FOMC α and β parameters from IORE C_0, N and k parameters are provided in **APPENDIX C**.

It may be necessary for global reviews to report the parameter χ^2.

5.5   Additional References

Draper, N. and H. Smith (1981) *Applied Regression Analysis*, John Wiley & Sons, New York.

Motulsky H. and A. Christopoulus (2003) *Fitting Models to Biological Data Using Linear and Nonlinear Regression. A Practical Guide to Curve Fitting*, Graph Pad Software Inc. San Diego, CW, www.graphpad.com.

NAFTA. 2011. *Guidance for Evaluating and Calculating Degradation Kinetics in Environmental Media*. December 2011. NAFTA Technical Working Group on Pesticides. Available at http://www.epa.gov/oppfead1/international/naftatwg/guidance/degradation-kin.pdf (Accessed June 12, 2012).

USEPA. 2009. *SAP Minutes No. 2009-01. A set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Selected Issues Associated with the Risk Assessment Process for Pesticides with Persistent, Bioaccumulative, and Toxic Characteristics. October 28-31, 2008., January 29, 2009*. Available at http://www.epa.gov/scipoly/sap/meetings/2008/102808_mtg.htm (Accessed July 9, 2009).

USEPA. 2012. *Guidance for Reviewing Environmental Fate Studies.* Environmental Fate and Effects Division. Office of Pesticide Programs. United States Environmental Protection Agency.

APPENDIX A

PestDF Instruction Manual

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October 3, 2012

Installing and Using PestDF

PestDF is a useful tool for estimating degradation inputs for regulatory transport models. Other tools commonly used in EFED that are also suitable for use include Sigmaplot and MS Excel. The current filename for PestDF is xxDeg_0.8.4.zip.

Abiotic studies (hydrolysis and phototransformation), which generally follow SFO and the SFO model should typically be chosen to describe the transformation kinetics. However, in some cases[8], if the data for these studies deviate beyond the restrictive NAFTA selection criteria for SFO, the DFOP and IORE models can be selected. For such cases, users should examine the data to understand why this deviation is occurring. Users should bring these cases to the attention of the Fate Tech Team (FTT) for review.

For **biotic studies**, all three kinetic models are considered. The following sections explain how to format the data for PestDF and how to use the results from PestDF fitting routines to select the appropriate model fit and representative half-life values (t_{rep}) for the dataset.

Installation and Setup of "R"

Step 1: Download "R". Evaluators will need to create an R folder on their computer to save the executable R file. The executable file is distributed by the FTT or can be downloaded free from the internet. There are a number of sources of R provided at http://www.r-project.org/.

Step 2: Install Current Version of PestDF Package. Evaluators will need to install the PestDF package in order to access necessary functions for running the analysis in a more automated fashion. The zip file for the current version of PestDF is available through the FTT.

Save the zip file within your "R" file. Within the "R console," click "Packages" on the top menu bar and select "Install package(s) from local zip files…" from the dropdown menu. Use the browser to locate the desired zip file.

Once the PestDF package has been installed on the "R Console," it will not need to be installed again. In addition, when updating the version of PestDF, the "R" program will automatically over ride the previous versions of the package.

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[8] Examples include: experimental error (*e.g.*, sampling errors) or pesticide sorption to either glass or soil during the course of the experiment.

Tool Use

Step 1: Data Entry. Data will need to be in column format with a title row AND a dataset title (see **Table A.1**). Excel can be used to format the data. Be sure to enter a title describing the data. This may include the chemical name, the soil name, MRID number or other information useful for identifying the data. The title is limited to a single line. Enter two descriptive column headings under the title, (*e.g.*, "Time" and "Concentration" or "percent applied"). Then enter data into two columns: the first column should contain sampling times, and the second column should contain concentrations as shown in **Table A.1**. The units for the time and concentration values do not matter, but results from PestDF will be in the time units entered. If the time is entered in days, then t_{rep}, rate constants (k), as well as DT50/DT90 values will all have units of days (or days^{-1}). As explained in the data handling section, enter all available true replicate[9] data. Data do not have to be sorted and placed in any specific order.

If a title is not included, R will use a default title for the graph. If a title (header row) is not included, R will use the first row of data as the header and not include the data in the analysis. R may not run correctly if special characters such as %, &, ^, etc. are used in the title rows. Additionally, PestDF does not run if a zero is reported as the percent applied or concentration.

Table A.1. Format Example for Data Used in PestDF Package Analysis

ExampleRun Chem X in Soil Y MRID 555555

Days Post treatment	Percent Applied
0	95
0	95
10	99
10	88
20	78
20	77
40	72
40	72
60	66
60	64
80	65
80	69
122	64
122	59
241	72
241	58
367	43
367	50

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[9] True replicates are data points from separate test systems.

13

Step 2: Running PestDF. Load the following libraries (see below) by copying ("Ctrl" and "c") and pasting ("Ctrl" and "v") into the "R console".

library(grid)
library(xxDeg)

Type or copy ("Ctrl" and "c") and paste ("Ctrl" and "v") the commands into the R console and click "enter" on the keyboard to run the command. The commands are run separately.

The libraries contain the necessary functions to run the analysis and create the graph. You will need to load these libraries each time you start a new "R" session; however, the user will not need to reload the PestDF package. An alternative to loading the library is to select "load package" from the "Packages" drop down menu and selecting "grid" and "xxDeg."

Step 3: Load Data and Fit the Models. Copy the data from source such as Excel onto the clipboard by highlighting the data table formatted as described in **Step 1** and pressing "Ctrl" and "c" at the same time or by using edit and copy commands. Return to R and run the fit and plot command shown below in R when the data is on the clipboard by typing or copying ("Ctrl" and "c"), paste ("Ctrl" and "v") it into the R console, and press "enter." Selection of the data source should be completed before clicking "enter" as the data needs to be copied to the clipboard in order to process.

fitandplot("clipboard")

The script will run automatically and details of the analysis will display in the "R Console." A new window will appear with the graphic representation of the kinetic analysis (see **Figure A.1**). This figure highlighted in red text will be the appropriate representative half-life value for use in modeling as described in the NAFTA degradation kinetics guidance. The results can be saved by clicking "File" and selecting "Save as" from the drop down menu. The image will be saved as it appears on the screen. Make sure the results of the analysis are not cut off in the window. If results are cut off, expand the window until the entire image is visible.

ExampleRun Chem X in Soil Y MRID 555555

Days Posttreatment	Percent Applied
0	95.0
0	95.0
10	99.0
10	88.0
20	78.0
20	77.0
40	72.0
40	72.0
60	66.0
60	64.0
80	65.0
80	69.0
122	64.0
122	59.0
241	72.0
241	58.0
367	43.0
367	50.0

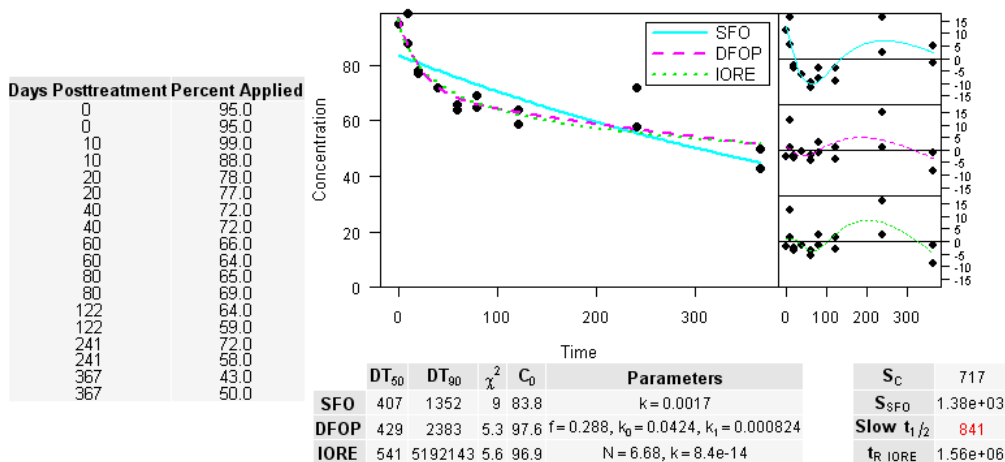|	DT50	DT90	χ²	C0	Parameters		
SFO	407	1352	9	83.8	k = 0.0017	Sc	717
DFOP	429	2383	5.3	97.6	f = 0.288, k0 = 0.0424, k1 = 0.000824	SSFO	1.38e+03
IORE	541	5192143	5.6	96.9	N = 6.68, k = 8.4e-14	Slow t1/2	841
						tR IORE	1.56e+06

14

Figure A.1. Example Graphic Representation of Kinetic Analysis Using R and PestDF

Most values are reported in data evaluation records, and exposure assessments can be found in the main table (bottom of **Figure A.1**) of the PestDF output.

Precautions and Additional Information

As mentioned in the main document, it is possible that programs, including PestDF, may occasionally give unreasonable results for one or more curve fits. This may be due to the way that it performs calculations, or it may be due to the nature of the degradation data. Any time the results from PestDF appear unreasonable, the results should be brought to the FTT for discussion.

Output Interpretation

For output, PestDF draws a set of plots and tables (**Figure A.1**) divided into five parts.

1. The top center of the output is a plot of all three curve fits (SFO, DFOP and IORE). The left hand side is a table of raw data. This data should be used to verify the values used in fitting.

2. The plots on the upper right hand side show the residuals corresponding to the three curve fits (SFO, DROP, and IORE). A smooth curve is drawn over the individual points to assist in recognizing any patterns in the residuals. Better fits are indicated by the lack of a pattern and smaller residuals.

3. The table in the bottom center summarizes the fitted parameters and a chi squared percent error for each of the three plots. This table contains information about all three model fits. The DT50 for the SFO model is used to estimate a model input value if the SFO model is deemed acceptable. Other DT50/DT90 values and parameters may be useful or needed for reporting in global joint review summary tables and for descriptive characterization (see **Section 4.5**).

4. The right most column in the table contains two separate pairs of values. The top pair is a sum of squares for the SFO model (S_{SFO}) and a critical value (Sc). These values are compared to determine if the SFO model is adequate (see NAFTA guidance document). The bottom two values contain the representative half-life values (*tR*) determined from the DFOP and IORE curves, which are used as a representative model input value when the SFO fit is deemed unsuitable. The value from DFOP, labeled "Slow t1/2," is a half-life determined from the slow (k_1) degradation rate from the DFOP model. The value from IORE, labeled "tR IORE," is the half-life of an exponential curve passing through the DT90 of the IORE model fit (*i.e.*, IORE DT90/3) and labeled T_{IORE}[10] in Appendix B.

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[10] T_{IORE} is the label used in the "*Guidance for Evaluating and Calculating Degradation Kinetics in Environmental Media.*"

5. After the run has been completed. Statistical data can be observed using the statistics command (see **Step 4** above). The statistical data is automatically saved to the clipboard when the analysis is complete and can be viewed by pasting ("Ctrl" and "p") the data into Excel.

The output figure can be saved by selecting "file" and "save as" or copying the figure to the clipboard by selecting "file" and "copy to clipboard." The image will be saved as it appears on the screen as discussed in **Step 3**.

APPENDIX B

Quick Reference Guide for Using PestDF

Prepared by: Katrina White
October 3, 2012

PestDF package (current filename xxDeg_0.8.4.zip) is available at (G:\Teams and Panels\Tech Teams\Fate-Chemistry(FTT)\Current Projects\Degradation Kinetics Case Studies\R program). The number in the filename may change over time for different versions.

Current version of R (available from http://www.r-project.org/)

1. Install R (only needs to be completed once)
2. Open R from start menu
3. Go to Packages>Install package(s) from local zip files>choose directory>xxDeg_0.8.4.zip or current filename>Open
    o This step only needs to be completed when you are loading a new package. Once it is installed, you can skip this step.
4. Type library(grid) into R console and press enter
5. Type library(xxDeg) into R console and press enter
6. Put data in the appropriate format, row for table heading, row headings, then data.

Table Title	
Days	**Data**
0	101.4
0	97.4
5	93.0
5	92.0

7. Copy data onto the clipboard (*e.g.*, highlight data and press ctrl and c at same time)
8. Type fitandplot("clipboard") into the R console and press enter
9. A new window will open with results. Resize it so that all information is visible. If the software does not work, remove any special characters from the headings and remove zero values from the data.

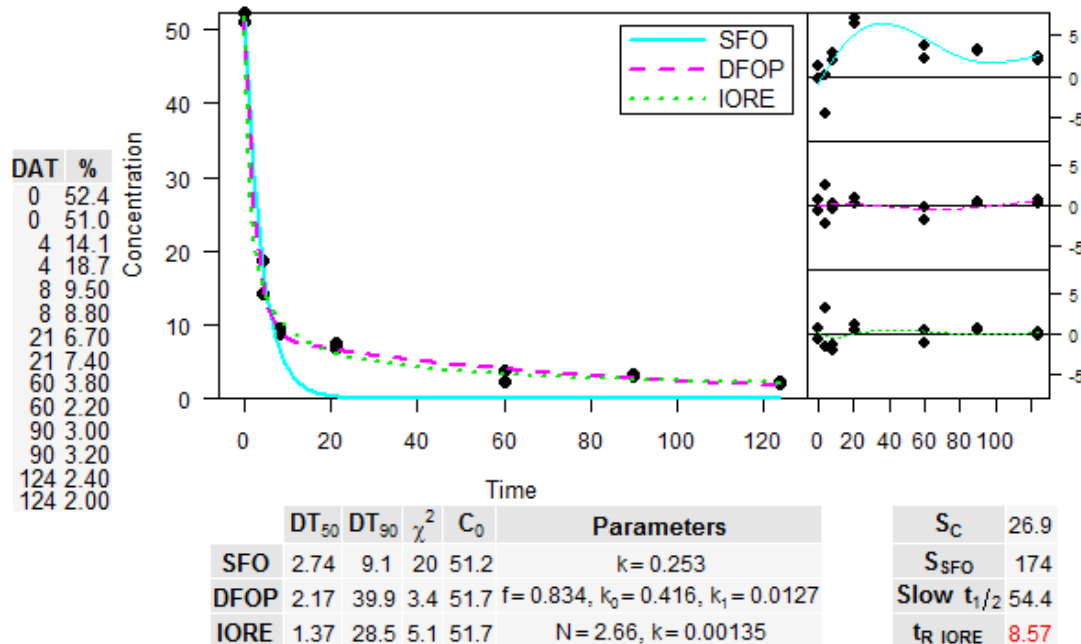   EFED guidance on handling zeros in datasets is as follows and discussed in the "*Standard Operating Procedure for Using the NAFTA Guidance to Calculate Representative Half-life Values and Characterize Pesticide Degradation*":
    • Omit all samples < LOD (unless later samples > LOD, see text).
    • Set samples between LOD and LOQ to measured value, or 0.5 (LOQ + LOD) if the value was not reported.

- When a reported <LOD has detections later in sampling, set the value equal to the LOD.
- No data points should be dropped from a dataset to achieve a better fit.

10. Save the file in the format you wish. It is easiest to copy (ctrl c) and paste (ctrl v) the image next to the data within the Excel or Word file from which the data were copied.

11. On the R console if you click the "up arrow," R will place the last command entered into R.

Example Results:

anaerobic aquatic

DAT	%
0	52.4
0	51.0
4	14.1
4	18.7
8	9.50
8	8.80
21	6.70
21	7.40
60	3.80
60	2.20
90	3.00
90	3.20
124	2.40
124	2.00

	DT_{50}	DT_{90}	χ^2	C_0	Parameters
SFO	2.74	9.1	20	51.2	$k = 0.253$
DFOP	2.17	39.9	3.4	51.7	$f = 0.834, k_0 = 0.416, k_1 = 0.0127$
IORE	1.37	28.5	5.1	51.7	$N = 2.66, k = 0.00135$

S_C	26.9
S_{SFO}	174
Slow $t_{1/2}$	54.4
$t_{R\ IORE}$	8.57

The DT50 and DT90 values are used to describe the kinetics reported for the corresponding kinetic equation. The DT50 and DT90 displayed for DFOP are overall values for the DFOP equation. The Slow $t_{1/2}$ and t_{rep} IORE are representative model inputs for those equations. Slow $t_{1/2}$ is the DFOP slow half-life (*e.g.*, based on k1). t_{rep} IORE is $t_{r\ IORE}$. f=g in the DFOP equation in the NAFTA degradation kinetics document. The red value is the value for estimating a model input value recommended by the NAFTA degradation kinetics guidance.

18

Degradation Kinetics Equations

Single First-Order Rate Model (SFO)

$$Ct = C_0 e^{-kt}$$ (equation 1)

Where, Ct = concentration at time t
C_0 = initial concentration or percent applied radioactivity
e = base e
k = rate constant of decline 1/days
t = time

SFO is solved by adjusting C_0 and k to minimize the objective function shown in equation 10:

DT50 = natural log (2)/k (equation 2)
DT90 = ln (10)/k (equation 3)

The linear form of the single first-order equation is shown in equation 4.

$\ln C_t = \ln C_0 - kt$ (equation 4)

where,
ln=natural log

The linear SFO equation is solved by adjusting C_0 and k to minimize residuals.

Nth-Order Rate Model or Indeterminate Order Rate Equation Model (IORE)

$$C = \left[C_0^{(1-N)} - (1 - N)k_{IORE}t \right]^{\left(\frac{1}{1-N}\right)}$$ (equation 5)

This model is solved by adjusting C_0 and k_{IORE}, and N to minimize the objective function (S_{IORE}) for IORE, see equation 10. An estimated SFO model input value using the IORE model is estimated by approximating the SFO model half-life that would have a DT90 that passes through the IORE DT90 and is estimated as shown in equation 6. Traditional DT50 and DT90 for the IORE model are calculated using equations 7 and 8.

$$t_{IORE} = \frac{\log(2)}{\log(10)} \frac{C_0^{1-N}(1 - 0.1^{1-N})}{(1-N)k_{IORE}}$$ (equation 6)

$$DT50 = \frac{(C_0/2)^{(1-N)} - C_0^{(1-N)}}{k_{IORE} \times (N-1)}$$ (equation 7)

$$DT90 = \frac{(C_0/10)^{(1-N)} - C_0^{(1-N)}}{k_{IORE} \times (N-1)} \qquad \text{(equation 8)}$$

Double First-Order in Parallel (DFOP)

$$C_t = C_0 g^{-K_1 t} + C_0(1-g)^{-K_2 t} \qquad \text{(equation 9)}$$

Where g is the fraction of C_0 applied to compartment 1
k_1 = rate constant for compartment 1 in1/days
k_2 = rate constant for compartment 2 in 1/days

DFOP is solved by minimizing the objective function for DFOP (Equation 10) and solving for g, C_0, k_1, and k_2. In Sigmaplot, C_0 x g is equal to a and $C_0(1-g)$ = c. The equation is solved by changing a, c, k_1, and k_2 to minimize the objective function as described in equation 10. The g described in the NAFTA degradation kinetics document and here corresponds to the f in the R output. The g or *f* parameter from the DFOP fit indicates the fraction of the initial chemical that degrades at the fast rate.

Fast and slow DT50 and DT90 are calculated using equations 3 and 4 and k_1 or k_2 in place of k. These fast and slow rates only describe a subset of the data. An overall value is reported in R based on the point on the curve where 50% of the chemical has declined.

Objective Function: SFO, IORE, and DFOP

$$\text{Objective function } S_{model} = \sum(C_{model} - C_d)^2 \qquad \text{(equation 10)}$$

where
S_{SFO} = objective function of the SFO fit to be minimized
S_{IORE} = objective function of IORE fit to be minimized
S_{DFOP} = objective function for DFOP fit to be minimized
C_{model} = modeled value at time corresponding to C_d
C_d = data

Critical Value to Determine Whether SFO Will Be Used to Estimate a Model Input Value

If S_{SFO} is less than S_c, the SFO model is used to describe kinetics for modeling. If not, use IORE or DFOP for modeling.

$$S_c = S_{IORE}\left(1 + \frac{p}{n-p}F(p, n-p, \alpha)\right) \qquad \text{(equation 11)}$$

where
S_c = the critical value that defines the confidence contours
p = number of parameters, (3 in this case)
α = the confidence level (0.50 for this guidance)

$F(a,b,c)=$ F distribution with a and b degrees of freedom and level of confidence c

Gustafson and Holden Model or FOMC Model

$$C_t = \frac{C_0}{\left(\frac{t}{\beta}+1\right)^{\alpha}}$$

(equation 12)

where:
α = shape parameter determined by coefficient of variation of k values
β = location parameter

This model is not solved using a regression model in EFED. Model parameters for FOMC are converted from IORE results using the following equations.

$$\alpha = \frac{1}{N-1}$$

(equation 13)

and

$$\beta = \frac{C_0^{1-N}}{k(N-1)}$$

(equation 14)

APPENDIX D

Example Kinetics Tables for Use in Exposure Assessments and DERs

The minimum information to be reported in a risk assessment is provided in **Table D.1.** The minimum information to be reported in a DER is provided in **Table D.3.** along with the PestDF output image (example shown in **Figure D.1**).

ExampleRun Chem X in Soil Y MRID 555555

Days Posttreatment	Percent Applied
0	95.0
0	95.0
10	99.0
10	88.0
20	78.0
20	77.0
40	72.0
40	72.0
60	66.0
60	64.0
80	65.0
80	69.0
122	64.0
122	59.0
241	72.0
241	58.0
367	43.0
367	50.0

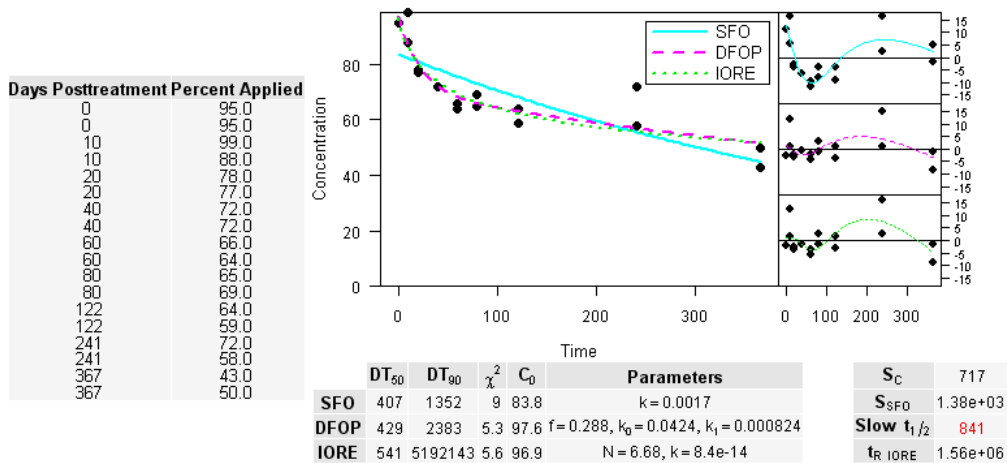|	DT_{50}	DT_{90}	χ^2	C_0	Parameters		
SFO	407	1352	9	83.8	$k = 0.0017$	S_C	717
DFOP	429	2383	5.3	97.6	$f = 0.288, k_0 = 0.0424, k_1 = 0.000824$	S_{SFO}	1.38e+03
IORE	541	5192143	5.6	96.9	$N = 6.68, k = 8.4e-14$	Slow $t_{1/2}$	841
						$t_{R\ IORE}$	1.56e+06

Figure D.1. Example Graphic Representation of Kinetic Analysis Using R and PestDF

Table D.1. Example Summary of Environmental Fate Properties and Values Used to Derive Model Input Values for Use in Exposure Assessments

Study	System Name/ Characteristics	Kinetic Model Fitted[1] Value and Unit *(Fitting Equation)*		Representative Half-life Value --Value Used to Derive Model Input Values (days)[2]--	Reference or (MRID #), Study Classification and Comments
		DT50 (days)	DT90 (days)		
Abiotic Hydrolysis	pH 5, temp	XX (SFO)	XX (SFO)	Not applicable	555555, Acceptable
	pH 7, temp	XX (SFO)	XX (SFO)	SFO DT50=XX	
	pH 9, temp	XX (SFO)	XX (SFO)	Not applicable	
Air Photolysis	temp	XX (SFO)	XX (SFO)	Not applicable	555555, Acceptable
Atmospheric Degradation	Hydroxyl radical Ozone reaction	XX estimated	XX, estimated	Not applicable	Estimated using EPI Suite v.4.1
Direct Aqueous Photolysis	pH, temp	XX (SFO)	XX (SFO)	SFO DT50=XX	555555, Acceptable; reported value is dark control corrected and corrected for 40°N latitude, 12 hours light and dark.
Soil Photolysis	texture, pH, OM temp	XX (SFO)	XX (SFO)	Not applicable	555555, Acceptable; reported value is dark control corrected and corrected for 40°N latitude, 12 hours light and dark.
Aerobic Soil Metabolism	soil texture, pH, OM, temp	XX (IORE)	XX (IORE)	T_{IORE}=X	555555, Supplemental; Soils were foreign soils. WRB classifications were not provided, and it was not determined whether soils were representative of a U.S. use site.
	soil texture, pH, OM, temp	XX (DFOP)	XX (DFOP)	Slow $t_{1/2}$ DFOP=X	
Aerobic Aquatic	Water/Sediment X: texture, pH, OM, temp	XX (IORE)	XX (IORE)	T_{IORE}=X	555555, Supplemental; Soils were foreign soils. WRB classifications were not provided , and it was not determined whether soils were representative of a U.S. use site.
	Water/Sediment X: texture, pH, OM, temp	XX(DFOP)	XX (DFOP)	Slow $t_{1/2}$ DFOP=X	
Anaerobic Aquatic	Water/Sediment X: texture, pH, OM, temp	XX (IORE)	XX (IORE)	T_{IORE}=X	555555, Supplemental; Soils were foreign soils. WRB classifications were not provided, and it was not determined whether soils were representative of a U.S. use site.
	Water/Sediment X: texture, pH, OM, temp	XX (DFOP)	XX (DFOP)	Slow $t_{1/2}$ DFOP=x	

[1] DT50 and DT90 values were calculated using nonlinear regression and single first-order (SFO), double first- order in parallel (DFOP), or indeterminate- order equation (IORE). For DFOP, the overall DT50 and DT90 are reported when available. Otherwise, a first and second DT50 are reported. The equations can be found in the document, *Standard*

Study	System Name/ Characteristics	Kinetic Model Fitted[1] Value and Unit *(Fitting Equation)*		Representative Half-life Value --Value Used to Derive Model Input Values $(days)^2$--	Reference or (MRID #), Study Classification and Comments
		DT50 (days)	DT90 (days)		
Operating Procedure for Using the NAFTA Guidance to Calculate Representative Half-life Values and Characterize Pesticide Degradation, U.S. Environmental Protection Agency August [x], 2012. [2] The value used to estimate a model input value is the calculated SFO DT_{50}, T_{IORE}, or the 2nd DT_{50} from the DFOP equation. The model chosen is consistent with that recommended using the, *Guidance for Evaluating and Calculating Degradation Kinetics in Environmental Media*, Health Canada, U.S. Environmental Protection Agency, December 21, 2012. The same model used to estimate the value used to derive a model input, is used to describe the DT50 and DT90 results.					

Table D2. Example Transformation Kinetics Table for Use in DER

Conditions of Test	Observed DT_{50} (days)	Observed DT_{90} (days)	Represetative Half-Life Value --Value Used to Estimate Model Input (days)--	Kinetic Model Fitted DT50 (days)	Kinetic Model Fitted DT90 (days)	Kinetics Model [C]	Model Parameters	Justification for model input and model chosen for degradation kinetics
Parent Only								
Soil type, pH 0.1 mg/kg	8-12	60-90	T_{IORE}=25	17.3	57.6	SFO	C_0=90.4, k=0.04, S_{SFO}=950	IORE for descriptive analysis was chosen because IORE predicted DT50 and DT90 closest to observed intervals, and it is the simplest model. T_{IORE} was recommended by NAFTA degradation kinetics guidance for model input estimate..
				13.0*	83.1*	IORE*	C_0=98.6, k=0.003, n=1.7, S_{IORE}=647, S_C=856	
				2nd=38.8 Overall=12.3	84.1	DFOP	C_0=99.6, f=0.55, k_1=0.111, k_2=0.0179, S_{DFOP}=610	
Soil type, pH 0.1 mg/kg	12-15	30-45	SFO DT50=12.1	12.1*	40.1*	SFO*	C_0=98.7, k=0.0574	SFO for descriptive analysis was chosen because SFO predicted DT50 and DT90 fall within the observed intervals, and it is the simplest model. The SFO value was also recommended based on NAFTA degradation kinetics guidance for model input estimate.
				12.0	41.1	IORE	C_0=98.9, k=0.049, n=1.04, T_{IORE}=12.4	
				2nd=-64.9 Overall=11.8	41.4	DFOP	C_0=99.3, f=0.989, k_1=0.059, k_2=-0.011	
Parent and Unextracted Residues								
Soil type, pH 0.1 mg/kg	8-15	60->120 9.6% at 90 days and 12%AR at 180 days	T_{IORE}=44.9	22.4	74.2	SFO	C_0=88.4, k=0.031	IORE for descriptive analysis was chosen because IORE predicted DT50 and DT90 fall within or is closer to the observed intervals. T_{IORE} was recommended by NAFTA degradation kinetics guidance for model input estimated.
				13.5*	149*	IORE*	C_0=98.6, k=0.0004, n=2.17	
				2nd=79.2 Overall=12.7	144	DFOP	C_0=99.1, f=0.65, k_1=0.099, k_2=0.009	
Soil type, pH 1 mg/kg	12-15	45->120 8% at 60 days and 13%AR at 180 days	SFO DT50=13	13	43.3	SFO	C_0=98.1, k=0.0531	IORE for descriptive analysis was chosen as it predicts the highest DT90 and DT90 not reached. SFO DT50 recommended by NAFTA degradation kinetics for model input estimate. DFOP slow rate was a negative value and should not be used.
				12*	60.3*	IORE*	C_0=100, k=0.008, n=1.46	
				2nd=-101 Overall=12.2	Not applicable	DFOP	C_0=100, f=0.96, k_1=0.0611, k_2=-0.007	
Parent, Unextracted, and Unidentified Extracted Residues								
Soil type, pH	70% remaining at 180 days		SFO DT50 = 299	299*	993*	SFO*	C_0=85.6, k=0.002	Use SFO as the model input and for descriptive analysis as 70% remained at
				1190	1.9×10^8	IORE	C_0=99.7, k=7.58×10^{-12}, n=9.89	

Conditions of Test	Observed DT$_{50}$ (days)	Observed DT$_{90}$ (days)	Represetative Half-Life Value --Value Used to Estimate Model Input (days)--	Kinetic Model Fitted DT50 (days)	Kinetic Model Fitted DT90 (days)	Kinetics Model [C]	Model Parameters	Justification for model input and model chosen for degradation kinetics
0.1 mg/kg 0.1 mg/kg	60-90			NA	NA	DFOP	Did not converge	the end of the study.
Soil type, pH 0.1 mg/kg 1 mg/kg	96% remaining at 180 days		Stable	Not Determined				Assumed stable due to amount remaining after 180 days.

* Asterick and red/brown values are the values and model recommended for descriptive analysis.

[A] See Attachment 3 for calculations.

[B] Calculated half-lives and model parameters are in accordance with the NAFTA kinetics guidance (USEPA, 2011).

[C] Kinetics models: Single First-Order (SFO); Double First-Order in Parallel (DFOP), and Indeterminate Order Rate Equation (IORE).

[D] DT50 is defined as the time it take for 50% of the amount applied to be lost. For the single first-order model, the DT50 is the same as the half-life. The half-life is essentially a DT50 with the single first-order model.

Table D3. Alternative Example Transformation Kinetics Table for Use in DER; model outputs are provided in the appendix that include all model parameters including the representative half-life value

Study Parameters/ Reference Information	Observed DT_{50} (days)	Observed DT_{90} (days)	Kinetic Model Fitted[C] DT50 (days)	Kinetic Model Fitted[C] DT90 (days)	Representative Half-life Value --Value to Use to Estimate Model Input Value--	Kinetics Model [C]
[Soil Location] [USDA Soil Series] [Soil Texture] [# °C, pH #]	[#]	[#]	[#]	[#]	SFO $T_{1/2}$ =[#]	SFO
			[#]	[#]	T_{IORE}=	IORE
			[#]	[#]	DFOP slow $t_{1/2}$=	DFOP [if applicable]
[Soil Location] [USDA Soil Series] [Soil Texture] [# °C, pH #]	[#]	[#]	[#]	[#]	SFO $T_{1/2}$ =[#]	SFO
			[#]	[#]	T_{IORE}=	IORE
			[#]	[#]	DFOP slow $t_{1/2}$=	DFOP [if applicable]

[A] Data were obtained from [location of data in study report] and calculations in the attached Excel workbook [name(s) of worksheets, if needed]. See Attachment 3 for calculations.
[B] Calculated half-lives and model parameters (determined in accordance with the NAFTA kinetics guidance (USEPA, 2011)), are in bold.
[C] Kinetics models: Single First-Order (SFO); Double First-Order in Parallel (DFOP), and Indeterminate Order Rate Equation (IORE).