Impact of Non-Constant Concentration Exposures on Lethality of Inhaled Hydrogen Cyanide

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Abstract

The toxic load (TL) model is an empirical approach to hazard assessment modeling for estimating the relationship between a chemical’s inhalation (HI) toxicity and the exposure duration. The TL is normally expressed as a function of vapor concentration (C), duration (t), and a constant (C). Hypothetically, any combination of C and t that yields the same TL will give a constant biological response. These formulas have been developed and tested using controlled, constant concentration animal studies, but the validity of applying these assumptions to time-varying concentration profiles has not been tested. Experiments were designed to test the validity of the model under conditions of non-constant acute exposure—the first of its kind. Over two separate experiments, mice Sprague-Dawley rats inhaled constant concentrations of hydrogen cyanide (HCN) generated in a dynamic and particle-free exposure system to determine whether the TL model’s ability to adequately describe the HI toxicity under the conditions of non-constant HI exposure. The model was found to be applicable under the tested conditions, with the exception of the median lethality of very brief, high concentration, discontinuous exposures. The implication of these results directly extends to the substantial effort from both the military and industrial sectors to develop TL databases for high priority toxic industrial chemicals. These agencies are required by their mandates to estimate causality from possiblehosts of toxic industrial chemicals against military and/or civilian target. The predictable (x, y, z) parameter values, invertably based on traditional constant concentration/time laboratory animal studies, form the basis for planning response actions and logistical supply decisions in response to public health emergencies (e.g., potential terrorist attacks).

Objective and Introduction

Objective: Conduct inhalation exposures that can be used to compare relative inhalation toxicity of constant and non-constant concentration-time (C-t) exposure profiles. Assess traditional quantitative toxicity parameters, e.g., toxic load (TL), developed from traditional laboratory constant C-t studies against the non-constant C-t profiles more applicable in real world exposure to hazardous chemicals.

Introduction: All current chemical, transport and dispersion models for chemical warfare agents base hazard prediction output on a mathematical assumption: toxicity parameters developed from non-fluctuating C-t profiles studies in laboratory animal species are relevant to real world which is highly variable various hazards and factors. The Toxic Load (TL) or the Bergog model is based on a constancy function of duration. Determining how to properly integrate (C-t) C-t for TL model will require toxicity data fluctuating C-t profiles. Currently, no adequate toxicity assessment tools for such profiles are.

Toxic Load Model—How Best to Integrate?

The Toxic Load (TL) model is an empirical approach to hazard assessment modeling for estimating the relationship between a chemical’s inhalation (HI) toxicity and the exposure duration. The TL is normally expressed as a function of vapor concentration (C), duration (t), and a constant (C). Hypothetically, any combination of C and t that yields the same TL will give a constant biological response. These formulas have been developed and tested using controlled, constant concentration animal studies, but the validity of applying these assumptions to time-varying concentration profiles has not been tested. Experiments were designed to test the validity of the model under conditions of non-constant acute exposure—the first of its kind. Over two separate experiments, mice Sprague-Dawley rats inhaled constant concentrations of hydrogen cyanide (HCN) generated in a dynamic and particle-free exposure system to determine whether the TL model’s ability to adequately describe the HI toxicity under the conditions of non-constant HI exposure. The model was found to be applicable under the tested conditions, with the exception of the median lethality of very brief, high concentration, discontinuous exposures. The implication of these results directly extends to the substantial effort from both the Department of Defense and the Department of Homeland Security Chemical Security Analysis Center to develop TL models for high priority toxic industrial chemicals. These agencies are required by their mandates to estimate causality from possible hosts of toxic industrial chemicals against military and/or civilian target. The predictable (x, y, z) parameter values, invertably based on traditional constant concentration/time laboratory animal studies, form the basis for planning response actions and logistical supply decisions in response to public health emergencies (e.g., potential terrorist attacks).

Materials and Methods

Exposure System

- Aqueous cyanide in 21% O2, balance N2
- HCN shown because its well studied & characterized
- Two separate gas generation systems
- Mass flow controllers to meter gas and dilution air
- Mixing prior to entering chambers
- Solenoid valves to start and stop flows
- Monitor using FT infrared spectroscopy
- Enables generation of pulsed C-t profiles
- Goal is to study TL model under HCN toxicity

Pulsed-Style Experiments

(Finnery 1971) 5-A groups of 10 subjects per exposure profile
- Median effective CIC calculated for each profile
- All dose and exposure variations overlaid

Animals and Methods

- How best to integrate C-t: fluctuating
- How to properly integrate C-t
- Toxic load TL model under HI toxicity

Design

- Aqueous cyanide in 21% O2, balance N2
- HCN shown because of its well studied characterizations
- Two separate gas generation systems
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Animal Care and Use

The experiments using this system were conducted in compliance with the Animal Welfare Act and with all applicable animal care and use procedures with the exception of the guidelines established in the Guide for the Care and Use of Laboratory Animals (1996). The experiments were conducted under the aegis of the Naval Medical Research Unit-Dayton at the Animal Care and Use Protocol (ACUP) approved by the University of Dayton Institutional Animal Care and Use Committee (IACUC). The views expressed in this presentation are those of the authors and represent the official policy of the Department of Defense or the U.S. Government.

References


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