Toxicology 355–356 (2016) 49–53

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Review

Influence of exposure time on toxicity—An overview

Des W. Connell[a,*], Qiming J. Yu[b], Vibha Verma[b]

[a] Griffith School of the Environment, Griffith University, Nathan 4111, Qld, Australia
[b] Griffith School of Engineering, Griffith University, Nathan 4111, Qld, Australia

ARTICLE INFO

Article history:
Received 12 April 2016
Received in revised form 19 May 2016
Accepted 19 May 2016
Available online 20 May 2016

Keywords:
Lethal concentrations
Lethal dose
Habers Rule
Reduced Life Expectancy (RLE) model
Life expectancy
Fish

ABSTRACT

Data on toxicity of chemicals is usually reported as the LD_{50}, or LC_{50}, with the exposure time from experimental testing in the laboratory reported. But the exposure time is not considered to be a quantifiable variable which can be used to evaluate its importance in expressed toxicity, often described in general terms such as acute, chronic and so on. For the last hundred years Habers Rule has been successfully used to extrapolate from reported exposure times to other exposure times which may be needed for setting standards, health risk assessments and other applications. But it has limitations particularly in environmental applications where exposure levels are low and exposure times are relatively long. The Reduced Life Expectancy (RLE) model overcomes these problems and can be utilised under all exposure conditions. It can be expressed as

$$\ln(LT50) = -a\,(LC50)^{\nu} + b$$

where the constants ν, a and b can be evaluated by fitting the model to experimental data on the LC_{50}, and corresponding LT_{50}, together with the Normal Life Expectancy (NLE) of the organism being considered as a data point when the LC_{50} is zero. The constant, ν, at a value of unity gives a linear relationship and where $\nu < 1$ the relationship has a concave shape. In our extensive evaluations of the RLE model for fish, invertebrates and mammals involving 115 data sets and with a wide range of organic and inorganic toxicants the RLE model gave correlation coefficients of >0.8 with 107 sets of data. The RLE model can be used to extrapolate from a limited data set on exposure times and corresponding LT_{50} values to any exposure time and corresponding LT_{50} value. The discrepancy between Haber's Rule and RLE model increases as the exposure time increases.

Contents

1. Introduction . . . 50
   1.1. Historical perspective . . . 50
   1.2. Habers Rule variants . . . 50
2. An explanation of the principals of Habers Rule . . . 50
3. Limitations with Habers Rule . . . 51
4. Development of the Reduced Life Expectancy (RLE) model . . . 51
   4.1. Characteristics of the RLE model . . . 51
   4.2. Advantages of the RLE model . . . 51
5. Evidence for the Reduced Life Expectancy (RLE) model . . . 52
6. Use of the RLE model . . . 52
7. Comparision between Haber's Rule and the RLE model . . . 53
8. Conclusions . . . 53
   Conflict of interest . . . 53
   References . . . 53

* Corresponding author.
E-mail address: D.Connell@griffith.edu.au (D.W. Connell).

http://dx.doi.org/10.1016/j.tox.2016.05.015

1. Introduction

1.1. Historical perspective

This year is one year in excess of the Centenary Year of the first mass gas attack of the Great War using chlorine. It was organised by Fritz Haber the controversial recipient of the 1918 Nobel Prize for chemistry for developing a process for fixing nitrogen from the atmosphere to produce ammonia principally for use as an agricultural fertilizer. Another of his achievements is described as Habers Rule for evaluating the effects of exposure time on toxicity which resulted from his studies of the effects of poison gases on the Western Front. Currently toxicological data is usually reported as the LD_{50} or LC_{50} while the exposure time to reach that toxicity, often relatively short times, is recorded but regarded as a factor which is fixed. It is usually not considered to be a variable in the toxicity model which has a quantitative role in the expressed toxicity (Ashauer and Escher, 2010; Rozman and Doull, 2000; Rozman and Doull, 2001a,b). Often broad and imprecise terms such as acute, subacute, chronic and subchronic are used to describe the exposure time conditions. The lethal toxicity, at another exposure time other than that reported, may be required for risk assessment or to set guidelines in air, food, soil and water. This is usually obtained by extrapolation using Habers Rule. Haber's Rule is usually expressed as

$$C \times t = k \quad (1)$$

where C is the lethal concentration of the toxicant; t, the exposure time and k, a constant.

This can be expressed in a more precise form where the lethal concentration of a toxicant is expressed as the LC_{50} which is the lethal concentration of the toxic chemical to the average organism over the time the organism is exposed. The empirical constant, k, is then related to the organisms being evaluated, experimental conditions, units used and so forth. In fact the inherent toxicity of the substance does not change during the exposure, irrespective of the exposure time involved, but the toxic effect on the organism has a longer duration with longer exposure times and consequently there is a lethal toxic effect at a lower concentration.

1.2. Habers Rule variants

This rule has been used extensively for evaluation of effects of exposure time on toxicity for about a century. Many variants of Habers Rule have been proposed based on sets of data derived from laboratory tests on a limited range of organisms with generally specific toxicants and a summary of some of these is shown in Table 1. It is noteworthy that approximately two decades before Haber's Rule came into existence Warren (1900) tried to quantitatively relate exposure time and toxic concentration by utilising the concentration of a toxicant below which no measurable effects take place (C_0). Soon after this, another somewhat similar quantitative relationship of exposure time and concentration was proposed by Ostwald and Dernoscheck, 1910 which has the importance of the concentration elevated by raising ($C-C_0$) to the power α. Later Bliss (1940) evaluated the limitations of previous relationships using the dose – mortality and time – mortality curves for insecticides and proposed the use of the general equation $C\alpha \times t = k$ as well as the equation $(C - C_0)\alpha \times t = k$ given by Ostwald and Dernoscheck, 1910. British pharmacologist Clark (1937) while working on various drugs used Haber's Rule to describe their action and proposed a different form (Table 1) where t_0 is threshold time below which no measurable effects are observed. Later Druckrey and Kupfmuller (1948) gave the same emphasis to exposure time by raising this factor to the power of β as well thus giving an exponent on both concentration and time. Similarly more recently Miller et al. (2000) has proposed the use of an exponent on either *C* or *t*.

Table 1
Haber's Rule and some variants.

Mathematical Expressions	References
$C \times t = k$	Haber (1924)
$(C - C_0) \times t = k$	Warren (1900)
$(C - C_0)\alpha \times t = k$	Ostwald and Dernoscheck (1910)
$(C - C_0) \times (t - t_0) = k$	Clark (1937).
$C\alpha \times t = k$	Bliss (1940).
$C\alpha \times t = k$	Druckrey and Kupfmuller (1948).
$C \times t\beta = k$	
$C\alpha \times t\beta = k$	
$(C - C_0)\ \alpha \times t\beta = k$	Miller et al. (2000).

Where, C is lethal concentration, C_0 is threshold concentration below which no toxic effects are observed, t is exposure time, t_0 is threshold exposure time below which no toxic effects are observed, k, a and b are constants, α and β are exponents.

Over the last century there have been few quantitative scientific relationships which have survived in an unaltered form. Habers Rule has not only survived but prospered with many new applications. It has stood the test of time in setting standards, extrapolating effects from chronic to subchronic exposure, setting exposure limits for workplaces and even setting guidelines for maximum permissible limits for chemicals in spaceships. Generally it can be concluded that Habers Rule, and its variants, have been extremely valuable with toxicants at relatively high levels and short exposure times. However the experimental data on which Habers Rule is based is limited to some specific organisms and toxicants and more verification and development with different organisms and toxicants is required.

2. An explanation of the principals of Habers Rule

An explanation of the principals underlying Habers Rule for gaseous toxicants can be obtained as outlined below. A toxicant in air is taken up through the lungs and distributed throughout the body by the circulatory fluid and finally reaches the active site to give the toxic effect. The LC_{50} is usually measured in terms of concentration in the atmosphere. Thus when the toxicant reaches the lethal level then

$$LC_{50} = T/V = T_T/V_T \quad (2)$$

where T is the amount of toxicant and V, the volume of air in which it is contained and thus T_T is the total toxicant taken up to give the toxic effect and V_T, the total volume breathed in by the organism giving exposure to the toxicant.

The total volume can also be expressed as

$$V_T = t \times B_R \quad (3)$$

where t is the exposure time and B_R, the breathing rate (V_T/t). Thus combining Eqs. (2) and (3)

$$LC_{50} = T_T/(t \times B_R) \text{ and } LC_{50} \times t = T_T/B_R$$

Since B_R is constant and if T_T is constant then the expression T_T/B_R is constant. Then

$$LC_{50} \times t = \text{constant}$$

This is the expression for Habers Rule as expressed in Eq. (1)

$$LC_{50} \times t = k$$

This derivation of Habers Rule rests principally on the assumption that the total amount of toxicant (T_T) taken up by an organism to give lethality is constant irrespective of exposure time. It applies for organisms which are exposed to the toxicant in the atmosphere as is the assumption with Habers Rule. This group