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Comparison of models to analyze mortality data and derive concentration–time response relationship of inhaled chemicals

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ABSTRACT

The derivation of thresholds for lethal effects for inhaled chemicals is a key issue in accidental risk management because they largely determine the outcome of land use planning, among which localization of habitations in the vicinity of a factory. This derivation is generally performed on the basis of rodent lethality data analyzed by statistical models able to extrapolate effects for different times and concentrations of exposure. A model commonly used in France is the standard probit model. In this model, effects is related to exposure concentration and duration according to the Haber's law and considers that individual thresholds, corresponding to the maximum tolerated effects before dying, are log-normally distributed among the population. This approach has been criticized for its lack of biological parameters and its inability to treat data characterized by only one time of exposure. In order to improve the current state of modeling, we proposed three alternative models. Two of them (DEBtox and Haber-TKTD models) incorporate the kinetics of the chemicals. The third one (Loguniform model) is a linearization of the standard probit model. We evaluated their performance by analyzing real data and simulated data generated with each model. For data characterized by several times of exposure, the standard probit model outperformed all other models in terms of goodness of fits and estimation of parameters. For data characterized by only one time of exposure, only DEBtox model was able to fit the data and estimate parameters, provided we dispose of several observation times, typically just after exposure and a long period afterwards.

1. Introduction

To prevent risks related to accidental releases of dangerous chemical substances in the atmosphere, risk managers need acute toxicity thresholds in association with accident scenarios to produce safety reports and design emergency plans. In France, they usually determine the zones of lethal, irreversible and reversible effects relative to the location of plants storing, producing or using toxic substances, especially for land use planning. The lethality threshold is related to a certain percentage of death occurring during the experimental test or in the following 14 days post-exposure (including animal sacrificed for ethical reasons). The "irreversible effects" correspond to the persistence over time of a lesion or a functional damage induced by an exposure. Three types of irreversible effects are pointed out, lesion without functional repercussions, lesion with functional repercussions (like bronchopneumopathy, pulmonary fibrosis, necrosis of olfactory epithelium with anosmia) and the functional irreversible impairment (like asthma). The "reversible effects" correspond to a return to the level of health prior to exposure (immediately or in a reasonable time after).

It is therefore crucial to evaluate properly the thresholds, because they determine the distances of effects. Indeed, if the thresholds are overestimated, distances are overprotective with economic impact. In contrast, if the thresholds are underestimated, the health of the exposed population is threatened.

A French methodology was developed to evaluate the quality of the data available and to deduce from these data acute toxicity thresholds. It comprises many steps. The first step is the selection of an experimental key study (mainly, an animal study) for each effect, based on the method developed by Klimisch et al. (1997) for quality assessment and on expert judgment for relevance of the observed effects related to the type of threshold. The second step consists in finding the relevant critical toxic effect for the two types of effects which are considered in addition to lethal effects, *i.e.* irreversible and reversible effects. The third step is the data analysis based on a statistical model. The fourth step considers the extrapolation from animals to humans (with or without uncertainty factors). Here we focus on lethality data only.

Usually, the data to analyze are rodent lethality measurements for different exposure concentrations and different exposure durations, observed after at least a 14 day period. It can however happen that the information is available only for single exposure duration.

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Standard dose–response models are generally based on the Haber's law, or its generalizations (ten Berge et al., 1986). These generalizations state that the effect for exposure to concentration C during a period of time t is a function of $(C^n t)$, named fixed effect level (Jarabek, 1995), where n is called the Haber constant. Thus, in the standard probit model, the probability of death equals:

$$P(\text{death}) = F\left(\frac{n\log(C) + \log(t) - \mu}{\sigma}\right)$$

where F is the cumulative distribution function of a normal distribution with mean μ and standard deviation σ (Diack and Bois, 2005). In this formulation, each individual has a given threshold, log-normally distributed. If he is exposed to an effect level exceeding this threshold, death will occur.

There are many limits to this model. First, it is not possible to analyze data for which only one exposure time is available, because only two combinations of parameters (n/σ and $(\log(t) - \mu)/\sigma$) could be identified in this case. This model has also been criticized for its lack of biological parameters by Diack and Bois (2005) who have proposed an alternative model (the so-called PKPD model). However, the model they propose has even more limitations in a risk assessment perspective.

First, the gain in terms of realism compared to the standard probit approach is far from obvious. Indeed, the proposed equation for kinetics is the following one:

$$\frac{dQ}{dt} = kaC^n - keQ$$

with Q the internal quantity of substance in the tissue, C the exposure concentration, k_a the pulmonary ventilation rate, k_e the elimination rate, and n an unknown parameter analogous to the Haber constant. This is a very unusual kinetics equation, because there is no reason for the parameter n to be different from 1, *i.e.* for the intake rate of the substance not to be proportional to its concentration in the air. Authors try to justify their equation with some biological consideration in their discussion, but their reasoning would be acceptable only for very rapid kinetics.

Second, there are five parameters to estimate (k_a, k_e, n, but also μ and σ as in the probit model), compared to the three ones in the probit approach. In practice, when analyzing data for accidental risk assessment, with both the PKPD model and the standard probit model, we found that the common parameters have similar estimates but that the remaining parameters have large confidence intervals. This observation indicates an excessive number of parameters to estimate. In particular, the estimation of the kinetics parameters is not feasible when only data for one time of exposure are available.

Here, we propose to evaluate three alternative models. These models have the same numbers of parameters (three) as the standard probit model. The first two models incorporate chemical kinetics through a one-compartment model to add realism relative to compound uptake and elimination. They differ in the toxicodynamics part. The first one, which is called DEBtox (Bedaux and Kooijman, 1994), is based on a threshold approach which has already been used in ecotoxicology. The second one is based on the Haber's law and will be here referred to as Haber-TKTD. The third approach we propose is an approximation of the probit standard by using a loguniform statistical distribution for F instead of a normal one. The comparison of the models we propose is based on the analysis of datasets generated from simulations with each of the models and on actual data which have already been used to derive toxicity threshold for accidental risk assessment.

2. Materials and methods

2.1. Mathematical models to analyze survival data

2.1.1. Standard probit

As already presented in the introduction, in the standard probit model, the probability of death equals:

$$P(\text{death}) = F\left(\frac{n\log(C) + \log(t) - \mu}{\sigma}\right)$$

where F is the cumulative distribution function of a normal distribution with mean μ and standard deviation σ. It consequently assumes that the individual threshold for response follows a lognormal distribution. When the product $C^n t$ exceeds its threshold, the individual dies.

2.1.2. Loguniform model

In this model, the probability of death equals:

$$P(\text{death}) = F\left(\frac{n\log(C) + \log(t) - a}{b - a}\right)$$

where F is the cumulative distribution function of an uniform distribution with lower and upper bounds 0 and 1, and where a and b are bounds of the response. As for the standard probit, when the product $C^n t$ exceeds the threshold of an individual, the individual dies. There is no individual having a threshold below a and above b, which means that no individual are expected to die for $C^n t$ values below a and no individual are expected to survive for $C^n t$ values over b. The Loguniform model can be seen as a linearization of the standard probit model. The comparison will permit to assess the relevance of the choice of the statistical distribution for F.

2.1.3. DEBtox model

DEBtox model is a mathematical model that has first been developed to analyze aquatic ecotoxicological survival data. It has been proposed by Bedaux and Kooijman, 1994. It is particularly adapted for the analysis of toxicological data obtained under time-varying exposures (Pery et al., 2001, 2002).

In DEBtox model, a kinetics module, accounting for the dynamics of compound body concentration is coupled with an effects module. To keep the same number of parameters as for the standard probit, we assumed, as in the standard DEBtox model, that all individuals have a common threshold for effects. Once this threshold is exceeded by the dose at target organ level, the probability to die is not 100% but increases linearly as a function of this dose.

Dose at target level is described using the following linear one-compartment kinetics model:

$$\frac{dc_i}{dt}(t) = k_e(C(t) - c_i(t))$$

where k_e is the elimination rate, C is the concentration measured in exposure air, and c_i the scaled body concentration. This parameter corresponds to the ratio of the amount of compound in the whole body to the body volume. It is scaled by the bioconcentration factor (a constant corresponding to the ratio of the concentration in the target organ to the concentration in air at toxicokinetics steady state) in order to ensure the feasibility of parameters estimation. Toxic effects occur only when $c_i(t)$ exceeds a threshold, the No Effect Concentration (*NEC*), which corresponds to the maximal toxicant concentration at target organ level that can be handled by regulation systems without generating detectable effects on mortality. Survival probability in exposed organisms is described based on $c_i(t)$, which drives toxicodynamics. Death being assumed to be a