



Energy-based modelling to assess effects of chemicals on *Caenorhabditis elegans*: A case study on uranium



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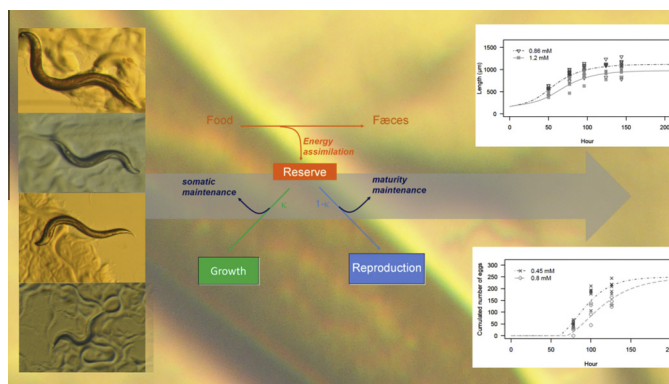
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HIGHLIGHTS

- We proposed an improved bioenergetic model to assess effects on nematodes.
- The numerical behaviour of this model was evaluated.
- The model proved to handle a wide range of plausible biological parameters values.
- Uranium is likely to decrease the assimilation of energy by *C. elegans*.

GRAPHICAL ABSTRACT



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ABSTRACT

The ubiquitous free-living nematode *Caenorhabditis elegans* is a powerful animal model for measuring the evolutionary effects of pollutants which is increasingly used in (eco) toxicological studies. Indeed, toxicity tests with this nematode can provide in a few days data on the whole life cycle. These data can be analysed with mathematical tools such as toxicokinetic-toxicodynamic modelling approaches. In this study, we assessed how a chronic exposure to a radioactive heavy metal (uranium) affects the life-cycle of *C. elegans* using a mechanistic model. In order to achieve this, we exposed individuals to a range of seven concentrations of uranium. Growth and reproduction were followed daily. These data were analysed with a model for nematodes based on the Dynamic Energy Budget theory, able to handle a wide range of plausible biological parameters values. Parameter estimations were performed using a Bayesian framework. Our results showed that uranium affects the assimilation of energy from food with a no-effect concentration (NEC) of 0.42 mM U which would be the threshold for effects on both growth and reproduction. The sensitivity analysis showed that the main contributors to the model output were parameters linked to the feeding processes and the actual exposure concentration. This confirms that the real exposure concentration should be measured accurately and that the feeding parameters should not be fixed, but need to be reestimated during the parameter estimation process.

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1. Introduction

The evaluation of the long term effects of pollutants on the environment is required for an effective protection of the

ecosystems. According to Yeates and Bongers (1999), a useful bioindicator of ecosystemic stress should be the nematodes since they are abundant key decomposers in soil ecosystem. Within this phylum, a powerful animal model for measuring the effects of pollutant is the ubiquitous free-living nematode *Caenorhabditis elegans*. It measures 250 μm at hatching and up to 1.4 mm at adult stage. It has several advantages for ecotoxicological assessment such as (i) a short life cycle (*C. elegans* breeds in three days after hatching at 20 °C), (ii) a short life span (21 days at 20 °C), and (iii) a high fecundity (Byerly et al., 1976). *C. elegans* allows the assessment of life-history traits such as length, reproduction, or survival at various time steps during an experimentation. Therefore, this nematode is widely used to produce data for the assessment of chemical effects on the environment (Smith et al., 2009; Boyd et al., 2010; Swain et al., 2010; Dutilleul et al., 2013; Goussen et al., 2013).

The assessment of (eco) toxicological data through models based on the Dynamic Energy Budget (DEB) theory (Kooijman and Bedaux, 1996; Billoir et al., 2008b), known as DEBtox models is relevant to assess the effects of toxic compounds on organisms. Indeed, this method allows the simultaneous modelling of multiple endpoints (growth and reproduction) and the parameters estimated are independent of the exposure time (Jager et al., 2004; Billoir et al., 2008b). Such models can be used to assess physiological modifications (e.g. changes in growth rate, maximal length, reproduction rate, cumulated reproduction) (Billoir et al., 2008a; Massarin et al., 2011; Augustine et al., 2012a), or differential life strategy responses (Alda Álvarez et al., 2005) of an organism exposed to a pollutant. DEB modelling can also be adapted to other types of analysis. Thereby, individual based model (IBM) based on DEB modelling can permit to analyse population level data, especially multi-generation studies (Beaudouin et al., 2012; Martin et al., 2013).

Uranium, a pollutant of growing interest (OECD and International Atomic Energy Agency (IAEA), 2012), is a radioactive heavy metal that can be found naturally in the environment. It is both a chemical and a radiological toxic but its chemical toxicity is considered to be dominant (Sheppard et al., 2005; Zeman et al., 2008).

We recently produced multi-generation data for nematodes exposed to uranium (Goussen et al., 2013). These data will be analysed with a DEBtox model for nematodes. Prior to this, we had to propose a relevant and robust DEBtox modelling approach for nematodes. This is the aim of this paper.

Jager et al. (2005) presented a DEB model applied to the nematode. This model has been adapted to the assessment of ecotoxicological data (resulting in a so called DEBtox model) and used several times (Alda Álvarez et al., 2005, 2006; Swain et al., 2010). In the present study, we proposed an augmented version of the DEBtox equations for nematodes by Jager et al. (2005) based on biological characteristics that were not covered. We evaluated both nematode DEBtox models to analyse data on the effects of the uranium on the free living nematode *Caenorhabditis elegans*. We also assessed the output robustness and sensitivity to parameters.

2. Materials and methods

Experimental data were extracted from (Goussen et al., 2013). Extended description is presented in supplementary information.

2.1. Model description

The Dynamic Energy Budget (DEB) theory (Kooijman, 2010) is based on a mathematical description of the uptake and use of energy within an organism. The general DEB framework generally predicts that individuals' growth follows a von Bertalanffy growth curve provided feeding is *ad libitum* or at constant density

(Kooijman, 2010) and the growth is isomorphic (*i.e.* the organism shape do not change with growth). However as demonstrated by Byerly et al. (1976), *C. elegans* growth curve deviates from the expected von Bertalanffy curve. According to Knight et al. (2002), the *C. elegans* buccal cavity grows in a stepwise manner at each moult whereas the rest of the body growth is linear between the moults. Knight et al. (2002) assumed that this process induces a food limitation thus resulting in an initial growth slower than the later growth. Jager et al. (2005) dealt with this particularity assuming the *C. elegans* ingestion rate follows a size-dependent feeding limitation function and incorporated this in their nematode DEB model. These authors also assumed an immediate stop of the reproduction when the sperm runs out. Nevertheless, experimental data do not show an immediate stop of reproduction, but rather a more smooth transition (see for example Byerly et al. (1976) Figs. 6 and 8 and Muschiol et al. (2009) Fig. 2). We here propose two modifications of this set of equations in order to take into account some known biological specificities of the nematode. (i) The *C. elegans* male gamete limitation induces a progressive stop of the egg laying (Maupas, 1900; Ward and Carrel, 1979). (ii) We also modified the size-dependent feeding limitation function by adding a new parameter which allows the nematode to access food whatever its length. Indeed, the approach from Jager et al. (2005) assumed that a small nematode would never be able to access enough food to growth if food is just sub-optimal (see section results in this paper). With our approach, we assumed that this nematode will be able to access to a sufficient small quantity of food, such as small bacteria (bacteria is the main food source of *C. elegans* Abada et al., 2009), to initiate growth. The set of equations in our DEBtox model for nematodes is thus:

$$s_f(l) = \alpha \left[1 - \left(1 + \frac{l_f^3}{l^3} \right)^{-1} \right] \quad (1a)$$

$$\frac{dl}{dt} = r_B [(1 - s_f)f - l] \quad (1b)$$

$$\frac{dR}{dt} = \frac{R_M}{1 - l_p^3} \left[\frac{g + l}{g + (1 - s_f)f} (1 - s_f)fl^2 - l_p^3 \right] \frac{R_{Max} - R}{R_{Max}} \quad (1c)$$

with s_f the size-dependent ingestion limitation function, $(1 - \alpha)$ the proportion of food available whatever the length, r_B (h^{-1}) the von Bertalanffy growth rate, f the actual ingestion rate divided by the maximal ingestion rate for a body size, R (#) the cumulated reproduction, R_{Max} (#) the maximal cumulated reproduction, R_M ($\# \text{h}^{-1}$) the maximum reproduction rate, and g (-) the investment ratio. L (μm) represents the body length at time t , L_0 (μm) the body length at birth (*i.e.* the start of feeding in the DEB framework), L_f (μm) the body length at which the ingestion rate is half the maximum ingestion rate, and L_p (μm) the body length at puberty. All these length data are scaled by the maximal length L_{inf} (μm) resulting in scaled parameters l , l_0 , l_f , and l_p (-).

The internal concentration of the pollutant scaled by the ratio between the uptake rate and the elimination rate (which can be regarded as the bioconcentration factor; Péry et al., 2001), c_q , has been calculated as described by Kooijman and Bedaux (1996). These authors described a one-compartment toxico-kinetic model with growth dilution, chemical exchanges depending on a surface area:volume ratio, and an elimination rate depending on food availability. This equation has been modified with the s_f function resulting in the following equation:

$$\frac{dc_q}{dt} = C \frac{k_e(1 - s_f)f}{l} - c_q \left[\frac{k_e(1 - s_f)f}{l} + \frac{d \ln l^3}{dt} \right] \quad (2)$$

where k_e (h^{-1}) is the elimination rate and C (mM) the real exposure concentration. The toxic stress function, s , was calculated as

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