Effects of Long Term Exposure on Toxicity

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**ABSTRACT**

In environmental investigations the effects of relatively long exposure times, often over a lifetime or decades, are of particular importance. Considering the importance of exposure time for toxicity to occur, the relationship between the lethal exposure time ($LT_{50}$) and lethal exposure concentration ($LC_{50}$) has been evaluated over relatively long exposure times using Normal Life Expectancy (NLE) as a reference point. The innovatory approach of using NLE as a reference point is important since it limits the data to the range where toxicity occurs.

A model based on this concept has been developed which has the normal life expectancy (NLE) as a fixed limiting point for a species. The model is based on the equation ($LC_{50} = a \ln(LT_{50}) + b$) where $a$ and $b$ are constants. It was evaluated by plotting $\ln LT_{50}$ against $LC_{50}$ with data on organic biocides with fish and metal, metalloid and organic compounds with zooplanktons obtained from the scientific literature.

Most of the experimental data sets can be satisfactorily correlated by use of the RLE (Reduced Life Expectancy) model, but deviations occurred for some data sets. Those data sets were satisfactorily fitted by a Two Stage RLE model. This model was based on two phases: one in the peripheral system and other in the central system. Both the Single and Two Stage RLE model support the hypothesis that toxicity is time dependent and decreases in a systematic way with increasing exposure time. A Calculated NLE was derived from the plots. The Calculated NLE obtained was in good agreement with the Reported NLE obtained from literature. Estimation of toxicity at any, particularly long exposure time and concentration is possible using the model.

In conjunction with aquatic organisms, the relationship between $LC_{50}$ and $\ln LT_{50}$ has been evaluated over relatively long exposure times with terrestrial mammal. The model was evaluated by plotting $\ln LT_{50}$ against $LC_{50}$ using available toxicity...
data related to terrestrial mammals from the literature. The model equation is
\[ \ln(LT_{50}) = a \cdot LC_{50} + b, \]
where a, b and \( a' \) are constants. The constant \( a' \) is the slope coefficient, \( b \) is related to NLE and the exponent \( (\cdot) \) applied to \( LC_{50} \) controls the degree of nonlinearity. A consistent nonlinear relationship was observed with the exponent value \( (\cdot) \) always < 1.

Use of NLE as a reference point provided a valuable limiting point for long exposure times beyond which no toxic effects can occur. The relationships between log octanol-water partition coefficient (Kow) and model constants a and \( a' \) were also evaluated and can be used to calculate model constants. According to this model toxicity is not dependent on body size of the organisms but principally on exposure concentration and exposure time and particularly at relatively long exposure times. The model can be used to characterise toxicity to specific mammals and then be extended to estimate toxicity to other mammals (similar type).

Though Haber’s Rule \( (C.t = k) \) has been an appropriate and effective tool for evaluation of effects of exposure time on toxicity with pharmaceuticals and military gases. But in recent years there has been an increase in chemicals released to the environment. The environmental concentrations of these chemicals are usually low and the exposures times are relatively long, often a life time. According to Haber’s Rule when lethal exposure concentration \( (LC_{50}) \) approximates zero, then the exposure time \( (LT_{50}) \) approaches infinity. So in this situation Haber’s Rule is quite inappropriate and a new approach is needed.

The RLE model \( (LC_{50} = [\ln(NLE) - \ln(LT_{50})]/d) \) which is based on a linear relationship between \( LC_{50} \) and \( \lnLT_{50} \) and uses NLE as a reference point as well as a long term data point has been proposed as an alternative to Haber’s Rule. After a direct comparison of both models it was observed that the RLE model has the benefit of using the NLE as a long term data point. According to the RLE model, unlike Haber’s Rule when \( LC_{50} \) approaches zero, then in place of being infinity the \( LT_{50} \) is limited by NLE. Though when the \( LT_{50} \) is short and the \( LC_{50} \) is high, Haber’s Rule showed consistency with the RLE model. But the difference between the two was evident in the situation when the \( LT_{50} \) is relatively long and the \( LC_{50} \) is
very low. This novel approach is a more appropriate and effective alternative to evaluate long term effects of exposure. In fact the RLE model is a marked departure from Haber’s Rule. It can be used to estimate the long term effects of exposure accurately and easily.
STATEMENT OF ORIGINALITY

“This thesis is submitted to Griffith University to fulfil the requirements of the degree of Doctor of Philosophy. I hereby declare that the work embodied in this thesis is my own original work and this work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.”

Vibha Verma

date
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DEDICATION

To my parents.
LIST OF PUBLICATIONS

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CONFERENCE PRESENTATION


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1. Verma, V., Yu, Q. J., Connell, D.W., A comparison of the Reduced Life Expectancy (RLE) model with Haber’s Rule to describe the effects of exposure time on toxicity.
LIST OF ACRONYMS & ABBREVIATIONS

a       Slope
a´      Slope Coefficient
As      Arsenic
ATSDR   Agency for Toxic Substances Data Registry
b      Intercept Related to NLE
C      Exposure Concentration
C_{\frac{1}{2}}      Exposure Concentration
C_{B}   Toxicant Concentration in the Organism Body
C_{w}   Toxicant Concentration in the Water
C_{o}   Toxicant Concentration below which no toxic effects are observed
CDCP   Centre for Disease Control and Prevention
ChEs   Cholinesterase
CPF    Chlorine Pentafluoride
d      Empirical Constant
d´      Empirical Constant
EPA    Environmental Protection Agency
FEPA   Food and Environmental Protection Act
GA     Tabun
GB     Sarine
GD     Soman
GF     Cyclosaine
gm/L   Gram per Litre
HSDB   Hazardous Substances Database
ILC_{50}   Internal Lethal Concentration
ILL    Incipient Lethal Level
IMI    Imidacloprid
K_{B}   Bioconcentration Factor
K_{R}   Constant
K_{ow}  Octanial Water Partitioning Coefficient
LC_{50}  Lethal Exposure Concentration
ln      Natural logarithm
log logarithm on Base 10
LT₅₀ Lethal Exposure Time
mg/L Milligram per Litre
MMH Monomethyl hydrazine
MSA Molecular Surface Area
NCEH National Centre for Environmental Health
NF Nitrogen Trifluoride
NLE Normal Life Expectancy
NOEL No Observed Effect Level
NOAEL No Observed Adverse Effect Level
NRC National Research Council
OEHHA Office of Environmental Health Hazard Assessment
OP Organophosphorus
PNS Peripheral Nervous System
POPs Persistent Organic Pollutants
ppb Parts per billion
ppm Parts per million
R² Regression Coefficient
RLE Reduced Life Expectancy
T Exposure Time
TCE Trichloroethane
TRVs Toxicity Reference Values
t₀ Exposure Time below which No Toxic Effects are Observed
UDMH Unsymmetrical dimethyl hydrazine
µg/L Microgram per Litre
Exponent
Yₗ Lipid Concentration
KEYWORDS

Alternative to Haber’s Rule
Aquatic Toxicity
Calculated NLE
Effects of Exposure Time
Estimation of Toxicity
External Lethal Concentration
Haber’s Rule
Inhalation Exposure
Intermediate Phase
Internal Lethal Concentration
Lethal Exposure Time
Lethal Exposure Concentration
Lethal Toxicity
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Normal Life Expectancy
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Reduced Life Expectancy Model
Reduction in Life Expectancy
Reported NLE
Single Stage RLE Model
Terrestrial Mammal Toxicity
Two Stage RLE Model