Nanotechnology Risk Assessment Models

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Outline

- Overview & Motivation
  - High commercialization of nanotechnology
  - Health, economic, and regulatory uncertainties

- To-Date Nanotoxicology literature review
  - Huge concern, huge uncertainty

- Potential Modeling Approaches & Applications
  - Monte Carlo risk models
  - Multi-criteria models
  - Stochastic programming
  - Desirability functions

- Conclusions / Future Work
Nanomanufacturing Promise and Perils

**Promise**
- Over 800 commercial nanotech products on the market
- Main application areas:
  - Health & Fitness - 62%
  - Home & Garden - 11%
  - Food & Beverage - 10%
  - Electronics & Computers - 7%
- Full-scale production costs

**Perils**
- Possible negative attributes:
  - Penetrate dermal barriers
  - Cross cell membranes
  - Reach the gas exchange regions of the lung
  - Travel from the lung throughout the body
  - Interact at the molecular level

**Social Benefits**

**Health & Eco Risks**

**Manufacturing Economics**

**Regulatory Uncertainties**

**Future regulatory standards**

**Growing concerns**

**Next industrial revolution**
Global Distribution of Nanotoxicology Literature

- 1,935 items of peer-reviewed literature on nanotoxicology
- Period of year 2000 to year 2007
- English journals, letters, and reviews

Global Distribution of Nanotoxicology Scientific Literature

<table>
<thead>
<tr>
<th>Number of Publications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unites States</td>
<td>768</td>
</tr>
<tr>
<td>China</td>
<td>191</td>
</tr>
<tr>
<td>Germany</td>
<td>116</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>103</td>
</tr>
<tr>
<td>Japan</td>
<td>101</td>
</tr>
<tr>
<td>France</td>
<td>80</td>
</tr>
<tr>
<td>India</td>
<td>74</td>
</tr>
<tr>
<td>Italy</td>
<td>56</td>
</tr>
<tr>
<td>South Korea</td>
<td>56</td>
</tr>
<tr>
<td>Canada</td>
<td>42</td>
</tr>
<tr>
<td>Spain</td>
<td>34</td>
</tr>
<tr>
<td>Taiwan</td>
<td>34</td>
</tr>
<tr>
<td>Switzerland</td>
<td>30</td>
</tr>
<tr>
<td>Brazil</td>
<td>21</td>
</tr>
<tr>
<td>Netherlands</td>
<td>21</td>
</tr>
<tr>
<td>Australia</td>
<td>20</td>
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<tr>
<td>Russia</td>
<td>17</td>
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<tr>
<td>Singapore</td>
<td>15</td>
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<tr>
<td>Belgium</td>
<td>12</td>
</tr>
<tr>
<td>Israel</td>
<td>11</td>
</tr>
<tr>
<td>Denmark</td>
<td>11</td>
</tr>
<tr>
<td>Poland</td>
<td>10</td>
</tr>
<tr>
<td>Romania</td>
<td>10</td>
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</tbody>
</table>

Growing Nano-EHS Concerns...

- 600% increase in total number of studies since 2000
- Growing concerns for consumer risk group
- Little research on ecological risk assessment

Data input from ICON

Fullerenes, quantum dots, and carbon nanotubes

Metal nanoparticles: copper, aluminum, nickel, and cobalt

Little research on ecological risk assessment - particularly on aquatic ecosystems
Making Informed Decisions

- Numerous nanotoxicity and ecotoxicity questions
  - Example: Carbon nanotubes are among the most studied nanomaterials, the differences in behavior of single versus multi-carbon nanotubes remain unclear.
- Uncertainty in dose-response relationships and long-term accumulation affects
- Lack of data limits the utility of methods such as life cycle assessment

Risk

Exposure assessment

Toxicological studies

Mathematical and optimization models

Developing comprehensive risk analysis methods
# Risk Assessment Models

- Potential nanomanufacturing risk assessment modeling approaches
- Differ in the manner by which they handle uncertainty, multiple criteria, and risk-benefit trade-offs

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages &amp; Disadvantages</th>
<th>Contexts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monte Carlo simulation</td>
<td>+ Allows modeling uncertainty</td>
<td>Random sampling for output distribution</td>
</tr>
<tr>
<td></td>
<td>– No tradeoff framework</td>
<td></td>
</tr>
<tr>
<td>Multi-criteria decision making</td>
<td>+ Tradeoff frontiers</td>
<td>Tradeoff or compromise solutions</td>
</tr>
<tr>
<td></td>
<td>– Deterministic</td>
<td></td>
</tr>
<tr>
<td>Stochastic programming</td>
<td>+ Allows stochastic parameters</td>
<td>Probabilistic constraints or objectives</td>
</tr>
<tr>
<td></td>
<td>– Computational time</td>
<td></td>
</tr>
<tr>
<td>Desirability functions</td>
<td>+ Can compare discrete alternatives, robust</td>
<td>Balance weighted total multi-criteria</td>
</tr>
<tr>
<td></td>
<td>– Abstract approach, arbitrary weights</td>
<td></td>
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</tbody>
</table>
Monte Carlo Model

- Cost-exposure trade-off analyses for HiPco single wall carbon nanotube manufacturing

- Uncertainties – costs, occupational health risks, and EHS standards – modeled as probabilistic events
  - Largely unknown
  - Difficult to estimate

- Similar analyses for
  - Best worker protection
  - Cost effective plant design
  - Optimum technology investments
Given Current Uncertainty…

<table>
<thead>
<tr>
<th>Engineering Controls</th>
<th>None</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Exhaust - Ventilation</td>
<td>24 hours, 1,000 cfm ventilation rate, $10,000 capital cost, $3,000/year operating cost</td>
<td>24 hours, 1,000 cfm ventilation rate, $10,000 capital cost, $3,000/year operating cost</td>
<td>24 hours, 1,000 cfm ventilation rate, $10,000 capital cost, $3,000/year operating cost</td>
<td></td>
</tr>
<tr>
<td>Fume hoods</td>
<td>$4,000 capital cost for 6.25 ft² equipment and $9,500 for 25 ft² equipment</td>
<td></td>
<td>$4,000 capital cost for 6.25 ft² equipment and $9,500 for 25 ft² equipment</td>
<td></td>
</tr>
<tr>
<td>Enclosure of processes</td>
<td></td>
<td></td>
<td></td>
<td>50% decrease in labor productivity, 50% extra equipment cost</td>
</tr>
</tbody>
</table>

| Administrative Controls                  |                                           |                                           |                                           |                                           |
| Annual worker training                   | 8 hours of training, $560/year instructor cost | 8 hours of training, $560/year instructor cost | 8 hours of training, $560/year instructor cost |                                           |
| Air monitoring                           | Monthly monitoring, $20K/equipment capital cost | Weekly monitoring, $20K/equipment capital cost | Biweekly monitoring, $20K/equipment capital cost |                                           |
| Medical monitoring                       |                                           |                                           |                                           | $950/worker/year                           |

| Personal Protective Equipment            |                                           |                                           |                                           |                                           |
| Gloves                                   |                                           |                                           |                                           |                                           |
| Latex                                    | 5 pairs/shift, $0.06/pair                 |                                           |                                           |                                           |
| Nitrile                                  |                                           |                                           |                                           |                                           |
| Disposable                               | 1/shift, $0.70                           |                                           |                                           |                                           |
| HEPA filters                             |                                           |                                           |                                           |                                           |
| Tyvek suits                              |                                           |                                           |                                           |                                           |

Four general levels of environmental, health, and safety (EHS) standards defined…
HiPco Production Costs Determined

**Base case assumptions**
- Production volume: 10,000 g/yr
- Operating hours: 2000 hr/yr
- Capital recovery rate: 10%
- Overhead cost: 40% of direct labor
- Maintenance cost: 5% equip. cost
- Labor wage: $20/hr
- Electricity cost: $0.10/kW*hr
- Building cost: $13/ft²*yr
Scenario Analysis Results

- Expected costs alone are insufficient for informed decision making
- Difficulty in decision making due to overlapping cost and exposure distributions

**Potential 10-year Cost**

**Potential 10-year Exposure**

**Joint Cost-Exposure Density**

**Total Manufacturing + Exposure Cost**
Multi-criteria Models

- Many multi-criteria methods available that are applicable to a wide range of nanomanufacturing applications

Goal Programming Example:
- Balance reliability, production rate, and workplace exposure in a nanomanufacturing process
- Decision variables: pH (x1), conductivity (x2), temperature (x3)
- Objective: To identify values of decision variables that minimize a weighted total deviation from set goals for the three criteria

<table>
<thead>
<tr>
<th>Priority</th>
<th>Factor</th>
<th>Goal</th>
<th>Penalty Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-priority</td>
<td>Reliability rate</td>
<td>≥90%</td>
<td>M</td>
</tr>
<tr>
<td>Second-priority</td>
<td>Production rate</td>
<td>≥10 gr/hr</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Exposure level</td>
<td>≤5 units</td>
<td>3</td>
</tr>
</tbody>
</table>

Problem formulation

\[
\text{leq min}\left\{d_1^-; d_2^-; d_3^+\right\} \text{ is equivalent to } \\
\min \quad Md_1^- + 5d_2^- + 3d_3^+ \\
s.t. \quad 0.098x_1 + 0.00014x_2 - 0.0004x_3 + d_1^- \geq 90\% \\
\quad \quad \quad - 0.27x_1 - 0.0167x_2 + 0.058x_3 + d_2^- \geq 10 \\
\quad \quad \quad \quad \quad \quad \quad - d_3^+ \leq 5 \\
\quad \quad 7 \leq x_1 \leq 11, \quad 100 \leq x_2 \leq 1000, \quad 50 \leq x_3 \leq 200 \\
\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{all } d_i \geq 0
\]
Probabilistic Bounds & Trade-off Frontiers

- Sensitivity to weights and constraints – experimental errors
- Optimal trade-off frontiers/surfaces – mapping all optimal solutions of the multiple criteria
Stochastic Programming

- Treating secondary objectives as chance constraints – Chance-constrained models
  - Example: To ensure low probability that exposure exceeds some limit

  Minimize: $f(x_1, x_2, x_3, x_4)$
  subject to:
  $\Pr(c^1x \geq g_1) \geq \alpha_1$
  $\Pr(c^2x \geq g_2) \geq \alpha_2$
  $\Pr(c^3x \leq g_3) \geq \alpha_3$
  $x \geq 0$
  where $0 < \alpha < 1$

- Using probabilistic objective functions
  - Example: To minimize expected exposure or the probability that cost exceeds some amount

- Developing sequential multi-period contingency decision schedules
  - Example: To produce a schedule of present and future workplace safeguard decisions to minimize expected total societal costs
As new technologies developed, probability thresholds might be relaxed to reduce cost but still meet a target with some lesser probability.

Decision variables: pH ($x_1$), conductivity ($x_2$), temperature ($x_3$), occupational health protection level ($x_4$)

Objective: To identify values of decision variables that minimize cost while satisfying reliability, production rate, and workplace exposure constraints with some specified probability

**Problem formulation**

Minimize

\[ 6.5x_1 + 0.7x_2 + 3.25x_3 + 10x_4 \]

subject to

\[ P(0.137x_1 + 0.007x_2 - 0.0023x_3 + 0.033x_4 \geq 60\%) \geq 0.95 \]
\[ P(1.82x_1 - 2.34x_2 + 7.1x_3 - 1x_4 \geq 10) \geq 0.90 \]
\[ P(0.94x_1 - 0.0043x_2 + 0.13x_3 - 10x_4 \leq 2) \geq 0.95 \]
\[ 7 \leq x_1 \leq 11, 100 \leq x_2 \leq 1000, 50 \leq x_3 \leq 200, 1 \leq x_4 \leq 4 \]
\[ x_1, x_2, x_3, x_4 \geq 0, \text{ and } x_4 \text{ integer} \]

Optimal solution:

$x_1$ (pH) = 11, $x_2$ (conductivity) = 292.5, $x_3$ (temperature) = 97.9, $x_4$ (occupational health protection level) = 3, and Cost = $624.57
Desirability Functions

Framework for
- Choosing between finite number of alternatives
- Identify optimal process variable settings

- Each criteria $Y_i$ transformed to a dimensionless value $d_i$
- $d_i$ increases as the desirability of $Y_i$ increases
  - $0 \leq d_i \leq 1$
  - $d_i = 0.00$ completely unacceptable (undesirable)
  - $d_i = 1.00$ completely acceptable (desirable or ideal)
- Individual $d_i$ values combined into an overall desirability value, $D$

Larger-is-better transformation

$$d_i = \begin{cases} 
0 & Y_i \leq Y_{i-min} \\
\left[ \frac{(Y_i - Y_{i-min})}{(Y_{i-max} - Y_{i-min})} \right]^R & Y_{i-min} \leq Y_i \leq Y_{i-max} \\
1 & Y_i \geq Y_{i-max}
\end{cases}$$

Nominal-is-better transformation

$$d_i = \begin{cases} 
\left[ \frac{(Y_i - Y_{i-min})}{(\tau_i - Y_{i-min})} \right]^S & Y_{i-min} \leq Y_i \leq \tau_i \\
\left[ \frac{(Y_i - Y_{i-max})}{(\tau_i - Y_{i-max})} \right]^T & \tau_i \leq Y_i \leq Y_{i-max} \\
0 & Y_i < Y_{i-min} \text{ or } Y_i > Y_{i-max}
\end{cases}$$

+ Center for High rate Nannomaterials
+ Quality & Productivity Laboratory
**Fume Hood Selection Example**

- Criteria: cost ($Y_1$), air flow ($Y_2$), and ease of use ($Y_3$)

<table>
<thead>
<tr>
<th>Candidate Fume Hood</th>
<th>Individual Criteria and Desirabilities ($d_i$)</th>
<th>Overall Desirability D ($w_1$, $w_2$, $w_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost $d_1$</td>
<td>Air Flow $d_2$</td>
</tr>
<tr>
<td>F1</td>
<td>$7,500$</td>
<td>0.56</td>
</tr>
<tr>
<td>F2</td>
<td>$9,500$</td>
<td>0.30</td>
</tr>
<tr>
<td>F3</td>
<td>$6,000$</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Best selection in balancing the three properties against each other
Conclusions

- Challenges with nanotechnology risk assessment
- Inherent tradeoffs and enormous uncertainty exist for nanomanufacturing economics and workplace exposure
- Probabilistic, optimization, and multi-criteria models allow a characterization of a range of possible consequences
  - Examples shown for application of several modeling approaches
  - Focus expansion of desirability functions modeling on tradeoffs for safe handling of engineered nanomaterials with safe fume hoods
- Until sufficient toxicology and other studies progresses, these type of risk assessment models can help private & regulatory decision-makers to protect workers, consumers, and the environment
Acknowledgements

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