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Evaluation of effects of long term exposure on lethal toxicity with mammals

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ABSTRACT

The relationship between exposure time (LT_{50}) and lethal exposure concentration (LC_{50}) has been evaluated over relatively long exposure times using a novel parameter, Normal Life Expectancy (NLT), as a long term toxicity point. The model equation, $\ln(LT_{50}) = aLC_{50}^{v} + b$, where a, b and v are constants, was evaluated by plotting $\ln LT_{50}$ against LC_{50} using available toxicity data based on inhalation exposure from 7 species of mammals. With each specific toxicant a single consistent relationship was observed for all mammals with v always <1. Use of NLT as a long term toxicity point provided a valuable limiting point for long exposure times. With organic compounds, the Kow can be used to calculate the model constants a and v where these are unknown. The model can be used to characterise toxicity to specific mammals and then be extended to estimate toxicity at any exposure time with other mammals.

1. Introduction

Toxicity is generally a function of exposure time and concentration or dose (Baas et al., 2010; Connell and Yu, 2008; McCarty et al., 2011; Tennekes and Sanchez-Bayo, 2011; Zhao and Newman, 2004). However, conventionally exposure time is usually kept constant and not used as a quantifiable variable in toxicological studies (Rozman and Doull, 2000; 2001). In relatively fewer studies time has been studied as a quantifiable variable but these are limited to short term exposure only. In environmental investigations the effects of relatively long exposure times, often over a lifetime or decades, are of particular importance. In some instances the presence of toxicant in very low concentrations can cause toxic effects if the exposure time is relatively long (Tennekes, 2010). Nevertheless information related to effects of long term exposure is scarce in the scientific literature (Simonton and Spears, 2007; Townsend and Maynard, 2002).

The relationship ($C \times t = k$) proposed by Haber (1924) is regarded as the first relationship established between exposure concentration (C) and time to a specific effect (t), where k is a constant for a given system. According to this relationship, when exposure concentration is C, then t is the exposure time to a fixed level of adverse biological (often lethality) response and at a continuous and constant exposure concentration, the product (k) will be a constant (Druckrey and Kupfmuller, 1948; Haber, 1924; Ostwald and Dernoscheck, 1910; Rozman, 1999; Saghir et al., 2005). However some observers have concluded that Haber's rule is not always followed, especially when exposure concentration is relatively low and/or exposure time is very long (Druckery, 1967; Gardner et al., 1979; Henschler, 1984; Hulet et al., 2007; Kodavanti et al., 1997; Mioduszewski et al., 2002).

A reduced life expectancy (RLE) model based on the influence of exposure time has been developed to study the effects of relatively long exposure times (Chaisuksiant et al., 1997; Connell and Yu, 2008; Yu et al., 1999). The model establishes a linear relationship between the Internal Lethal Concentration (ILC_{50}) and the natural log of the exposure time with the normal life expectancy of the organisms as a limiting point. The RLE model has been evaluated with fish and zooplanktons using data from the scientific literature by plotting $\ln LT_{50}$ (exposure time required for 50% of the organisms to die) against LC_{50} (lethal concentration to 50% of organisms) in ambient water (Verma et al., 2011, 2012). The RLE model successfully fitted most of the fish and zooplankton data sets. However some sets of data were best fitted by a two stage version of the RLE model (Verma et al., 2012). Reduction in life expectancy of terrestrial animals as a measure of toxicity has also been reported by Rozman et al. (2005) while studying effects of chronic exposure of heptachlorobenzo-p-dioxin on rats.

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Only aquatic organisms were evaluated in the research described above, however there is a need to evaluate effects of long term exposure on toxicity by the RLE model with terrestrial organisms. Thus the objective of this current research was to evaluate the application of the RLE model to terrestrial animals using data from the scientific literature.

2. Theory

2.1. Reduced life expectancy (RLE) model

The original RLE model was based on a linear relationship between Internal Lethal Concentration (ILC_{50}) and the natural logarithm of the corresponding exposure time (LT_{50}) (Yu et al., 1999). The relationship could be described by the equation given below,

$$ILC_{50} = [\ln(NLT) - \ln(LT_{50})]/d \quad (1)$$

where LT_{50} is the exposure time; ILC_{50} the Internal Lethal Concentration causing the death of 50% of the organisms exposed for the time LT_{50}; NLT is the normal life expectancy of the organisms without exposure and d is a constant. Constant d is a measure of toxicity representing the reduction in life expectancy of the organism per unit concentration of the toxicant.

However the limited availability of ILC_{50} data in the scientific literature (Maeder et al., 2004) restricted the evaluation of the RLE model. Therefore the relationship was extended from using ILC_{50} to using LC_{50} with the proposal that the relationship between LC_{50} and exposure time period (LT_{50}) could be used to estimate the reduction in life expectancy of organisms. The concentration of toxicant in ambient water and internal concentration both are interrelated parameters (Connell and Yu, 2008). Thus,

$$LC_{50} \propto ILC_{50} \quad (2)$$

Where LC_{50} is the lethal concentration in water and ILC_{50} is the corresponding Internal Lethal Concentration (ILC_{50}).

The relationship obtained after replacing ILC_{50} with LC_{50} in Equation (1) was given below:

$$LC_{50} = [\ln(NLT) - \ln(LT_{50})]/d \quad (3)$$

So

$$LC_{50} = a\ln(LT_{50}) + b \quad (4)$$

Where a is $-1/d$ and b is $\ln(NLT)/d$

According to this model, in a toxicant free environment (at LC_{50} zero) organisms would be expected to live their normal life expectancy (NLT).

2.2. Nonlinear RLE model

The original RLE model was based on the concept that there was a linear relationship between exposure time period (LT_{50}) and concentration (LC_{50}). However, nonlinear relationships between LT_{50} and LC_{50} have been already reported at low concentrations and longer exposure durations (Bliss, 1940; Wuhrmann, 1952; Zhao and Newman, 2006).

Equation (4) can be rewritten as,

$$\ln(LT_{50}) = a\,LC_{50} + b \quad (5)$$

A nonlinear RLE model was developed based on the concept that the curvature could be described by taking the LC_{50} to an exponent value v. The nonlinear relationship can be expressed as:

$$\ln(LT_{50}) = a\,(LC_{50})^{v} + b \quad (6)$$

where, a is a slope coefficient, b the intercept related to NLT and v the exponent for LC_{50}. The value of v controls the nonlinearity. When the value of v was negative plots of the relationship between exposure time ($\ln LT_{50}$) and LC_{50} were nonlinear with negative curvature and a corresponding situation when v was positive. However when v was unity, then the relationship reduces to the original model with a linear shape.

3. Methodology

3.1. Organisms and toxicants with sufficient data available for evaluation

The terrestrial mammals were used as study organisms in this study which are used as surrogates for humans in laboratory research. The data were reported as the LC_{50} recorded at various exposure times. The groups of mammals with data available were strains of rats (*Rattus norvegicus*), mice (*Mus musculus*), Gottingen minipig (*Sus domestica*), beagle and mongrel dog (*Canis lupus familiaris*), rhesus monkey (*Macaca mulatta*) and squirrel monkey (*Saimiri sciureus*). The rat strains used in these studies were Sprague–Dawley, Long Ewans, Fischer-344, Wistar rats weighing 100–209 g. The mice strains were CF-1, Swiss, ICR, CD-1 weighing 17–34 g on average. The Gottingen Minipigs were the miniature pigs developed at Gottingen University (Kohn et al., 2007). On average temperature range was between 21° ± 1–22° ± 3 °C but with pentaborane-9 the temperature was relatively low (2.0° ± 0.1 °C). Humidity was between 35 and 70% during the exposure with 12 h light and dark cycles. In the literature, toxicity data were available for both inorganic and organic compounds so both were used in this study.

3.2. Sources and collection of data

The data available from peer reviewed literature were used, where concentration and corresponding exposure time with mammals were reported (Table 1). All the datasets were based on inhalation exposure only. These data sets included records of LC_{50} at various exposure times. The data were in various units of concentration such as mg/m^3, g/m^3 and ppm, which for consistency had been converted into mg/m^3. Similarly the exposure time was also expressed in various units (hours, minutes and seconds), and all were converted into *days*. The normal life expectancy (NLT) of the mouse, rat, dog, Gottingen Minipig, squirrel monkey and rhesus monkey were reported in the literature as 550 days, 650 days (Derelanko and Hollinger, 1995; USEPA, 1996), 4700 days (Michell, 1999), 5400 days (Holtz, 2010) 5100 days (Hopfs and Ploog, 1979) and 9000 days (Jack, 2007; Mattison, 2012) respectively. The octanol–water partition coefficient (as log Kow) values of the organic toxicants were collected from the publications listed in Table 2. These values were the most recently published available in the scientific literature.

3.3. Processing of data

For each data set the values of a, b and v were obtained by plotting the LC_{50} values against $\ln LT_{50}$ values. (Example in Fig. 1). The NLT for each mammal (see Section 3.2) was not part of the experimental dataset but it was included for regression analysis. The NLT was used as a long term independent data point, when $LC_{50} = 0$ then $LT_{50} = NLT$. Regression analysis was then carried out between $\ln LT_{50}$ and LC_{50}^{v}. For this analysis LC_{50}^{v} was obtained by