Estimate of No Effect Concentrations from exposure experiments

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1. Introduction

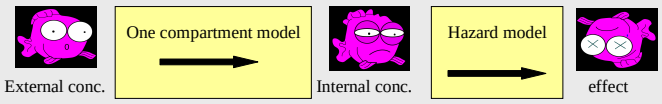
When a No Effect Concentration (NEC) is estimated from exposure data as a parameter in a model it is assumed that all individuals have the same NEC. We assigned each individual exposed organism its own NEC and we investigated to what extent individual differences in NEC affect the estimates of a NEC in the model for survival.

We used a process-based model (survival has to be followed in time) with a toxicological threshold (the NEC) that is already in use under the name DEBtox. We used a more elaborate form of the basic DEBtox model and extended it to cope with differences in the NEC of individual organisms.

2. Approach

Survival datasets were simulated for a variety of toxicological parameters, using Monte Carlo techniques. From these datasets the toxicological parameters were re-estimated with the same model enabling a comparison of the estimated parameters with their true values.

In the model we assume a gradual increase of the internal concentration in an organism in time (when exposed to a fixed external concentration). When the internal concentration exceeds a certain threshold (the internal NEC) the survival probability will start to increase compared to the control.



The model contains four parameters (all independent of time):

- the blanco killing rate, λ (dim: day^{-1})
- the no effect concentration, NEC (dim: µg/l)
- the killing rate, k_f (dim: $(\mu g/l)^{-1}day^{-1}$)
- the elimination rate, k_e (dim: day^{-1})

A fifth parameter, the standard deviation in the assumed lognormal distribution in the NEC, s_c (dimensionless), was added to investigate the properties of the estimates of the NEC. This parameter could also be estimated from the survival datasets.

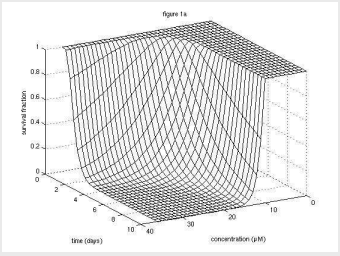


Fig 1a Identical NEC for all individuals, giving a sharp edge going from no effect to effect

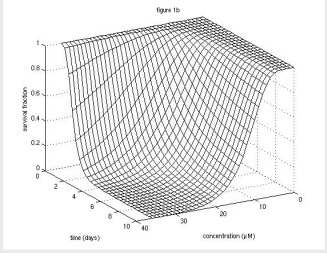
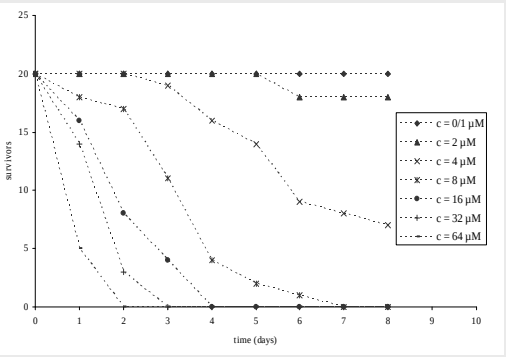


Fig 1b All individuals have their own NEC, derived from a lognormal distribution in the individual NEC values. Leading to a smooth transition from no effect to effect.

3. Example



Example of a calculated survival dataset.

Parameters:

NEC = 1.5 µM

k_f = 0.1 $\mu M^{-1}day^{-1}$

k_e = 0.4 day^{-1}

λ = 1 E-5 day^{-1}

4. Results

We derived a typical standard deviation in the assumed log-normal distribution in the NEC from survival measurements of 0.1, with a maximum of 0.32.

We run the simulations with a standard deviation of 0, 0.2, 0.5, 1 and 1.5. The result for sc values of 0.2, 0.5, 1.0 and 1.5 is shown in table 1.

Table 1 Simulation result with different values for the standard deviation in the lognormal distribution of the NEC

(exposed organisms/conc = n, k_f = 0.3, k_e = 0.2, λ = 0.05)

(c = 0, 1, 2, 4, 8, 16, 32 µM, t = 0 – 9 days)

true mean NEC = 1.0

n	estimated mean NEC	s_c true value	estimated s_c
20	1.09 (0.45)	0.2	0.14 (0.18)
20	0.97 (0.35)	0.5	0.33 (0.22)
20	1.00 (0.52)	1.0	0.77 (0.18)
20	1.42 (2.18)	1.5	0.81 (0.27)
50	0.98 (0.26)	0.2	0.16 (0.17)
50	0.95 (0.22)	0.5	0.44 (0.18)
50	1.04 (0.39)	1.0	0.85 (0.16)
50	1.47 (1.25)	1.5	0.81 (0.34)
100	1.00 (0.12)	0.2	0.20 (0.15)
100	0.92 (0.21)	0.5	0.43 (0.15)
100	0.89 (0.32)	1.0	0.85 (0.14)
100	1.16 (0.94)	1.5	0.85 (0.08)

The estimate of a NEC from survival data is robust, also when there are much larger differences between individual organisms than we encountered in the survival measurements. The standard deviation in the assumed lognormal distribution in the NEC itself can also be estimated from survival data but when it gets higher than 1 the true value is underestimated.

5. Summary and Conclusions

We tested the properties of the estimates of the NEC from an toxicity experiment when each individual organism in an exposure experiment was assigned an individual NEC, based on a log normal distribution.

•It proved that the derivation of a NEC from exposure data is robust either with a sharp or a smooth transition from no effect to effect.

•The standard deviation in the lognormal distribution in the NEC itself can also be estimated from survival datasets but the experimental setup has to be elaborate.

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