WP 4.1: Modelling effects of mixtures of compounds

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2006/10/02

This document summarises the progress in WP 4.1 since its start at 2005/10/01. Work in this package was in close collaboration with Mieke Broerse, Kees van Gestel, Daniel Bontje and Bob Kooi.

1 Results for RP3

We modelled the effects of mixtures of compounds on the survival of organisms using biology-based methods [5], which relate effects of compounds on the hazard rate of organisms to their internal concentrations. This model, therefore, involves a toxico-kinetic module, which is here taken to be a one-compartment model for simplicity's sake. We started to write a review on physiology-based toxico-kinetic models [4]. The interaction of compounds is taken to be proportional to the product of their internal concentrations. This way of modelling interactions originates from Taylor's theorem of the approximation of "smooth" functions by polynomials, and is standardly applied in the analysis of variance (ANOVA). The parameters of the model can be obtained from data using the Maximum Likelihood (ML) methods. We wrote code to apply the model as part of the DEBtool software package, that can be downloaded from `http://www.bio.vu.nl/thb/deb/deblab/`. This code also provides estimates for the variance-covariance matrix of the parameter values. The model turns out to have nice statistical properties. The code allows a variety of algorithms for the calculation of the ML estimates (scoring, simplex, genetic algorithms), varying from fast to robust. The use of these procedures, however, does require some experience.

We applied the model, using DEBtool, to data on the binary mixture of metal (Cu, Cd, Pd & Zn) on the survival of the springtail *Folsomia candida*, and found that the irreversible-binding variant of the model fitted the data best, and that the fit was very good indeed. We concluded that none of these metals showed interactions, except the mixture Cu & Pb, which showed slightly a antagonistic interaction.

The results are submitted for publication [1].

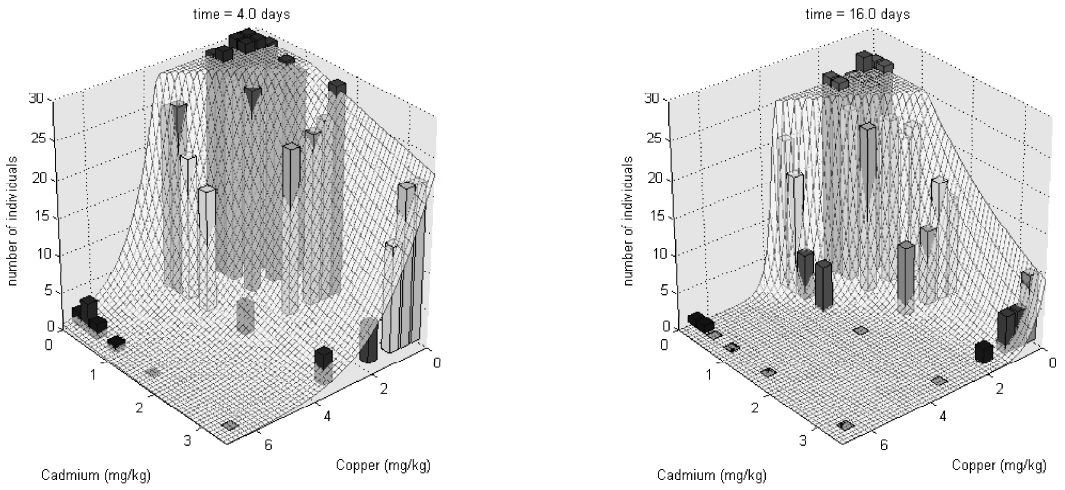

Figure 1: The survival frequency of *Folsomia candida* in a mixture of Cu & Cd at 4 (left) and 16 (right) day of exposure. All daily data are fitted simultaneously for the full period of 21 d of exposure.

2 Results for RP4

The OECD (Branschweig 1996) recommended the development of exposure-time explicit methods. This extension of the biology-based methods does exactly that, and it is still the only method that does so for lethal and sublethal effects in a single framework.

We developed theory for the derivation of the toxicity for compounds as function of their chemical properties of compounds. This theory has close links with other theory that we developed for the co-variation of parameter values across species. This paper [3] discusses the interrelationships between the two pieces of theories, which can be very useful for filling gaps in our knowledge on behalf of risk assessment applications.

We also did research on the effects of variation of parameter values among individuals, focusing on the statistical consequences for such a variation on the No Effect Concentration (NEC) [2]. We showed that NEC-estimates are really robust for such changes, and, therefore, the NEC is a natural successor of the still widely used No-Observed Effect Concentration. The OECD and the ISO recommended out-phasing on this misleading concept.

3 Publications since start at 2005/10/01

[1] J. Baas, B. P. P. van Houte, C. A. M. van Gestel, and S. A. L. M. Kooijman. Modelling the effects of binary mixtures on survival in time. *Environmental Toxicology & Chemistry*, 2006. subm 2006/08/24.

[2] J. Baas and S. A. L. M. Kooijman. The statistical properties of NEC estimates if values scatter among individuals. *Water Research*, 2006. in prep.

[3] S. A. L. M. Kooijman, J. Baas, D. Bontje, M. Broerse, T. Jager, C. van Gestel, and B. van Hattum. Scaling relationships based on partition coefficients and body sizes have similarities and interactions. *SAR and QSAR in Environ. Res.*, 2006. to appear.

[4] S. A. L. M. Kooijman, J. Baas, D. Bontje, M. Broerse, B. W. Kooi, B. van Hattum, C. van Gestel, and T. Jager. Toxico-kinetic models for ecotoxicological applications. *Ecotox. Environ. Saf.*, 2006. in prep.

[5] S. A. L. M. Kooijman, J. J. M. Bedaux, A. R. R. Péry, and T. Jager. Biology-based methods. In H. Magaud, editor, *Current approaches in the statistical analysis of ecotoxicity data: A guidance to application.*, volume 54, TC 147/ SC 5/ WG 10/ N0390 of *Series on Testing Assessment*, chapter 7. ISO and OECD, Paris, 2004.