Are toxic load-based toxicity models consistent with experimental observations?

Independent analysis of steady-exposure data from the 2012–2013 ECBC/NAMRU-D toxicological experiments

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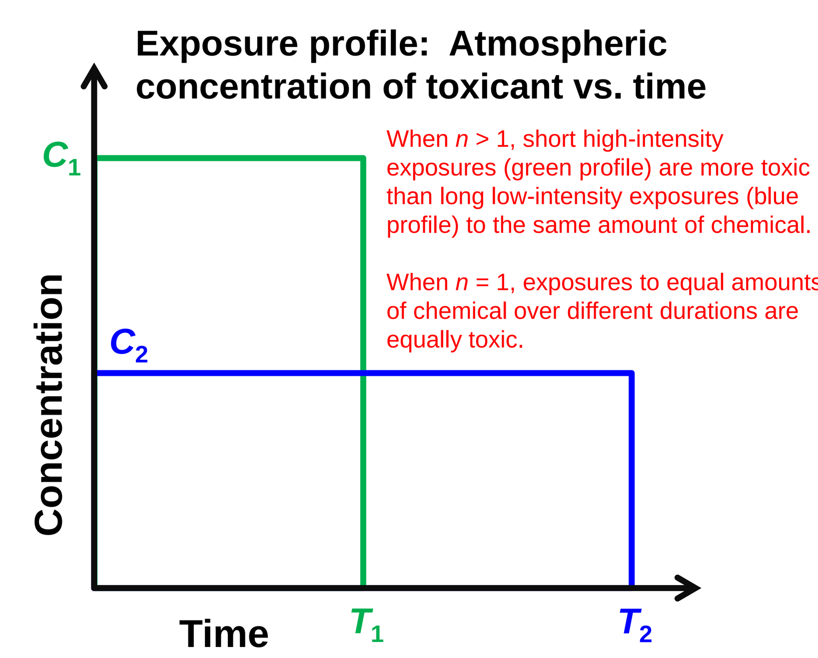
Introduction

Consequence assessment studies of hazardous airborne releases require accurate toxicity models that use airborne exposure levels to predict casualties. One such model, the "toxic load" model, has been increasingly adopted in atmospheric dispersion modeling studies. This model was developed and tested with time-independent ("steady") exposure profiles and has not been validated using profiles that emulate real-world fluctuating exposures.

In 2012–2013 the U.S. Defense Threat Reduction Agency (DTRA) sponsored a two-year set of toxicological experiments, conducted by the Edgewood Chemical and Biological Center (ECBC) and the Naval Medical Research Unit Dayton (NAMRU-D), to investigate proposed extensions of the toxic load model that use time-varying ("non-constant") exposure profiles. The experiments exposed rats to hydrogen cyanide (HCN) via the inhalation route. We used these data to independently assess the validity of 1) the basic toxic load model using steady exposure data [presented in this poster] and 2) the proposed extensions of the toxic load model using non-steady exposure data [presented separately].

The toxic load model



The *toxic load* is a measure of exposure:

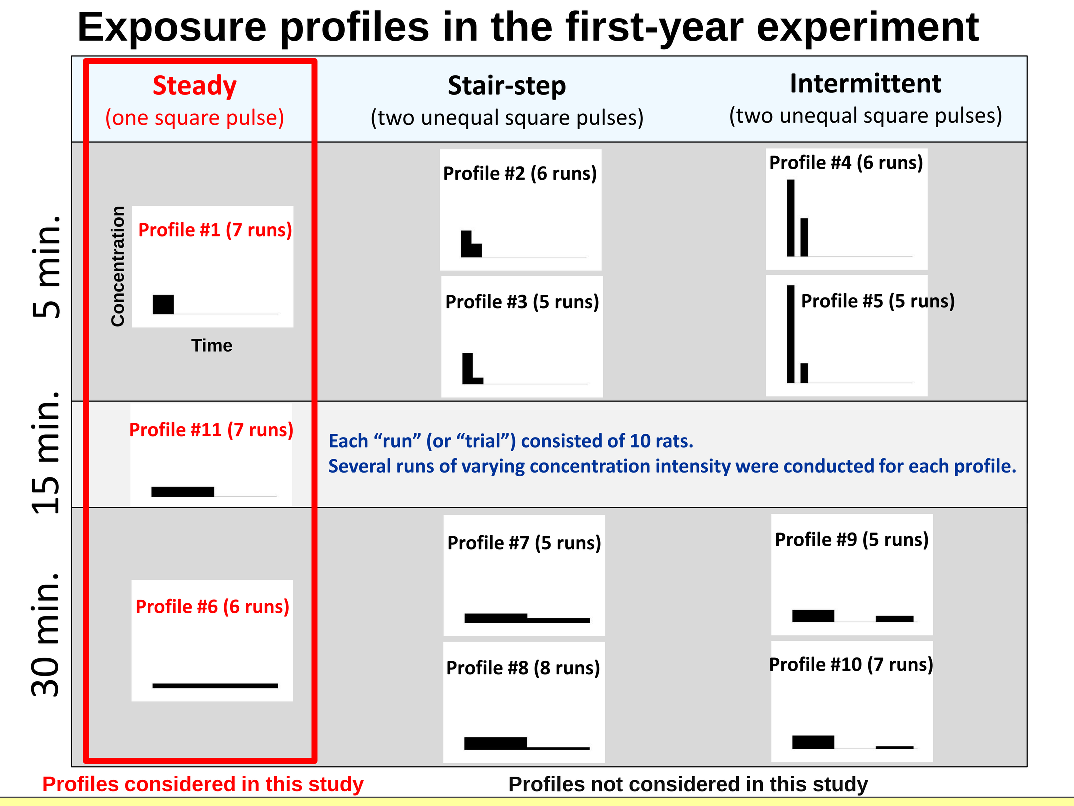
(Eq. 1) $$TL = C^n \times T$$

The *toxic load model* uses a probit exposure-response function to relate the toxic load to the probability of casualty (or "casualty fraction"):

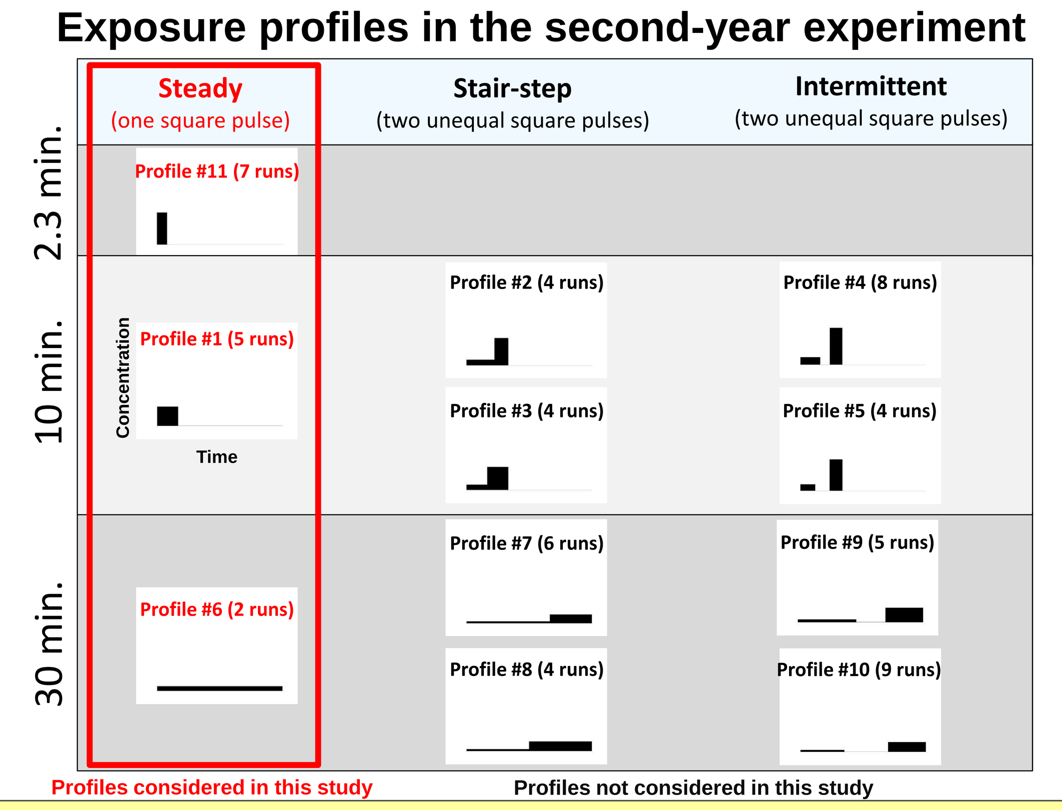
(Eq. 2) $$P = \{\mathrm{erf}[m \log_{10}(TL) - m \log_{10}(TL_{50})] + 1\}/2$$

n = toxic load exponent
m = probit slope
TL_{50} = median lethal toxic load
erf(x) = error function

Exposure profiles in the first-year experiment



Exposure profiles in the second-year experiment



Methodology

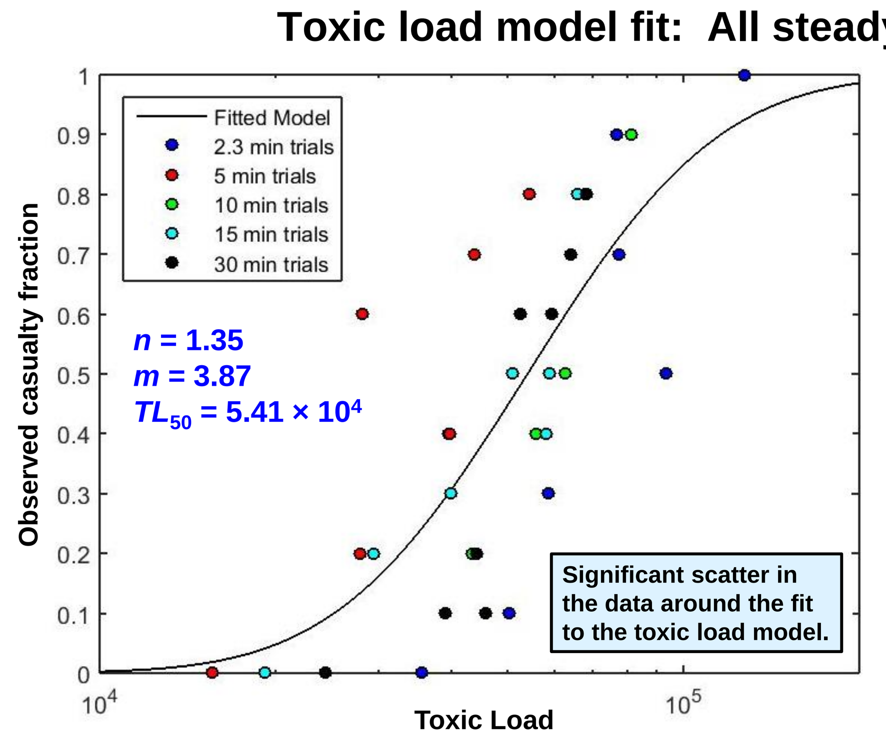
We assessed the validity of the toxic load model as applied to HCN inhalation exposures in rats by examining how well the model fits the ECBC/NAMRU-D data for steady exposures.

We performed a simultaneous 3-parameter fit of the toxic load model (Eq. 2) to the steady exposure data (i.e., observed casualties for each exposure with toxic load values calculated via Eq. 1). The goodness of fit was evaluated visually and by statistical measures.

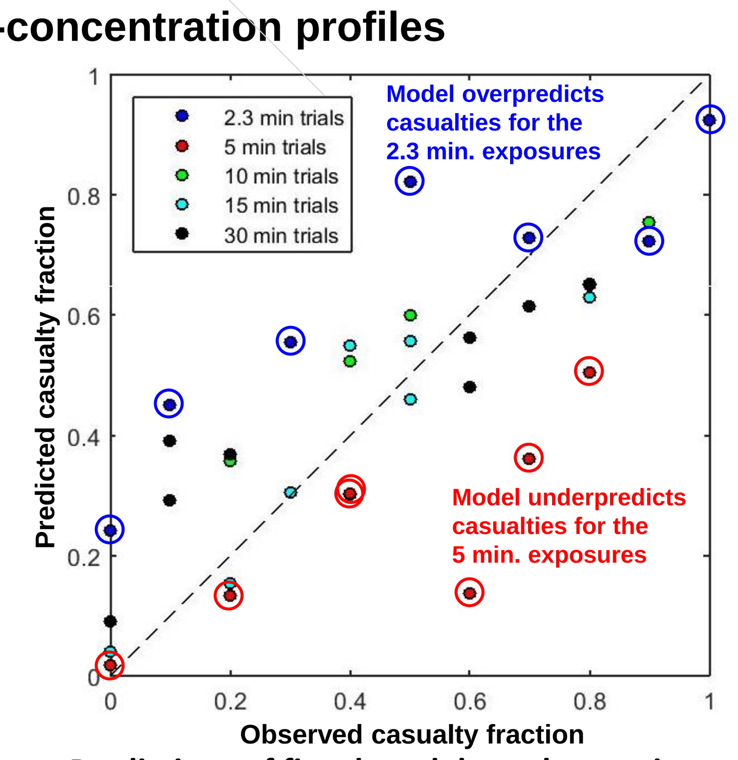
We also examined whether the toxic load model is valid across the whole range of exposure durations (2.3 to 30 min.) by assessing the goodness of fit for different subsets of exposure durations.

As an additional measure of the self-consistency of the model, we applied the fitted model to predict casualties using the same set of exposure data that was used to fit the model.

Toxic load model fit: All steady-concentration profiles

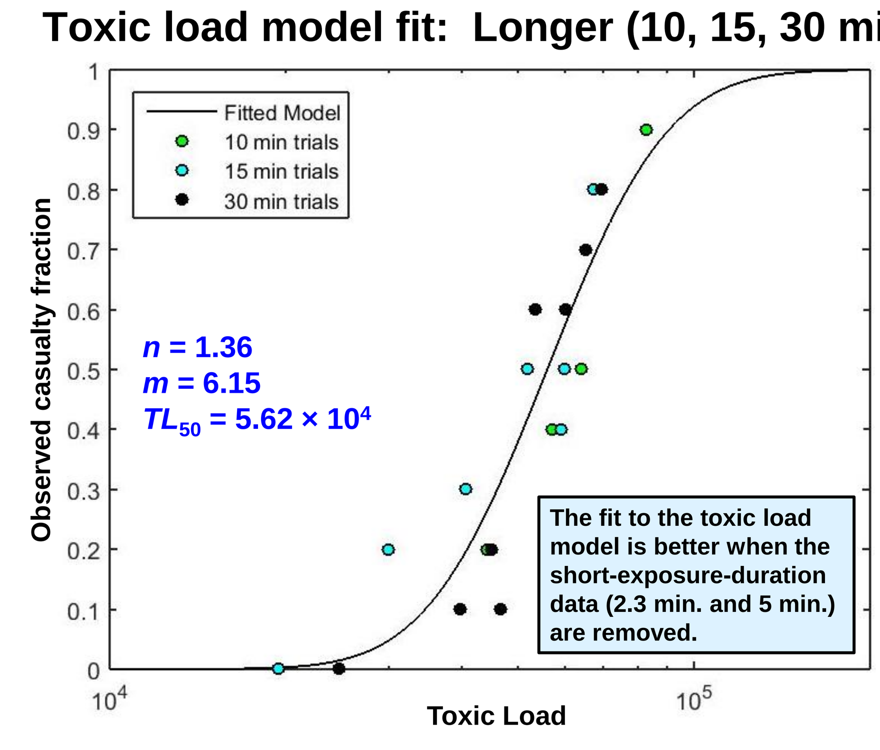


Fit of toxic load model to experimental observations

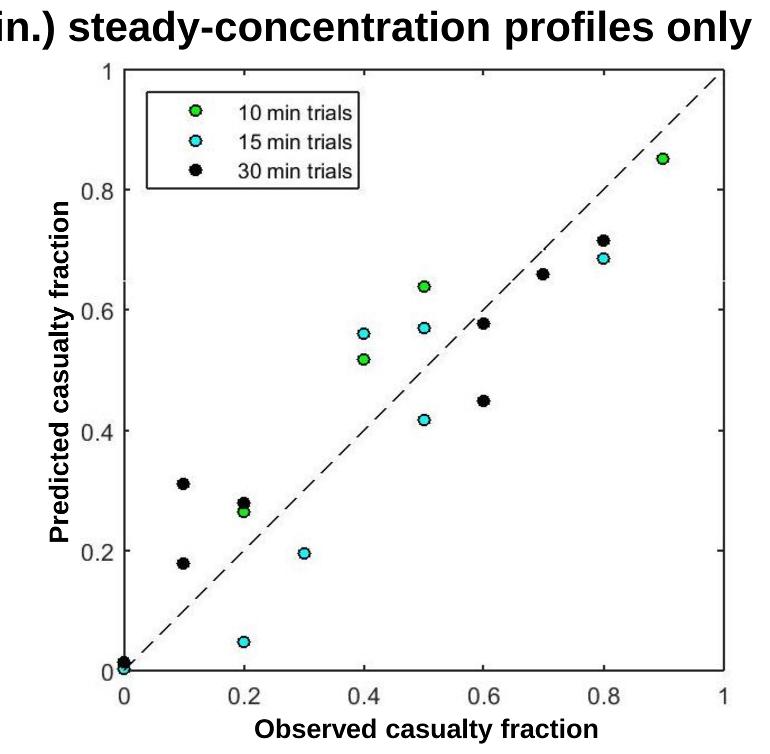


Predictions of fitted model vs. observations

Toxic load model fit: Longer (10, 15, 30 min.) steady-concentration profiles only



Fit of toxic load model to experimental observations



Predictions of fitted model vs. observations

Model parameters and goodness of fit statistics for different subsets of exposure durations

Exposure durations (min)	# of trials	Fitted model parameters: n	TL_{50}	m	Goodness-of-fit metrics: RMSE (Root-mean-square error)	p-value
2.3, 5, 10, 15, 30	34	1.35	5.41×10^4	3.87	0.187	0.000337
2,3, 10, 15, 30	27	1.23	2.71×10^4	7.04	0.124	0.221
5, 10, 15, 30	27	1.73	5.20×10^5	3.71	0.145	0.257
10, 15, 30	20	1.36	5.62×10^4	6.15	0.105	0.856
5, 15, 30	20	1.79	7.06×10^5	3.85	0.137	0.351
2.3, 5, 10	19	1.12	1.05×10^4	4.00	0.209	0.005
					(Smaller RMSE is better)	(Larger p-value is better)

The toxic load model has a poor fit to the complete set of all steady exposures. The model cannot simultaneously fit the short-duration and long-duration exposures adequately. The best fit is obtained when only longer exposures (10, 15, and 30 minutes) are considered.

The (10,15,30)-minute data set results in similar fitted model parameters to those of the full data set, except for the significant difference in probit slope m. This may be simply coincidental, as all three model parameters (n, m, and TL_{50}) vary independently during the fit.

Conclusions

The toxic load model is not suitable for describing the ECBC/NAMRU-D data on steady exposures of HCN to rats across the full range of the experiments' exposure durations (2.3 minutes to 30 minutes). The model fits the data adequately only if the short-duration exposures (2.3 minutes and 5 minutes) are dropped from the data set.

We note that a practical toxicity model should be able to describe toxicological effects across all timescales relevant to acute inhalation exposures of hazardous chemicals (i.e., minutes to tens of minutes).

Our analysis does not attempt to attribute a physical explanation to these results.

Acknowledgements

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Citations (ECBC/NAMRU-D experiments):

- Sweeney, et al., 2014: Impact of non-constant concentration exposure on lethality of inhaled hydrogen cyanide. *Toxicol. Sci.* **138**, 205–216.
- Sweeney, et al., 2015: Evaluating the validity and applicable domain of the toxic load model: Impact of concentration vs. time profile on inhalation lethality of hydrogen cyanide. *Regul. Toxicol. Pharmacol.*, **71**, 571–584.