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Independent analysis of toxic load based toxicity models using time-varying hydrogen cyanide exposure data

Alexander Slawik, Nathan Platt, Jeffry Urban, Kevin Axelrod, James Silva

Institute for Defense Analyses

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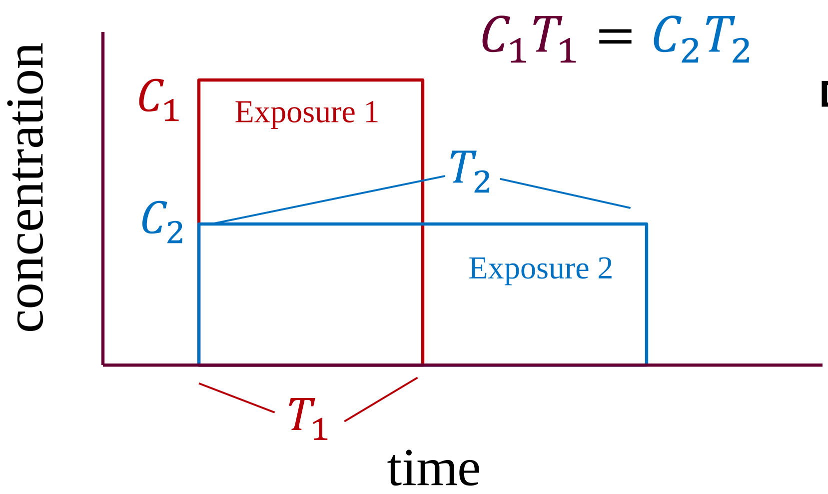
Motivation: Hazard Assessment

- Given a certain inhalation exposure to toxic chemicals, how do we assess the hazard this poses to a human population?

- Need models that link exposure to human response…

IDA | Haber's Law and Toxic Load Model

One of the simplest phenomenological models relating concentrations of toxic chemicals to casualties is Haber's law



Haber's law:
Dosage = $C \times T$ (~total amount of agent delivered)
Dosage uniquely determines casualties (ie. LD50)

Time history does not matter:
Exposure 1 and Exposure 2 will cause the same amount of casualties

Haber's law models casualties for certain chemicals under certain conditions

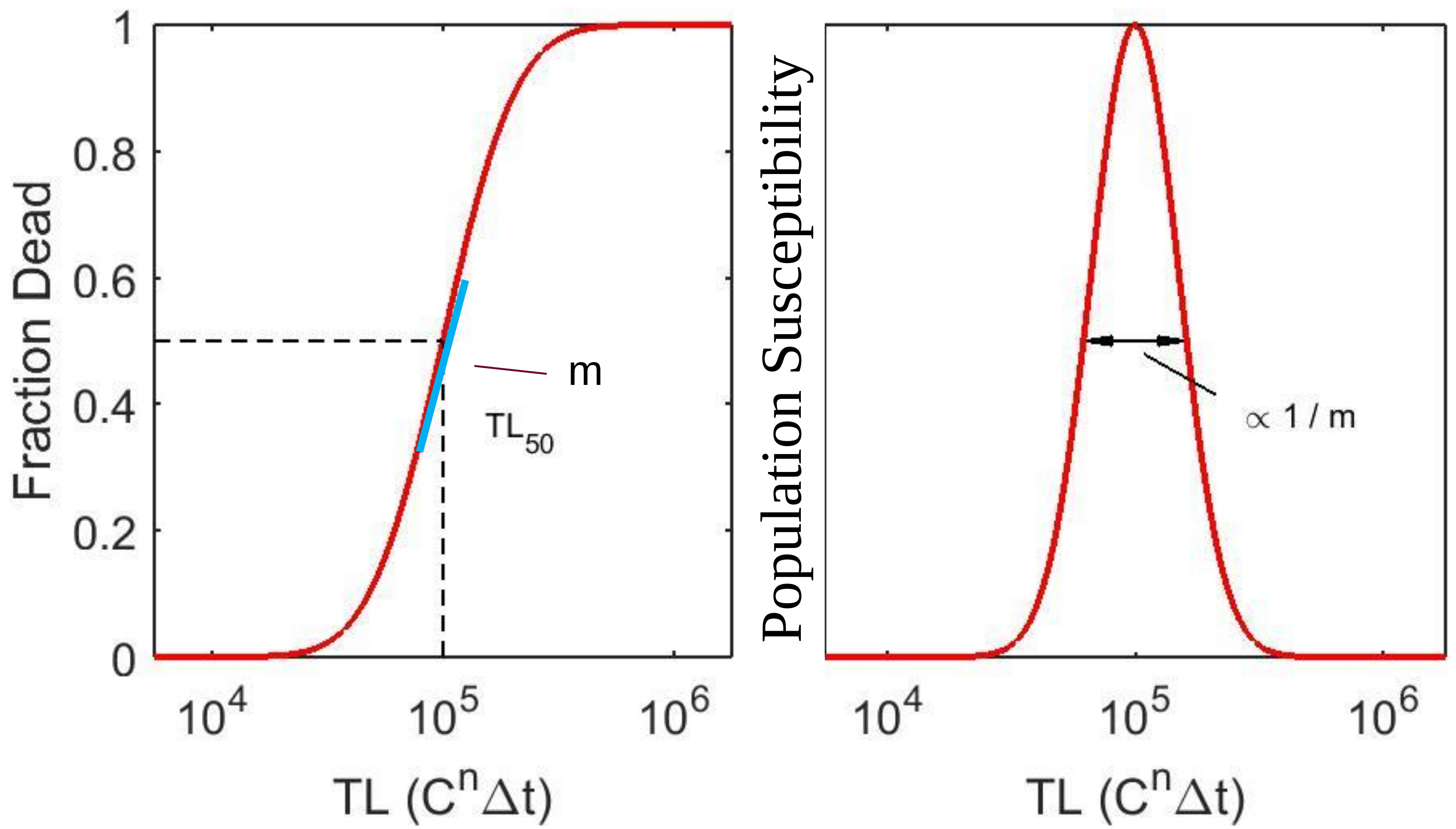
However, for some toxic agents, the population response depends upon the time history of the exposure

US EPA's AEGL methodology utilizes toxic load model

Toxic Load Model:
Toxic Load = $C^n \times T$ (depends on time history)
Toxic Load uniquely determines casualties (ie. TL50)
n>1: Exposure 1 will be more lethal than Exposure 2

TL Model and Population Statistics

- Physiological differences in a population leads to variability in lethal exposure, as observed in an experiment
- Toxic load model uses three parameters (n, TL50, m) to capture the statistics of population



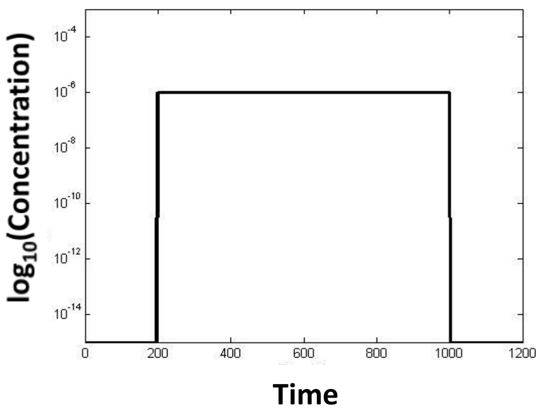
Toxic Load Model and its Extensions

The toxic load model was originally defined and validated for time-constant exposures (single square pulses).

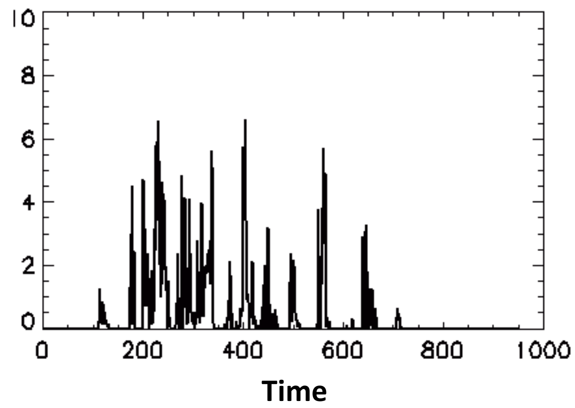
Real-world exposures are not time-constant.

Various extensions to the toxic load model are proposed to capture time dependence. None have been validated!

Laboratory Testing Profile



Possible Real-World Profile



Extensions to Toxic Load Models

If concentration is constant (ie. C(t) = C), all extensions reduce to: $TL = C^n \Delta t$

- Integrated Concentration (or ten Berge): $TL = \int C^n(t)\, dt$
  Common in dispersion modeling systems

- Average Concentration: $TL = \left(\frac{\int C(t)dt}{\Delta t}\right)^n \Delta t = \left(\overline{C(t)}\right)^n \Delta t$
  Avg. conc. over exposure period

- Griffiths and Megson: $TL = \left(\frac{\int C(t)dt}{\Delta t_{C>0}}\right)^n \Delta t_{C>0}$
  Accounts for intermittent exposures

- Peak Concentration: $TL = \left(\frac{\int C(t)dt}{\max\{C(t)\}}\right) \max\{C(t)\}^n$
  Max.conc. over exposure period

- Conc. Intensity: $TL = \left(\frac{\left(\int C(t)dt\right)^{2-n}}{\left(\int C^2(t)dt\right)^{1-n}}\right)$
  Related to SCIPUFF tox. model; accounts for conc. fluctuations

Extensions to the model provide significantly different casualty predictions for time-dependent exposures

US DTRA sponsored a set of experiments specifically designed to identify possible toxic load model extension

Exposure profiles in the 2012 DTRA experiment

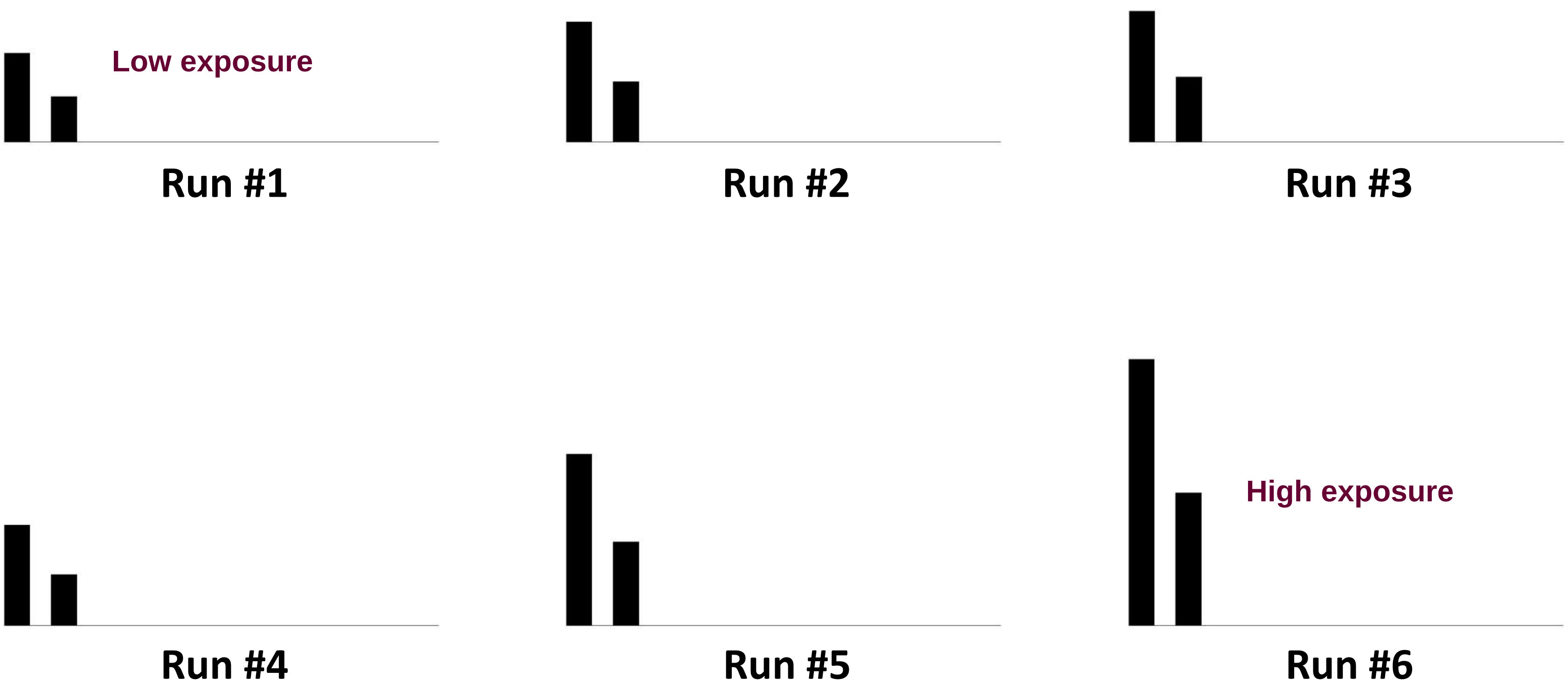
	Constant (one square pulse)	Stair-step (two unequal square pulses)	Intermittent (two unequal square pulses)
5 min.	Profile #1 (7 runs)	Profile #2 (6 runs) Profile #3 (5 runs)	Profile #4 (6 runs) Profile #5 (5 runs)
15 min.	Profile #11 (7 runs)		
30 min.	Profile #6 (6 runs)	Profile #7 (5 runs) Profile #8 (8 runs)	Profile #9 (5 runs) Profile #10 (7 runs)

Exposures for different runs within a profile (Example)

Profile #4

(2:1 pulse ratio is maintained, but overall intensity is varied)

(Each "run" consists of a batch of 10 rats)



Exposure profiles in the 2013 DTRA experiment

	Constant (one square pulse)	Stair-step (two unequal square pulses)	Intermittent (two unequal square pulses)
2.3 min.	**Profile #11 (7 runs)** 		
10 min.	**Profile #1 (5 runs)** 	**Profile #2 (4 runs)**  **Profile #3 (4 runs)** 	**Profile #4 (8 runs)**  **Profile #5 (4 runs)** 
30 min.	**Profile #6 (2 runs)** 	**Profile #7 (6 runs)**  **Profile #8 (4 runs)** 	**Profile #9 (5 runs)**  **Profile #10 (9 runs)** 

IDA

Outline of our Analysis

- Identify the subset of time-constant concentration data that is consistent with TL model
    - Determine baseline parameters
- For non-steady concentration data, compare predictions of different extensions of toxic load model to observations
    - Using baseline parameters
- Assess robustness of conclusions

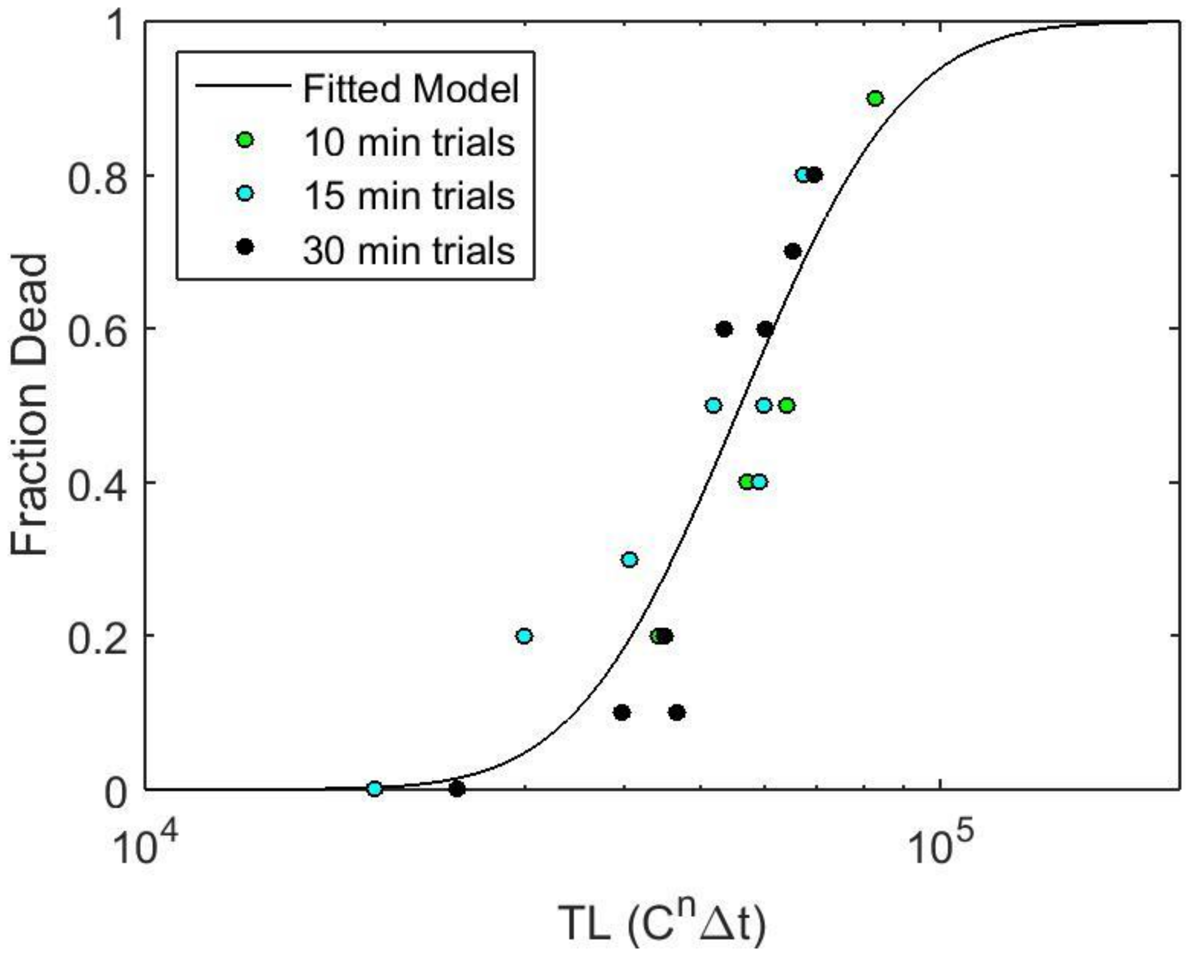
Fit of Toxic Load Model to Const. Conc. Data (10, 15, 30 minutes as baseline for fit)

n = 1.36
TL50 = 5.62 x 10^4
m = 6.15

Discrete values on the y-axis

Sampling error plays a significant role

Fit consistent with expected sampling error

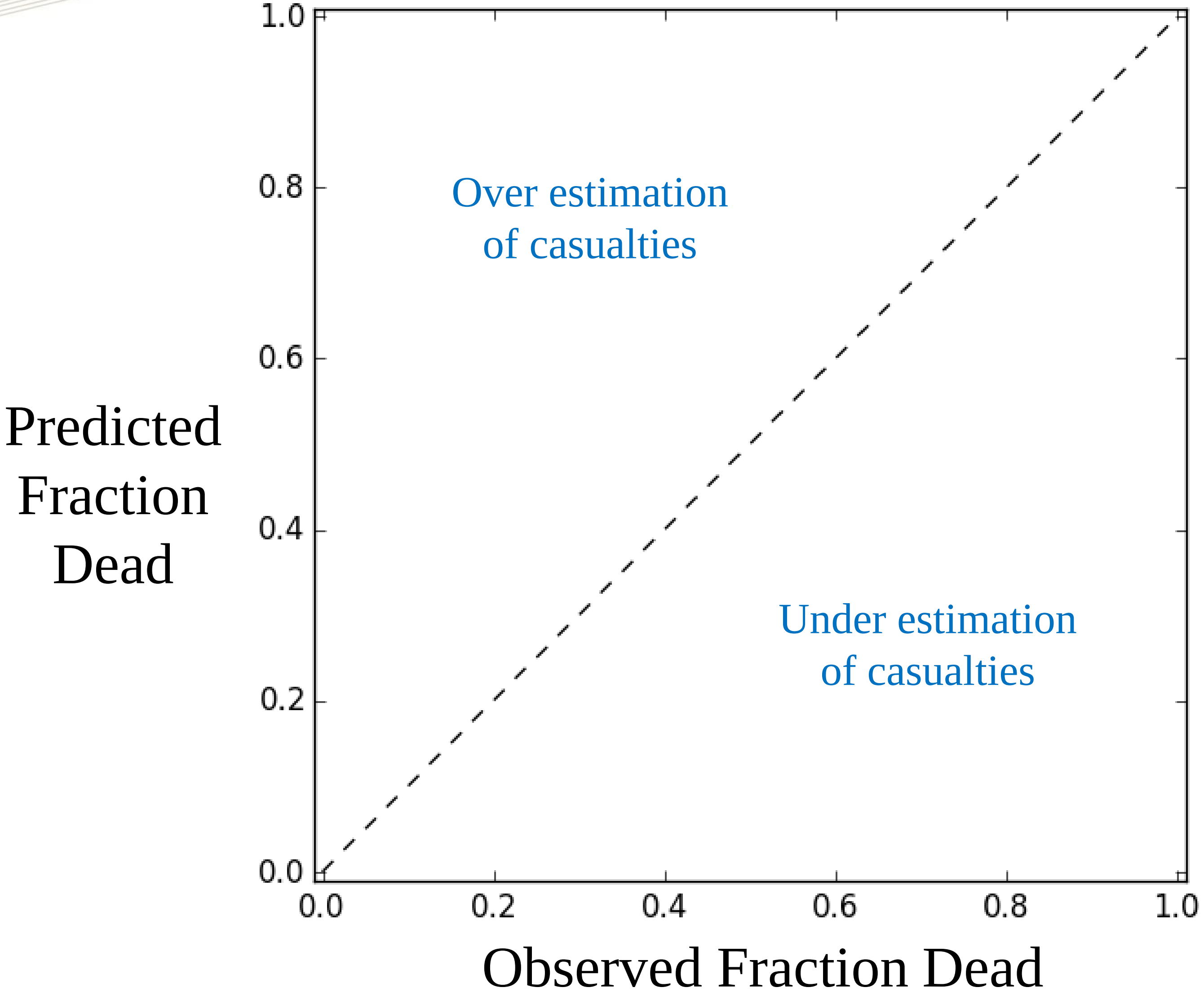


One dot = 10 rats… one trial

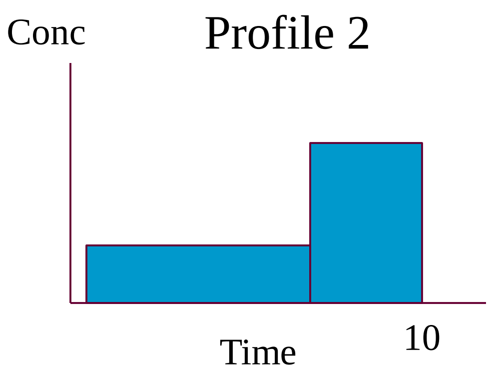
See Jeffry Urban's poster tonight for details (H17-112)

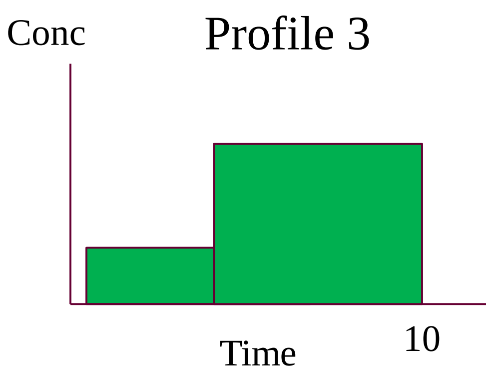
Do toxic load model extensions work for time-dependent exposures?

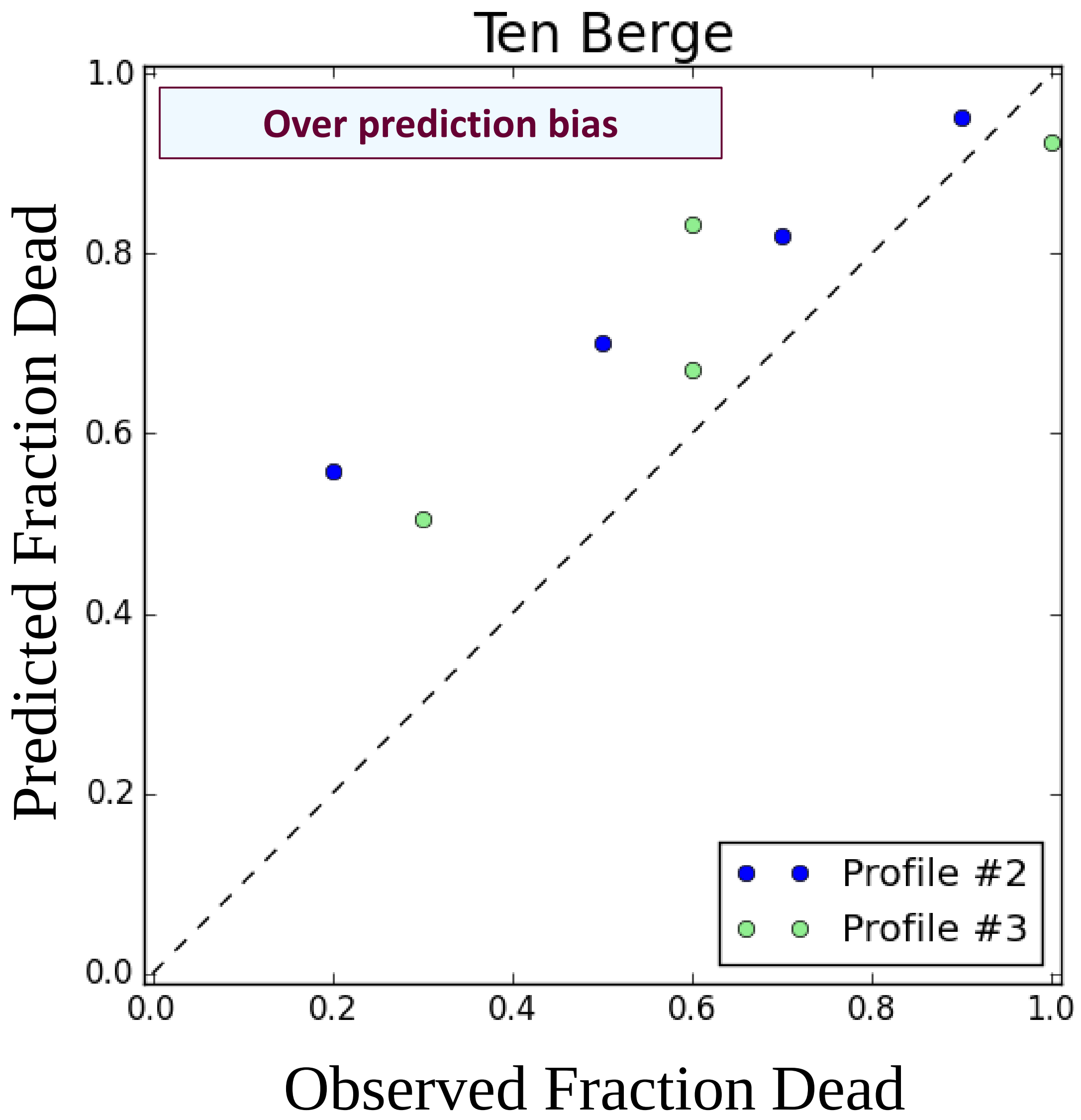
Accuracy of Casualty Model
Modeled vs Observed



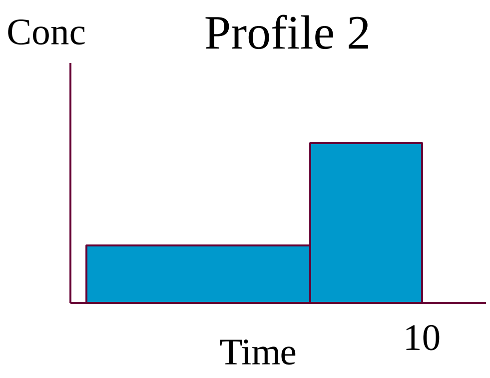
Ten Berge: Accuracy of Casualty Predictions
10 minute stair-step exposures

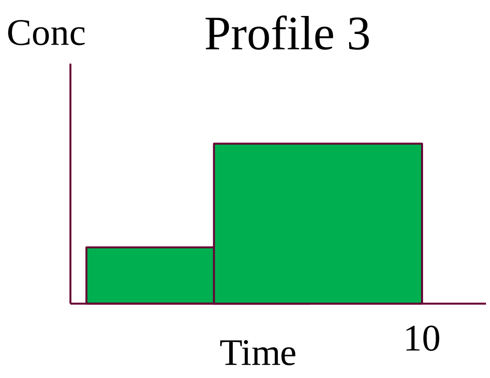


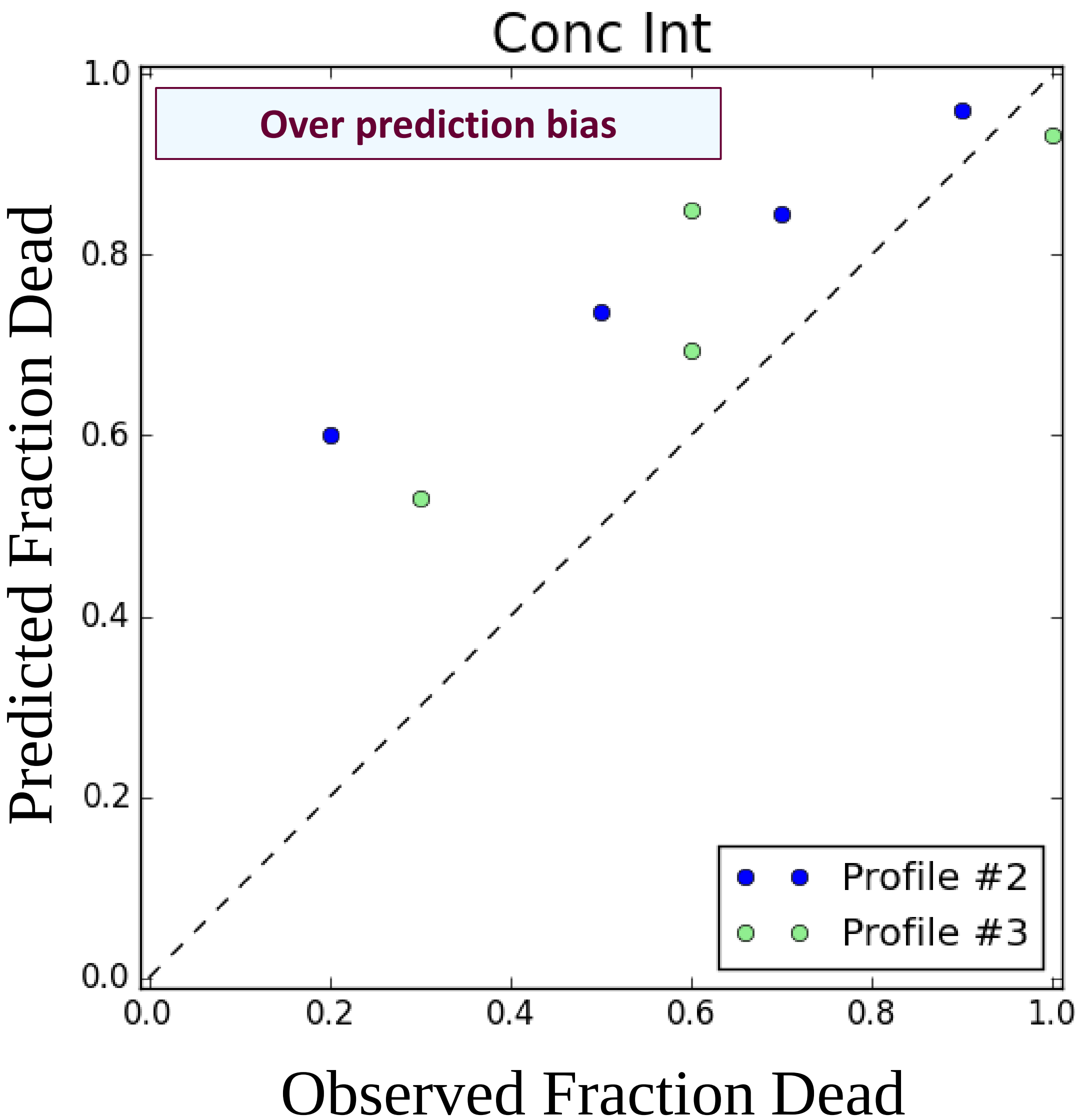




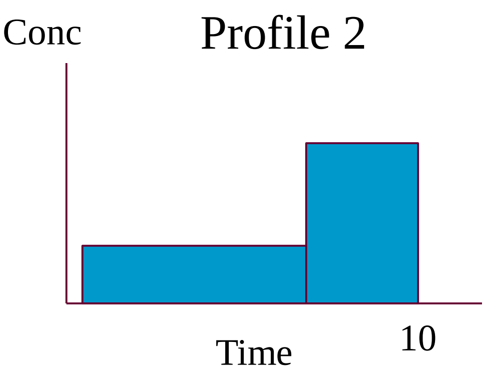
Conc Int: Accuracy of Casualty Predictions 10 minute stair-step exposures

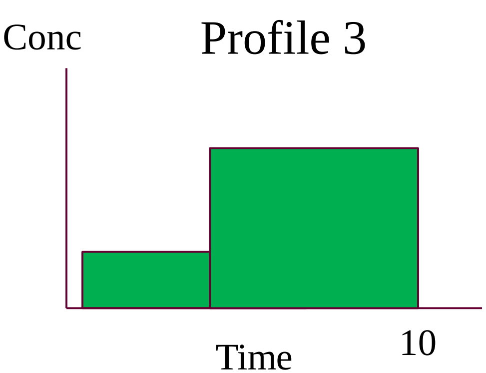


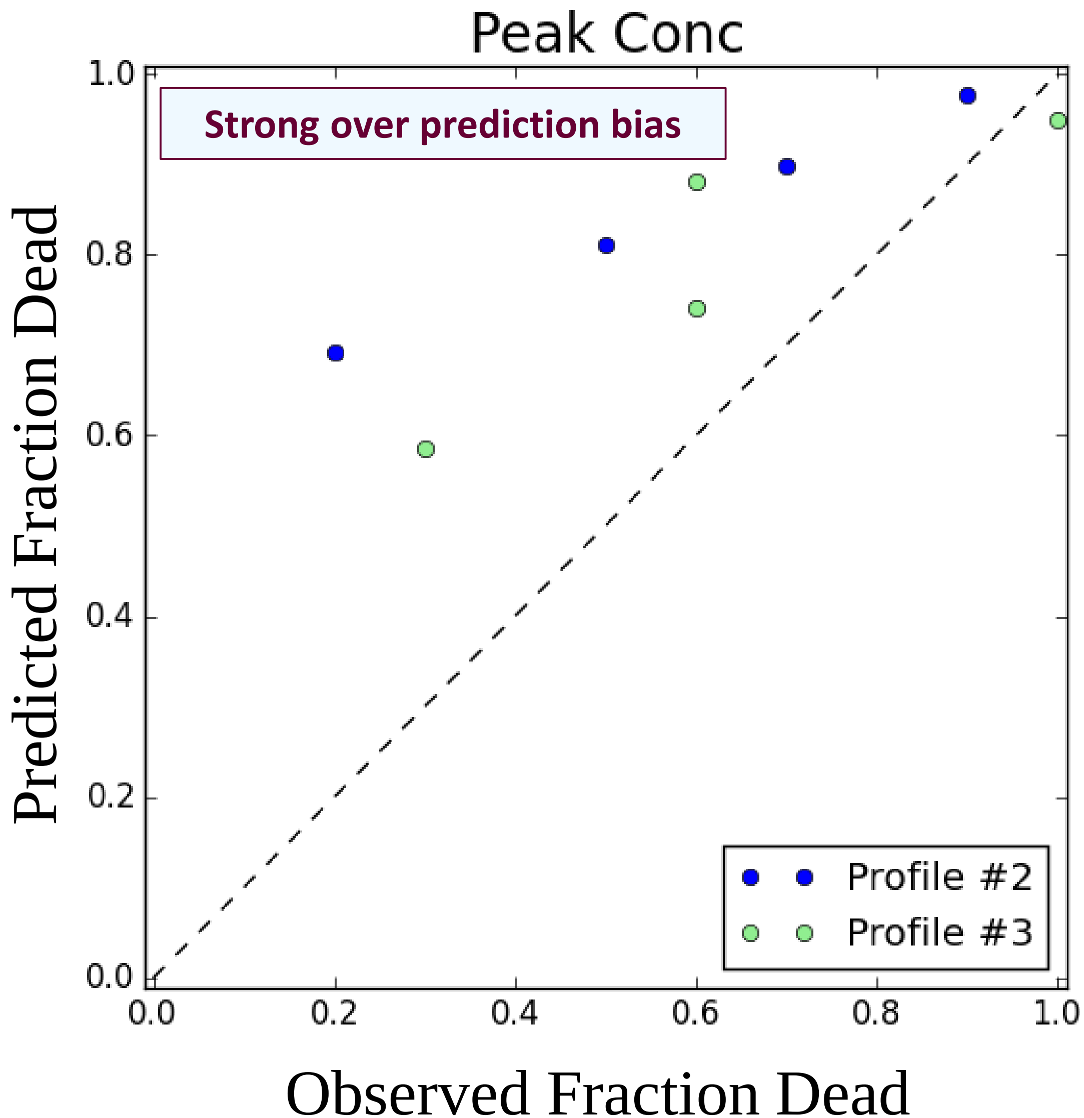




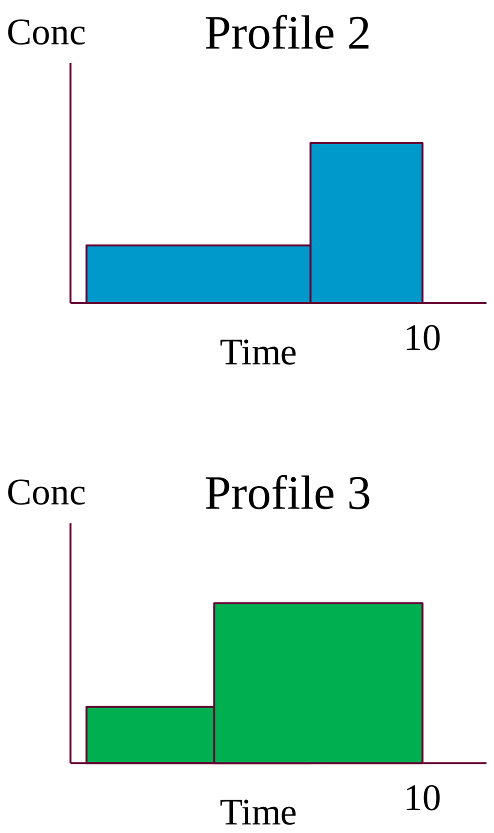
Peak Conc: Accuracy of Casualty Predictions
10 minute stair-step exposures

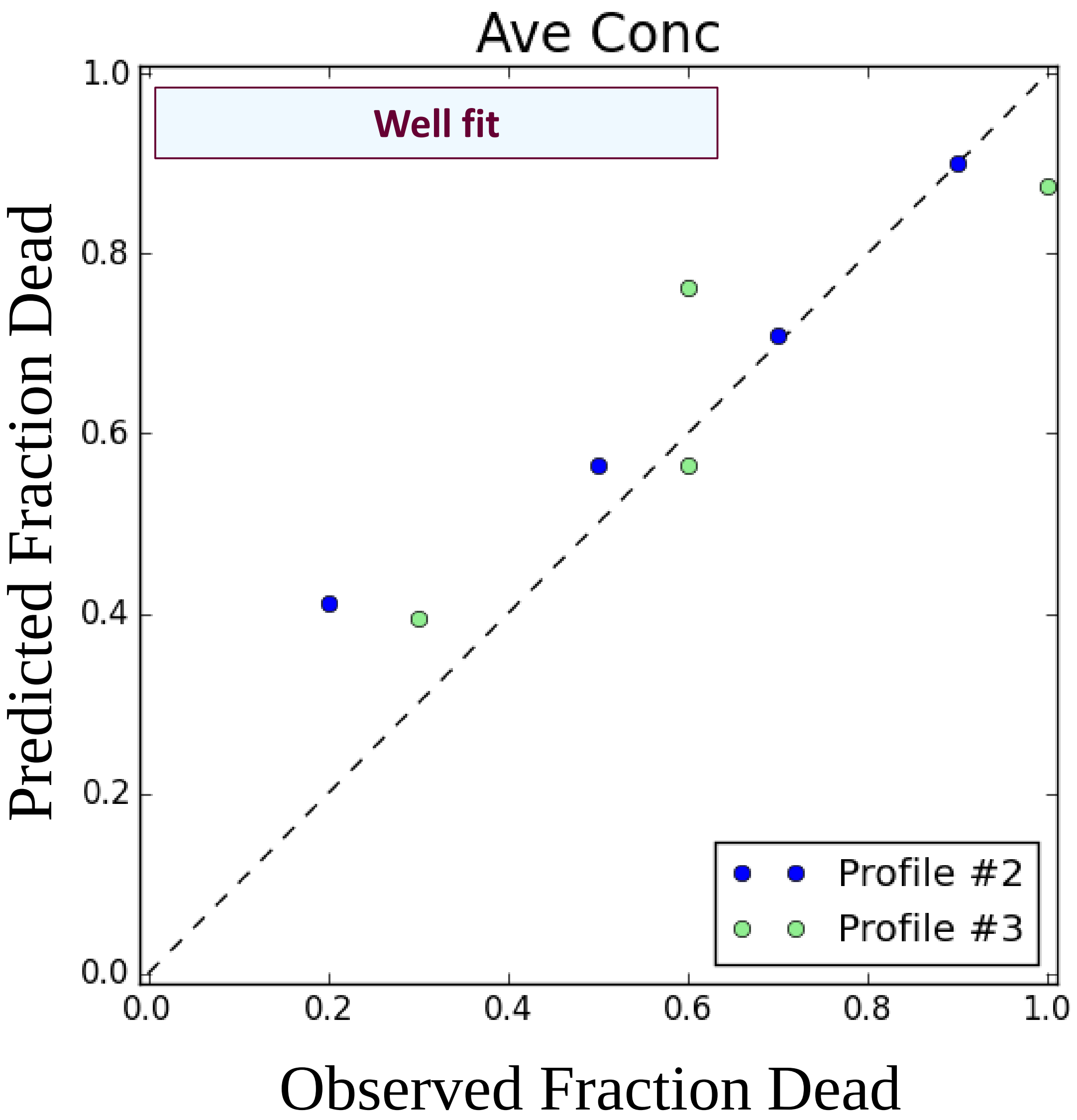




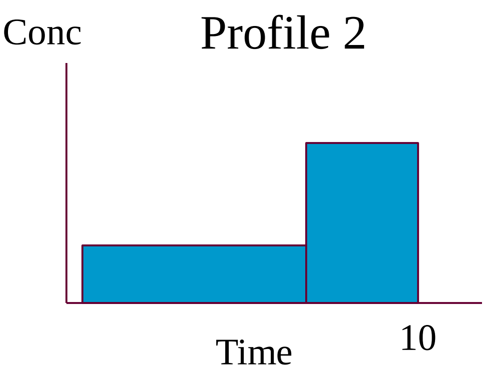


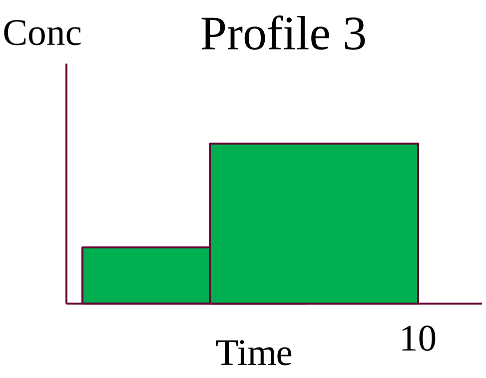
Ave Conc: Accuracy of Casualty Predictions 10 minute stair-step exposures

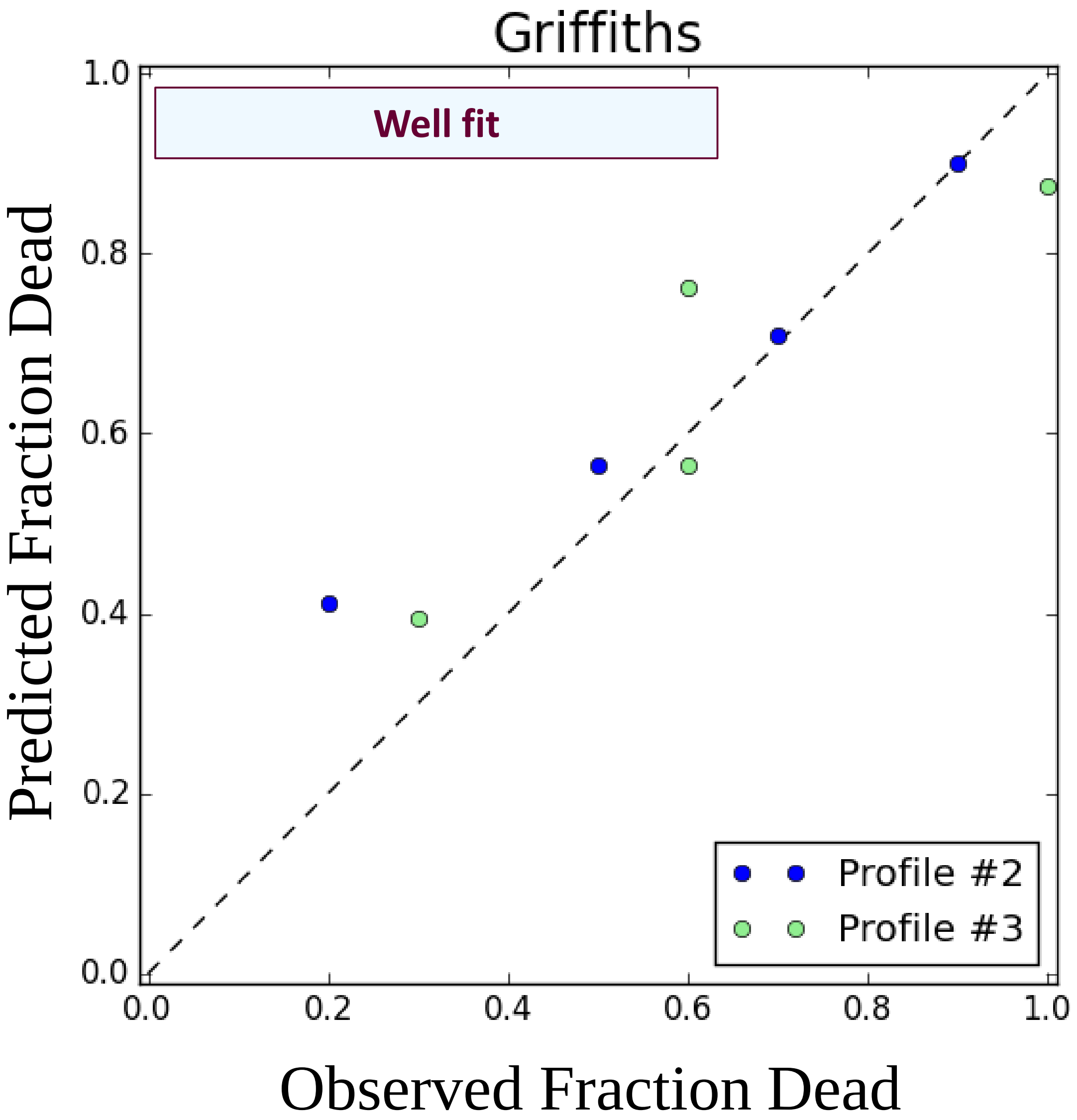




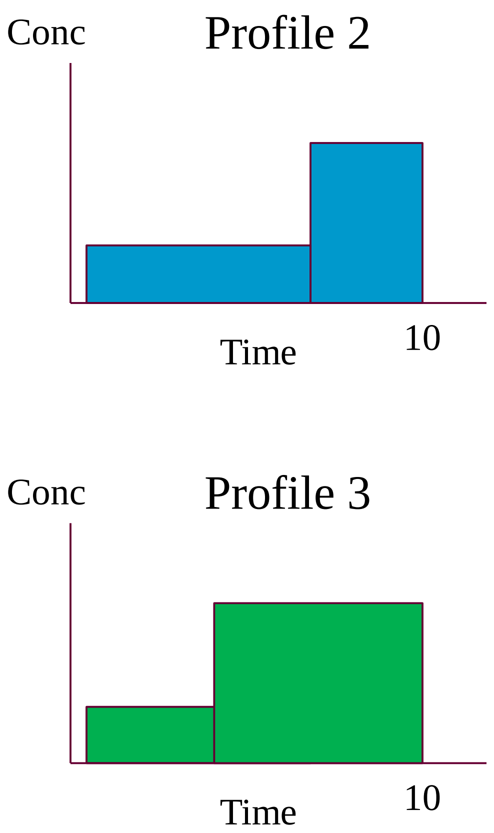
Griffiths: Accuracy of Casualty Predictions 10 minute stair-step exposures

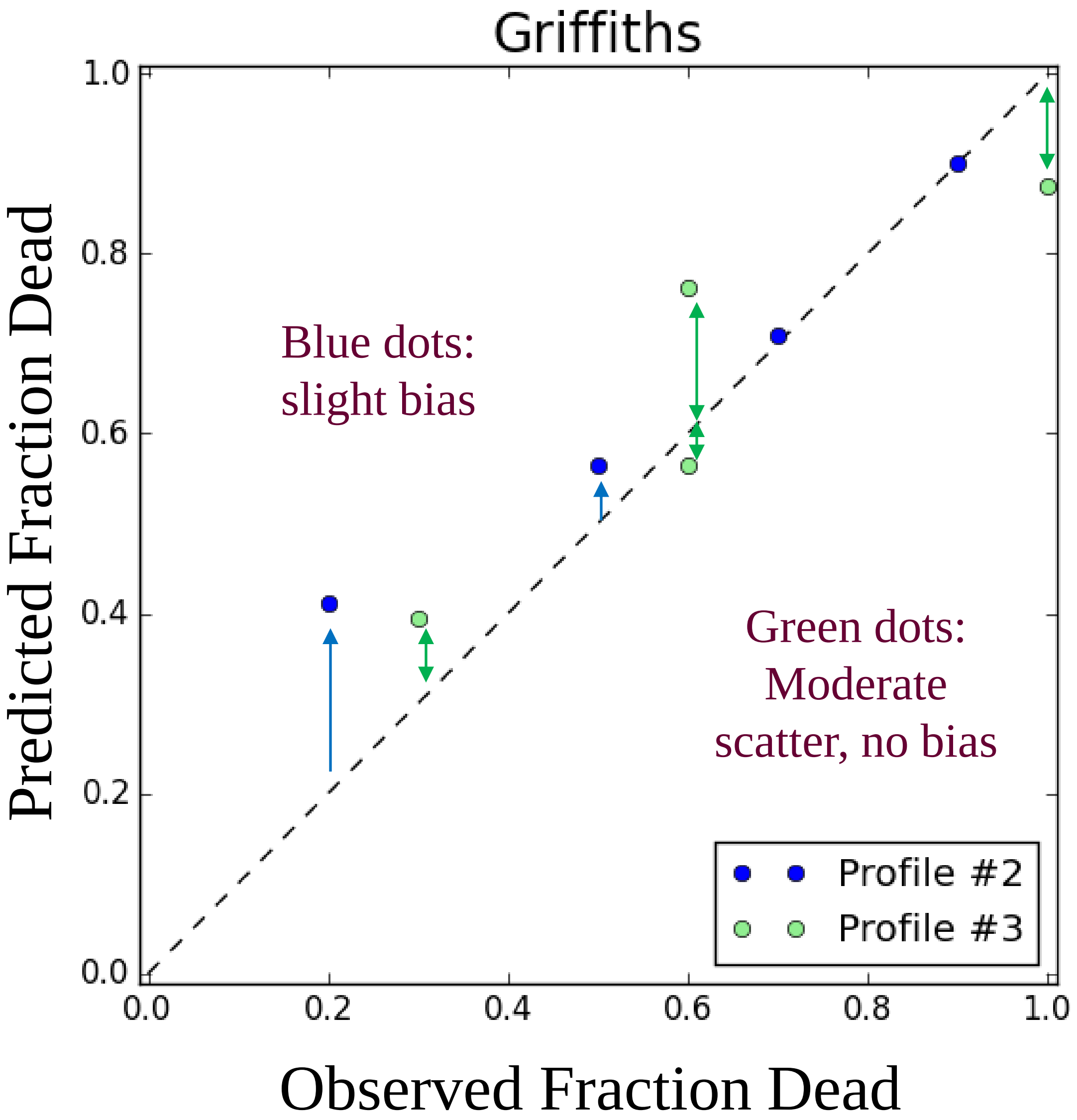






Visual depiction of bias and scatter

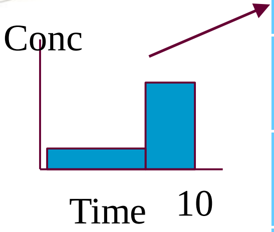




Quantifying Bias and Scatter

- Need a way to compare disagreement we observe to what we would expect by chance
- This indicates how well the TL model is predicting casualties
- Use p-values as an indicator of goodness of fit and define a “pass” or “fail”
    - If the bias/scatter of the data has a p-value less than 0.9, term the fit acceptable

TL Models' Performance for Scatter
P-values of mean square error statistic



Profile Desription	Griffiths-Megson p-values	Ave. Conc. p-values	Ten-Berge p-values	Conc. Int. p-values	Peak Conc. p-values
1:5, long-short, 10 mins total No time gap					
1:5, equal dur., 10 mins total No time gap					
2:1, equal dur., 30 mins total No time gap					
5:1, equal dur., 30 mins total No time gap					
1:5, long-short, 30 mins total No time gap					
1:5, equal dur., 30 mins total No time gap					
1:5, long-short, 10 mins total Time gap					
1:5, equal dur., 10 mins total Time gap					
2:1, equal dur., 30 mins total Time gap					
5:1, equal dur., 30 mins total Time gap					
1:5, long-short, 30 mins total Time gap					
1:5 equal dur., 30 mins total Time gap					

TL Models' Performance for Bias
P-values of absolute mean difference statistic

Profile Desription	Griffiths-Megson p-values	Ave. Conc. p-values	Ten-Berge p-values	Conc. Int. p-values	Peak Conc. p-values
1:5, long-short, 10 mins total No time gap	0.6882	0.6882	0.9964	0.9997	1.0000
1:5, equal dur., 10 mins total No time gap	0.4002	0.4002	0.9135	0.9681	0.9964
2:1, equal dur., 30 mins total No time gap	0.9864	0.9864	0.9979	0.9990	1.0000
5:1, equal dur., 30 mins total No time gap	0.9211	0.9211	0.3071	0.5740	0.9791
1:5, long-short, 30 mins total No time gap	0.5429	0.5429	0.9924	0.9986	0.9999
1:5, equal dur., 30 mins total No time gap	0.4322	0.4322	0.6243	0.7895	0.9328
1:5, long-short, 10 mins total Time gap	0.9314	0.2194	1.0000	1.0000	1.0000
1:5, equal dur., 10 mins total Time gap	0.9639	0.2483	0.9996	0.9999	1.0000
2:1, equal dur., 30 mins total Time gap	0.4431	0.9009	0.6398	0.7195	0.9513
5:1, equal dur., 30 mins total Time gap	0.8280	0.5758	0.9999	1.0000	1.0000
1:5, long-short, 30 mins total Time gap	0.0179	0.9852	0.9161	0.9460	0.9972
1:5 equal dur., 30 mins total Time gap	0.9363	1.0000	0.0301	0.2928	0.7334

TL Models' Overall Performance in Predicting Casualties

Metric	Griffiths-Megson	Average Conc.	Ten-Berge	Conc. Intensity	Peak Conc.
# profiles with acceptable scatter	6 of 12	5 of 12	4 of 12	4 of 12	2 of 12
# profiles with acceptable bias	7 of 12	7 of 12	4 of 12	4 of 12	1 of 12
# profiles with acceptable bias and scatter	5 of 12	4 of 12	3 of 12	3 of 12	0 of 12

Poor performance

Very poor performance

- The experiments indicate that the time-dependent toxic load models are not accurate for HCN exposures in rats

IDA | Recap and Conclusions

- For constant concentration profiles:
  - A single toxic load model cannot accurately predict casualties across the full time scale from 2.3 to 30 minutes.
  - However, we found that a single toxic load model can accurately predict casualties across a time-scale of 10 to 30 minutes.
    - On this time scale, the best fit parameters were…

$$n = 1.36, TL50 = 5.62 * 10^4, m = 6.15$$

IDA | Recap and Conclusions

- For time varying concentration profiles:
  - No model fits the data particularly well.
  - The Average Concentration model and the Griffiths-Megson model provide the least inaccurate predictions
    - Both models provide inaccurate predictions for seven of twelve profiles in the 10-30 minute exposure range where the toxic load model is applicable.

- Our conclusions about model accuracy hold only if the dominant source of error is small sample size (10 rats per trial).
  - Potential systematic errors are not considered in this analysis
  - Some physiological effects cannot be captured by any toxic load model. New toxicity models may be needed.