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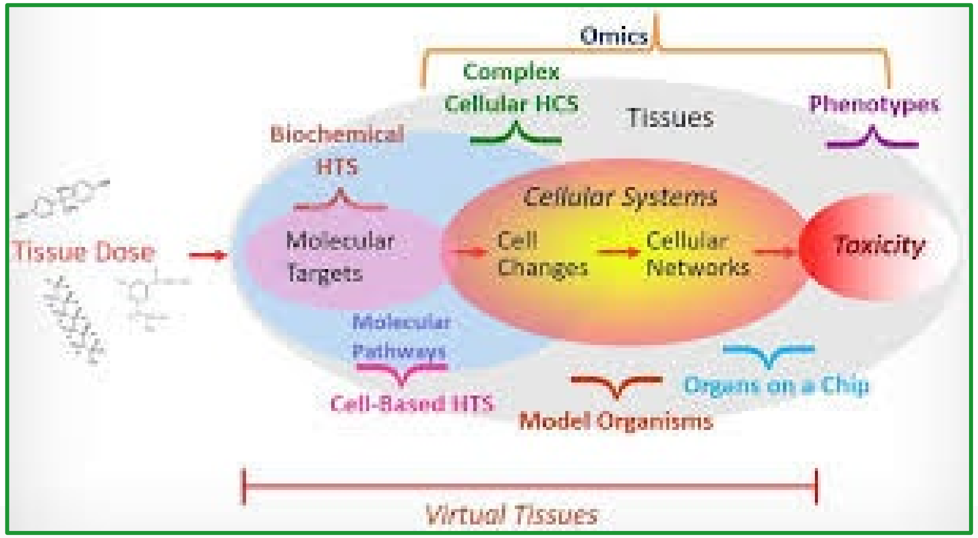
Application of Cost Effectiveness and Value of Information Analyses in Evaluating the Utility of Toxicity-Testing Methodologies



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Accelerating the Pace of Chemical Risk Assessment (APCRA)
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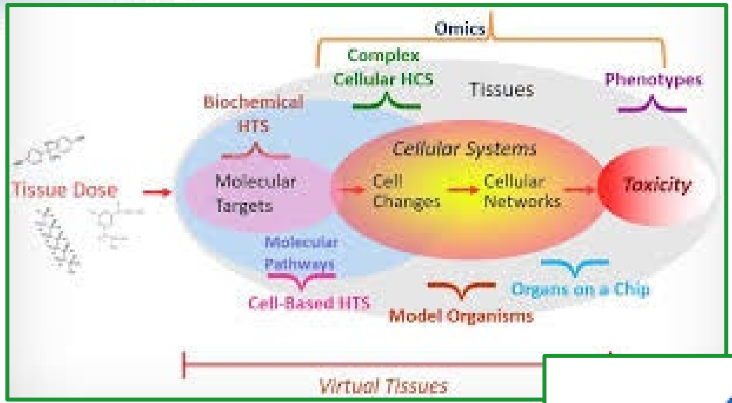
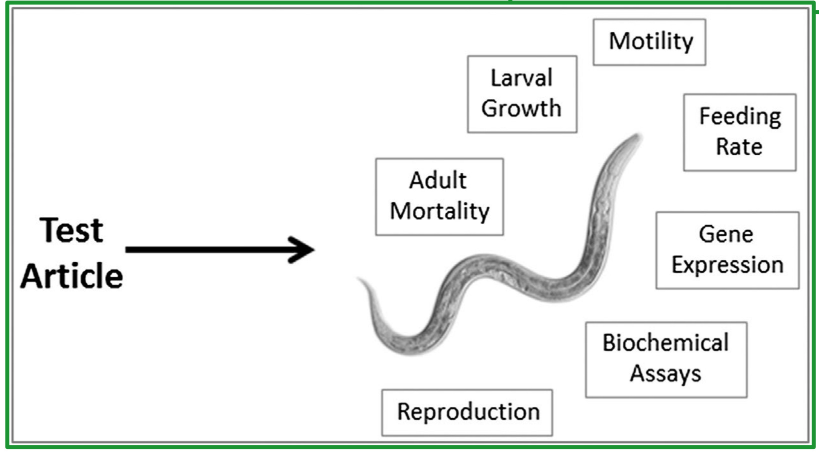
Purpose of the project

- Toxicology continues to develop new testing methodologies
- A framework is needed to evaluate the new tests –
  - Are they better then 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
  - Very different aspects of a test
  - How to do tradeoffs?





The impact of the cost of testing

- The vast majority of the more than 100,000 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
- Decreasing the cost directly increases the number of chemicals that can be assessed under a given budget

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

The impacts of the duration of testing

- Complete testing of a substance using traditional testing methods can take from 3 to > 8 years
- Impacts of testing duration vary with the timing of the need:
  - Traditional toxicology could not address immediate needs (e.g., 4-methyl-cyclohexanemethanol spill or surfactants used to control the gulf oil spill)
  - Preference for immediate versus delayed action in regulation. Long durations reduce value.

Impacts of the uncertainty in toxicity findings

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- Regulatory agencies have historically used *in vivo* toxicity data of varying levels of uncertainty
- Uncertainty in toxicity data increases probability of under or overestimating the need for controls leading to higher social costs
- Larger uncertainty in data→ larger uncertainty factors → increased probability of overregulation

Evaluating toxicity tests using tools from decision analysis

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- The project investigated the use of two tools
  - Cost Effectiveness Analysis (CEA)
  - Value of Information (VOI)
- CEA and VOI
  - Each has different strengths and limitations
    - CEA addresses binning decisions (above or below acceptable level of risk)
    - VOI addresses calibrated decisions (optimal levels of control)
  - Both have the ability to assess the impacts of cost, duration, and uncertainty
    - Both deal with the impacts of the cost and duration in similar ways
    - Different and complimentary approaches for uncertainty
- CEA work was recently published in Risk Analysis. VOI work has been submitted to Risk Analysis.

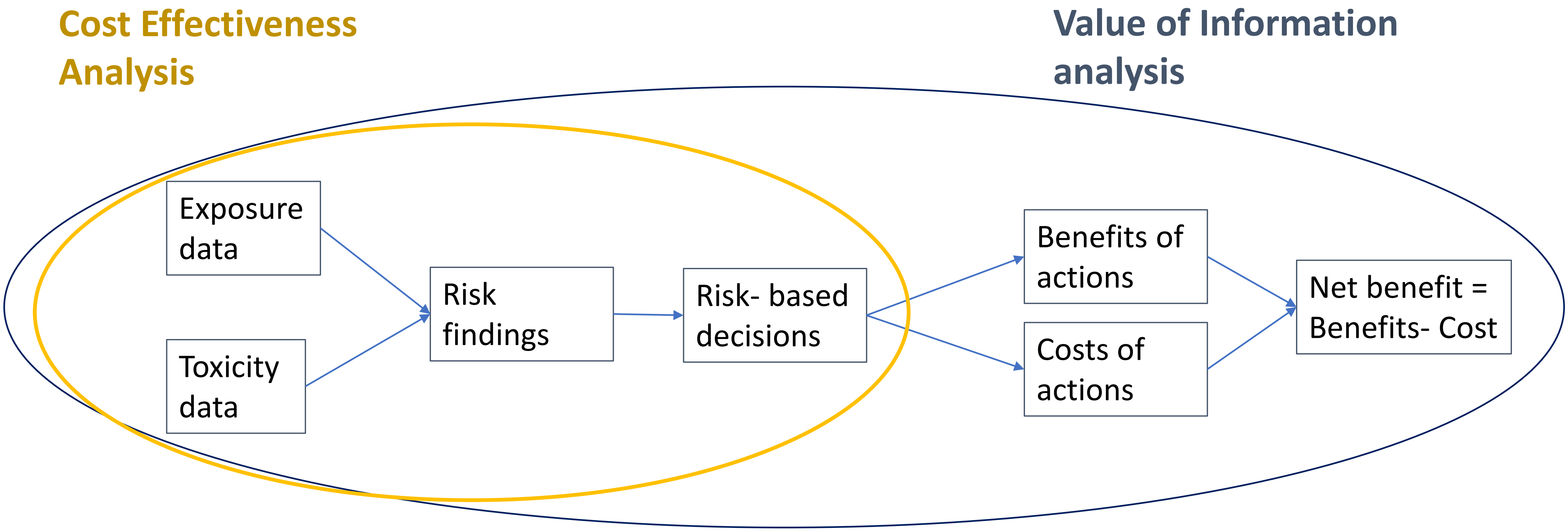
Cost Effectiveness Analysis:

"What is the most cost effective test for correctly determining if a chemical's risk is above or below a target risk level?"

Value of Information:

"Is it worth spending additional money to reduce the uncertainty in an estimate of toxicity that is driving a regulatory action?"

Scopes of CEA and VOI approaches

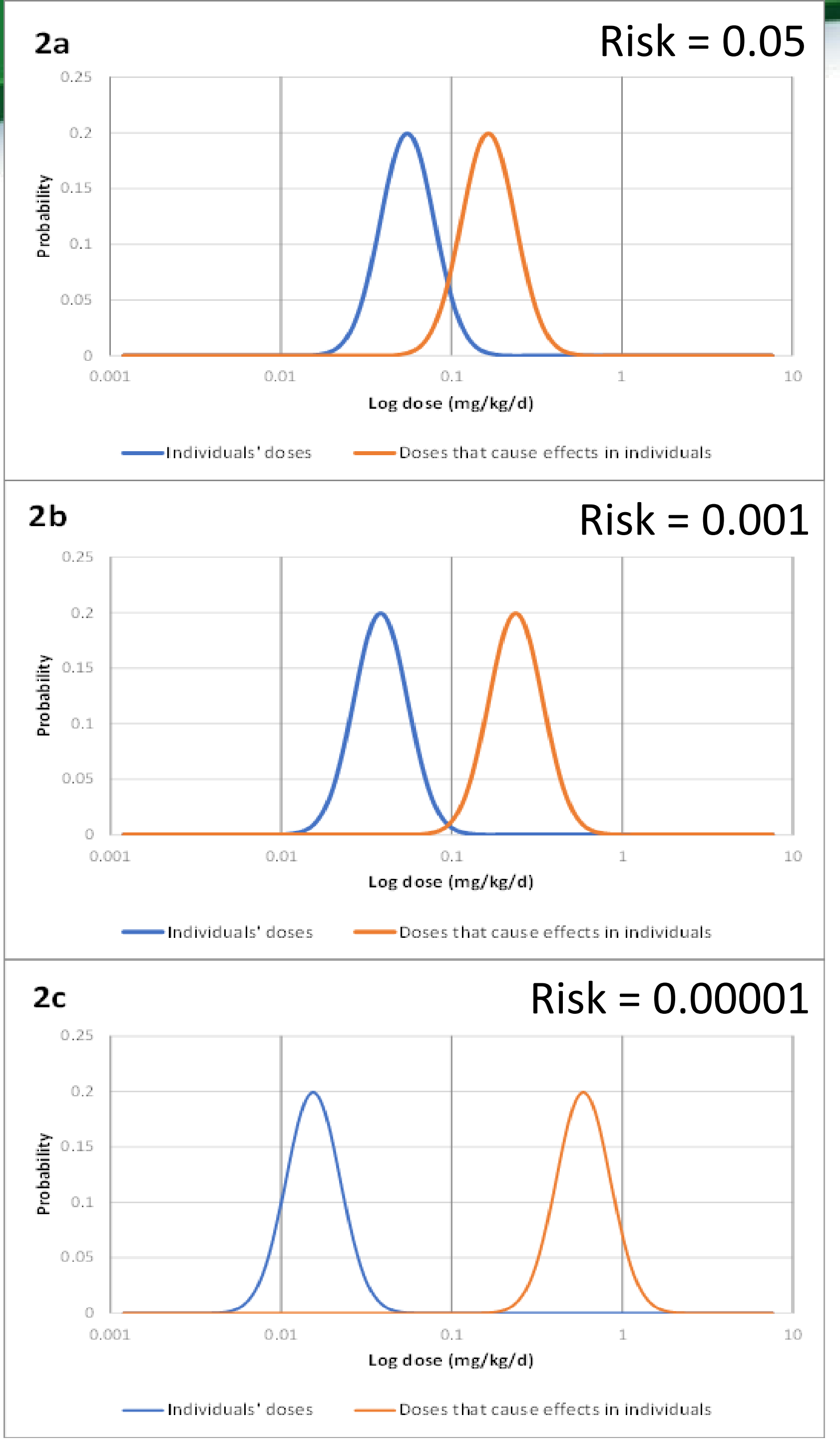


Risk model used by both approaches

When distributions of doses and toxicity thresholds across individuals follow log normal distributions the fraction of the population that is affected by a chemical is given by:

$$R = \Phi\left(\frac{\mu_{\text{exp}} - \mu_{\text{tox}}}{\sqrt{\sigma_{\text{exp}}^2 + \sigma_{\text{tox}}^2}}\right)$$

Using this model, the uncertainty in toxicity (μ_{tox} or σ_{tox}) can be converted into the uncertainty in risk (R)



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Cost Effective Analysis

Cost Effectiveness Analysis (CEA)

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- A tool for selecting a preferred option of achieving a desired outcome from a number of alternatives
- Based on Cost Effectiveness Ratio (CER). CER is defined as:

$$CER = \frac{Cost\ in\ dollars}{Desired\ outcome}$$

- The option with the lowest CER is preferred
- Long history of use

Cost Effectiveness Ratio

- The net present value of cost of a correct l^{th} decision for one chemical for one year using the j^{th} toxicity methodology
- DMV value is discounted to reflect delays in data availability
- Costs are discounted to reflect when they occur
- Time horizon (y_{TH})- period of time when costs and benefits accrue

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

Decision Making Value (DMV)

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- DMV is the probability that a decision made based on a test is correct.
- A correct decision is the decision that would be made with perfect toxicity data

Simple Decision: Is risk greater than Target Risk Level			
		Action taken based on uncertain toxicity data	
		Safe	Unsafe
Action taken based on perfect toxicity data	Safe	0.5	0.2
	Unsafe	0.1	0.2

DMV = 0.7

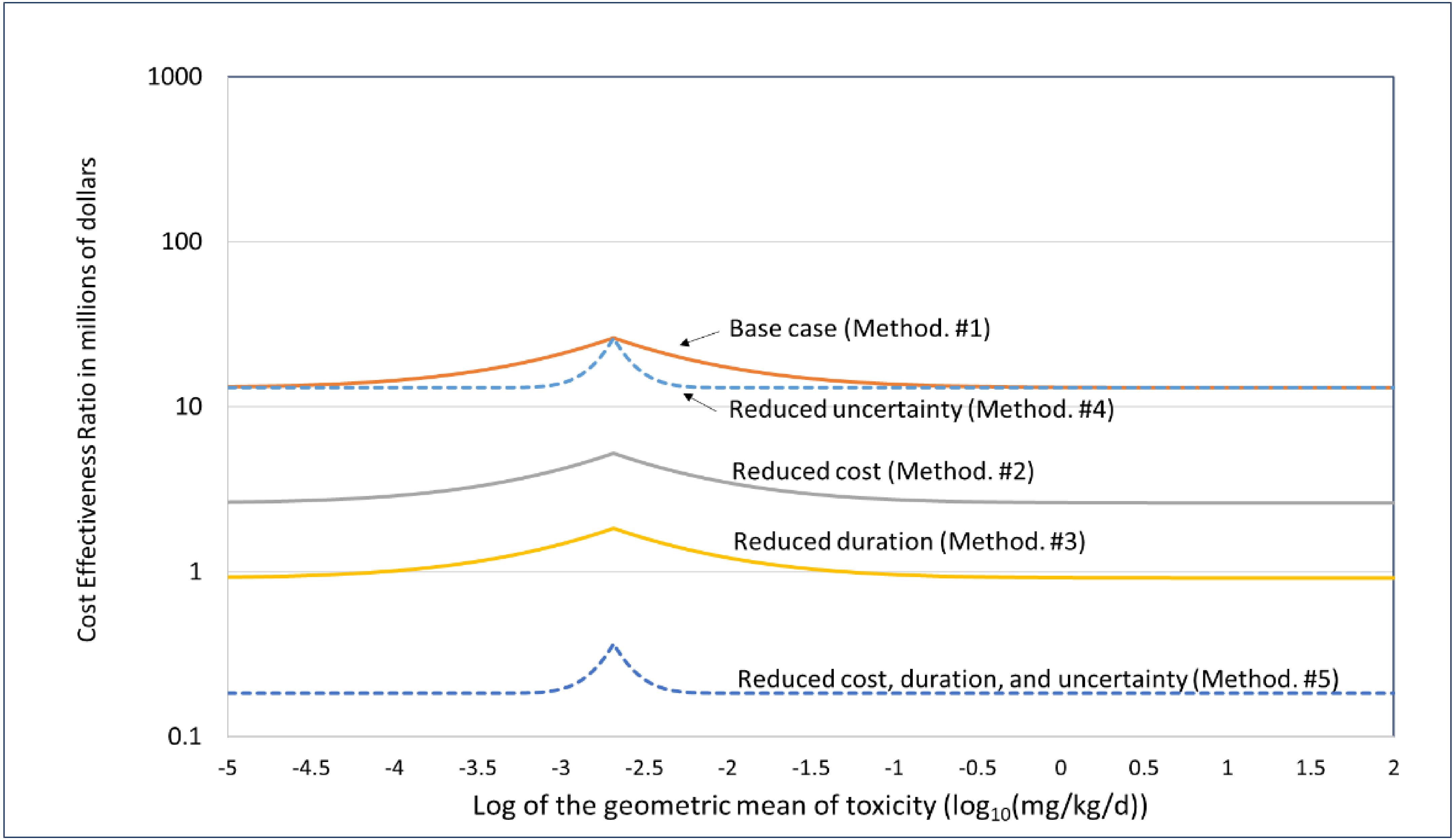
Complex decision: Selection of a regulatory action						
		Action taken based on uncertain toxicity data				
		No action	Regulatory action 1	Regulatory action 2	Regulatory action 3	Regulatory action 4
Action taken based on perfect toxicity data	No action	0.3	0.05			
	Regulatory action 1	0.1	0.1	0.05		
	Regulatory action 2		0.04	0.1		
	Regulatory action 3		0.01	0.04	0.05	0.05
	Regulatory action 4			0.01		0.1

DMV = 0.65

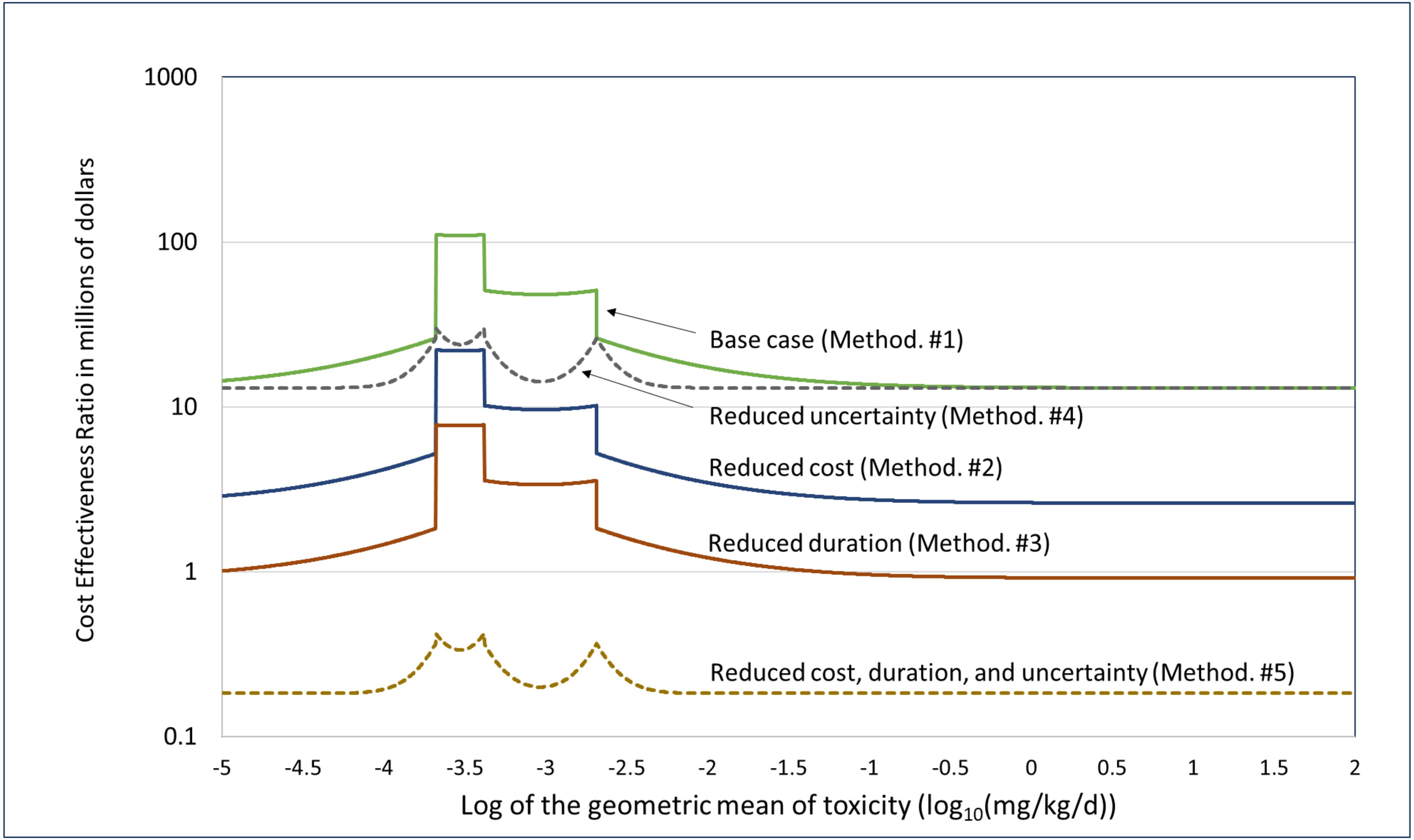
Setting up the CEA illustration

- A program is envisioned that tests large numbers of the chemicals every year
  - The tested chemicals include a wide range toxicities
  - Exposure data on the chemicals are available
- The results of the testing are used to generate risk estimates for two decision making processes (binning exercises)
  - Are exposures above a level of concern? (Yes/No)
  - Which level of regulatory action is needed (None, level 1, level 2, and level 3)
- Five toxicity-testing methodologies (hypothetical)
  - Base case: test with high cost, high uncertainty, and long duration
  - Four alternative tests that independently or together reduce cost, reduce uncertainty, and reduce duration

CER values for the 5000 chemicals for the simple decision



CER values for the 5000 chemicals for the complex decision



Findings on the relative importance of reducing cost, duration, and uncertainty

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- <u>In the example illustrations,</u> 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 and exposure findings
- There is no single standard for the "acceptable" level of uncertainty in a toxicity finding

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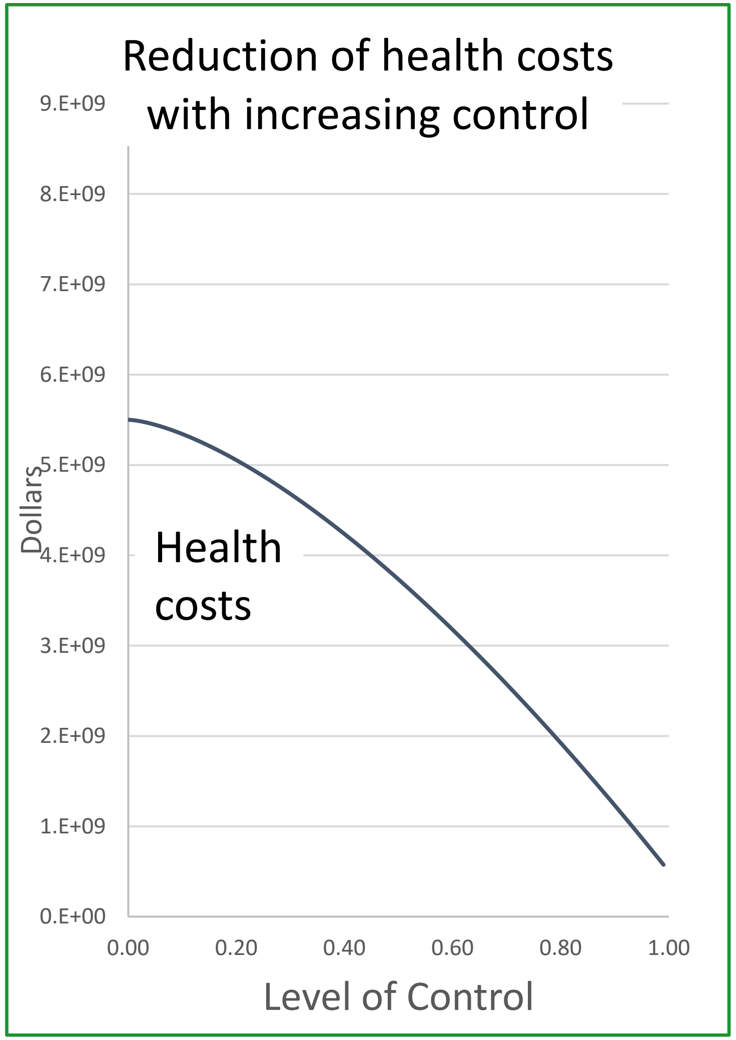
Value of Information

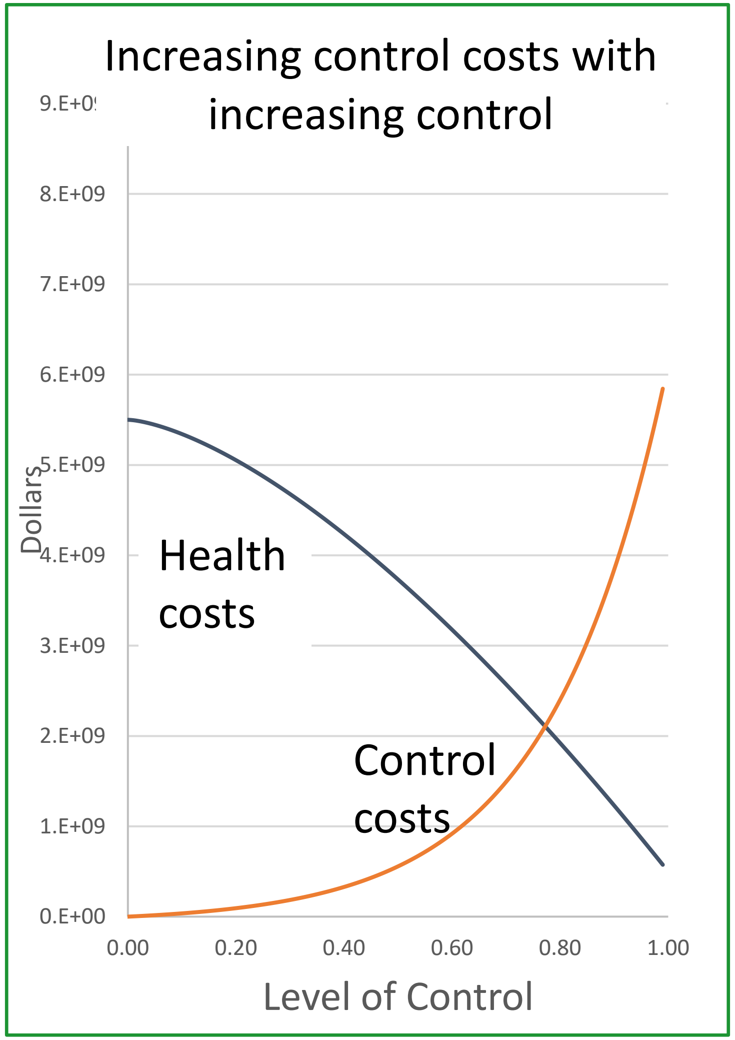
- Does the improvement in a decision that results from more certain data worth the time and cost of obtaining such data
- The metric to address this is the Total Social Cost (TSC) ($)

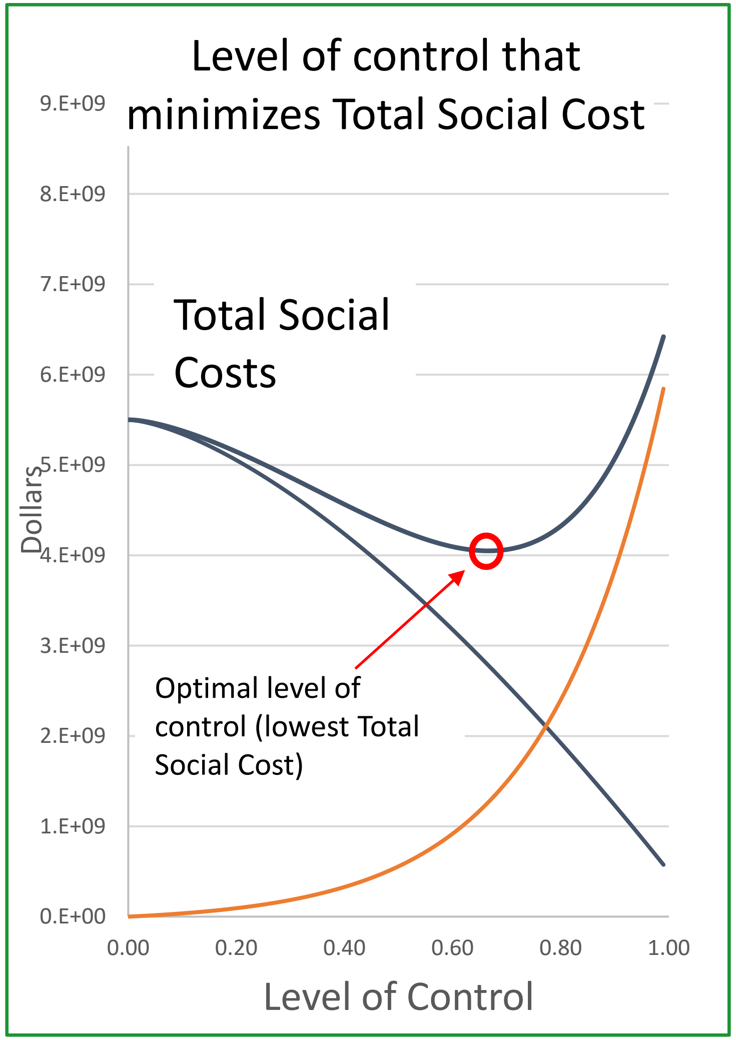
$$Total\ Social\ Cost = Total\ Health\ Cost + Total\ Control\ Cost$$

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

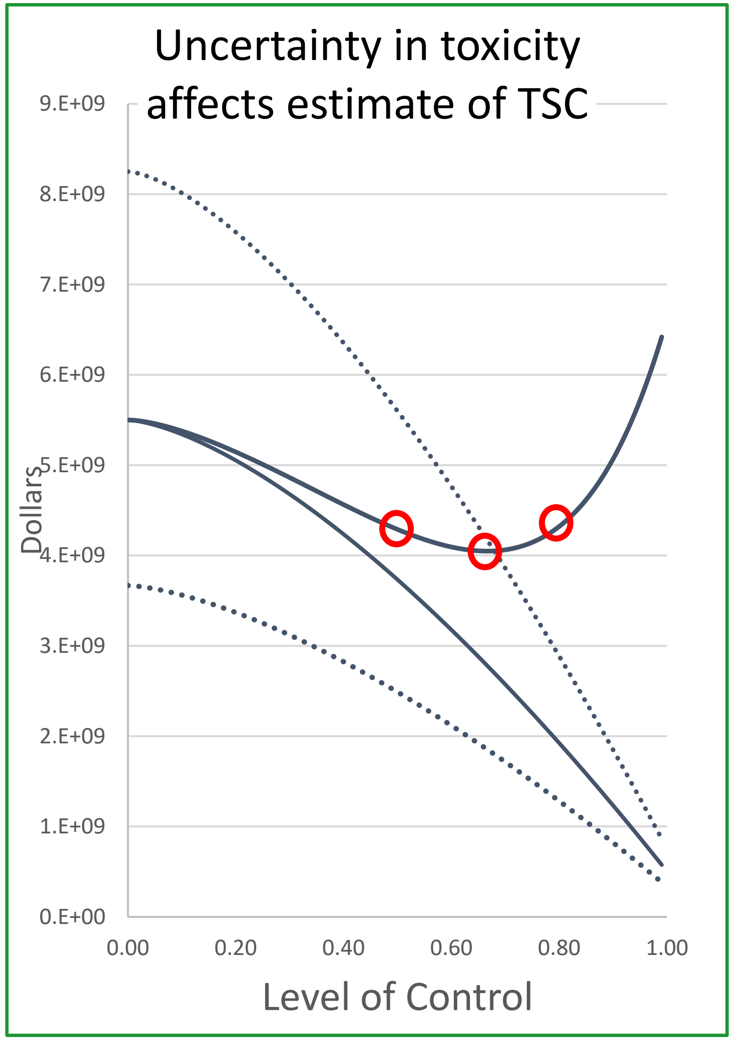
Determining the cost of uncertainty

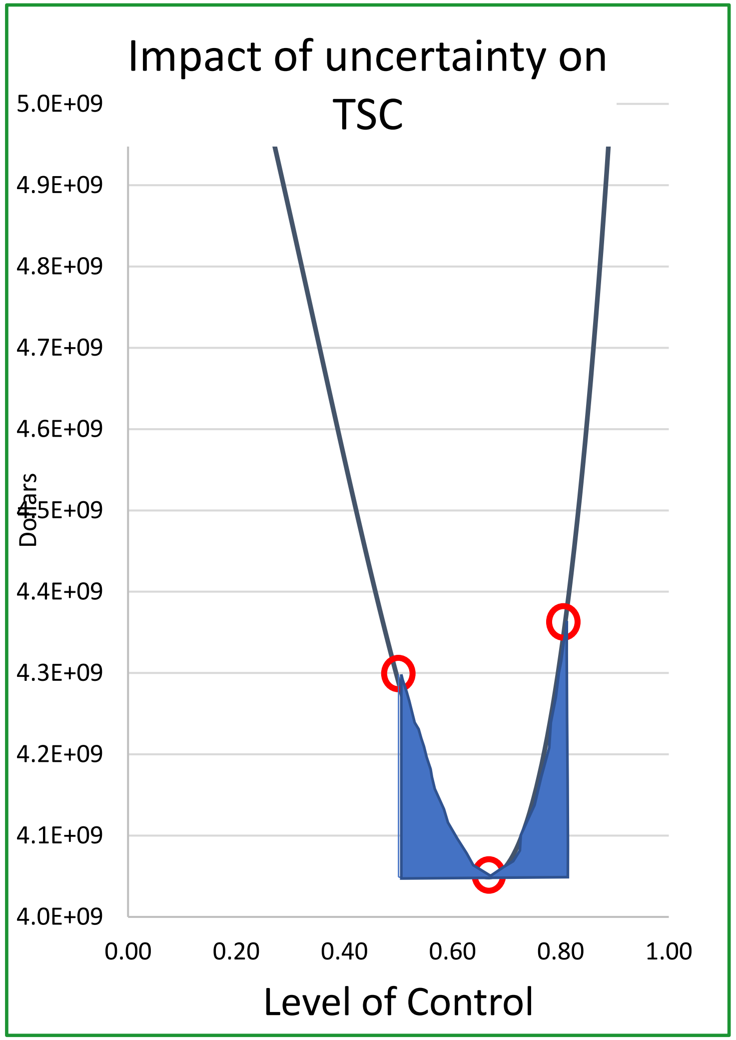


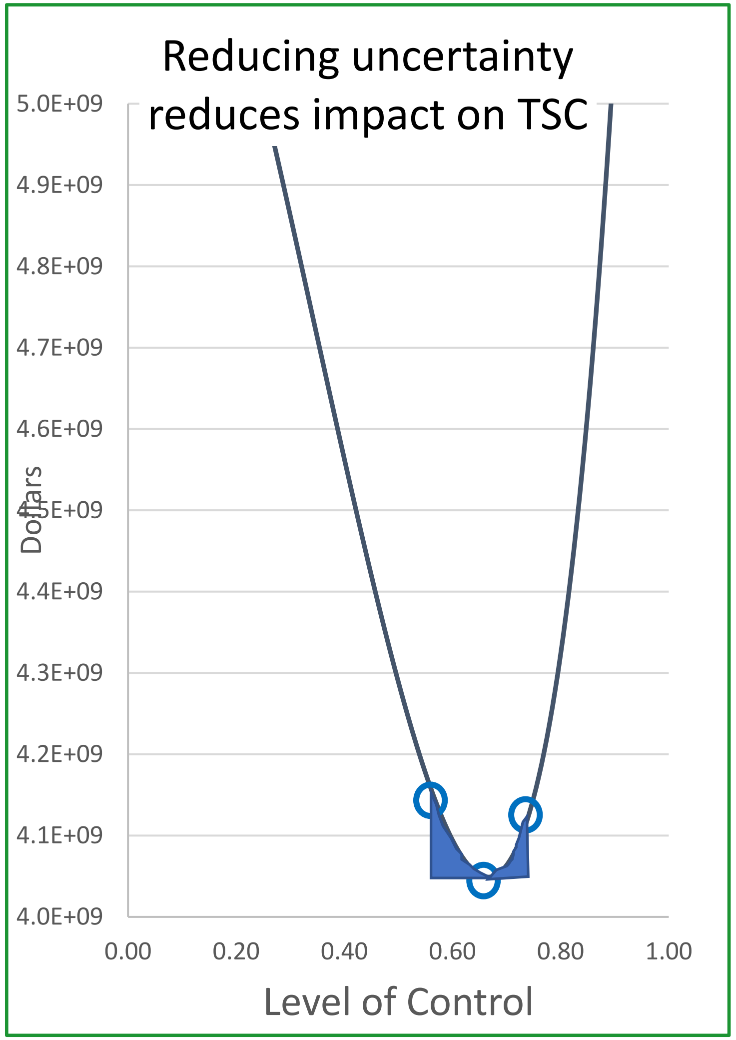




Determining the cost of uncertainty







VOI case studies

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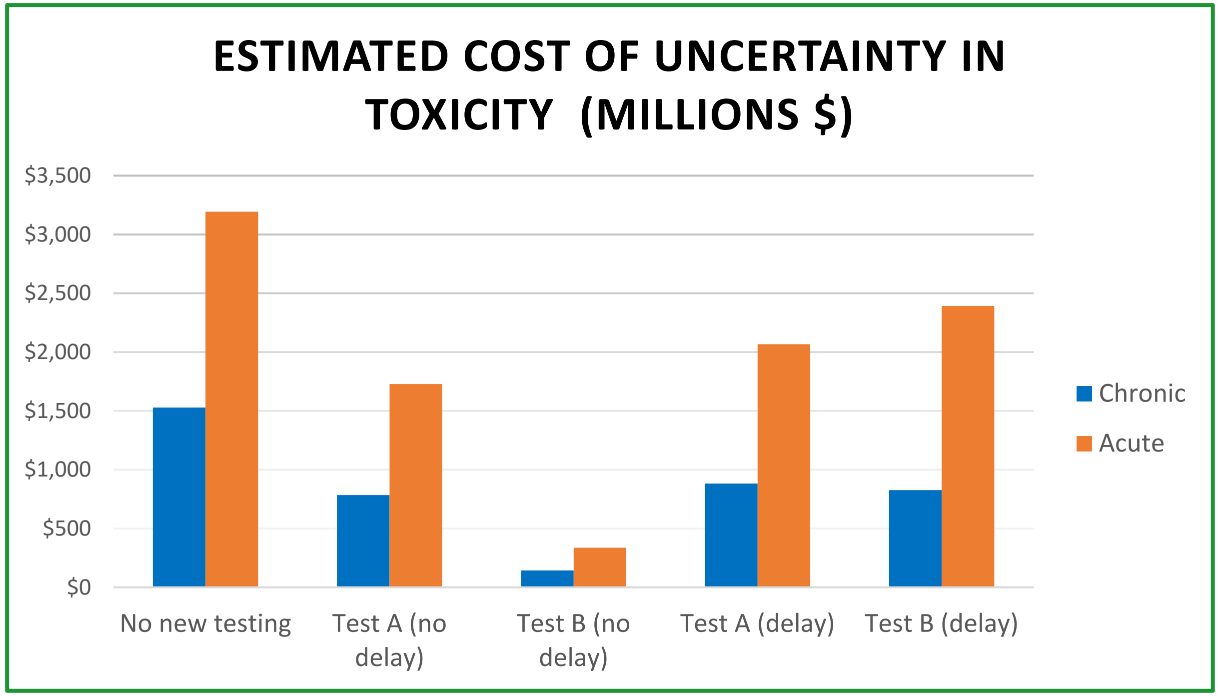
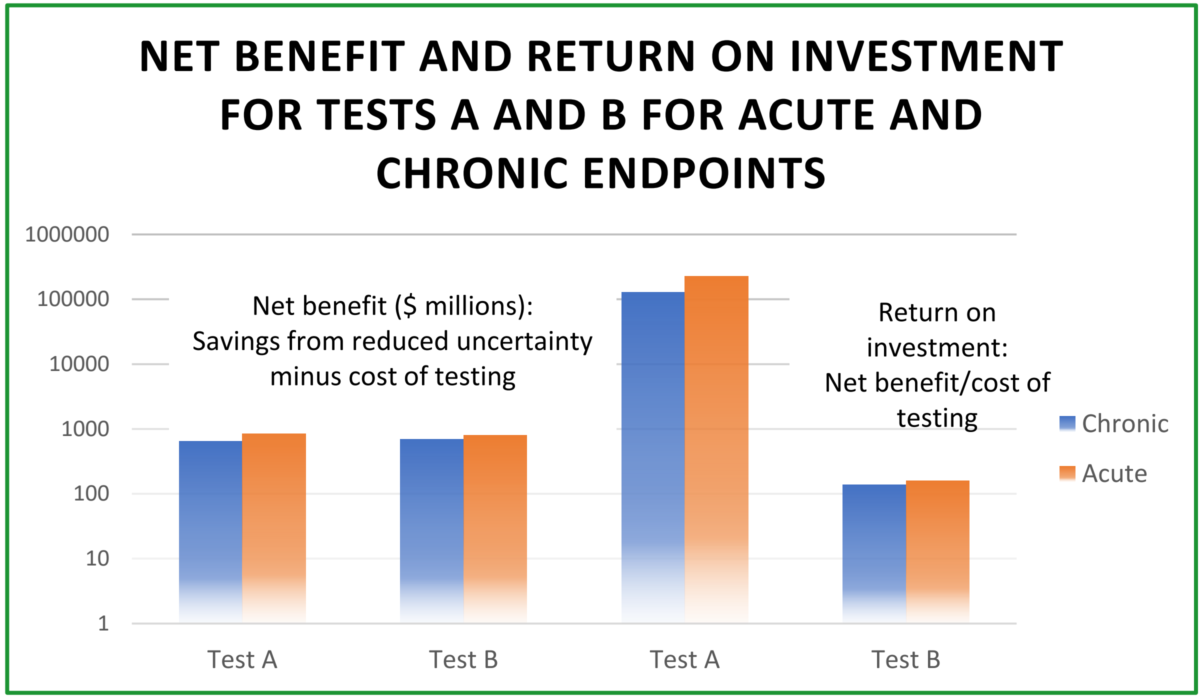
- Look at a range of chemicals and decisions
  - Chemicals with of high and relatively low uncertainty
  - Chemicals regulated based on benefit-cost analysis and target risk levels
- Evaluated two toxicity tests
  - Test A – lower cost, shorter duration, higher uncertainty
  - Test B – high cost, long duration, lower uncertainty
- Evaluated
  - Chronic effect leading to early mortality
  - Acute effect leading to multiple days of illness

Results





- Test B reduced cost of existing uncertainty compared to Test A
- The longer duration of Test B reduced this advantage
- The lower cost of Test A resulted in a dramatically larger return on investment

Findings for project

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- Two tools for determining preferred toxicity tests were developed
  - Both addressed duration, cost, and uncertainty
  - Approaches are complementary: addressing different aspects of testing
- Both approaches found similar patterns of impact for cost, duration, and uncertainty
  - Reduction in all three elements are desirable
  - Reduction in cost and duration can have effects equal to greater than reductions in uncertainty
- Impact of uncertainty varies with the decision, the toxicity of the chemical, and level of exposure

There is no single level of certainty that is required for a toxicity finding – different decisions required different levels of certainty

Outstanding issues and next steps

- The proposed framework has been demonstrated using a novel measure of risk and two example risk-based decisions.
- The framework needs to be applied to actual toxicity tests, actual chemicals, and using the risk-based decision making practiced by EPA.
  - Extend models to address the concept of uncertainty factors
  - Investigate the impact of giving greater weight towards avoiding underestimates toxicity than avoiding overestimates for CEA
  - Investigate tiered decision-making processes where an initial tier uses low-cost but more uncertain tests, and a higher tier uses more expensive but more accurate tests

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Thank you.

Questions?