Models in Toxicology

Budi Widianarko

Department of Food Technology
Soegijapranata Catholic University

ALL MODELS ARE WRONG AND SOME ARE USE(FUL)/(LESS)

Mathematical Model

To describe real world processes using a simple language, i.e. mathematical expression

The two most important mechanisms in **T**oxicology

- **DOSE-RESPONSE RELATIONSHIP** – a correlation between dose of a toxic substance administered or received and the incidence of an adverse (including health) effect in exposed population.
- **TOXICOKINETICS -** process of uptake of toxicants by the body of organism, the biotransformation they undergo, the distribution of the toxicants and their metabolites in the tissues, and the elimination of the toxicants and their metabolites from the body.

Dose-Response Models

Dose-response relationship (DRR) is fundamental to toxicology. Understanding the association between effect and dose is the basis of safety evaluation, assuming that the effect is the result of the substance administered. In toxicology, we can observe a quantal response (mortality or number of animals affected) and a graded or continuous response (weight, enzyme activity, etc).

When a sufficient number doses is used in an experiment with a sufficient number of animals, the result can be represented by a sigmoid dose-response curve. In classical analysis of dose-response data, probit or logit transformation is used to transform the sigmoid curve into a linear curve. Based on the slope and intercept of this linear curve, the values of LD_{50} or ED_{50} can then be derived.

Alternatively, **a logistic response model** can be used to describe the dose-effect relationship:

$$Y = \frac{c}{1 + e^{b(X-a)}} \qquad (18)$$

where **Y** is the observed biological rate, **X** is the (natural) logarithm of the concentration, **c** is the undisturbed level of the biological rate, **a** is the logarithm of the concentration at which the biological rate is half of the undisturbed level, and **b** is a slope parameter.

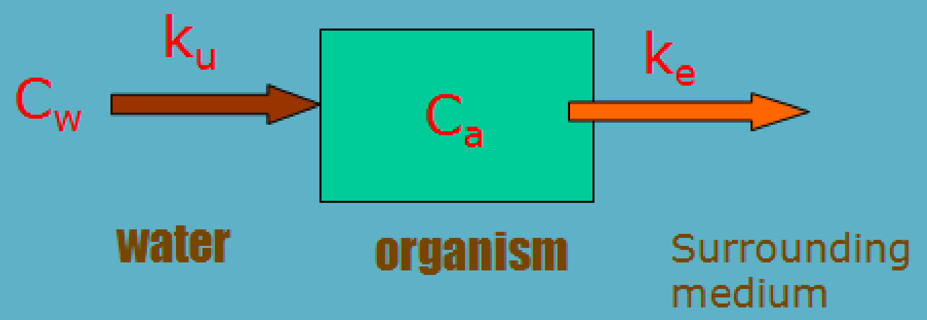
Parameter **b** indicates the rate of increase of inhibition with increasing concentration around ED_{50} concentration. The higher the value of **b**, the more abruptly the biological rate decreases, which would mean that the toxicant strongly acts on the organism. On the other hand a low value of b does not necessarily mean that a toxicant does not act strongly on the organism.

TOXICOKINETICS MODEL

- Compartment-based models describe toxicant movement between compartments.
- A compartment represents the amount of a compound that behaves as though it exists in a homogeneously well-mixed container and moves across the compartment boundary with a single uptake or elimination rate coefficient.

Click to add title

The model relates the amount or concentration of a compound in one compartment with that in another:



Compartment Models

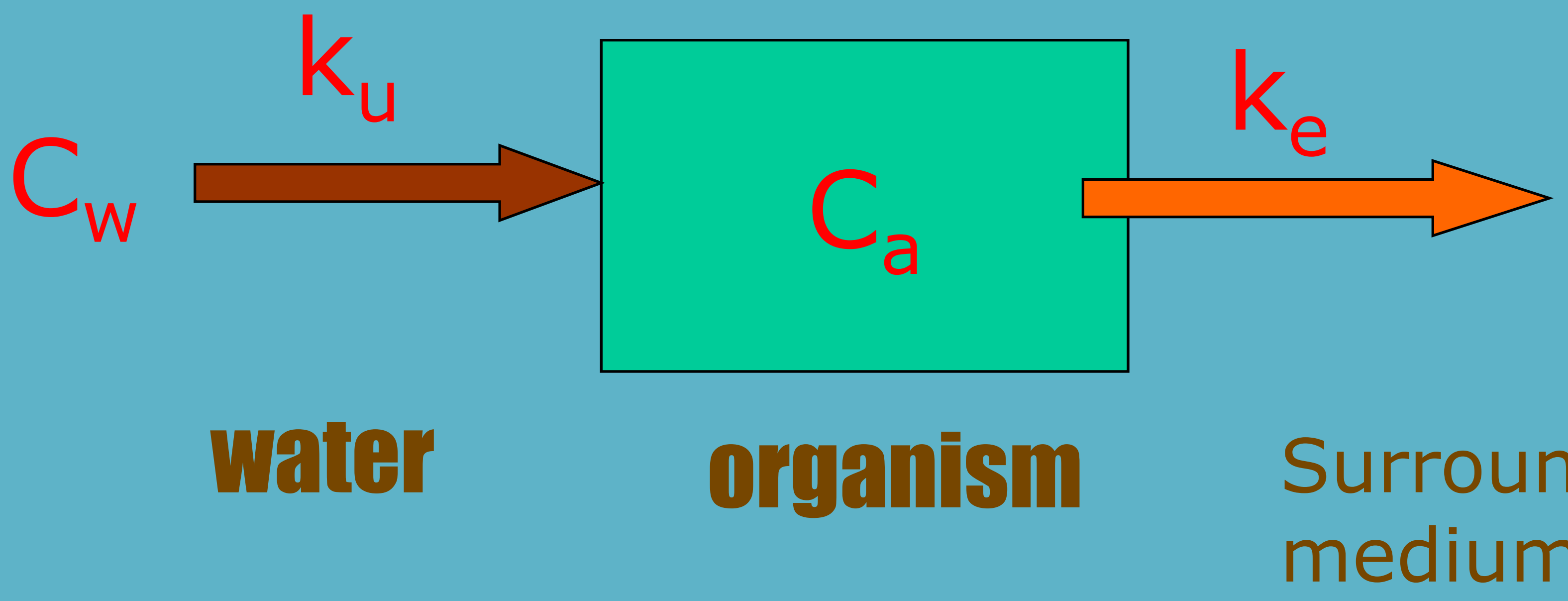
A simple compartment model containing water and organism compartments.

The water represents the source **Of toxicant and the organism represents** the toxicant sink**.**

ASUMPTIONS:

- The toxicant is well mixed and homogeneous within each compartment
- No compound biotransformation occurs
- The uptake rate constants and clearances remain constant over time (if the organism undergoes physiological change, this assumption can be violated)
- The transfer between compartment is first order. Thus, the flux across the boundary depends on the chemical activity (concentration) in the respective compartment. The net flux is the sum of the uptake and loss fluxes across the compartment boundaries

The model relates the amount or concentration of a compound in one compartment with that in another:



$$\frac{dC_a}{dt} = (k_u)(C_w) - (k_e)(C_a) \qquad (1)$$

Where

C_a = the concentration of the chemical in the organism (mol/kg)

C_w = the concentration of the chemical in the water (mol/L)

k_u = the uptake rate constant (L/kg.d)

k_e = the elimination rate constant (1/d)

t = time (d)

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If **Cw** is held constant, as ideally occurs in flow-through experiments and is often assumed for field exposures, Equation (1) can be exactly integrated to yield

$$Ca = \frac{k_u . Cw}{k_e} (1-e^{-k_e t})$$

The uptake rate constant can be derived from the initial uptake of the chemical by the organism, when elimination is asumed to be negligible

$$C_a = k_u \, C_w \, t$$

$$\frac{dCa}{dt} = (k_u.Cw) - (k_e.Ca) \quad (1)$$

Where

C_a = the concentration of the chemical in the organism (mol/kg)

C_w = the concentration of the chemical in the water (mol/L)

k_u = the uptake rate constant (L/kg.d)

k_e = the elimination rate constant (1/d)

t = time (d)

$$Ca = \frac{k_u.Cw}{k_e}(1\text{-}e^{-k_e t})$$

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After $t \longrightarrow \infty$

$dC_a/dt = 0$ --- steady state

$$\boxed{BCF = C_a/C_w = K_u/K_e}$$

Biological Concentration Factor

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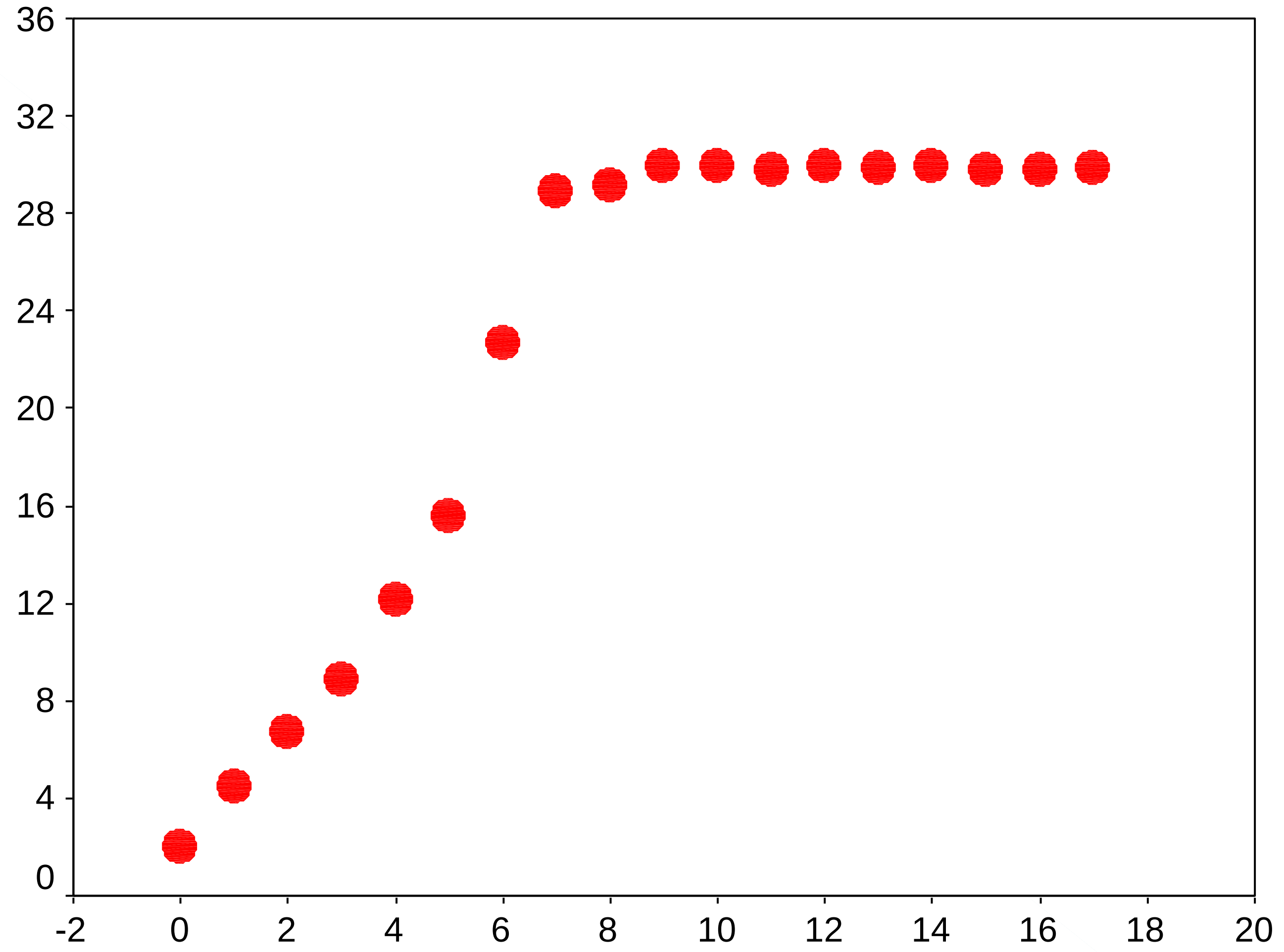
Typical Experimental Data

t	Ca
0	2.00
1	4.50
2	6.70
3	8.90
4	12.10
5	15.60
6	22.70
7	28.90
8	29.10
9	29.90
10	29.90
11	29.80
12	29.90
13	29.85
14	29.95
15	29.80
16	29.80
17	29.89



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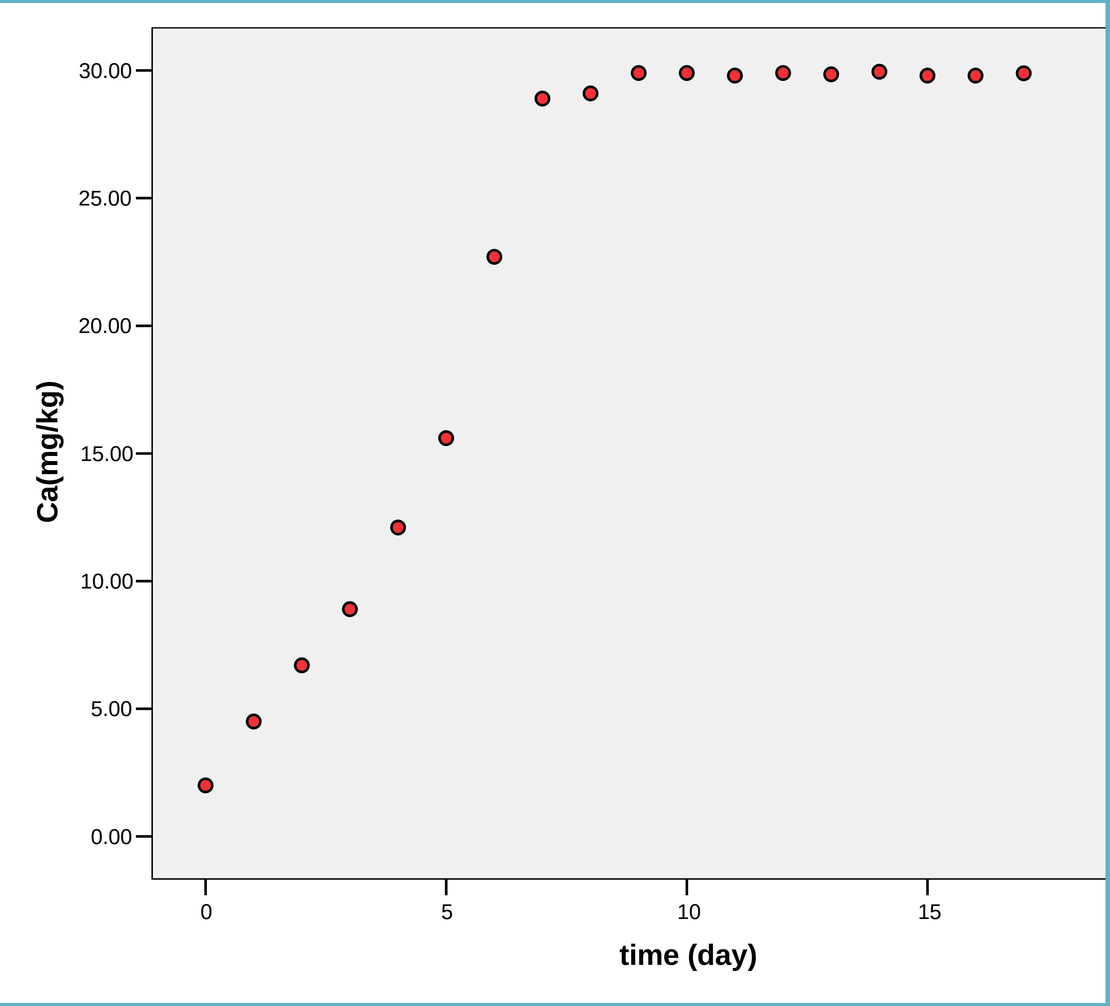

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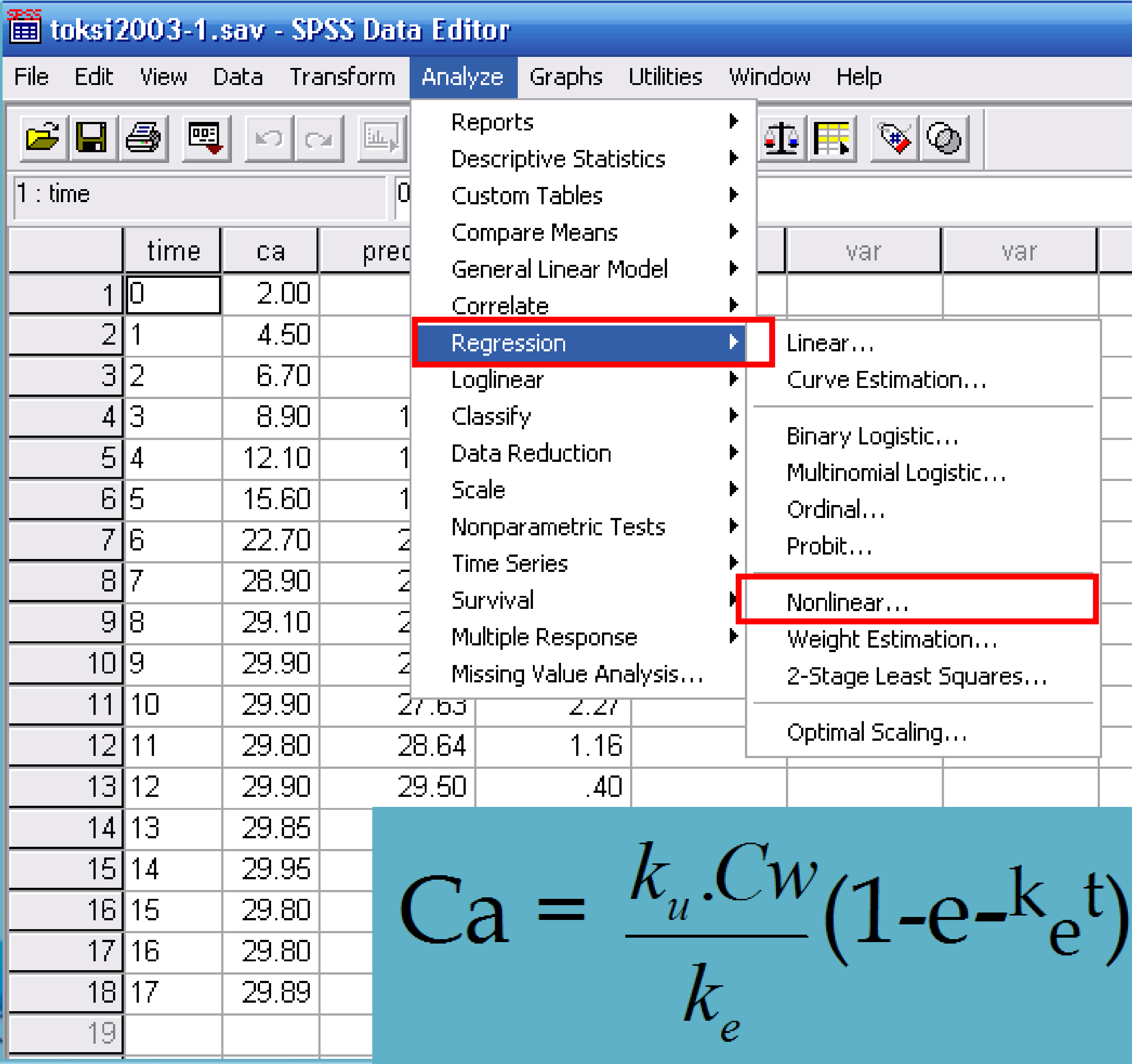
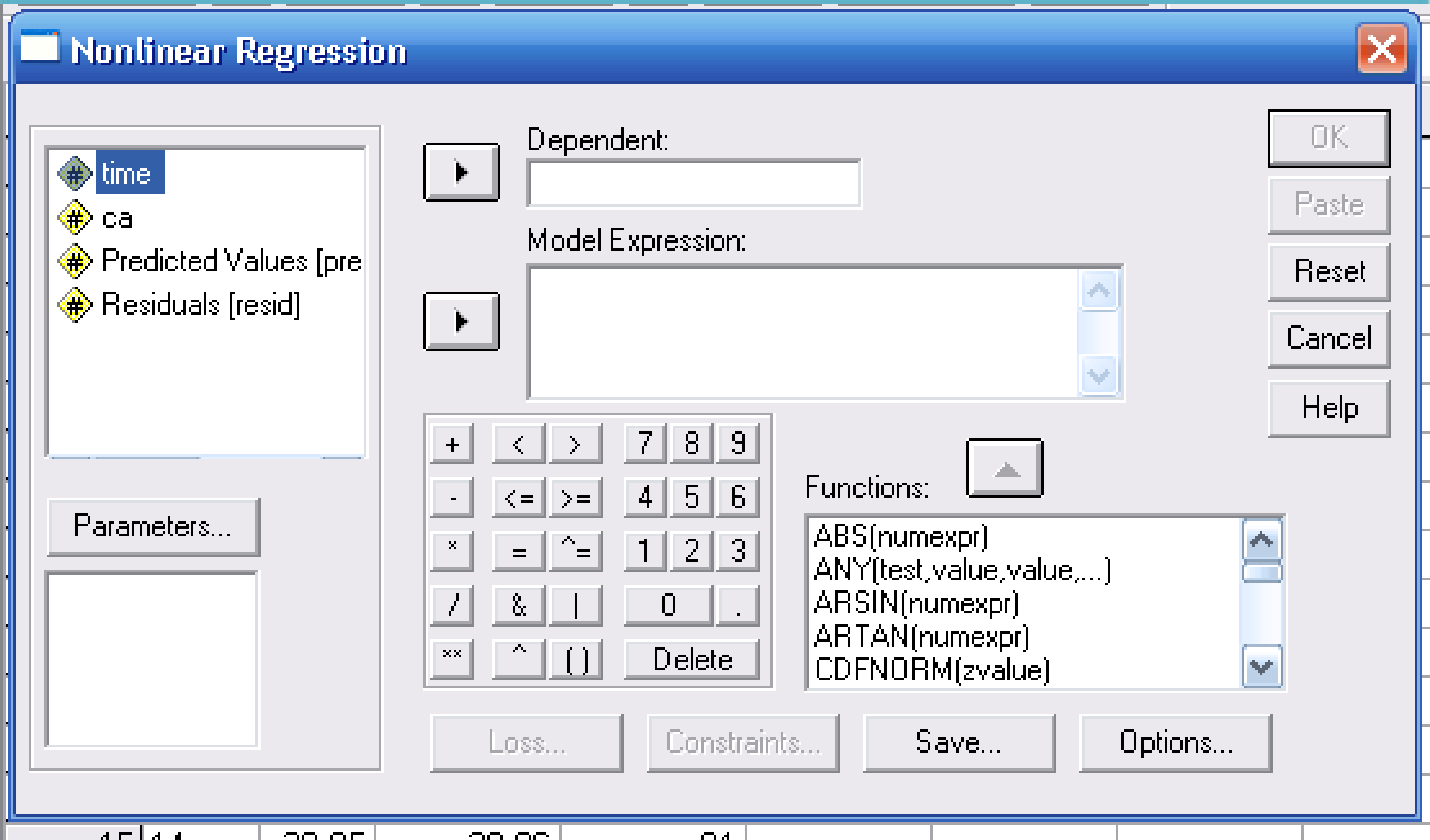
1 : time 0

	time	ca	var	var
1	0	2.00		
2	1	4.50		
3	2	6.70		
4	3	8.90		
5	4	12.10		
6	5	15.60		
7	6	22.70		
8	7	28.90		
9	8	29.10		
10	9	29.90		
11	10	29.90		
12	11	29.80		
13	12	29.90		
14	13	29.85		
15	14	29.95		
16	15	29.80		
17	16	29.80		
18	17	29.89		
19				



$$Ca = \frac{k_u . Cw}{k_e}(1 - e^{-k_e t})$$

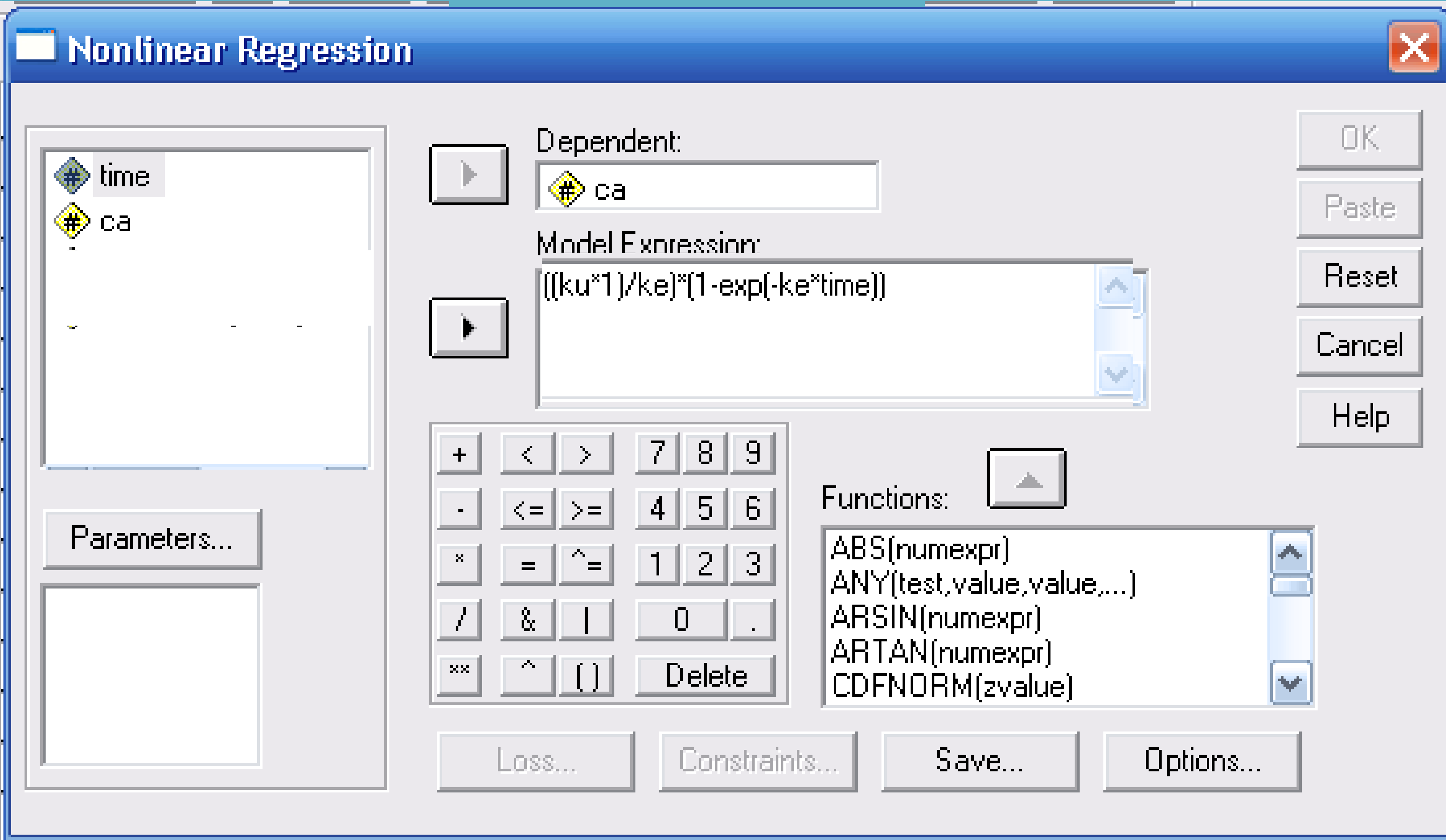
DIALOG BOX – NONLINEAR REGRESSION



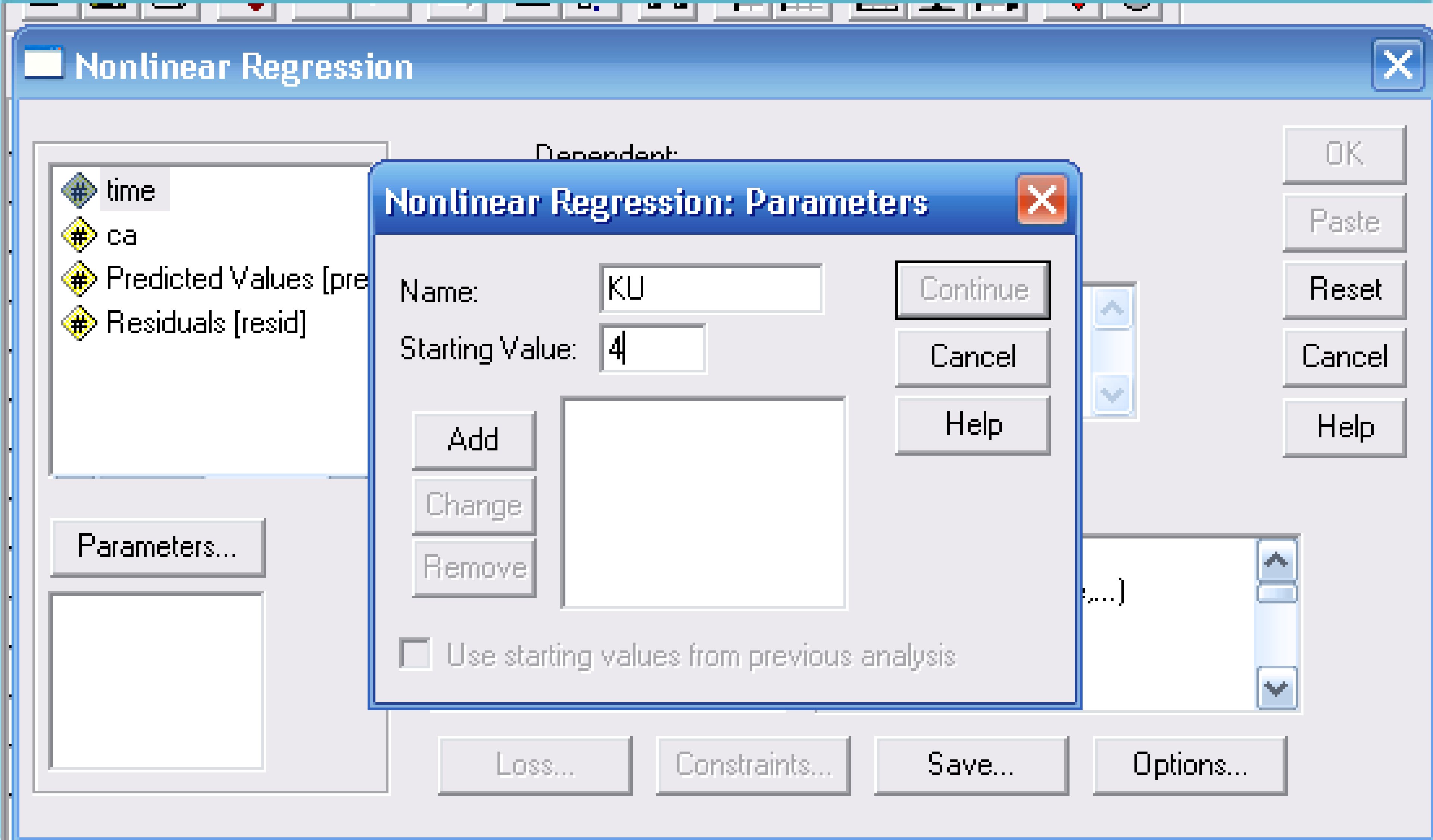
MODEL DEFINITION

$$Ca = \frac{k_u . Cw}{k_e}(1\text{-}e^{-k_e t})$$

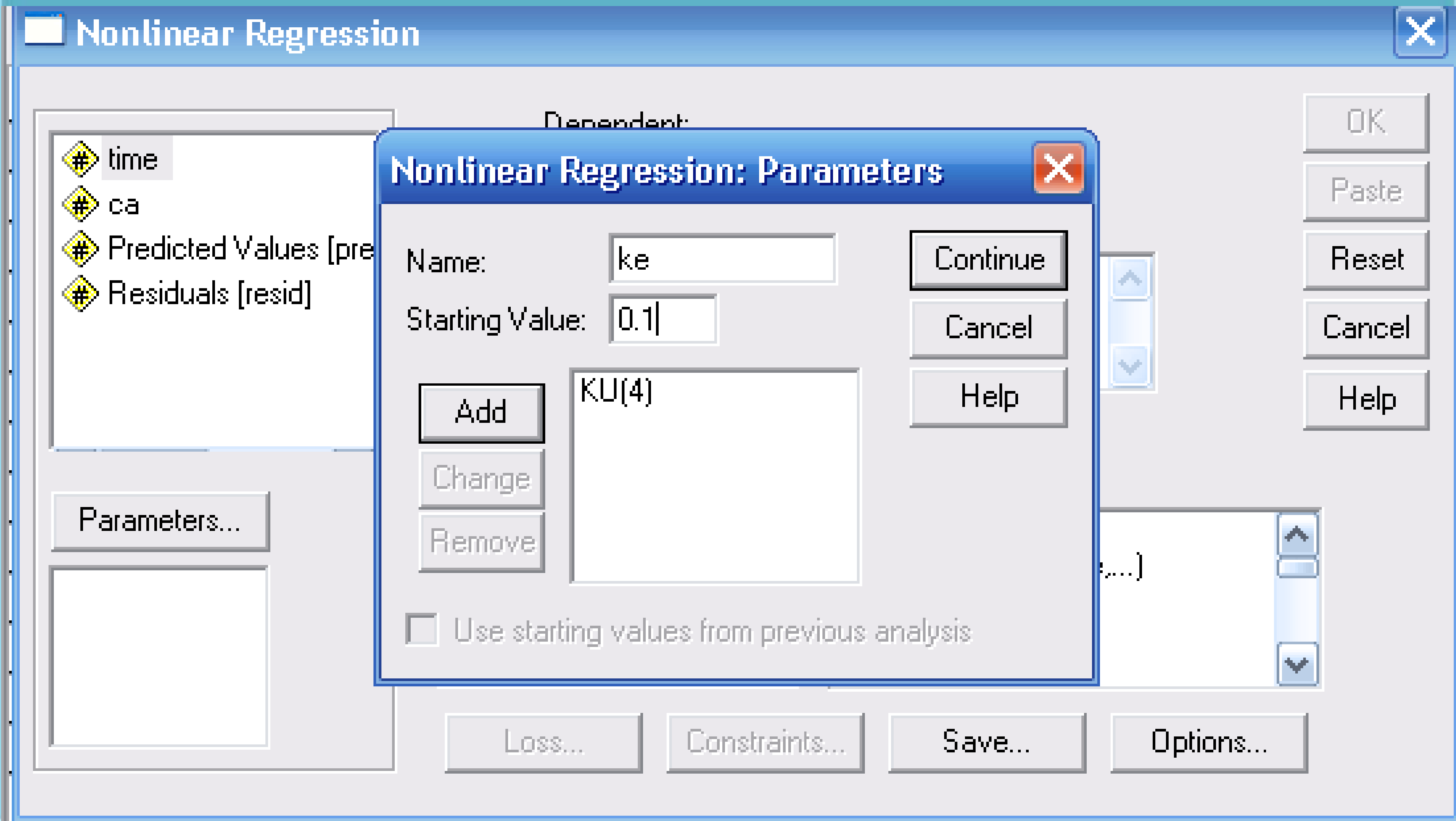
$C_w = 1$



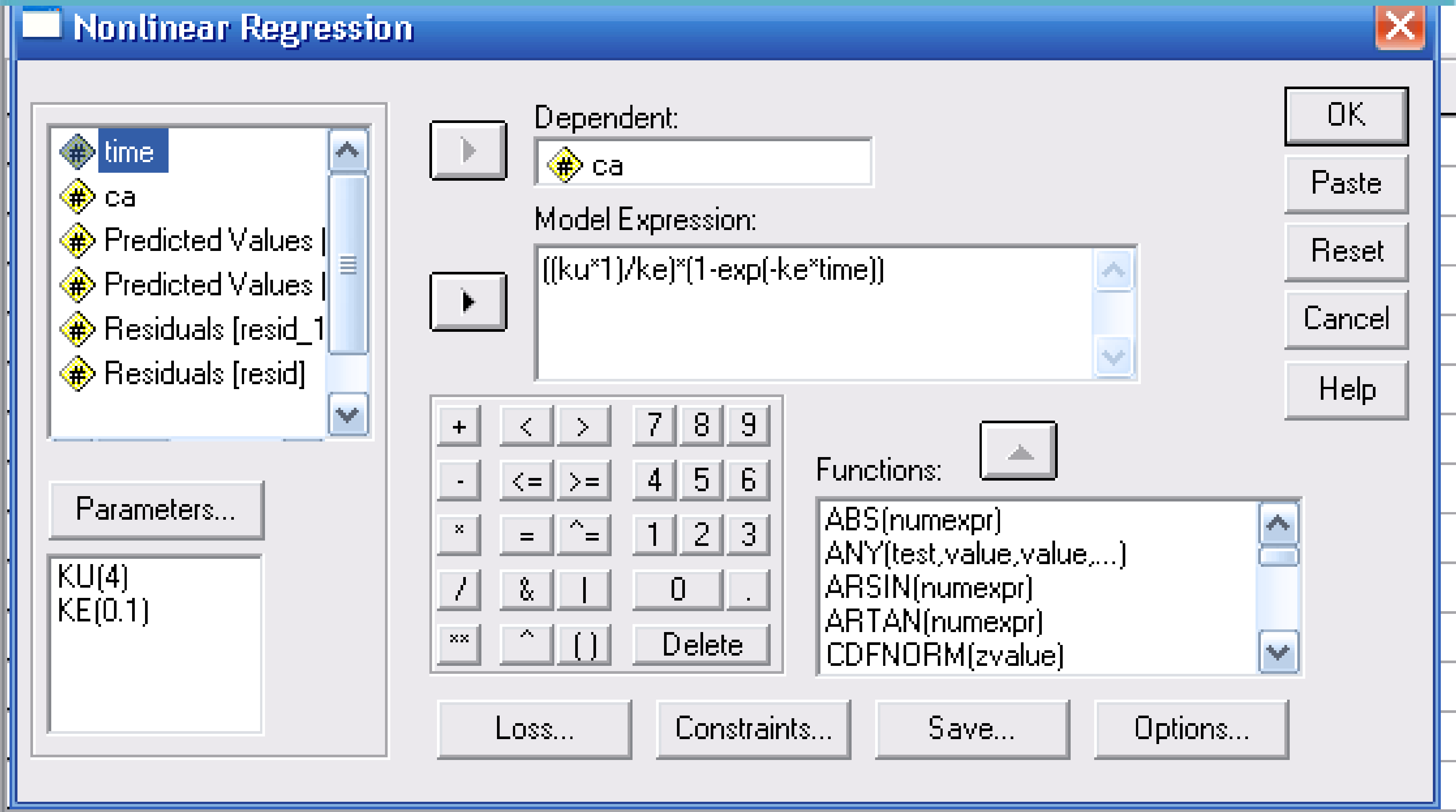
INITIAL (ESTIMATE) VALUE OF THE PARAMETER (1)



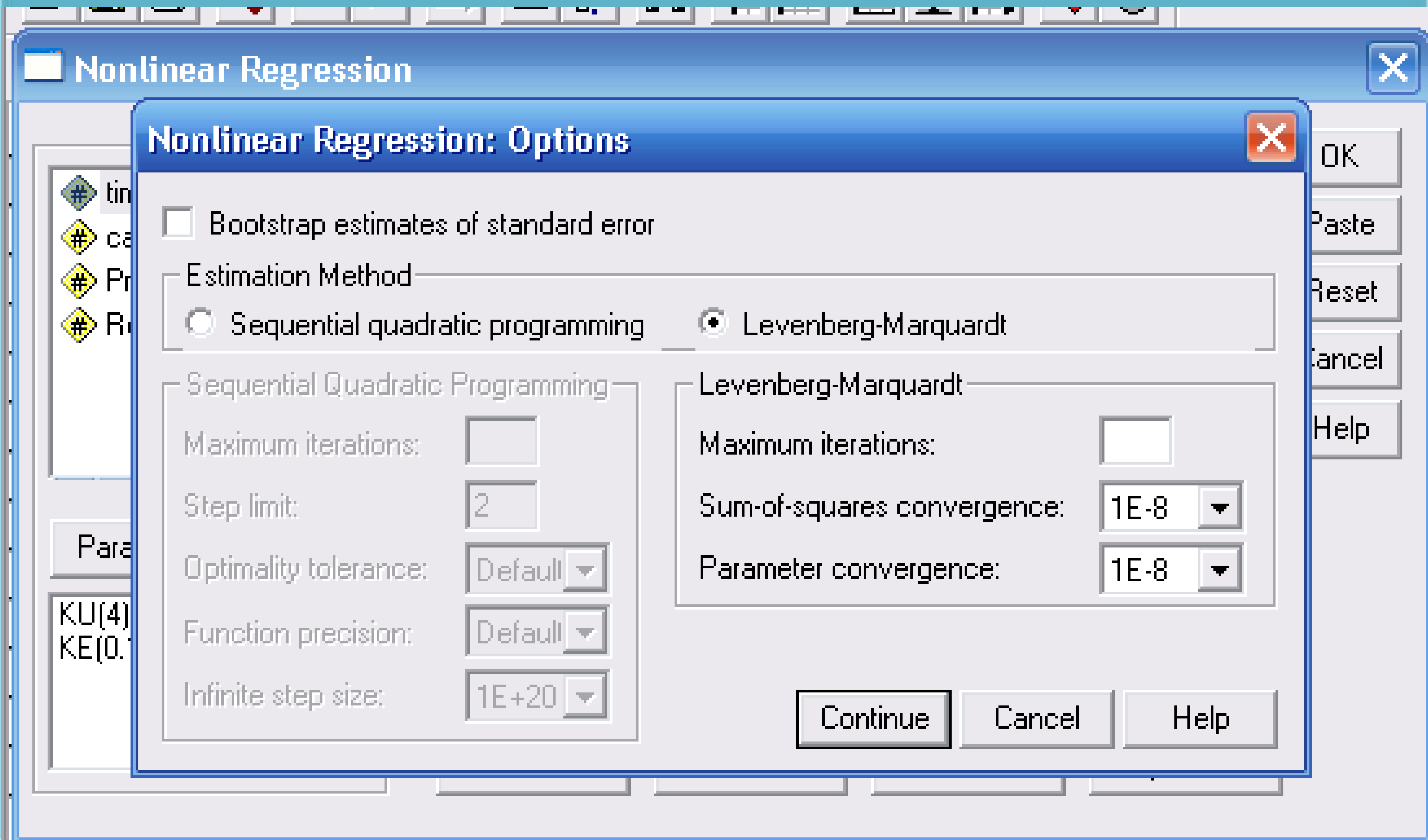
INITIAL (ESTIMATE) VALUE OF THE PARAMETER (2)



INITIAL (ESTIMATE) VALUE OF THE PARAMETER (3)



ESTIMATION PROCEDURE (algorithms, iterations, sensitivity)



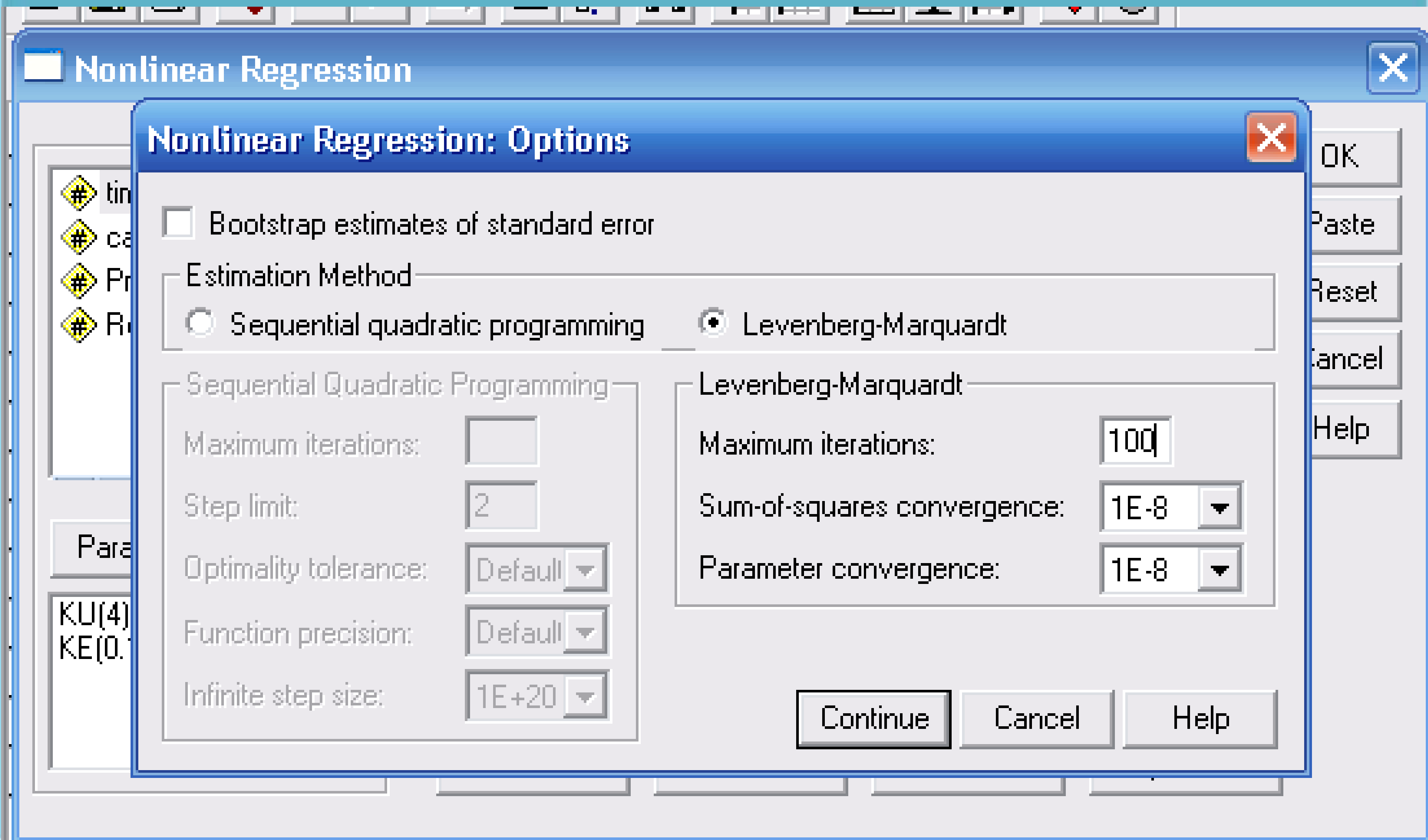
Iteration process

ku(1) .... ku(2)....ku(3).... ku(4).....
.........................ku(o-1).......ku(o)

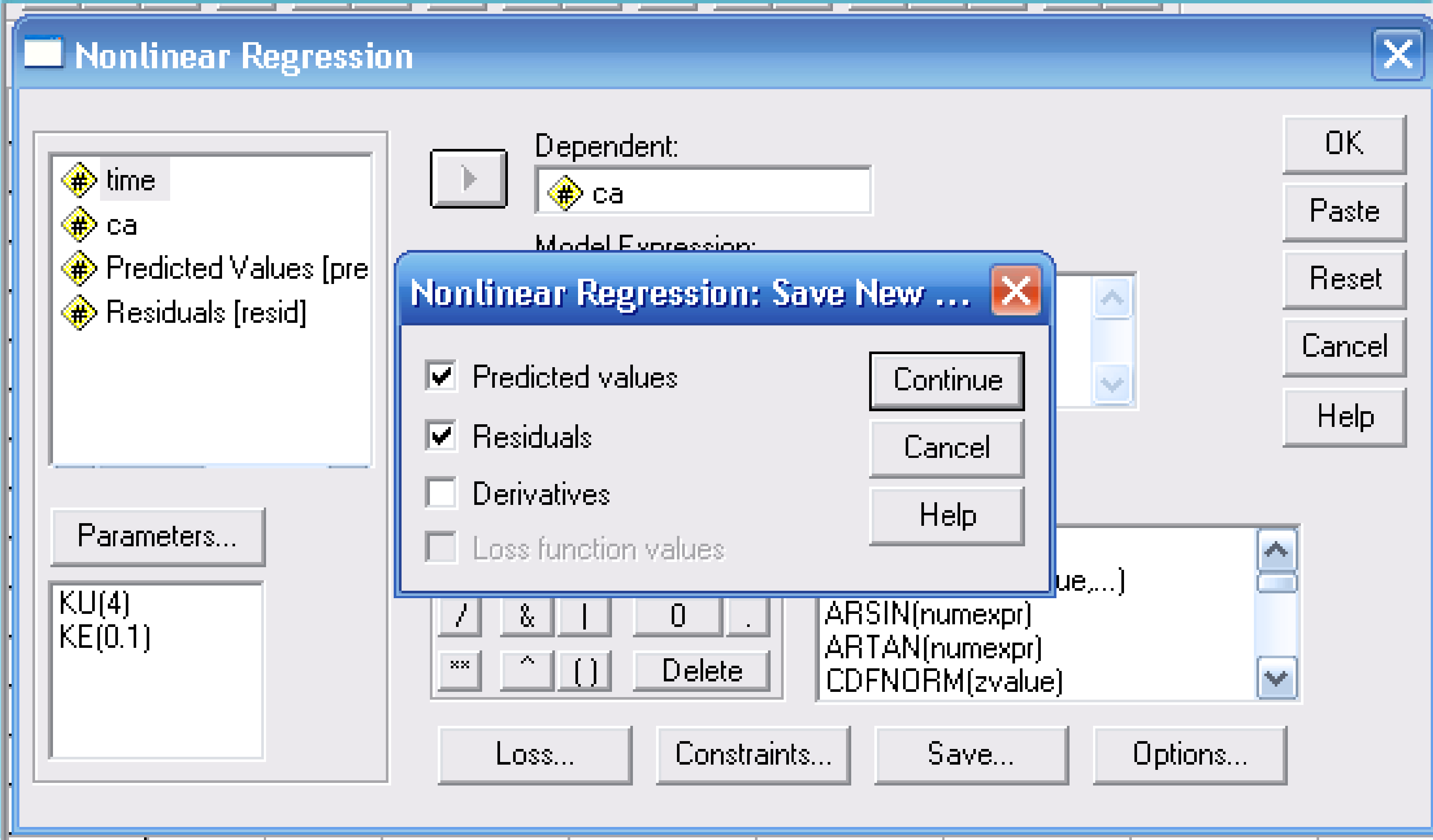
$< 1 \times 10^{-8}$

Ku(o) = ku optimum

NUMBER OF ITERATION



SAVING PREDICTED VALUES & RESIDUALS



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Non-linear Regression

All the derivatives will be calculated numerically.

The following new variables are being created:

Name	Label
PRED_1	Predicted Values
RESID_1	Residuals

Iteration	Residual SS	KU	KE
1	243.9776935	4.00000000	.100000000
1.1	154.1074970	5.61814910	.171690248
2	154.1074970	5.61814910	.171690248
2.1	143.7823735	5.54496196	.160166809
3	143.7823735	5.54496196	.160166809
3.1	143.6848572	5.61031957	.163439697
4	143.6848572	5.61031957	.163439697
4.1	143.6805519	5.59395216	.162688821
5	143.6805519	5.59395216	.162688821
5.1	143.6803067	5.59786037	.162867354
6	143.6803067	5.59786037	.162867354
6.1	143.6802930	5.59693934	.162825198
7	143.6802930	5.59693934	.162825198
7.1	143.6802923	5.59715734	.162835171

Run stopped after 14 model evaluations and 7 derivative evaluations.
Iterations have been stopped because the relative reduction between successive

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```
Run stopped after 14 model evaluations and 7 derivative evaluations.
Iterations have been stopped because the relative reduction between successive
residual sums of squares is at most SSCON = 1.000E-08


Nonlinear Regression Summary Statistics     Dependent Variable CA

  Source                     DF   Sum of Squares   Mean Square

  Regression                  2     10619.33681     5309.66840
  Residual                   16       143.68029        8.98002
  Uncorrected Total          18     10763.01710

  (Corrected Total)          17      1905.65576

  R squared = 1 - Residual SS / Corrected SS =     .92460

                                             Asymptotic 95 %
                            Asymptotic     Confidence Interval
  Parameter    Estimate     Std. Error     Lower          Upper

  KU         5.597157339   .672976652  4.170510568  7.023804111
  KE          .162835171   .029876905   .099498962   .226171380

  Asymptotic Correlation Matrix of the Parameter Estimates

                   KU         KE

  KU          1.0000      .9703
  KE           .9703     1.0000
```

Parameter Estimation

(SPSS for Windows 10.0)

- **ll the derivatives will be calculated numerically.**

Iteration	Residual SS	KU	KE
1	144.2117274	5.50000000	.160000000
1.1	143.6859841	5.61110738	.163502397
2	143.6859841	5.61110738	.163502397
2.1	143.6806092	5.59362163	.162673678
3	143.6806092	5.59362163	.162673678
3.1	143.6803099	5.59793821	.162870920
4	143.6803099	5.59793821	.162870920
4.1	143.6802932	5.59692098	.162824358
5	143.6802932	5.59692098	.162824358
5.1	143.6802923	5.59716166	.162835369

- **Run stopped after 10 model evaluations and 5 derivative evaluations.**
- **Iterations have been stopped because the relative reduction between successive residual sums of squares is at most SSCON = 1.000E-08**

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Curve Fitting

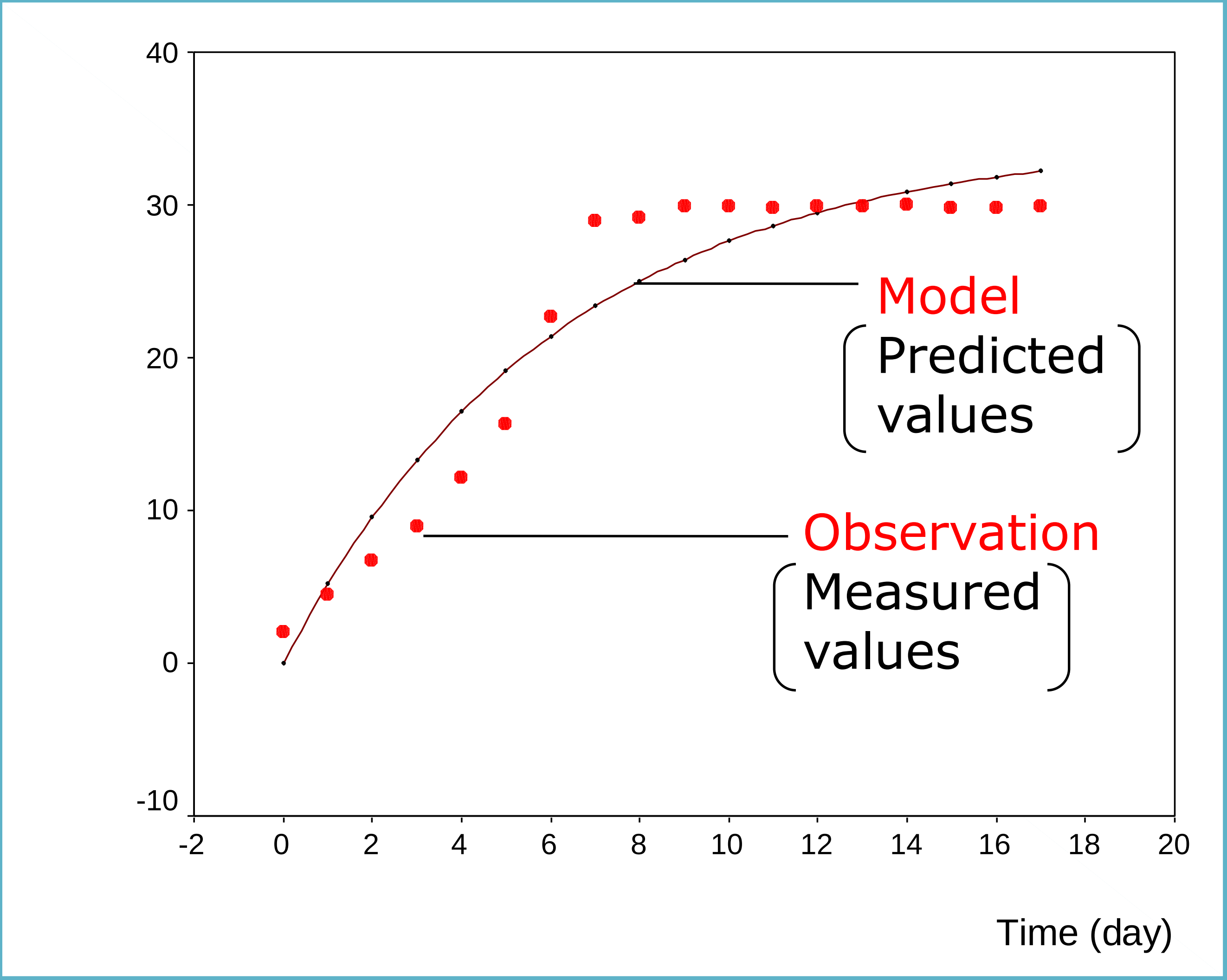

Figure 1. Dynamics of chemical concentration in organism

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Iteration	Residual SS	KU	KE
1	6606.044124	6.00000000	2.00000000
1.1	2.3679+301	-54.742782	-24.677153
1.2	89301381745	12.7747585	-.49618856
1.3	5693.251719	6.69601641	1.75940276
2	5693.251719	6.69601641	1.75940276
2.1	3989.165430	7.91880399	1.42238222
3	3989.165430	7.91880399	1.42238222
3.1	1579.618177	9.87011396	1.03883716
4	1579.618177	9.87011396	1.03883716
4.1	929.5788109	8.76624160	.591966797

Run stopped after 10 model evaluations and 4 derivative evaluations.
The iterations limit has been reached.

Single compartment model with time-varying input

In the real world situation, constant exposure to toxicants is a very special case. Mostly, levels of toxic substances released into environment are highly variable. Constant exposure will be realized only in the case of persistent toxicants in a well-buffered environment, *e.g.* heavy metals in soil. In almost all other cases, exposure is not constant. This may vary from erratic fluctuations to peaks followed by a gradual decrease. Concentrations of environmental pollutants can be variable due to varying rates of input and dilution, changes in chemical form and solubility, and degradation.

For non-persistent chemicals, such as pesticides, the half-life, or degradation time, is a very important variable determining ecological effects. Exposure concentrations in toxicity tests are characterized by an initial peak at time zero, followed by a gradual decrease. There is no theoretical framework for dealing with these non-constant exposures in the standard statistical analysis of concentration-response experiments.

Various terms have been used to describe the patterns of time-variable exposures, including pulse, plug, spike, episodic, fluctuating and intermittent exposures. In general these patterns can be simplified into two types of variable exposure: (1) pulse exposure which involves one or more isolated and brief exposure periods, and (2) fluctuating exposure which can be defined as a continuous exposure to varying toxicant concentrations .

The present model deals with a pulse exposure followed by exponential decay ("diluted pulse"). This type of exposure is not an uncommon phenomenon, and can be found both in terrestrial or aquatic environments. In the case of metal contamination in aquatic environments, such as urban streams, a decreasing exposure can occur when chemical discharges were released intermittently during production processes, so there will be a dilution driven by the flow and volume of water in the streams.

$$C_w(t) = C_{w_0}\, e^{-k_0 t} \qquad (13)$$

$$C_w(t) = C_{w0}\, e^{-k_0 t} \tag{13}$$

where:

Cw_0 = initial external concentration (*e.g.* in µg/g),

k_0 = rate constant for degradation of the chemical in the medium (*e.g.*, in day^{-1}).

The second assumption is that the kinetics of the concentration in the body follow a one-compartment model. This can be written as:

$$\frac{dC_a}{dt} = k_1 C_w(t) - k_2 C_a(t) \tag{14}$$

where $\mathbf{C_a(t)}$ = internal concentration at time **t**, $\mathbf{k_1}$= rate constant for uptake,

$\mathbf{k_2}$= rate constant for elimination, and other loss processes from the body, such as metabolism.

$$\frac{dC_a}{dt} = k_1 C_w(t) - k_2 C_a(t) \qquad (14)$$

where $\mathbf{C_a(t)}$ = internal concentration at time $\mathbf{t}$, $\mathbf{k_1}$= rate constant for uptake, $\mathbf{k_2}$= rate constant for elimination, and other loss processes from the body, such as metabolism.

Most toxicity experiments start with animals transferred from a clean environment, so equation (2) can be integrated with the initial condition, $C_a(0) = 0$. Application of standard techniques (*e.g.* Laplace transforms, see Jacques, 1972), yields:

$$C_a(t) = \frac{k_1 Cw_0}{k_2 - k_0}\left(e^{-k_0 t} - e^{-k_2 t}\right) \qquad (15)$$

(for the application, see Widianarko & van Straalen, 1996)

TERIMAKASIH

Kontak: widianarko@unika.ac.id

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