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

![Graph showing the proportion of dead organisms over time for different concentrations of exposure and post-exposure.](image)

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

\[ \text{Survival Time} = e^{b_1} e^{b_2 (\ln \text{Concentration})} e^{\varepsilon} \]

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

Exposure

Post-Exposure

Proportion Dead

Hours

153 ug/l
224 ug/l
302 ug/l
389 ug/l
Survival Model Contours - Phenanthrene

\[ \text{TTD}_{\text{PHEN}} = e^{12.9659} \times 1.5409 \ln C \times e^{0.3828W} \]

<5% of all mortality was post-exposure

LC50
### 48 h LC50 Probit Models

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

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

No Significant Post-exposure Mortality
Survival Models

\[ TTD = e^{b_1} e^{b_2 \cdot (\ln \text{Conc})} e^{b_3 W} \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>(b_1) (SE)</th>
<th>(b_2) (SE)</th>
<th>(b_3) (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethynaphthalene</td>
<td>15.3 (1.0)</td>
<td>-2.0 (0.2)</td>
<td>0.26 (0.01)</td>
</tr>
<tr>
<td>Dimethyl-naphthalene</td>
<td>14.9 (1.2)</td>
<td>-1.8 (0.2)</td>
<td>0.34 (0.03)</td>
</tr>
<tr>
<td>Phenanthrene</td>
<td>13.0 (1.1)</td>
<td>-1.5 (0.2)</td>
<td>0.38 (0.03)</td>
</tr>
<tr>
<td>Dibenzo-thiophene</td>
<td>17.4 (0.6)</td>
<td>-2.4 (0.1)</td>
<td>0.31 (0.02)</td>
</tr>
<tr>
<td>Fluorene</td>
<td>22.1 (1.6)</td>
<td>-2.8 (0.2)</td>
<td>0.41 (0.02)</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>52.2 (2.1)</td>
<td>-6.3 (0.3)</td>
<td>0.64 (0.03)</td>
</tr>
</tbody>
</table>

No Significant Post-exposure Mortality
Molecular weight is a good predictor of toxicity for unsubstituted compounds but seem to underestimate the toxicity of substituted PAH.

\[ y = -33.242x + 6278.5 \]
$K_{ow}$ QSAR Predicting LC50

Tatem (1975) and Current Study
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.

\[ y = 0.0952x - 20.366 \]
Mixture Experiment

Ethynaphthalene, Dibenzothiophene, Dimethynaphthalene 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.

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

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www.crrc.unh.edu