Survival time models quantitatively predict mortality from oil spill PAH exposures of different durations

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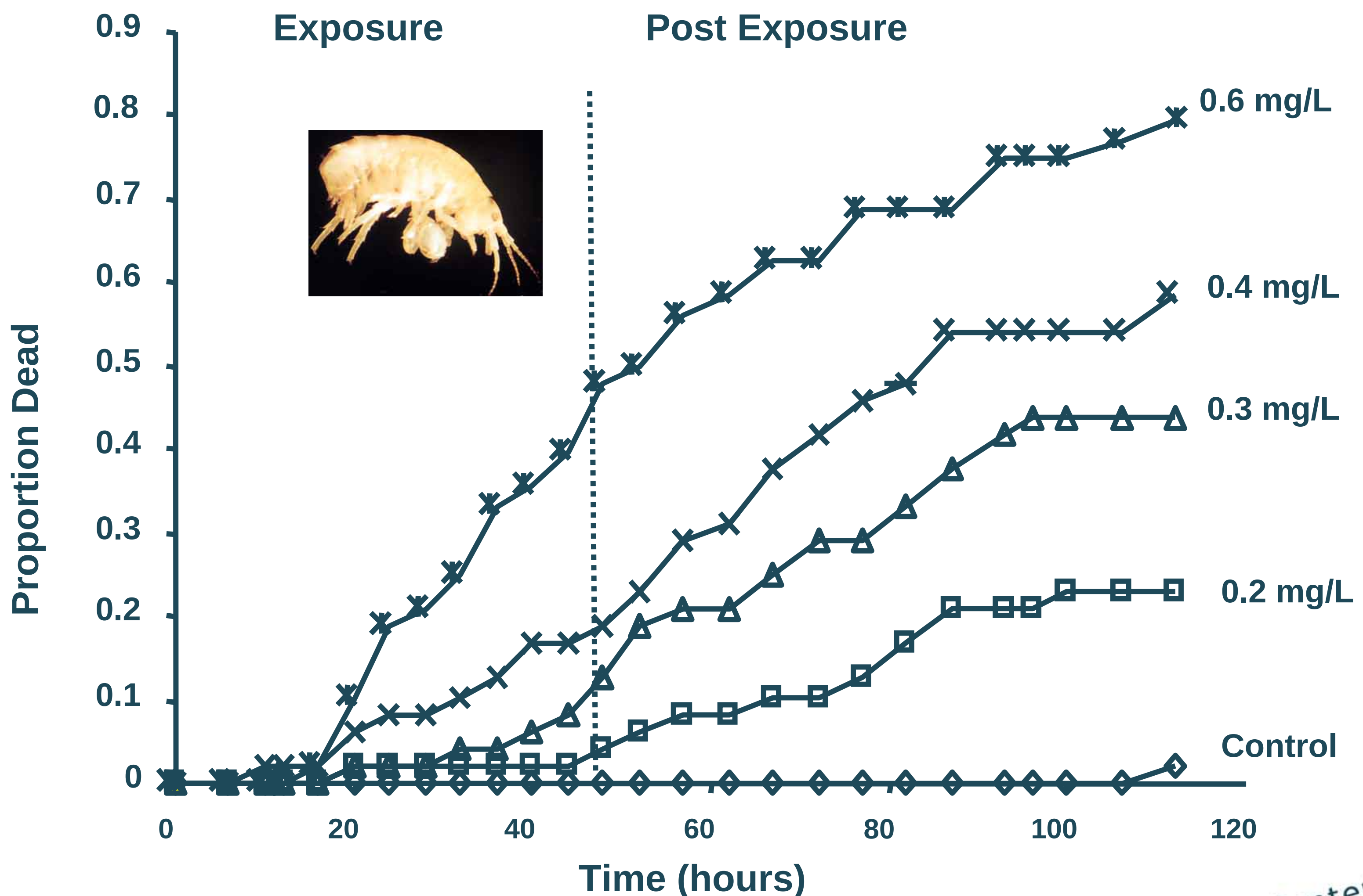
Rationale

Most toxicity data are derived from conventional concentration-effect test designs that produce an effect metric (e.g., LC50), at a set exposure time.

- **Only gross prediction if mortality not noted throughout the exposure.**
- **Post-exposure mortality is not included in predictions.**

This impedes accurate prediction for spilt oil exposures that vary in duration and concentration through time, and prediction of all mortality resulting from such exposures.

Post-exposure Mortality Example



From: Zhao & Newman. 2004. ETAC 23:2147-2153

Time-to-Death (Survival) Analysis As A Solution

Generally same test design but monitor time-to-death of individuals

Survivors are treated as censored in modeling

Fit data to best of several candidate models via MLE

$$Survival\ Time = e^{b_1} e^{b_2 (\ln Concentration)} e^{\varepsilon}$$

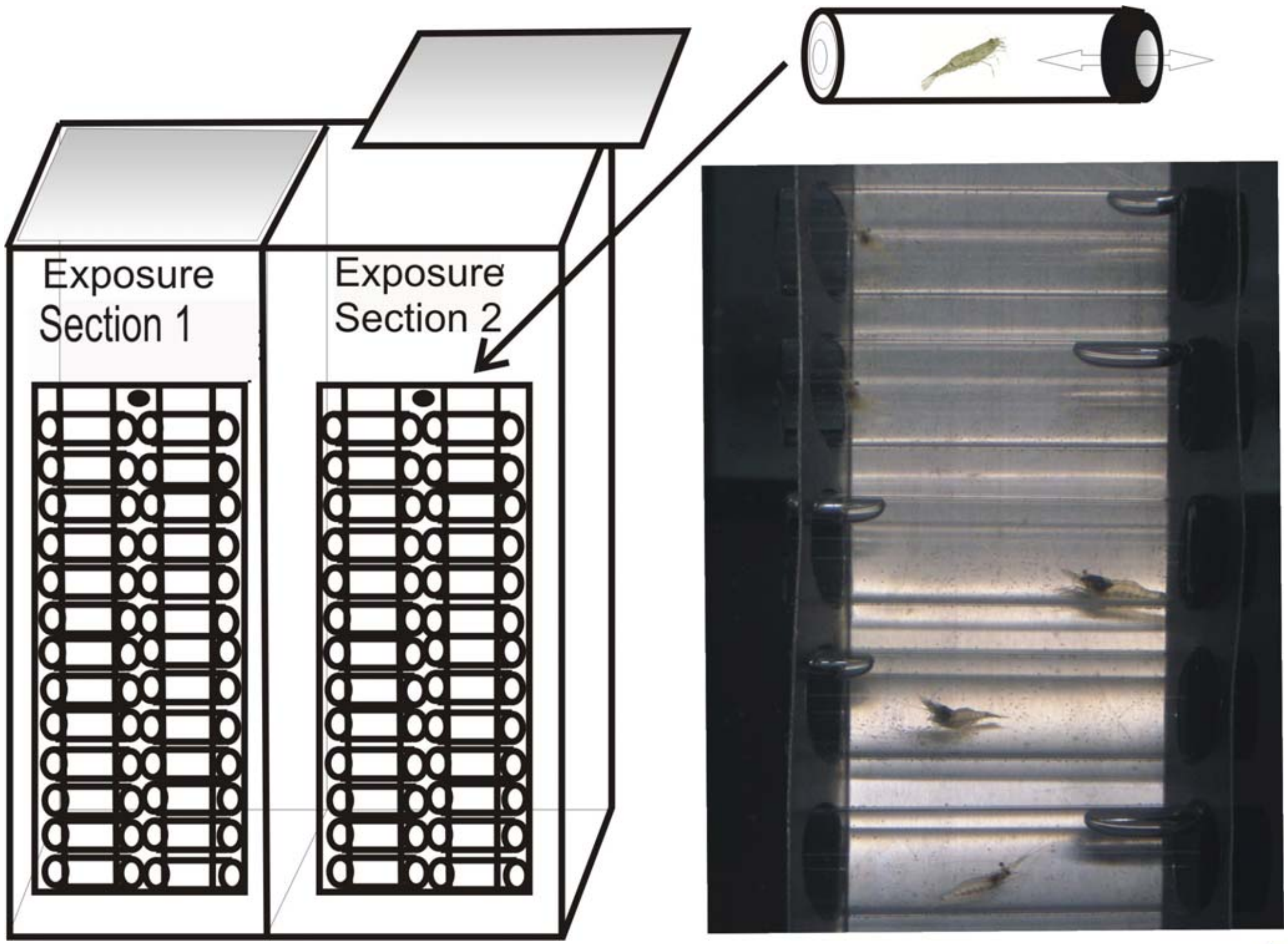
Why isn't this done? Advocated in classic books/papers.

Standard approach set before computations were easy.

Objectives

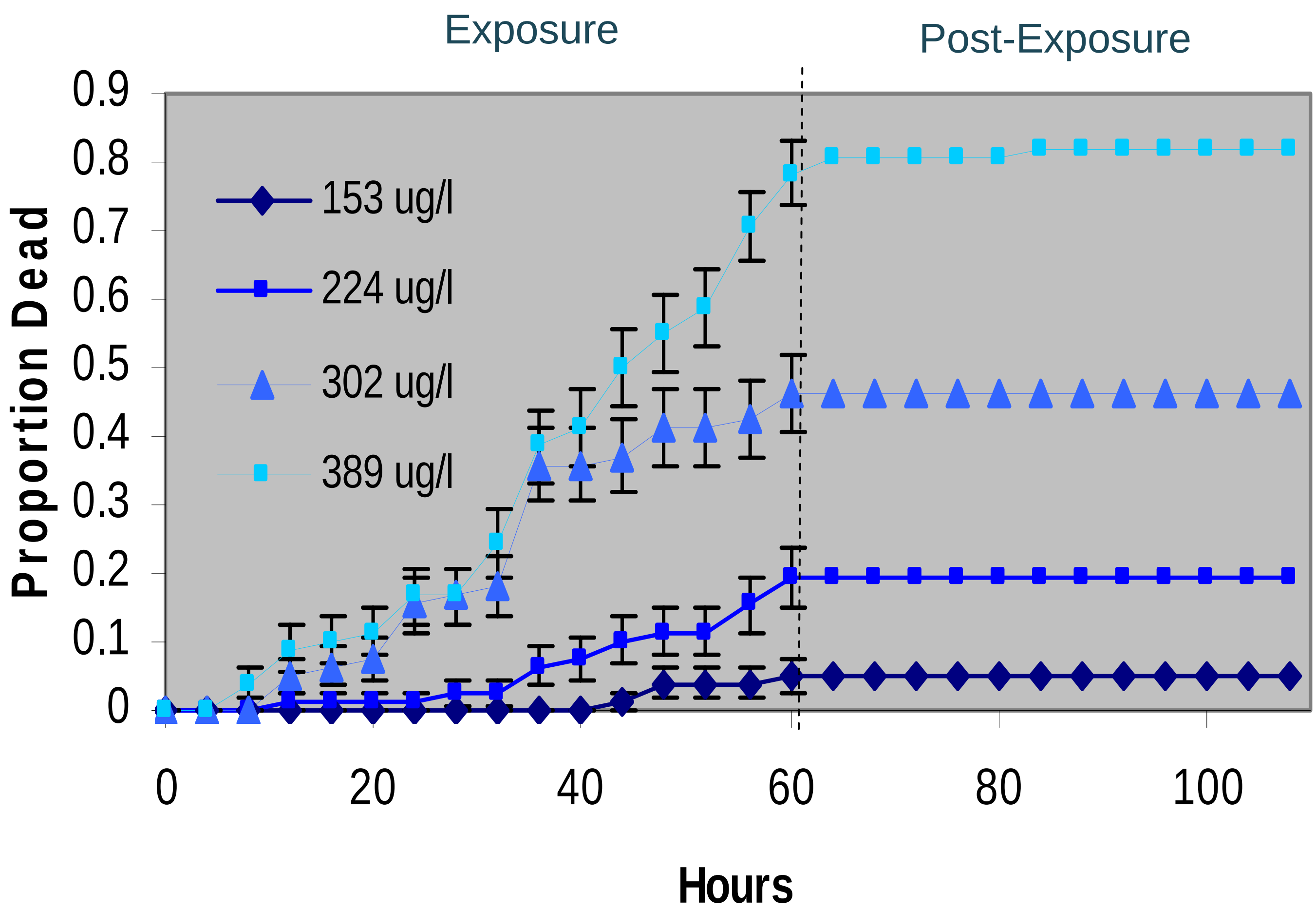
- Produce predictive survival time models for grass shrimp exposed to six representative PAH in weathered oil WAF.
- Produce predictive survival time models that include molecular qualities of the PAH.
- Produce predictive survival time models for shrimp exposed to a mixture of the PAH.

Exposure System

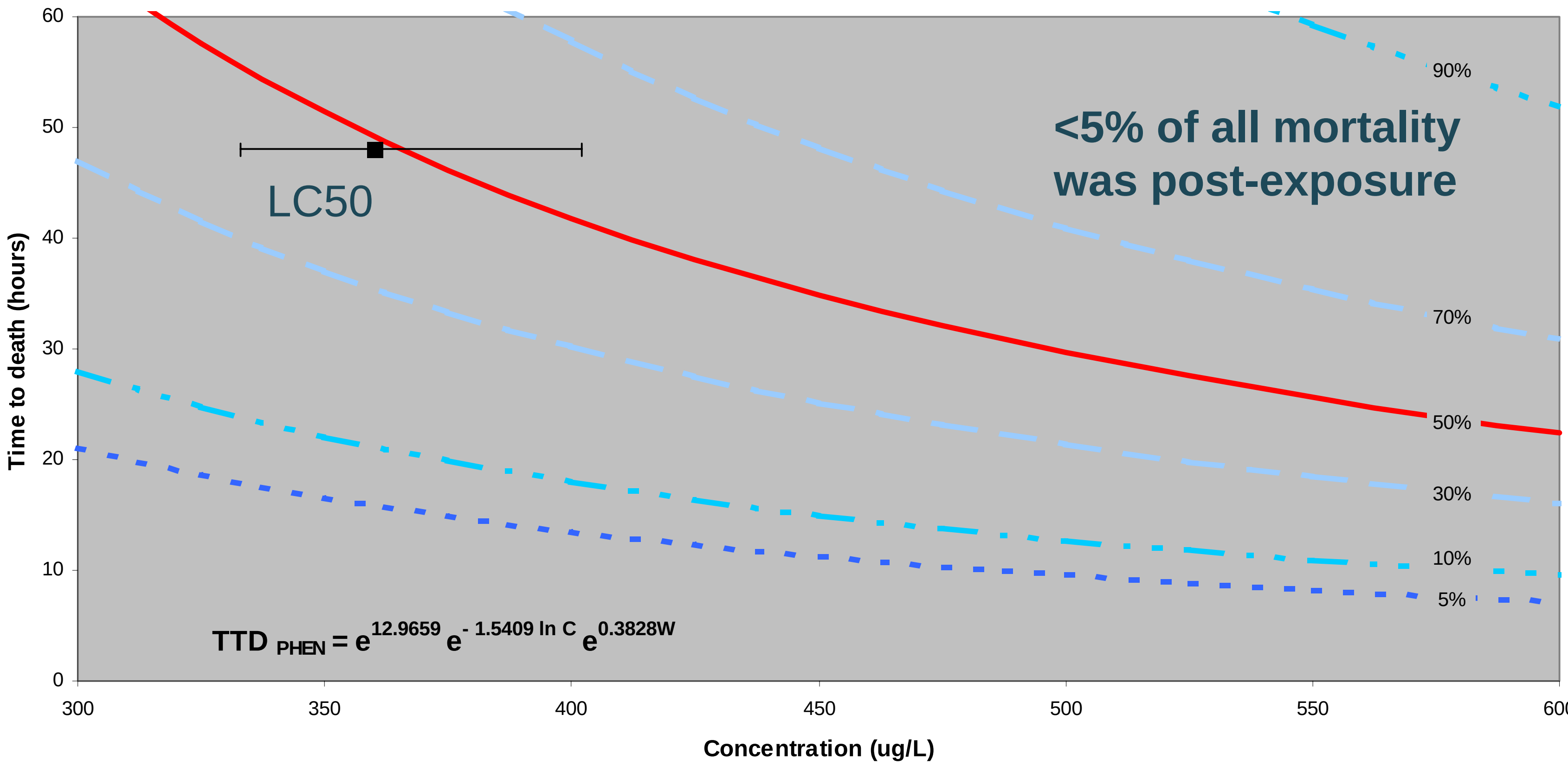


Survival Data

Phenanthrene



Survival Model Contours - Phenanthrene



$$TTD_{PHEN} = e^{12.9659} e^{-1.5409 \ln C} e^{0.3828W}$$

<5% of all mortality was post-exposure

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48 h LC50 Probit Models

$$P = P_{Threshold} + (1 - P_{Threshold})(\Phi(Intercept + Slope(\log Concentration))$$

Compound	LC50 (95% CI)	Intercept (SE)	Slope (SE)	Threshold Mortality (SE)
Ethylnaph-thalene	295 (162-308)	-31.4 (10.7)	12.7 (4.2)	0.06 (0.05)
Dimethyl-naphthalene	500 (467-535)	-20.4 (3.6)	7.5 (1.3)	0.06 (0.03)
Phenanthrene	360 (333-402)	-14.5 (2.4)	5.7 (1.0)	0.02 (0.01)
Dibenzo-thiophene	242 (228-253)	-35.4 (5.3)	14.9 (2.2)	0.06 (0.03)
Fluorene	615 (593-637)	-33.3 (3.6)	11.9 (1.3)	0.03 (0.02)
Naphthalene	2061 (2018-2106)	-60.3 (8.2)	18.2 (2.5)	0.01 (0.01)

No Significant Post-exposure Mortality

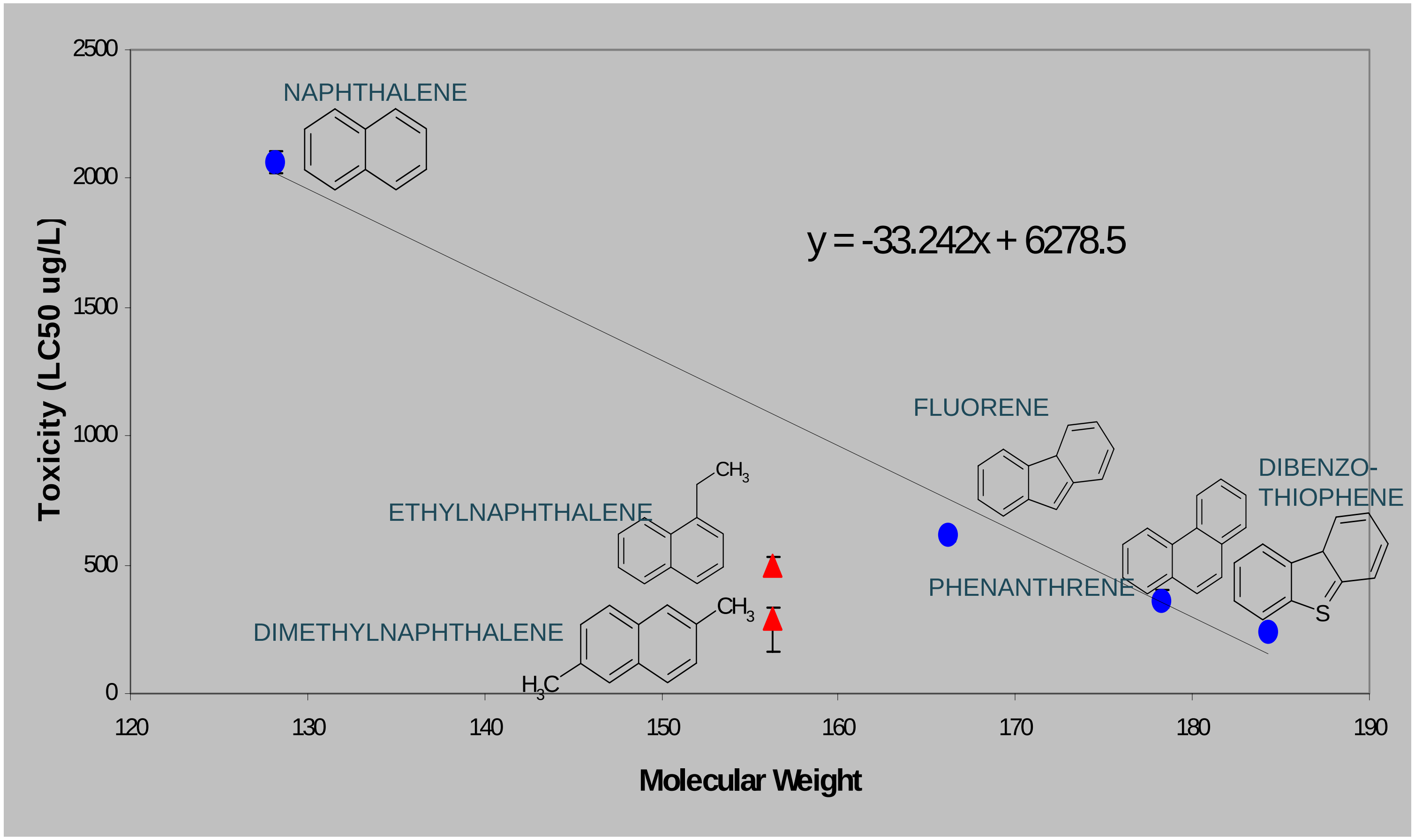
Survival Models

$$TTD = e^{b_1} e^{b_2 (\ln Conc)} e^{b_3 W}$$

Compound	b_1 (SE)	b_2 (SE)	b_3 (SE)
Ethylnaph-thalene	15.3 (1.0)	-2.0 (0.2)	0.26 (0.01)
Dimethyl-naphthalene	14.9 (1.2)	-1.8 (0.2)	0.34 (0.03)
Phenanthrene	13.0 (1.1)	-1.5 (0.2)	0.38 (0.03)
Dibenzo-thiophene	17.4 (0.6)	-2.4 (0.1)	0.31 (0.02)
Fluorene	22.1 (1.6)	-2.8 (0.2)	0.41 (0.02)
Naphthalene	52.2 (2.1)	-6.3 (0.3)	0.64 (0.03)

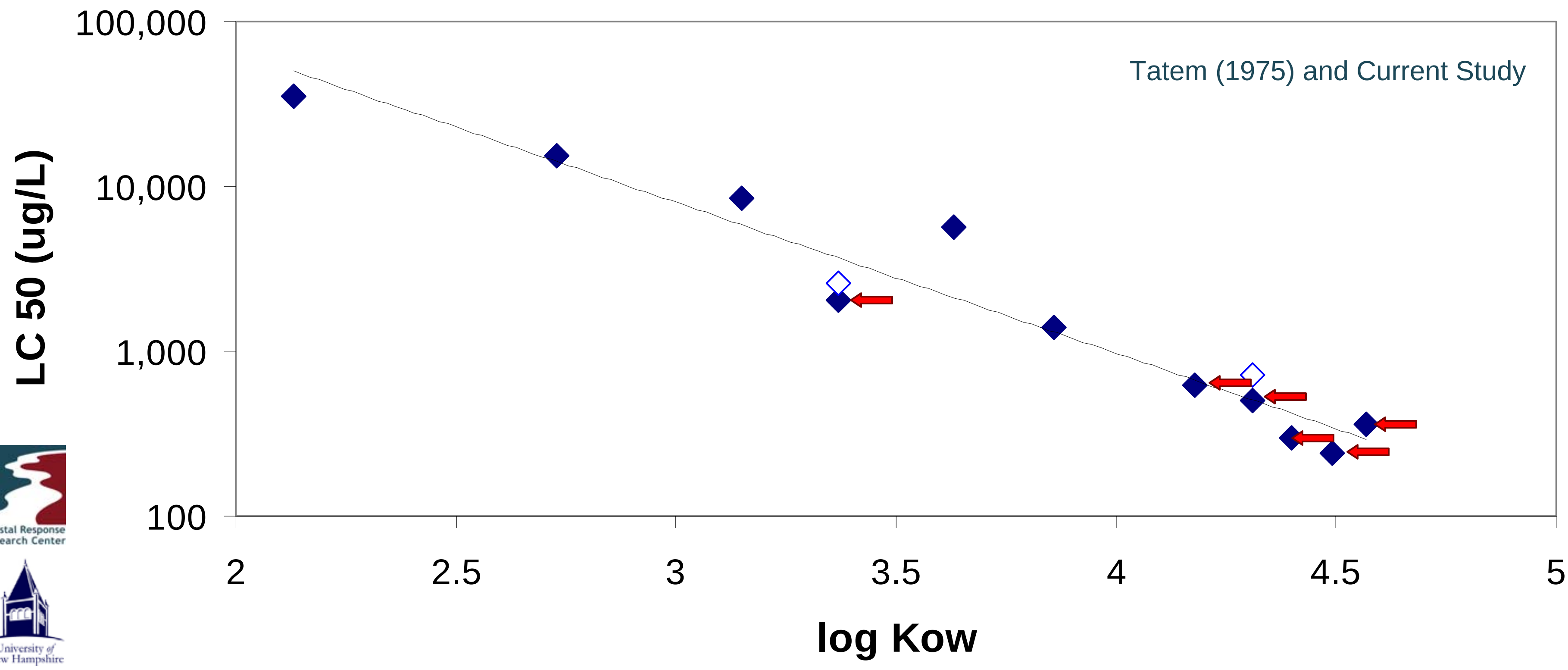
No Significant Post-exposure Mortality

MW QSAR Predicting LC50

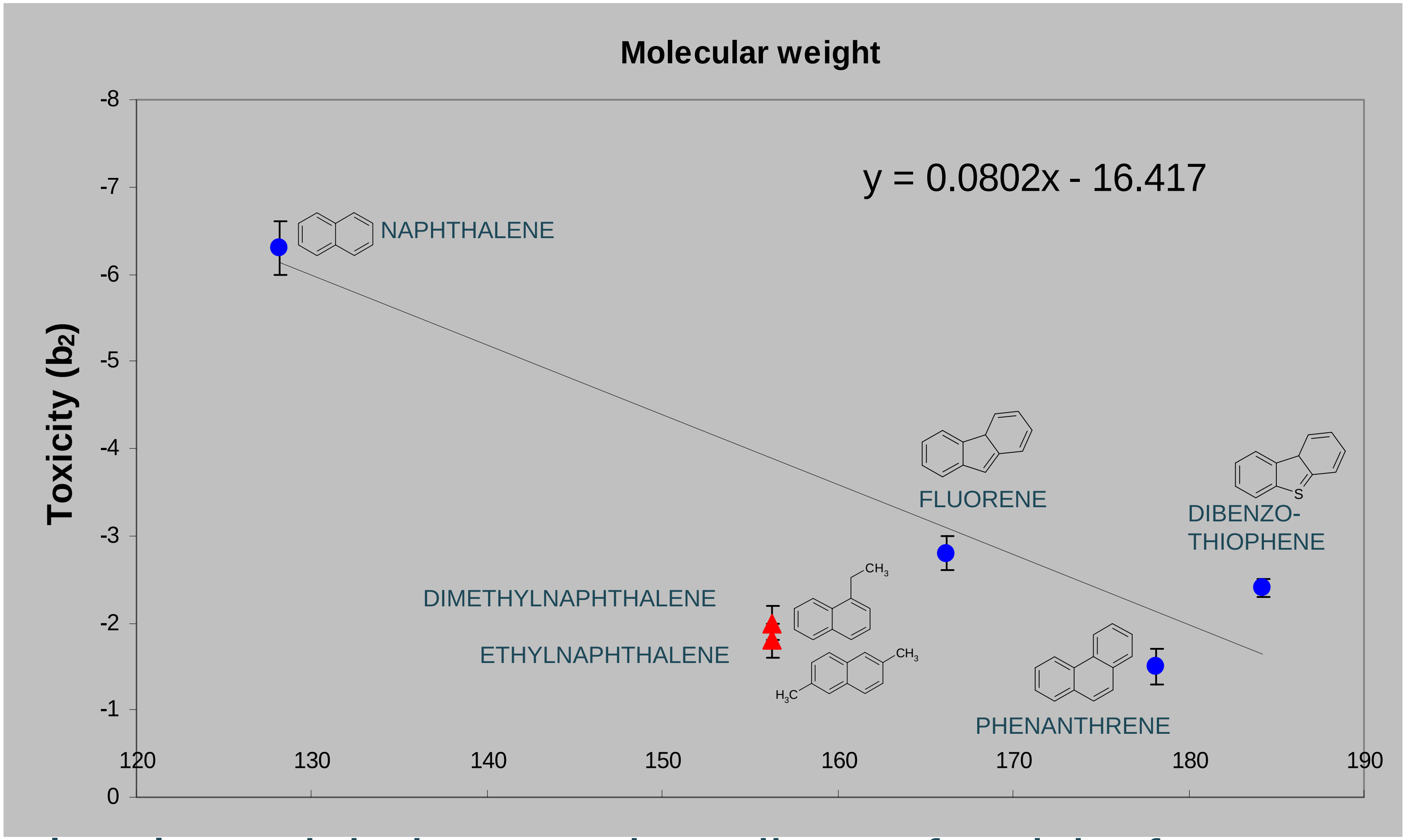


Molecular weight is a good predictor of toxicity for unsubstituted compounds but seem to underestimate the toxicity of substituted PAH

K_{ow} QSAR Predicting LC50

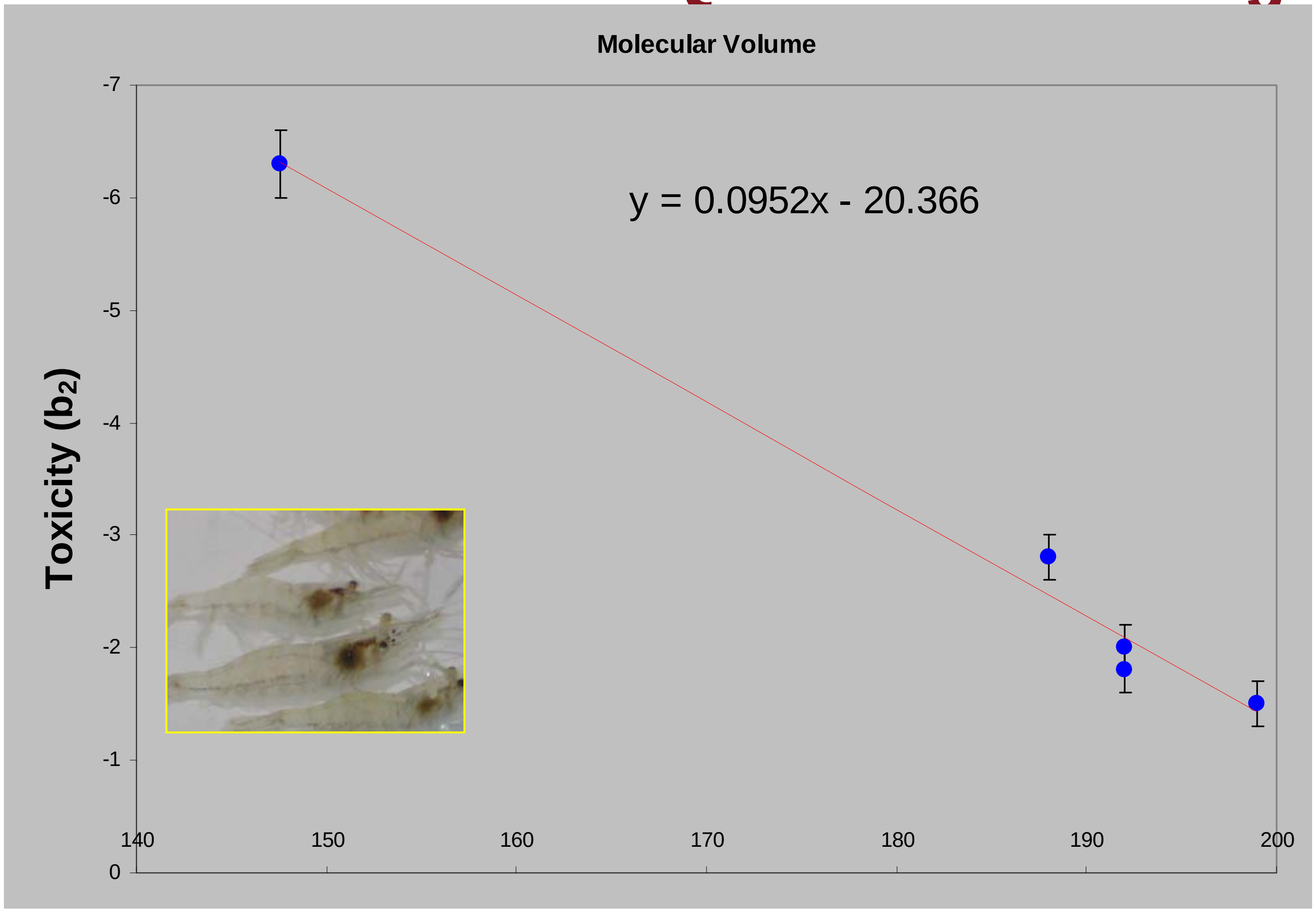


MW QSAR Predicting b_2



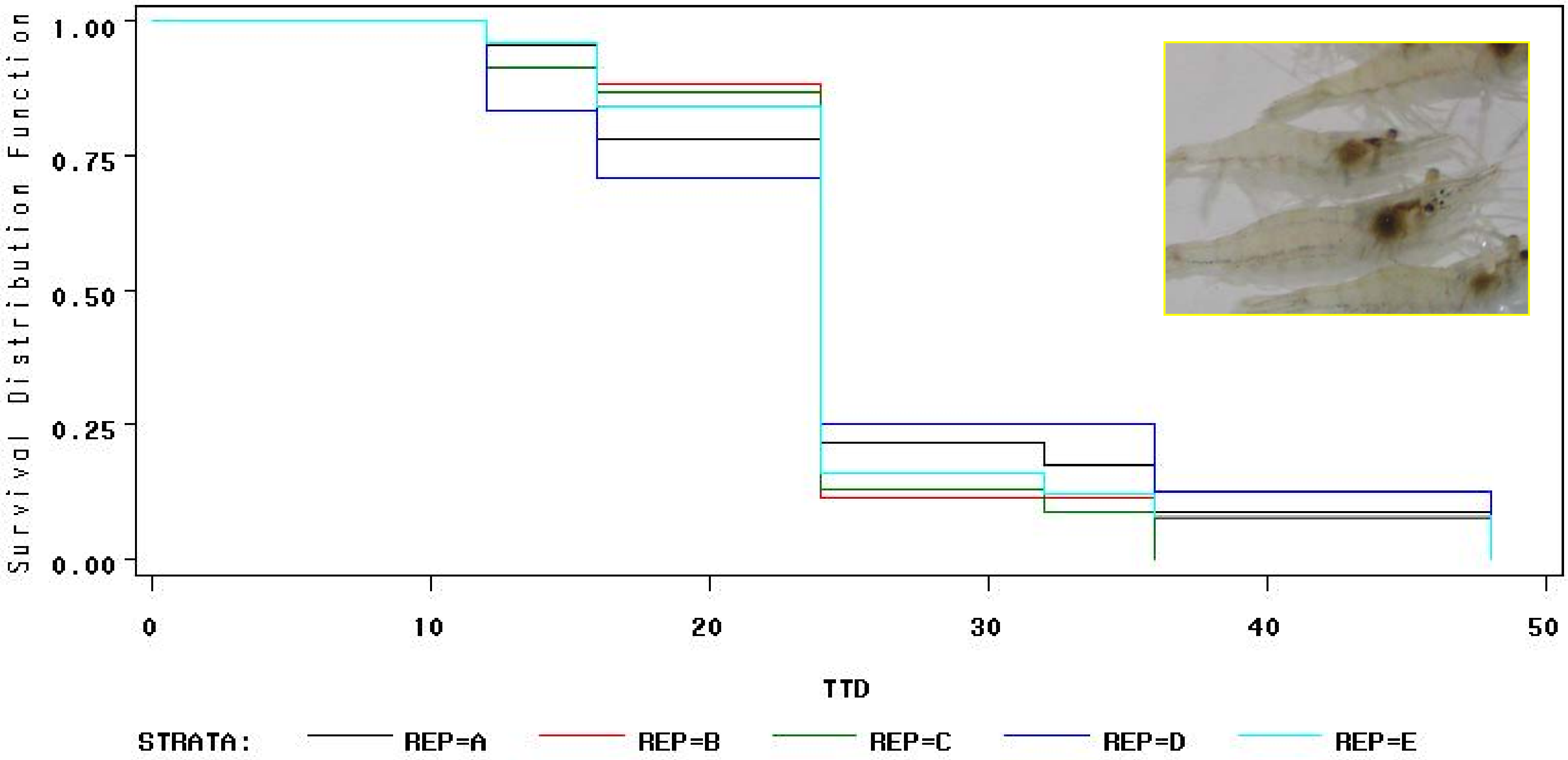
Molecular weight is a good predictor of toxicity for unsubstituted compounds but underestimates the toxicity of substituted PAH

Molecular Volume QSAR Predicting b_2



Molecular volume might be a better predictor for both unsubstituted and substituted compounds

Mixture Experiment



Ethylnaphthalene, Dibenzothiophene, Dimethylnaphthalene mixture predicted to kill 100% of shrimp by 48 hours

Generating ancillary data with easier Microtox® system

Applying Survival Analysis to Predict Oil Spill Toxicity

- Produced survival models for the six key compounds
- Minimal post-exposure mortality for these compounds
- Can predict mortality for different exposure scenarios
- QSAR models being built for survival model metrics
- Mixture experiment complete. Exploring data now.

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Much predictive promise for realistic exposure scenarios.
Survival models for 6 compounds and QSARs available soon.

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www.crrc.unh.edu

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