Predicting Effects of Toxic Inhalation Exposures[1]

Alexander J. Slawik, Nathan Platt, and Jeffry T. Urban

The toxic load model is a popular way to assess inhalation hazards posed by exposure to toxic chemicals. The model is well-defined for constant-concentration exposures, but several generalizations for time-varying exposures have not been validated by experimental evidence. We independently analyzed data from a three-year experiment on rats of time-varying exposures to inhaled toxins to assess the utility of the toxic load model and its proposed extensions to the hazard prediction modeling community.

Introduction

The toxic load model is a phenomenological exposure-response model of the effects of inhalation of toxic industrial chemicals. It was designed to improve upon Haber's Law, which states that toxic effects depend only on dosage, usually measured by the time-integrated airborne chemical vapor concentration. The toxic load model attempts to account for time-dependent biological response indirectly by replacing dosage as the measure of exposure with a quantity called the toxic load.

Our results raise the question of how best to model the toxic effects of acute inhalation exposures for the complex time-varying atmospheric concentration profiles characteristic of real-world airborne toxic release incidents.

[1] Based on A. Slawik, N. Platt, and J. T. Urban, "User-Oriented Independent Analysis of the Toxic Load Model's Ability to Predict the Effects of Time-Varying Toxic Inhalation Exposures," *Regulatory Toxicology and Pharmacology* 106 (August 2019): 27–42, https://doi.org/10.1016/j.yrtph.2019.04.003.

Previous research by ten Berge, Zwart, and Appelman (1986) showed that the toxic load model fits exposure-response data better than Haber's Law for certain chemicals. However, most experimental work to parameterize and validate the model used only steady exposures of constant concentration. This type of exposure is not representative of real-world atmospheric dispersion events, in which atmospheric turbulence can lead to highly fluctuating and intermittent chemical vapor concentrations due to in-plume turbulence and turbulent plume meander, respectively (Wilson 1995).

The Naval Medical Research Unit Dayton (NAMRU-D) conducted a three-year experimental campaign of the effect on rats of time-varying exposures to hydrogen cyanide (HCN) or carbon monoxide (CO) (Sweeney, Sharits, Gargas, et al. 2013; Sweeney, Summerville, and Channel 2014; Sweeney, Summerville, Channel, et al. 2015; Sweeney, Summerville, Goodwin, et al. 2016—collectively referred to hereafter as Sweeney et al.). The U.S. Army's Edgewood Chemical and Biological Center (ECBC) designed and managed the experiments.

We independently analyzed the ECBC/NAMRU-D data to assess the potential utility of the toxic load model and its proposed extensions to the hazard prediction modeling community. None of five proposed extensions to the toxic load model for the case of time-varying exposures in the literature have been validated. None of these proposed extensions have been definitively demonstrated to be preferred over another.

Methodology

Our analysis methodology focused on applying and assessing the toxic load model within a user-oriented context, which differs from that used in the ECBC/NAMRU-D experiments. We tried to emulate the hazard prediction modelers' practice of estimating the number of human casualties. They estimate casualties using time series of atmospheric concentrations. To do so, they apply a chosen extension of the toxic load model to the concentration time-series data. They typically express the toxic load model in terms of parameters using data from the toxicological literature. Our method follows a similar procedure to predict lethality for each trial in the ECBC/NAMRU-D experiments.

We generated predictions for each of five proposed extensions of the toxic load model to the case of time-varying chemical vapor concentrations. We applied statistical measures of scatter and bias to determine the degree of agreement between toxic load model predictions and observations, and performed statistical tests to determine whether any disagreement between predictions and observations is within the range that is expected from small sample size errors (i.e., variability due to small numbers of rats per exposure in the laboratory experiments). Our analysis methodology is not designed to explain differences between model predictions and experimental observations; it merely quantifies those differences so that model users can determine how much confidence they should have in their modeling protocols.

In our analysis protocol, we considered the HCN data and CO data separately, but combined the 2012 and 2013 HCN data sets. For each type of exposure, HCN or CO, we applied a multi-step analysis protocol:

1. Fit the toxic load model using constant-concentration exposure data to determine the toxic load model parameters
2. Determine regimes of exposure duration in which the constant-concentration exposure data are well-fit by the toxic load model
3. Compare model predictions to laboratory observations for all trials for each time-varying exposure profile and each proposed extension to the toxic load model
4. Assess the predictive performance of each proposed extension to the toxic load model
5. Determine regimes of exposure duration in which model predictions using the time-varying exposure data agree with observations

It's important to note that our method differs from the original work in several ways, leading to different conclusions. Our objective was to help the hazard prediction modeling community understand how much confidence they should have in their toxicology models, so our analysis methodology is designed to determine how well the predictions of the toxic load model and its time-varying extensions match experimental observations. We therefore compared the predicted and observed fractions of rats that died in each trial. Sweeney et al. used more indirect measures: they compared derived toxicity parameters to each other on a profile-by-profile basis. In general, Sweeney et al. sought to verify the applicability of the toxic load model to the case of time-varying profiles by demonstrating that the derived toxic load parameters were consistent from profile to profile.

We also employed a user-oriented approach in our data-fitting protocols. We fit the toxic load model using the constant-concentration data and then used the fitted parameters to frame the time-dependent extensions to the toxic load model. Constant-concentration exposure data is the type of data that is generally available in the inhalation toxicology literature, so any phenomenological toxicity model probably will need to be parameterized using constant-concentration exposure data for the time being. Our procedure of assessing the predictive performance of the time-varying extensions to the toxic load model using a different data set allowed us to avoid "tuning" the models with the same data used for the original experiments.

Some other ways in which our methodology differs from that of Sweeney et al. include the models we considered, the way we accounted for uncertainty, and the way we treated outliers. Our method of identifying exposure durations that result in poor fits of the toxic load model also differs somewhat from that of Sweeney et al., leading us to somewhat different conclusions.

Findings

We found that the constant-concentration exposure data are fit the toxic load model well for the full set of carbon monoxide exposures from 10 to 60 minutes although the data are sparse near the high and low ends of the exposure-response curve. The constant-concentration exposure data do not fit well for the full set of hydrogen cyanide exposures from 2.3 to 30 minutes although the hydrogen cyanide data fit well for exposures from 10 to 30 minutes. We used the fits to the constant-concentration exposure data to parameterize five proposed extensions of the toxic load model to the case of time-varying exposures. For the hydrogen cyanide exposures, we parameterized the models using the 10- to 30-minute exposure data and evaluated the model extensions using the same subset of exposure durations, although we also explored the sensitivity of our results to the choice of the set of exposure durations.

Our analysis of Sweeney et al.'s data on stair-step and intermittent exposures indicates that all five proposed extensions to the toxic load model have difficulty predicting lethality in rats. We also observed some systematic differences in predictive performance among the five models. In particular, the models that define toxic load as a monotonic function of time tend to over-predict lethality, but the time-averaging models do not consistently over-predict or under-predict rat lethality.

Although some of the five models perform better than others with particular data sets, all the models, when parameterized by the constant-concentration exposure data, show statistically significant systematic prediction biases on an individual profile-by-profile basis, and none of the models predict rat lethality within the bounds expected by small sample size errors. Furthermore, no one model appears to be clearly superior across both the hydrogen cyanide and carbon monoxide data sets. Consequently, although the toxic load model is thought to be a good phenomenological toxicity model, we urge caution within the hazard prediction modeling community when selecting and applying extensions of this model. We also recommend caution when applying this model to exposure durations shorter than 10 minutes, at least for hydrogen cyanide. Further work likely will be necessary to determine whether the toxic load model is "good enough" for specific hazard prediction modeling applications.

It is difficult to quantify how failures of toxicological models will affect hazard prediction modeling. The impact of an inaccuracy in the toxicological model will depend on the nature of the hazard event. For example, errors at the low end of the exposure-response curve (e.g., below 10 percent of the population responding) could result in large errors in the predicted size of the hazardous area, whereby edges typically consist of long spatial tails of low concentrations. The significance of errors in the predicted size of the hazardous area in turn depends on where the at-risk population is located.

Potential Approaches to Modeling Inhalation Toxicity

Our results raise the question of how best to model the toxic effects of acute inhalation exposures for the complex time-varying atmospheric concentration profiles characteristic of real-world airborne toxic release incidents. Real-world atmospheric concentration profiles are much more complex than the idealized laboratory profiles explored by Sweeney et al. and by Saltzman and Fox (1986). They may be composed of fluctuations that span several timescales and contain intermittent periods of various durations; total exposure durations may range from minutes (or shorter) to tens of minutes (or longer). A practical toxicological modeling approach—whether simple or complex—should be robust across the range of relevant exposure durations and profile shapes. We explored several potential approaches to modeling the effects of real-world inhalation exposures and came up with the following suggestions:

- Future research would benefit from closer collaboration between the toxicology community and hazard prediction modelers in the military, intelligence, emergency response, environmental regulation, chemical process safety, and transportation safety communities;
- Further research is needed to determine the answer to whether it is possible to build accurate and practical models for time-varying inhalation exposures that have reasonable data requirements; and
- Further development of the toxic load model is not warranted at this time.

We recommend that any new toxicological research in this area focus on theoretical efforts to develop new toxicological models, coupled with exploratory experiments to help develop the form of the models, experiments to determine the biologically based parameters for the models, and experiments to validate the models using laboratory exposures that are representative of real-world atmospheric exposures. Relevance to hazard prediction modelers should be considered throughout this effort from beginning to end. Any comprehensive effort to build new models should bring together theoretical toxicologists, experimental toxicologists, and hazard prediction modelers to guide each other's work.

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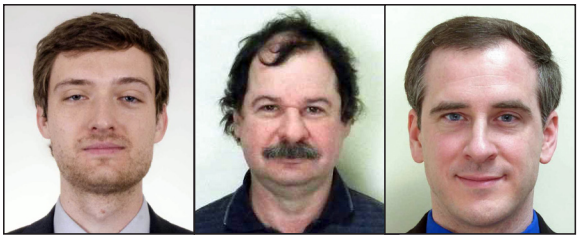
About the Authors



Alexander J. Slawik is a member of the research staff in SED. He earned both a PhD and a master's degree in applied mathematics from Northwestern University.

Nathan Platt is a member of the research staff in SED. He holds both a PhD and a master's degree in applied mathematics from Brown University.

Jeffry T. Urban is a member of the research staff in SED. He holds a PhD in chemistry from University of California at Berkeley.