NAFTA Technical Working Group on Pesticides
Grupo de Trabajo Técnico del TLCAN sobre Plaguicidas
Le groupe de travail technique de l'ALENA sur les pesticides

Guidance for Evaluating and Calculating Degradation Kinetics in Environmental Media

Introduction

This guidance covers the general methods to be used in determining the first-order degradation model input. Frequently, biotransformation laboratory studies do not follow a first-order degradation pattern; yet standard pesticide fate models (e.g. PRZM, EXAMS) require first-order degradation inputs. This interim guidance, which is based in part on FOCUS (2006), establishes a simple procedure for determining a first-order rate constant from biotransformation/ degradation studies, which include standard biotic studies conducted in soil, water, or mixed media (e.g., EPA 835.4300, EPA 835.4400, PMRA 8.2.3.5.4, PMRA 8.2.3.5.6, OECD 308, EPA 835.4100, EPA 835.4200, PMRA 8.2.3.4.2, PMRA 8.2.3.4.4, OECD 307). The standard abiotic studies (hydrolysis and photolysis) more commonly follow first-order patterns, and derivation of appropriate rate constants is straightforward. This guidance is not intended to speculate on the mechanism for the decline, and the procedures should not be used to imply a kinetic mechanism.

The guidance will be implemented by the United States Environmental Protection Agency and the Pest Management Regulatory Agency of Health Canada for one year, after which time the agencies will re-evaluate the guidance to determine if any changes are necessary. During the interim period, the NAFTA partners will gather knowledge to improve the robustness of the proposed approach.

Methods

To derive a representative half-life (t_{rep}), three models are used in a two-step process (Figure 1). First, the single first-order model (SFO) is compared to an n^{th} order model (Indeterminate Order Rate Equation - IORE) to determine if n can be considered statistically different from 1. If the test shows that n is different from 1, then a two compartment first-order model (Double First-Order in Parallel - DFOP) is also fitted with the slower rate taken as a lower bound on the representative degradation rate. The representative rate constant is taken as the rate constant defined by the exponential curve passing through the IORE DT_{90}, unless it is slower than the lower bound determined from the DFOP model. Mathematical descriptions of the models, including IORE equivalency to FOMC (First Order Multi-Compartment) used by FOCUS, are provided in Appendix 1.

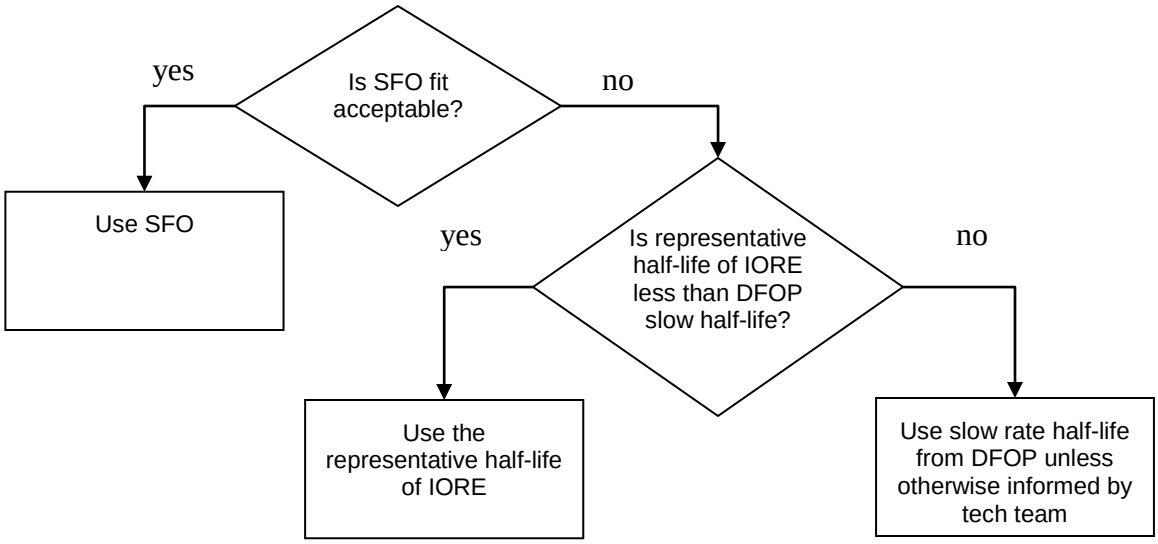

Figure 1. Process for choosing a model half-life.

Step 1: Prepare concentration (or mass) data from an acceptable degradation study. Determination of the acceptability of a study shall be in accordance with individual Agency guidance.

Step 2: Determine if the data set deviates from the Single First Order (SFO) model. The procedure adopted here is taken from Draper and Smith (1981) and Motulsky and Chistopoulus (2003). For this step, the exponent of the IORE model is used as an indicator of deviation from SFO. If the IORE exponent does not deviate significantly from 1, the data are deemed to be adequately represented by SFO. The process of determining a significant exponent deviation is as follows:

Best fits are made for both the 3-parameter IORE model (adjusting C_0, k_{IORE}, N) and the 2-parameter SFO model (adjusting (C_0 and k). Because SFO is a special case of IORE in which N=1, the significance of the additional parameter in IORE (the N value) can be tested to see if it differs significantly from 1. First, fit the SFO by minimizing:

$$S_{SFO} = \sum (C_{SFO} - C_d)^2 \quad (1)$$

where

S_{SFO} = objective function of the SFO fit to be minimized
n = number of data points,
C_{SFO}= SFO modelled value at time corresponding to C_d
C_d = data

Then fit the IORE model by minimizing:

$$S_{IORE} = \sum (C_{IORE} - C_d)^2 \quad (2)$$

where

S_{IORE} = objective function of the IORE fit to be minimized
n = number of data points,
C_{IORE}= IORE modelled value at time corresponding to C_d

A critical value is then calculated that defines a confidence region about S_{IORE}:

$$S_c = S_{IORE}\left(1 + \frac{p}{n-p}F(p, n-p, \alpha)\right) \quad (3)$$

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*

The 50% confidence level was chosen as it represents a level that provides more confidence in determining whether to choose a more complicated model (IORE) over a simpler one (SFO). In order to determine whether the IORE model is significantly better than SFO, compare S_{SFO} to S_c. If the S_{SFO} value is less than the S_c value, use the SFO model. Otherwise, use IORE and DFOP (see below).

Step 3: Half-Life Calculations from IORE and DFOP. When the SFO model does not fit the data well (as determined in Step 2), a first estimate of the representative half-life is made as follows:

$$t_{IORE} = \frac{\log(2)}{\log(10)} \frac{{C_0}^{1-N}(1 - 0.1^{1-N})}{(1-N)k_{IORE}} \quad (4)$$

where k_{IORE}, N, and C_0 are the fitted IORE parameters, and t_{IORE} is the representation of the half-life. (The t_{IORE} in equation (4) is the half-life of a SFO model that passes through a hypothetical DT_{90} of the IORE fit.)

An additional fit of the DFOP model will be made by least squares minimization. The DFOP model consists of the sum of two first-order terms (see Appendix 1). The term with the faster rate dominates the early degradation whereas the term with the slower rate dominates the later part of the degradation curve. This slower rate of degradation may be thought of as a lower bound on the observed degradation rate. Calculate the DFOP slow rate half-life (t_{DFOP2}), using the k_2 rate.

$$t_{DFOP2} = \frac{\ln(2)}{k_2} \quad (5)$$

Step 4: Compare t_{IORE} with t_{DFOP2}. If t_{IORE} is less than the t_{DFOP2}, then use t_{IORE} as the *representative half-life* (t_{rep}) for model input. If t_{IORE} is greater than t_{DFOP2}, then t_{IORE} is considered to be slower than the terminal degradation rate (see step 3) and t_{DFOP2} may be used as the t_{rep} for model input. This outcome indicates that a review of the data is also in order. Such chemicals should be brought to the attention of the NAFTA group. The scientist may want to

consider for example, whether the chemical appears to be persistent and whether sufficient degradation occurred and may offer alternative methods of representative half-lives for consideration. Visual inspection is an important tool for determining which chemicals should be reviewed by the NAFTA group.

Re-evaluation of guidance

During the period that this interim guidance is in place, the above guidance will be re-evaluated as to its effectiveness in delivering clear, fair, and sensible instructions. Problems that users have with the guidance should be brought to the attention of the NAFTA degradation team. This is especially necessary in the case of problematic chemicals in which the IORE representative half-life and the DFOP slow half-life values diverge considerably. After a period of one year, the NAFTA partners will re-evaluate this guidance.

References

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

FOCUS (2006) *Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration*, Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp.

Motulsky H. And Christopoulus, A. (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.

Appendix 1: Model descriptions

Single First-Order Rate Model (SFO)

The single first-order kinetics model (SFO) specifies that the rate of concentration decline is proportional to the concentration in the system The SFO is described by

$$\frac{dC}{dt} = -kC$$

For SFO kinetics, the time for a decrease in the concentration by a certain percentage is constant and independent of the initial concentration. For example, the time for a decrease in the concentration from 100% to 50% of the initial amount is identical to the time for a decrease from 50% to 25% of the initial amount. For a given initial concentration (C_0), the above equation can be solved to give

$$C = C_0 e^{-kt}$$

For SFO, there are two adjustable parameters: C_0 and k.

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

The IORE model is mathematically equivalent to the first-order multi-compartmental model (FOMC) used by FOCUS. The model is defined by:

$$\frac{dC}{dt} = -k_{IORE} C^N$$

Integrated form

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

For IORE, there are three adjustable parameters: C_0 and k_{IORE}, and N. The N parameter determines how fast the degradation rate declines with decreasing concentration and is an indicator of how far the data deviate from a first order model (where N =1).

Conversion between IORE and FOMC

FOCUS (2006) guidance on degradation kinetics includes use of the First Order Multi-Compartment (FOMC) model. The FOMC model has the following equation

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

The FOMC model is algebraically interchangeable with the IORE model used in this guidance. The parameters for FOMC can be calculated from IORE parameters as:

$$\alpha = \frac{1}{n-1} \quad \text{and} \quad \beta = \frac{C_0^{1-n}}{k(n-1)}$$

or IORE parameters can be calculated from FOMC parameters as:

$$n = \frac{1}{\alpha} + 1 \quad \text{and} \quad k_{IORE} = \frac{C_0^{1-n}}{\beta(n-1)}$$

Double First-Order in Parallel (DFOP)

The Double First-Order in Parallel (DFOP) model is a model which uses the sum of two first order equations, which allows the DFOP model to better conform to the data. The mass as a function of time is expressed as;

$$C = C_0 g^{-k_1 t} + C_0 (1 - g)^{-k_2 t}$$

Because of its two exponentials, there is no closed form equation for calculating the DT90, so an iterative procedure must be used. For DFOP, there are 4 adjustable parameters: C_0, g, k_1, and k_2, where g is the fraction of degradation occurring under rate constant k_1.

Appendix 2: Glossary of Terms

Degradation (also transformation): Degradation or transformation processes transform one compound to another through chemical or biological reactions in different environmental compartments. Degradation usually breaks down substances by such processes as hydrolysis or photolysis, but may also result in larger molecules by such processes as biosynthesis or polymerization.

Degradation Rate: A kinetic parameter describing an aspect of the rate at which a substance dissipates from the environment or an environmental compartment. Such parameters may be non-specific, simply describing net dissipation due to degradation and transfer processes, or they may be specific, describing dissipation due to degradation, formation, or transfer. The dimensions of these rate constants can vary. In a strict sense, rate constants will only depend on the temperature. Many of the rate constants considered in this document are pseudo-rate constants since they depend on other factors as well. However, the term "rate constant" is employed generically without specifying if it is a true or a pseudo-rate constant.

DT_{50}/DT_{90}: Time required for concentration/mass to decline by 50% or 90%, respectively. These terms are not associated with any particular type of kinetics to describe the time taken for a 50/90% decline in mass or concentration of a substance from the environment or an environmental compartment after it has been applied to, formed in, or transferred to, an environmental compartment. $DT_{50/90}$ does not differentiate between transfer processes and degradation processes. The first-order half-life of a substance may be identical to the DT_{50}, but a DT_{50} may not necessarily be a half-life depending upon kinetics. For the purposes of this document, the term half-life has been restricted to mean the half-life from fitting single first-order (SFO) kinetics to data to avoid confusion in the use of terminology.

Half-life: The time taken for 50% degradation/dissipation of a test substance described by single first-order kinetics and following the concept of exponential decay, where the rate constant is independent of concentration and time. The half life ($t_{1/2}$) is related to the degradation (k) by the following equation:

$$t_{\frac{1}{2}} = \frac{\ln(2)}{\mathbf{k}}$$

Kinetics models: Equation or set of equations used to describe the decrease of substances from the environment or an environmental compartment by various dissipation/degradation processes