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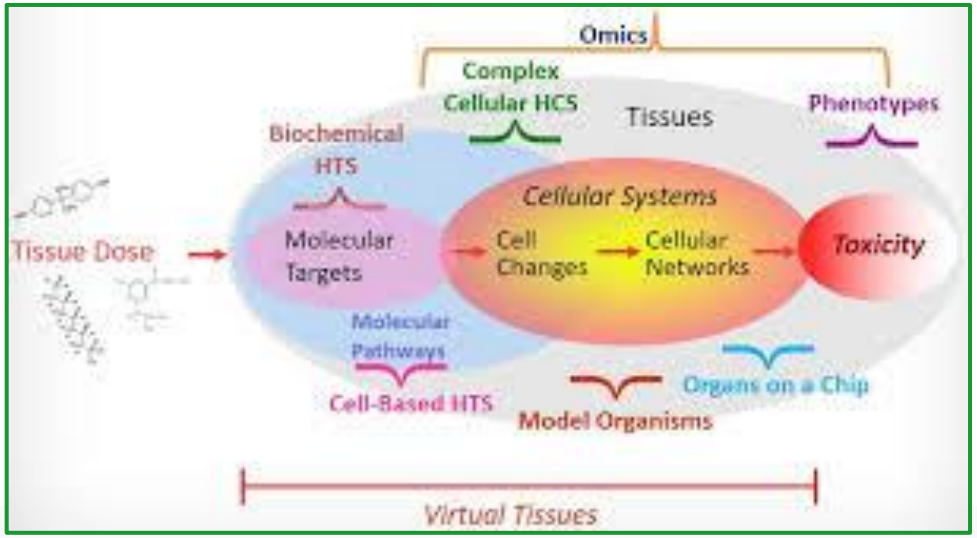
Application of Cost Effectiveness and Value of Information Analyses in Evaluating the Utility of Toxicity-Testing Methodologies



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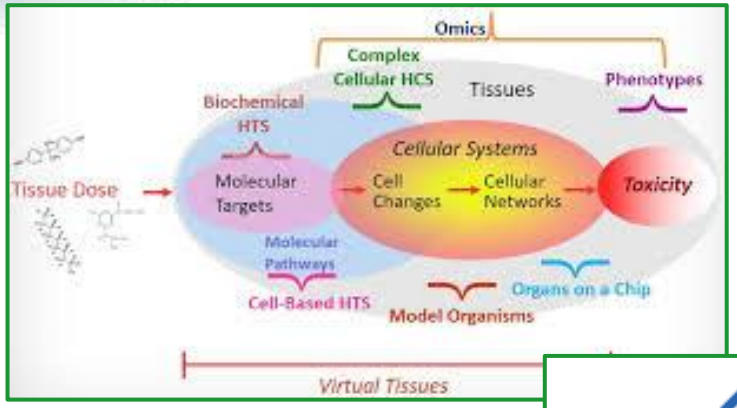
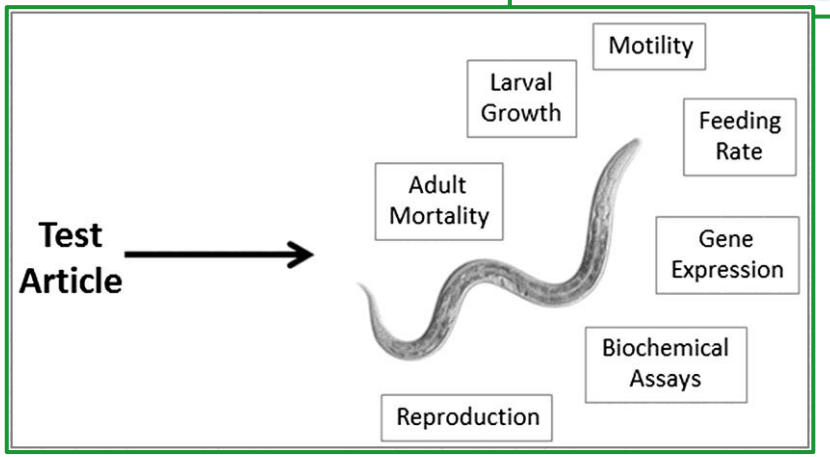
Purpose of the project

- Toxicology continues to develop new testing methodologies
- A framework is needed to evaluate the new tests –
  - Are they better than existing approaches?
  - In what ways?
  - Are they useful for testing large numbers of chemicals?
- Key elements to evaluate are– differences in cost, duration, and uncertainty
  - What are the tradeoffs?
  - Can the tradeoffs be quantitatively compared on similar scales (e.g., economic, public health)?





The impacts of cost, duration, and uncertainty

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- The vast majority of the 40,000+ chemicals in commerce have not been tested
  - Testing for a new pesticide: 8-16 million dollars
  - Cost has been identified as the major factor limiting testing
- Complete testing can take from 3 to > 8 years.
  - Exposures and risks are ongoing while we wait for test results
  - Can not address immediate needs (e.g., spills)
- Uncertainty in toxicity data increases probability of under or overestimating the need for controls leading to higher social costs

50-Million-dollar annual budget	
Cost per chemical	Annual number of chemicals tested
10 million dollars	**5**
50 thousand dollars	**1000**

Approaches used in the project

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Cost Effectiveness Analysis:

"What is the most cost-effective test for correctly determining if a chemical's risk is above or below a target risk level?" Measured using the cost effectiveness ratio.

$$Cost\ Effectiveness\ Ratio = \frac{Cost\ in\ dollars}{Desired\ outcome}$$

Value of Information:

"What is the return on money spent to reduce the uncertainty in an estimate of toxicity that is driving a regulatory action?"

$$Net\ Benefit = Costs\ saved\ by\ reducing\ uncertainty\ - cost\ of\ testing$$

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Cost Effective Analysis

Cost Effectiveness Ratio (CER)

- The net present value of cost of a correct l^{th} decision for one chemical for one year using the j^{th} toxicity methodology
- Decision Making Value ($DMV^{j|l}$) is the probability of reaching the conclusion of the l^{th} decision that would be made given perfect toxicity information when using the j^{th} toxicity methodology
- Costs and DMV are discounted to reflect differences in testing duration
- Time horizon (y_{TH})- period of time when costs and benefits accrue

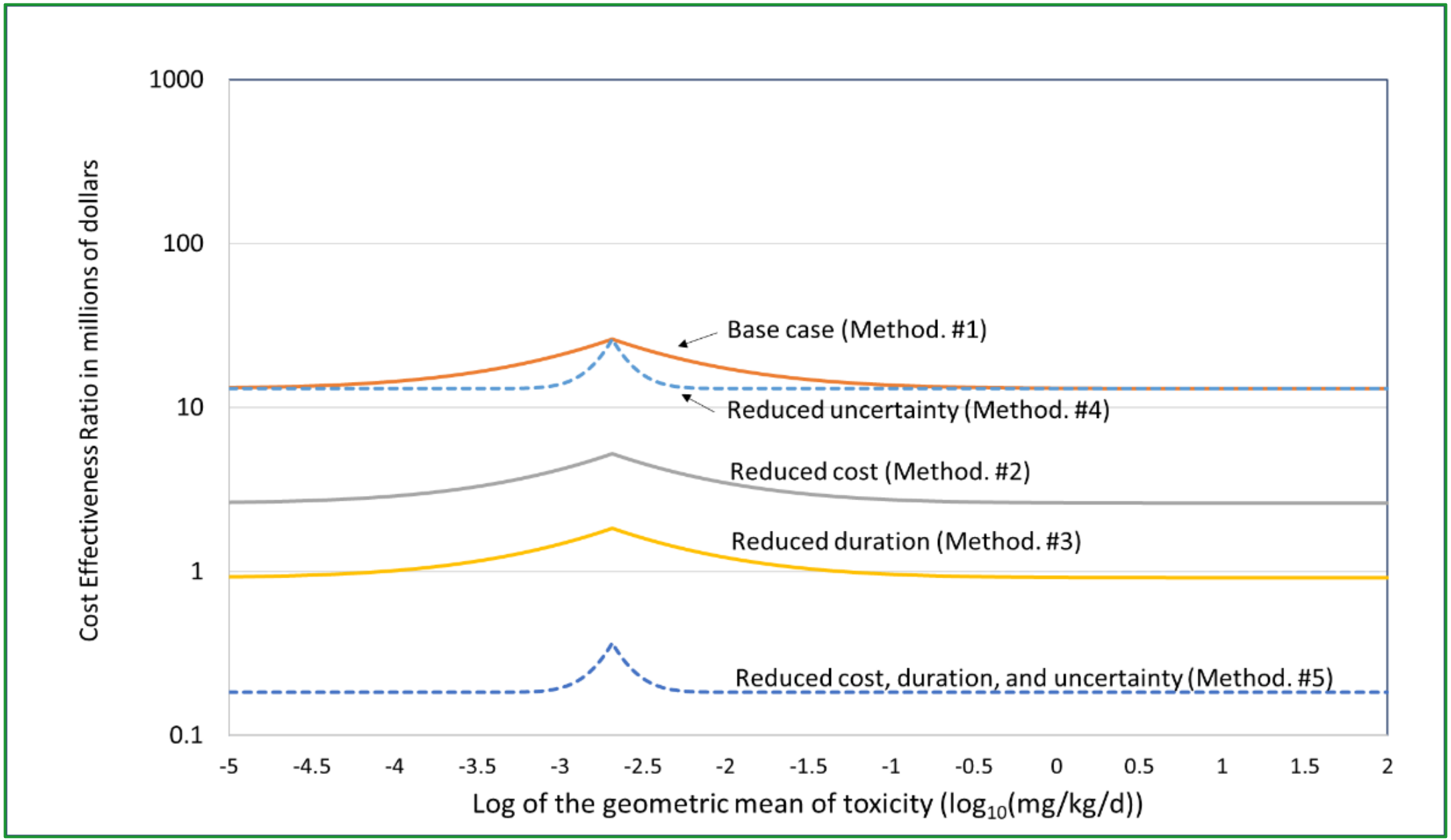
$$CER^{j|l} = \frac{\sum_{y=1}^{y_{T,j}} \frac{C_y^j}{(1+r)^{y-1}}}{\sum_{y=y_{T,j}}^{y_{TH}} \frac{DMV_y^{j|l}}{(1+r)^{y-1}}}$$

given

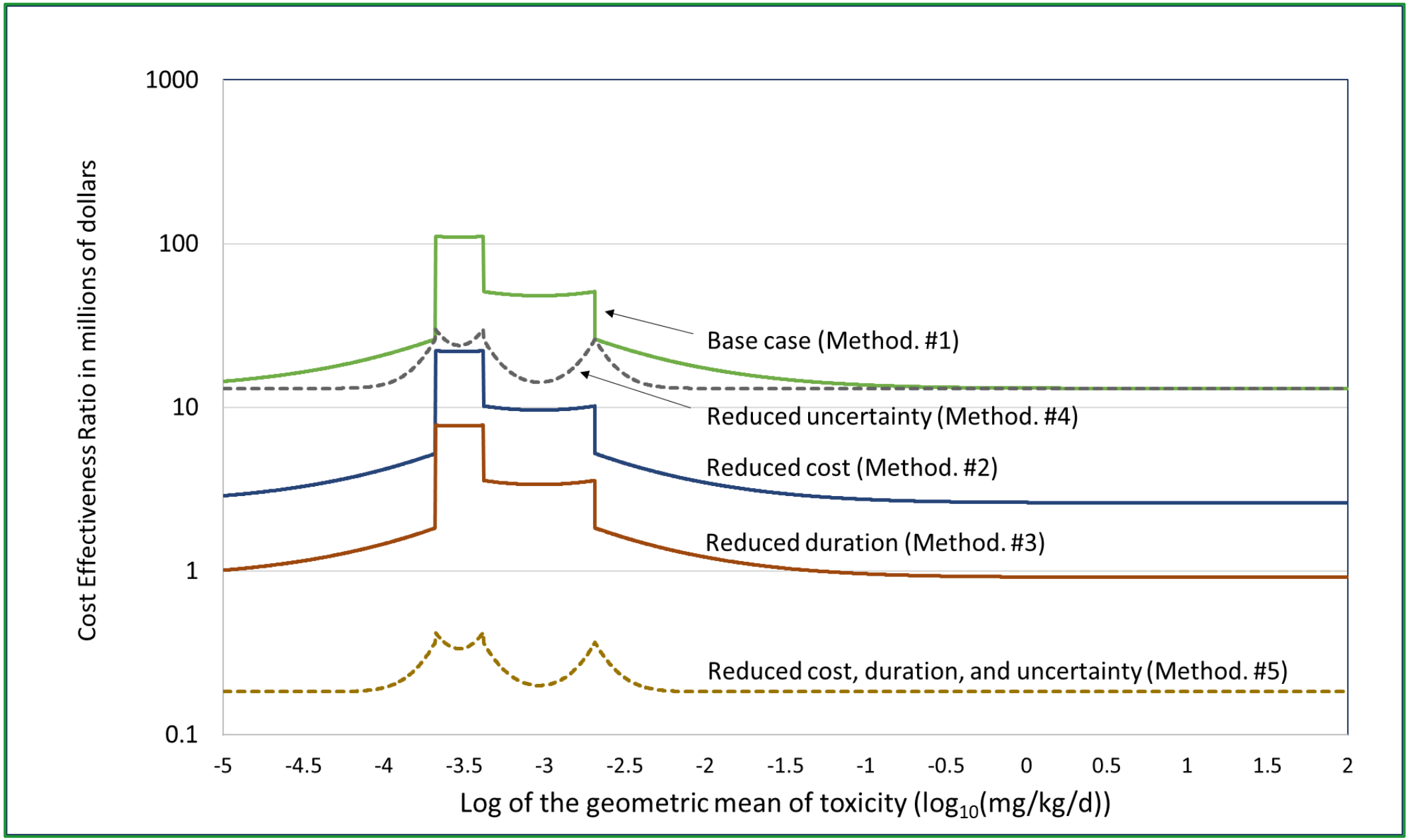
Setting up the CEA example analyses

- A toxicity testing program that is required to evaluate large numbers of the chemicals every year
- Evaluated CER for 5,000 chemicals of varying levels of toxicity
- Five hypothetical toxicity testing methodologies
  - Base case: high cost, high uncertainty, and long duration
  - Four alternatives: reduced cost (5X), reduce duration (5X), reduced uncertainty (5X reduction in GSD), reduce all three
- The results of the toxicity testing are used to generate risk estimates for two decision making processes
  - Simple Decision: Are exposures above a level of concern? (Yes/No)
  - Complex Decision: Which level of regulatory action is needed? (None, Level 1, Level 2, or Level 3)

CER values for the 5000 chemicals for the simple decision



CER values for the 5000 chemicals for the complex decision



CEA findings on the relative importance of reducing cost, duration, and uncertainty

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- In the example illustrations, proportional reductions in cost and duration have as large, or larger, impacts on CER than reductions in uncertainty.
- The impact of differences in uncertainty on decision making varies with the decision-making process and the chemical's toxicity.
- There is no single standard for the "acceptable" level of uncertainty in a toxicity finding.

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Value of Information

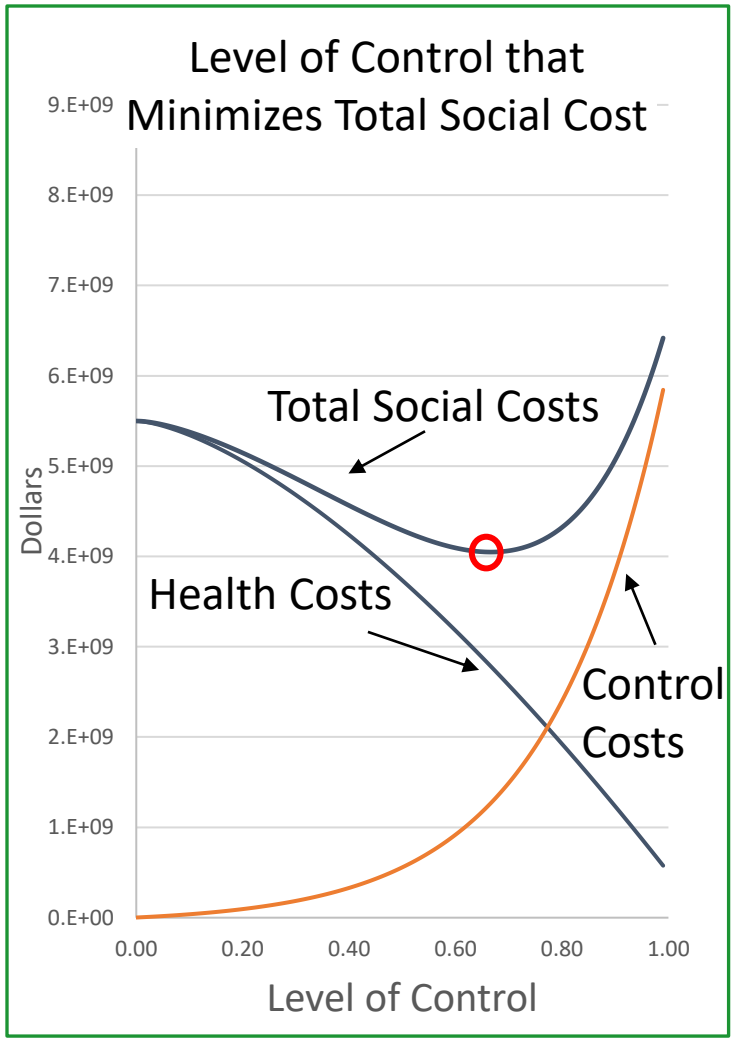
Value of Information approach

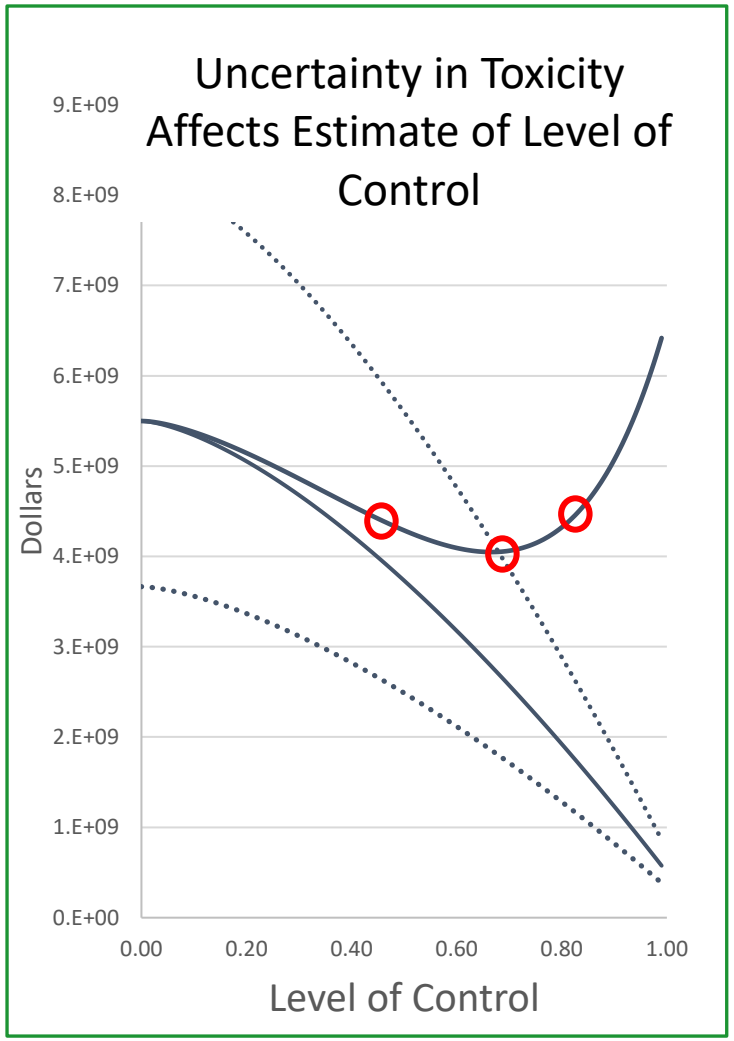
- Requires a mechanism for determining cost of uncertainty
  - The cost metric used is Total Social Cost (TSC) ($)

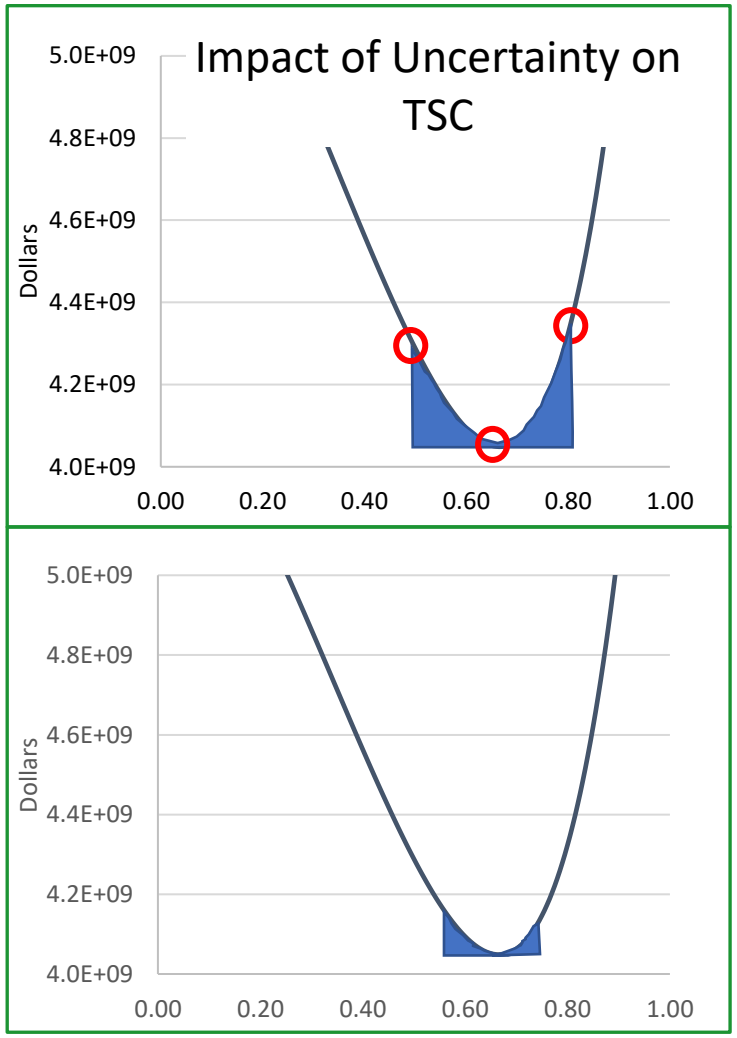
$$Total\ Social\ Cost = Total\ Control\ Cost + Total\ Health\ Cost$$

- Evaluate the error in the optimum degree of control and the resulting extra costs that occur from under or overestimating toxicity
- Total control and health costs occur over a 20-year period

Determining the cost of uncertainty for benefit cost analysis







Impact of delay

As with Cost Effectiveness Analysis, the VOI approach evaluates benefits over a 20-year time horizon. The impact of duration is accounted for using an annual discount of health and control costs “r“ for each year when health benefits and control costs occur.

$$Total\ Social\ Cost =$$

$$\sum_{y=y_{\mathrm{imp},j,k}}^{y_{TH}} \frac{C_k}{(1+r)^{y-1}} + \left[\sum_{y=1}^{y_{TH}} \frac{N_y B_y RV}{(1+r)^{y-1}} - \sum_{y_{\mathrm{imp},j,k}}^{y_{TH}} \frac{N_y B_y (R-R_k)V}{(1+r)^{y-1}}\right]$$

VOI case studies

- Two hypothetical toxicity tests
  - Test A – lower cost ($5K), shorter duration (1 yr), higher uncertainty (4 orders of magnitude)
  - Test B – higher cost ($5M), longer duration (5 yr), lower uncertainty (2 orders of magnitude)
- Different health endpoints
  - One with chronic effect leading to early mortality
  - One with acute effect leading to multiple days of illness
- A range of chemicals and decisions
  - Chemicals with high and relatively low prior uncertainties
  - Chemicals regulated based on benefit-cost analysis and target risk levels

Findings were similar in all examples

Results shown for benefit/cost assessment of chronic effects when some prior toxicity data are available

Impacts of different reductions in uncertainty and different testing durations

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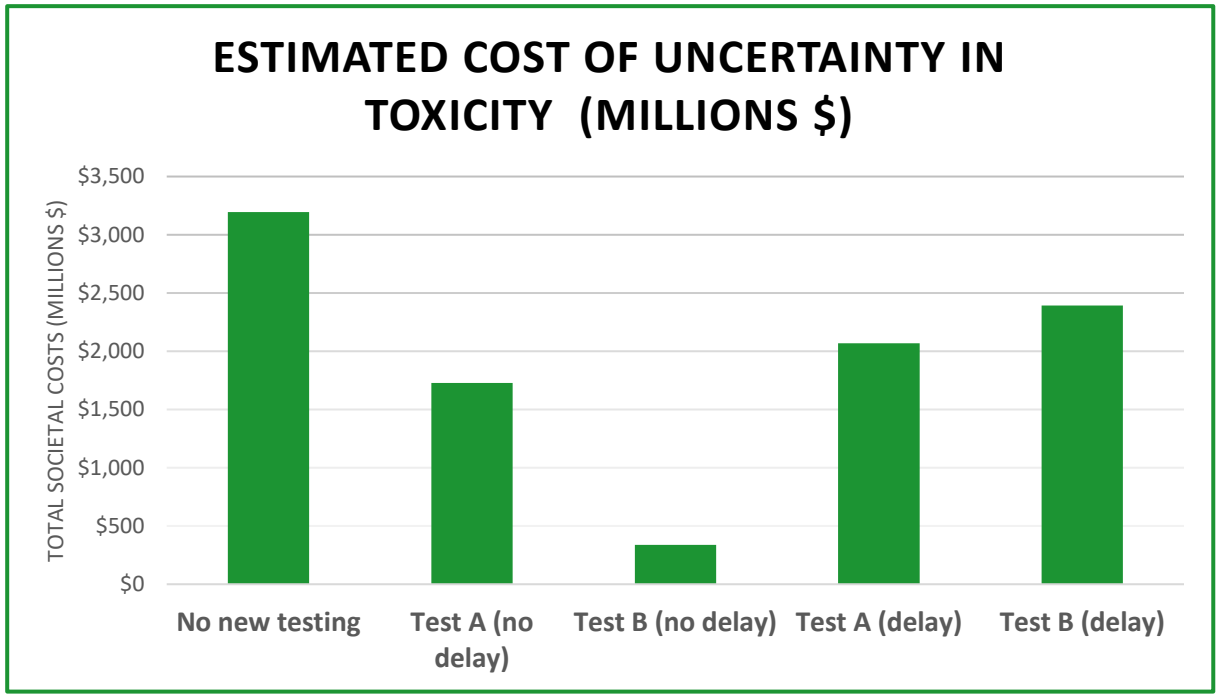
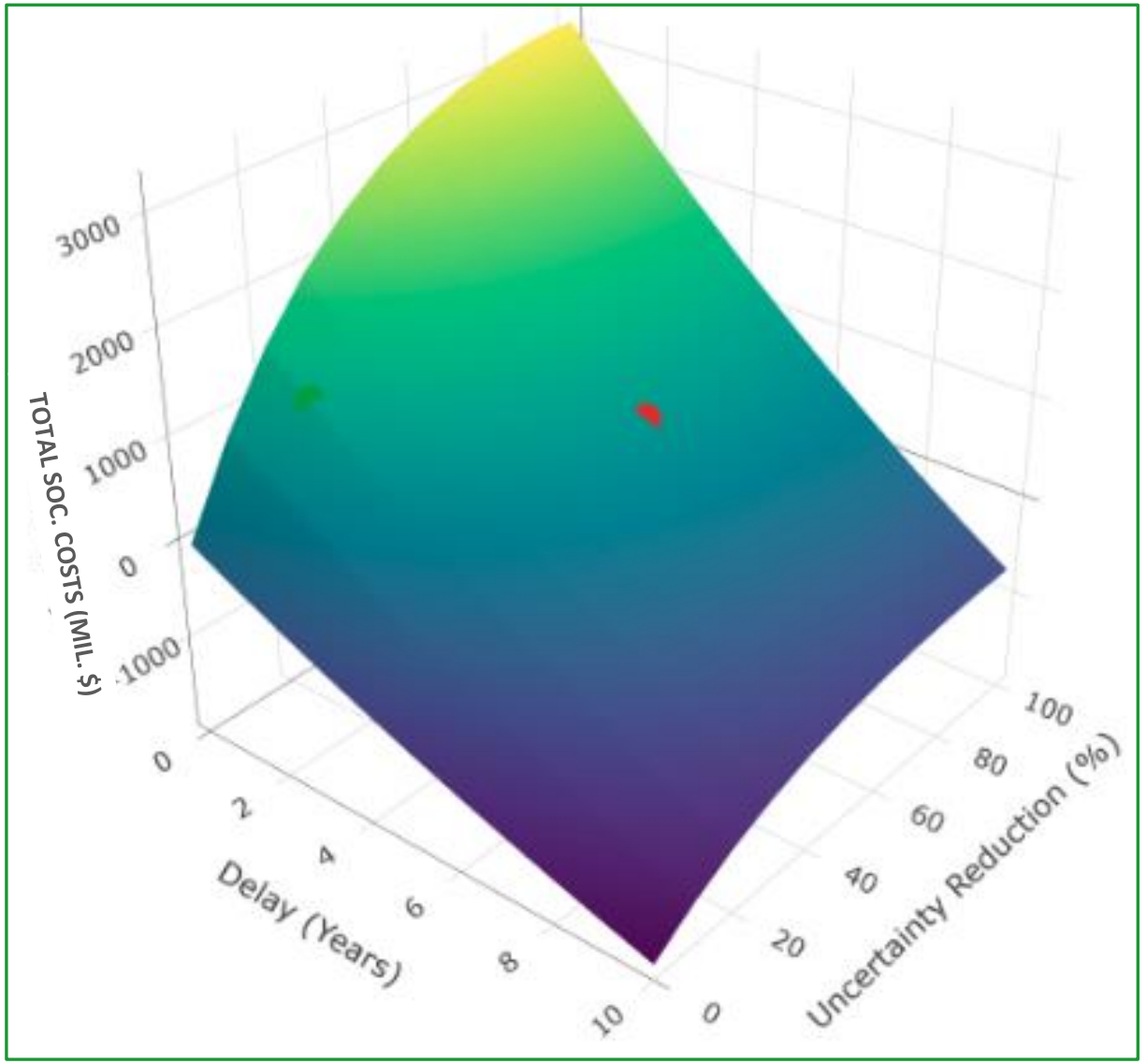
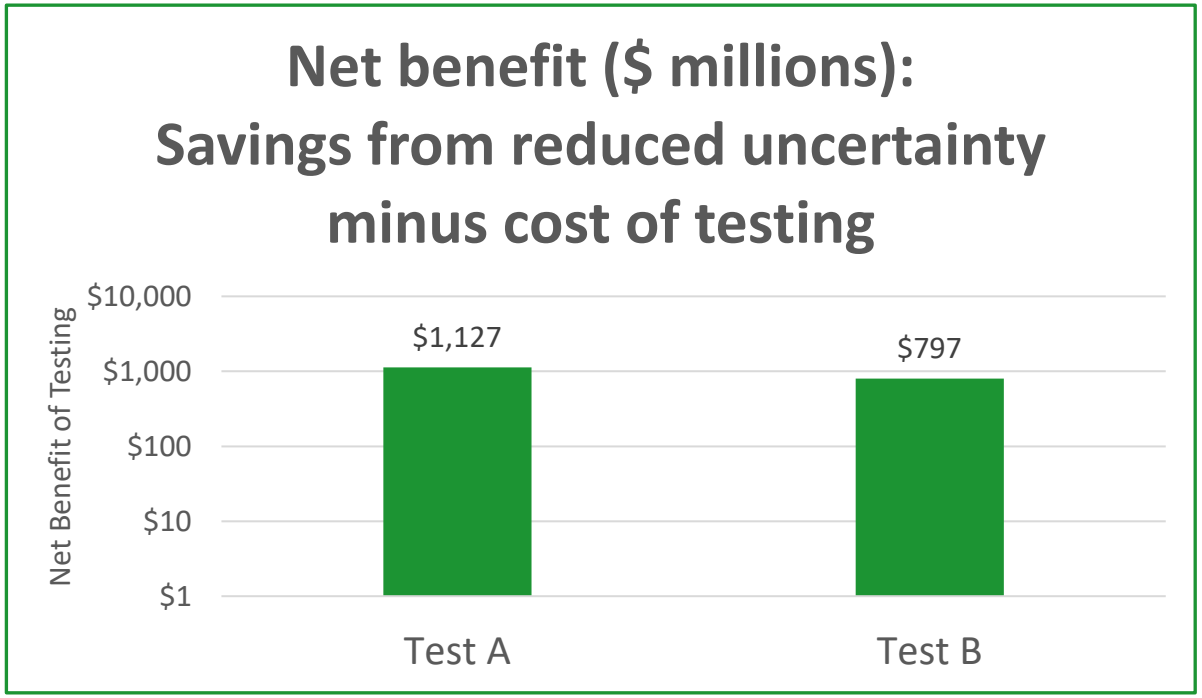
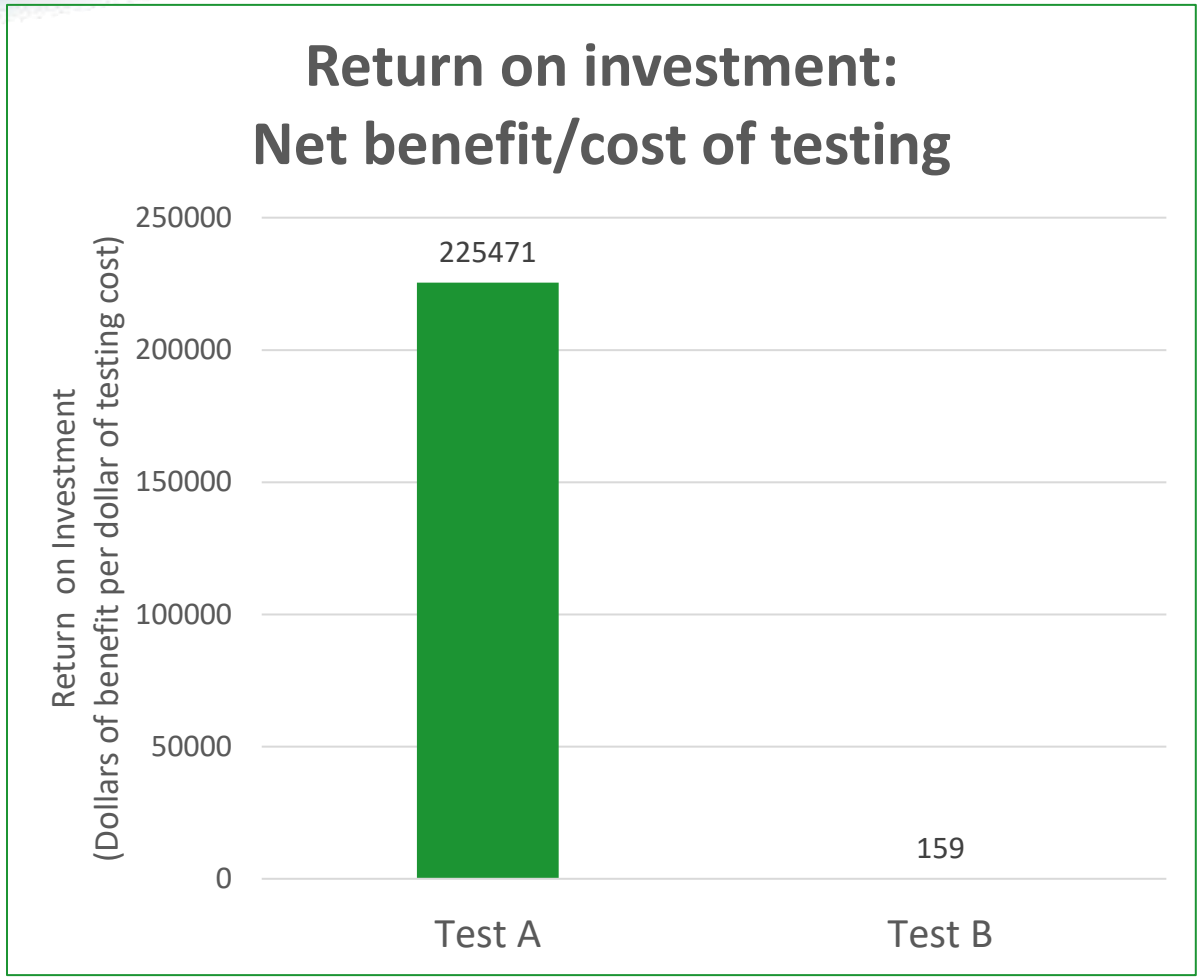




Impact of the cost of testing on VOI metrics





VOI findings

- Earlier availability of testing data results in higher VOI since the public health benefits of risk mitigation are realized earlier
- The impact of earlier data exceeded that of uncertainty reduction in many examples
- Reduced testing costs were small compared to health and control costs in the examples and did not change the choice of tests for a single chemical (Test A is slightly favored)
- The cost of testing, however, had a dramatic impact on Return on Investment - the metric relevant for programs testing large numbers of chemicals (Test A is greatly favored)

Overall conclusions

- Two complementary approaches were developed to evaluate trade-offs associated with duration, cost, and uncertainty in toxicity testing
- Similar patterns were observed for the impacts for cost, duration, and uncertainty
  - Reduction in cost and duration can have effects equal to or greater than reductions in uncertainty
  - Impact of uncertainty varies with the decision, the toxicity of the chemical, and level of exposure
- The two approaches allow for a systematic evaluation of the value of different methods of determining toxicity

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Thank you.

Questions?