Chemical Risk Assessment and Translation to Socio-Economic Assessments

Background Paper 1 Presentation for OECD Workshop on Socioeconomic Impact Assessment of Chemicals Management

7 July 2016

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Conflict of Interest Statement

- The author declares no relevant conflicts of interest with respect to the content of this presentation

- This presentation does not reflect the official views of the OCED, U.S. EPA, the State of Texas, or any other organization or third party, and contains personal opinions of the author

Acknowledgments

This work was supported by the OECD under Contract SRM #: 500044635

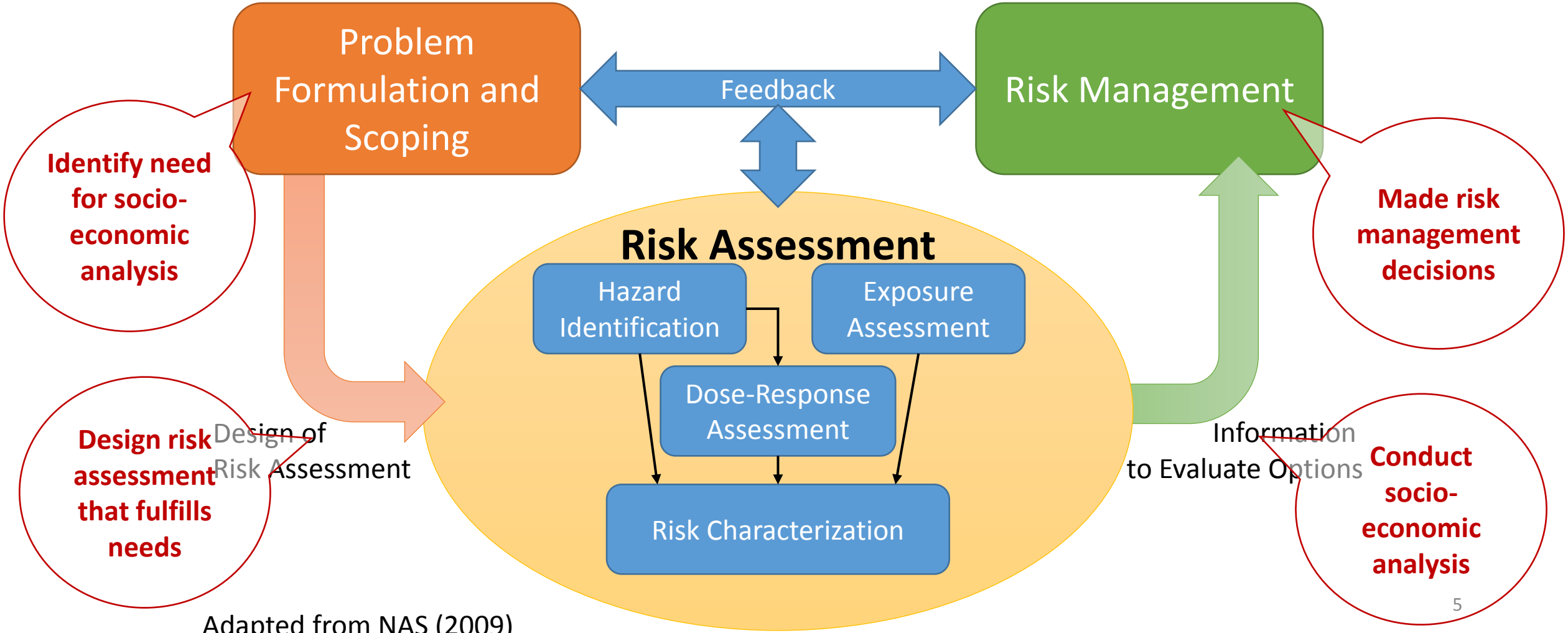
Colleagues and Reviewers

- Nour Abdo, JUST
- Daniel Axelrad, U.S. EPA
- Frederic Bois, INERIS
- Bernard Bottex, EFSA
- Nils Axel Braathen, OECD
- David Bussard, U.S. EPA
- Kenny Crump, consultant
- Christopher Dockins, U.S. EPA
- George Fotakis, ECHA
- Gary Ginsberg, Conn. DEPH
- Kate Guyton, WHO/IARC
- Al McGartland, U.S. EPA
- Andy Hart, FERA, UK
- Dale Hattis, Clark University, USA
- Matthias Herzler, BfR, Germany
- Kathy Hughes, IPCS (on detail from Health Canada)
- Juleen Lam, UCSF
- Eeva Leinala, OECD
- Qianwen Ouyang, TAMU (student worker)
- Greg Paoli, RSI
- Ivan Rusyn, TAMU
- Woody Setzer, U.S. EPA
- Wout Slob, RIVM, Netherlands
- David Threadgill, TAMU
- Theo Vermeire, RIVM, Netherlands
- Carolyn Vickers, IPCS
- Barbara Wetmore, Hamner
- Jessica Wignall, ICF
- Tracey Woodruff, UCSF
- Rick Woychik, NIEHS
- Fred Wright, NC State
- Lauren Zeise, California EPA

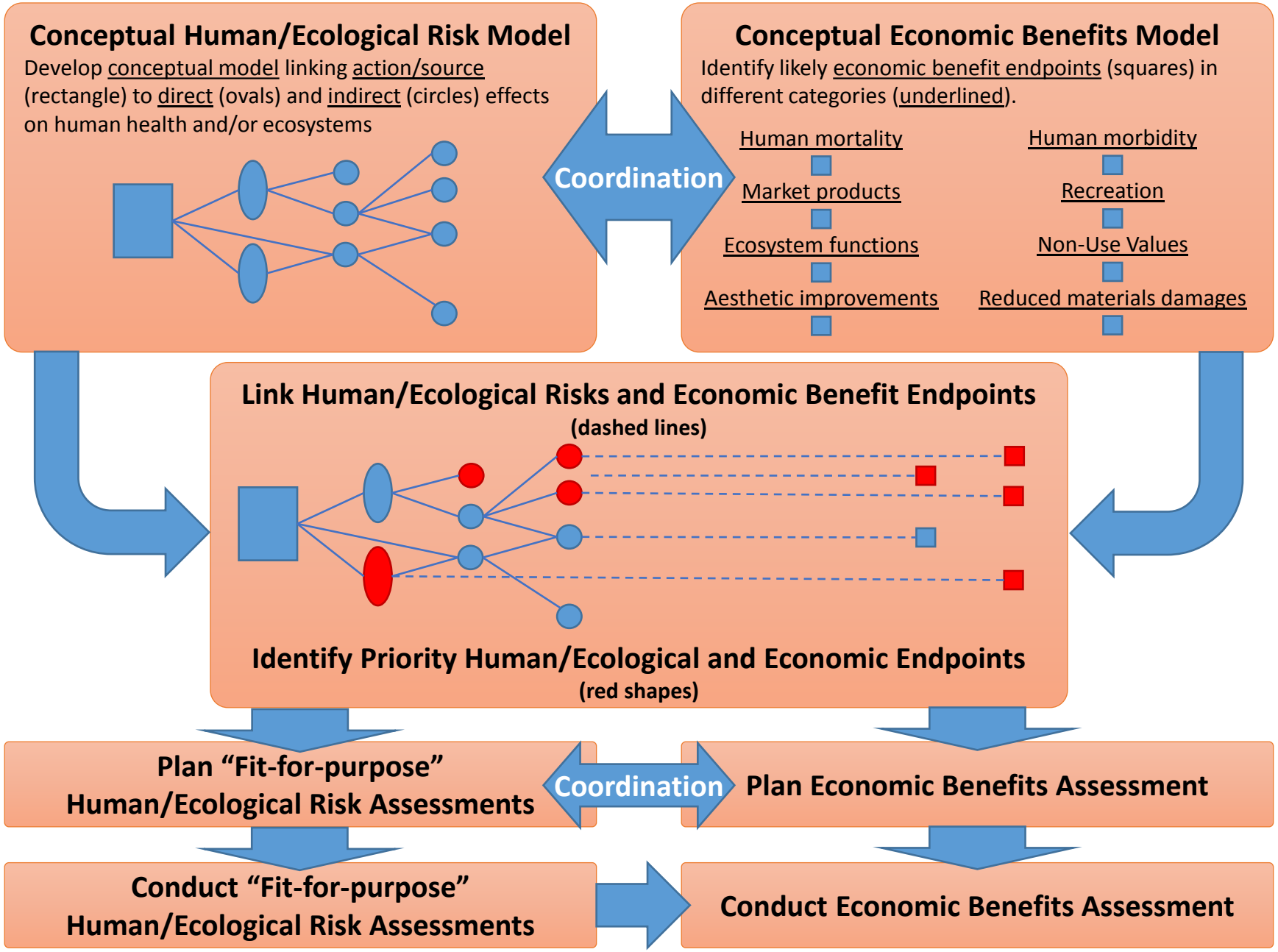
Outline

- Framing the Problem:
  Need to Adopt/Adapt Existing Risk Assessments for Use in Socio-Economic Analyses
- Identifying the Gaps:
  - Risk assessment information needed for socio-economic analyses
  - Information contained in “typical” chemical risk assessments
- Bridging the Gaps:
  Challenges, Opportunities, and Recommendations

Risk-Based Decision-Making: Developing "Fit for Purpose" Risk Assessments Supporting Socio-Economic Analyses



Adapted from NAS (2009)


Conceptual Human/Ecological Risk Model
Develop conceptual model linking action/source (rectangle) to direct (ovals) and indirect (circles) effects on human health and/or ecosystems
Coordination
Conceptual Economic Benefits Model
Identify likely economic benefit endpoints (squares) in different categories (underlined).
Human mortality
Market products
Ecosystem functions
Aesthetic improvements
Human morbidity
Recreation
Non-Use Values
Reduced materials damages
Link Human/Ecological Risks and Economic Benefit Endpoints
(dashed lines)
Identify Priority Human/Ecological and Economic Endpoints
(red shapes)
Plan "Fit-for-purpose" Human/Ecological Risk Assessments
Coordination
Plan Economic Benefits Assessment
Conduct "Fit-for-purpose" Human/Ecological Risk Assessments
Conduct Economic Benefits Assessment

Realities of expanding application of socio-economic analyses

- Most existing (and ongoing) chemical risk assessments are not designed to support socio-economic analyses.

- In most cases, there will not be the time or resources to iteratively "redo" chemical risk assessments to support socio-economic analyses.

- Economists need approaches to "adopt/adapt" existing risk assessments.

Outline

- Framing the Problem:
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- **Identifying the Gaps:**
  - Risk assessment information needed for socio-economic analyses
  - Information contained in “typical” chemical risk assessments
- Bridging the Gaps:
  Challenges, Opportunities, and Recommendations

Key needs for supporting typical socio-economic analyses

- **Exposure assessment**
  - Expected or central tendency values
  - Impact of risk management alternatives
- **Hazard identification**
  - Conclusion regarding causality
  - Economically-meaning endpoints
  - Non-overlapping endpoints
- **Dose-response assessment**
  - Functional relationship with exposure and time
  - Effects expressed as incidence or severity
  - Expected or central tendency values
- **Risk Characterization**
  - Change in incidence and severity of each endpoint under each alternative (including baseline), as a function of time
  - Expected or central tendency values

Comparison of human health risk assessments

U.S. National Ambient Air Quality Standards for Lead

Purpose: Selecting among alternative air pollution standards for lead.

- Baseline standard of 1.5 µg/m^3
- Proposed standards of 0.1, 0.15, 0.2, 0.3, 0.4, or 0.5 µg/m^3

Used directly in socio-economic benefit-cost analysis.

EU Risk Assessment Report for Hexabromocyclododecane (HBCD)

Purpose: Determining whether measures to address risks of exposure to HBCD are needed.

- Need for further information or testing
- Need for risk reduction measures to limit risks

Potential for use in socio-economic benefit-cost analysis?

Exposure Assessment

U.S. National Ambient Air Quality Standards for Lead

Blood lead levels in population of concern:

- Estimated annual mean air lead concentrations under different standards
- Estimated mean blood lead levels in children age<7 under different standards

EU Risk Assessment Report for Hexabromocyclododecane (HBCD)

Aggregate, multi-source, multi-pathway exposure estimates:

- Separate estimates for occupational workers and general public
- Estimated both “reasonable worst case” and “typical” exposure estimates

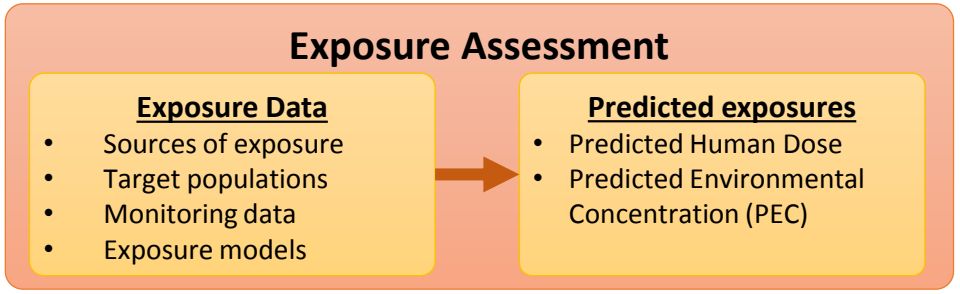
Suitable for supporting socio-economic analyses?

✓Expected or central tendency values

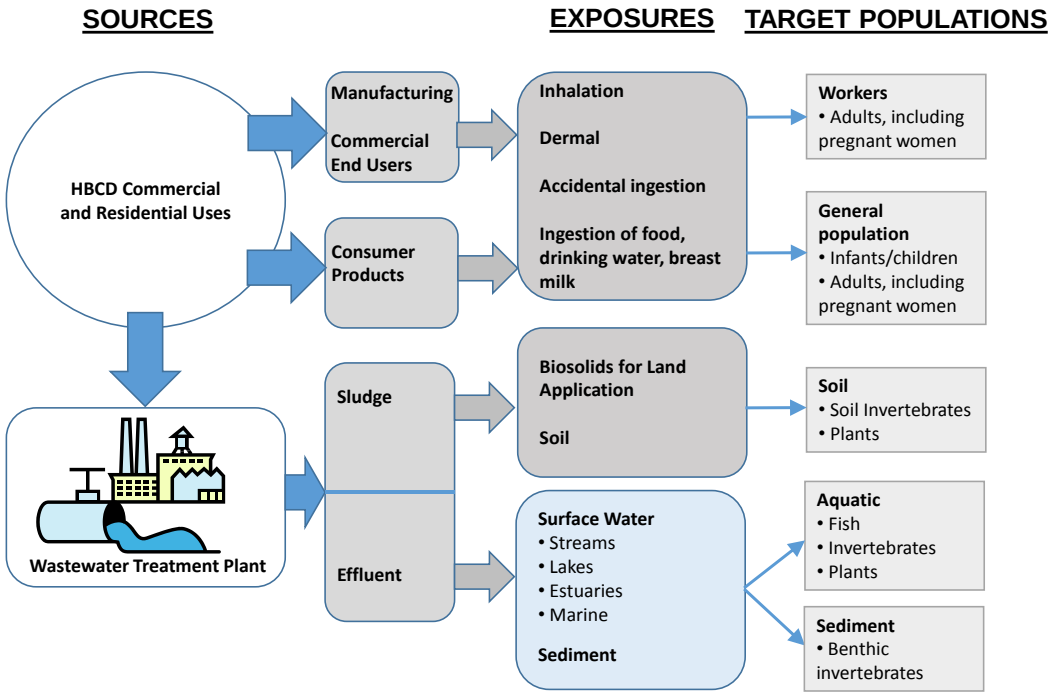
✓Impact of risk management alternatives

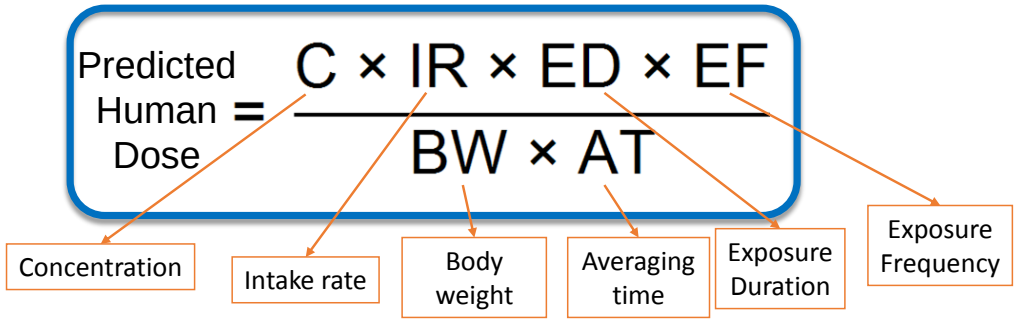
✓Expected or central tendency values

~ **Impact of risk management alternatives**



Key needs for supporting typical socio-economic analyses





- **Exposure Assessment**
  - Expected or central tendency values

Many include both “reasonable worst case” and “typical” exposure estimates.

  - Impact of risk management alternatives

Many include enough information to re-estimate exposure under risk management alternatives.

Hazard Identification

U.S. National Ambient Air Quality Standards for Lead

Health endpoints associated with lead exposure:

- "The overall weight of the available evidence provides clear substantiation of neurocognitive decrements being associated in young children with blood-Pb…"

EU Risk Assessment Report for Hexabromocyclododecane (HBCD)

Toxicological effects of HBCD exposure:

- "…proposed to base the NOAEL for repeated dose toxicity on … liver weight increase. Enzyme induction is a likely cause to the liver weight increase, and enzyme induction is clearly relevant also to humans."
- Effects on thyroid and pituitary – confidence in causality less clear.

Suitable for supporting socio-economic analyses?

✓ Conclusion regarding causality

✓ Economically-meaning endpoints

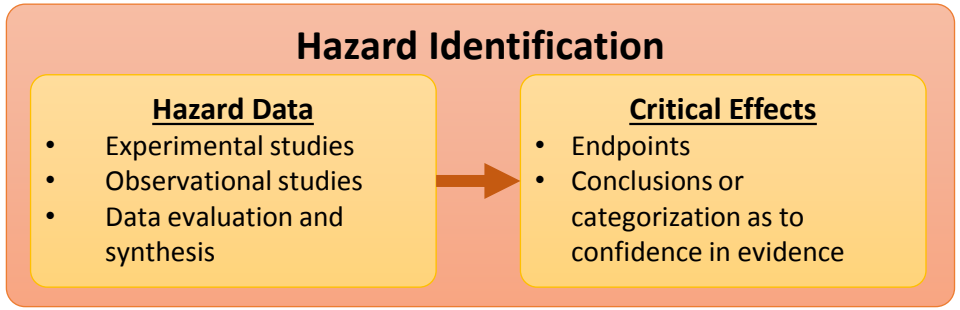
✓ Non-overlapping endpoints

~ **Conclusion regarding causality**

~ **Economically-meaning endpoints**

~ **Non-overlapping endpoints**

Key needs for supporting typical socio-economic analyses



Hazard identification categories

- Carcinogenic to Humans
- Likely to be Carcinogenic to Humans
- Suggestive Evidence of Carcinogenic Potential
- Inadequate Information to Assess Carcinogenic Potential
- Not Likely to be Carcinogenic to Humans

- **Hazard identification**
  - Conclusion regarding causality

Conclusions regarding causality are not always clearly stated.

  - Economically-meaning endpoints

Many endpoints not directly economically meaningful.

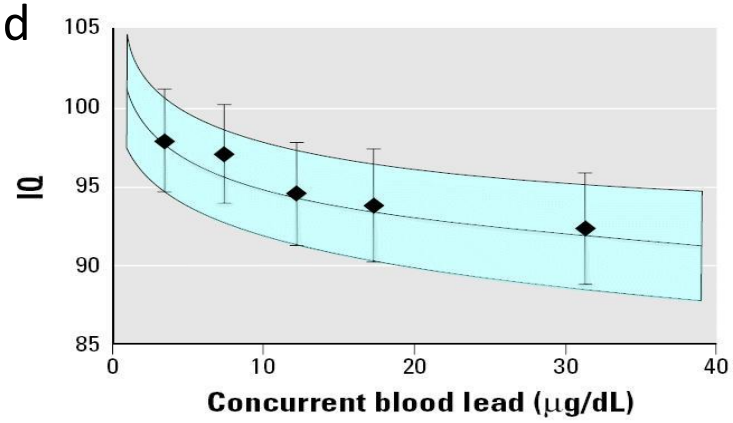
  - Non-overlapping endpoints

Limited to discussing endpoints that are “secondary” to other endpoints.

Dose-response Assessment

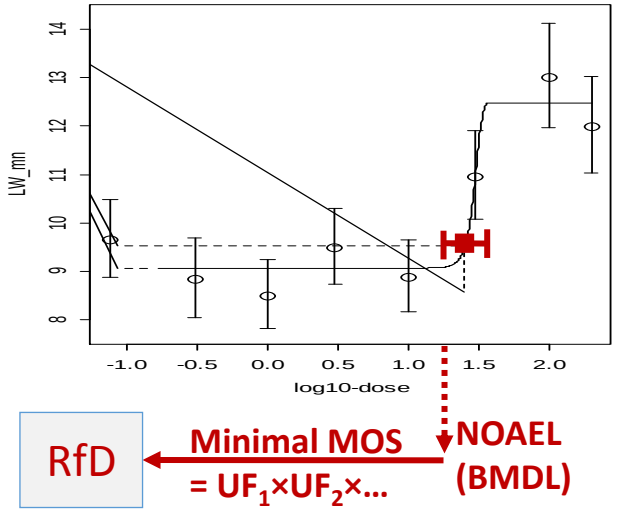
U.S. National Ambient Air Quality Standards for Lead

- Mean IQ loss in children under 7 as a function of blood lead



EU Risk Assessment Report for Hexabromocyclododecane (HBCD)

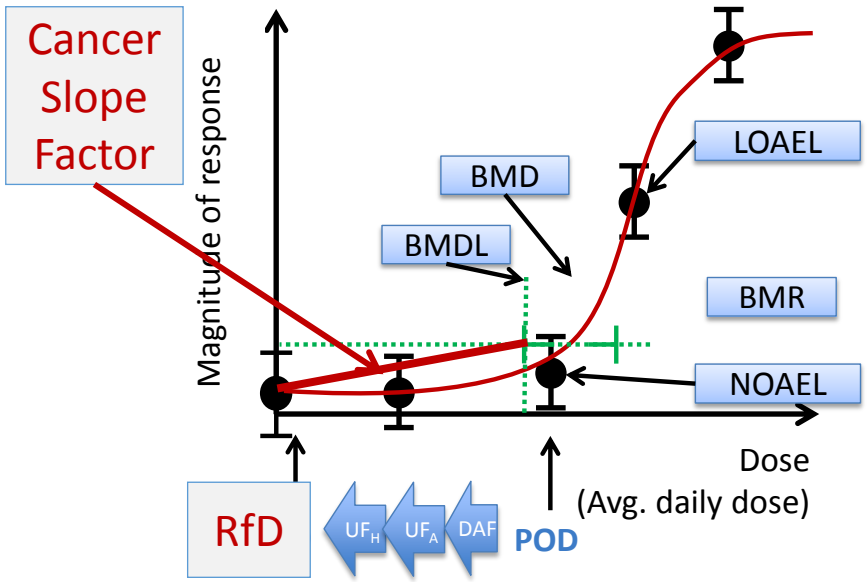
- NOAEL (BMDL) = 22.9 mg/kg-d for 5% increased liver weight
- Uncertainty factors to define "minimal Margin of Safety"

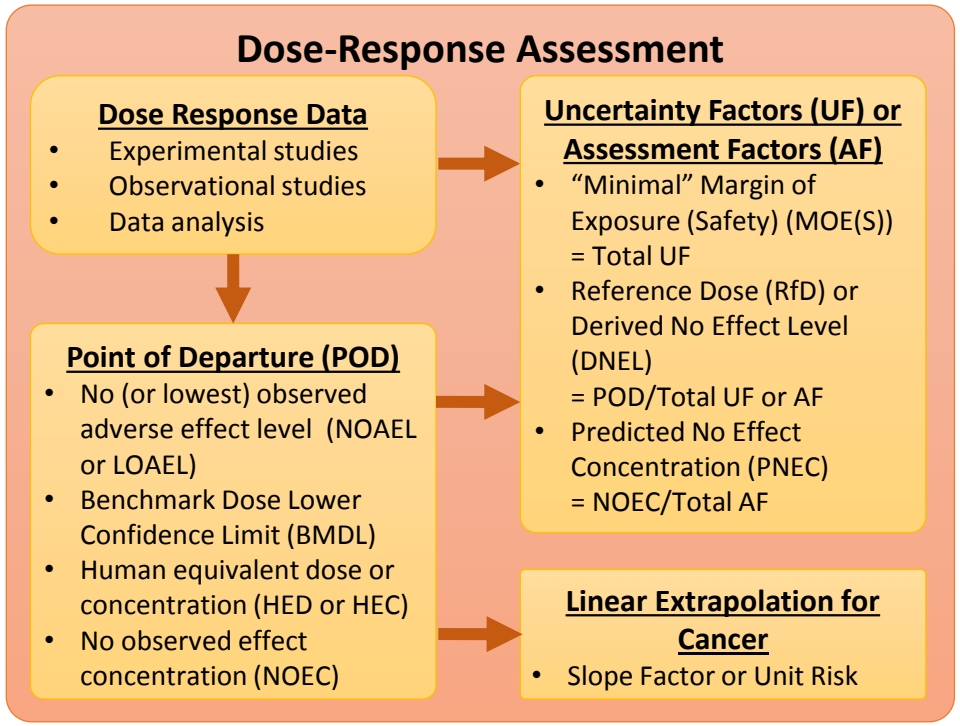


Suitable for supporting socio-economic analyses?

- ✓ Functional relationship with exposure and time
- ✓ Effects expressed as incidence or severity
- ✓ Expected or central tendency values

- ~ **Functional relationship with exposure and time**
- ✓ Effects expressed as incidence or severity
- ~ **Expected or central tendency values**





Key needs for supporting typical socio-economic analyses

- **Dose-Response**
  - Functional relationship with exposure and time

Only routinely estimated for cancer (linear relationship).

  - Effects expressed as incidence or severity

Only for cancer or when BMD modeling is conducted.

  - Expected or central tendency values

Central tendency values available from BMD modeling, but lacking for Uncertainty Factors.

Risk Characterization

U.S. National Ambient Air Quality Standards for Lead

- Total IQ points in population gained under alternative standards:
  - **0.5 µg/m³:** 230,000
  - **0.4 µg/m³:** 230,000
  - **0.3 µg/m³:** 270,000
  - **0.2 µg/m³:** 360,000
  - **0.15 µg/m³:** 400,000
  - **0.1 µg/m³:** 510,000

EU Risk Assessment Report for Hexabromocyclododecane (HBCD)

- Is ratio between NOAEL (BMDL) and Exposure larger than the minimal MOS?
  - **Yes:** "There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already."
  - **No:** "There is a need for limiting the risks; risk reduction measures that are already being applied shall be taken into account."

Suitable for supporting socio-economic analyses?

✓ Change in incidence and severity of each endpoint under each alternative (including baseline), as a function of time

✓ Expected or central tendency values

× **Change in incidence and severity of each endpoint under each alternative (including baseline), as a function of time**

× **Expected or central tendency values**

Key needs for supporting typical socio-economic analyses

- **Risk Characterization**
  - Change in incidence and severity of each endpoint under each alternative (including baseline), as a function of time

Only routinely available for cancer (linear relationships with dose and time).

  - Expected or central tendency values

Not generally available due to lack thereof in dose-response assessment.

Risk Characterization

Margin of Exposure (Safety) [Human]

MOE(S) = POD/Predicted Human Dose

- "Acceptable" risk if MOE(S) ≥ "minimal" MOE(S)
- "Unacceptable" risk if MOE(S) < "minimal" MOE(S)

Hazard Quotient (HQ) or Risk Characterization Quotient (RCR) [Human]

HQ or RCR = Predicted Human Dose/RfD

- "Acceptable" risk if HQ or RCR ≤ 1
- "Unacceptable" risk if HQ or RCR > 1

Excess Risk for Cancer [Human]

Excess Risk = Predicted Human Dose × Slope Factor or Unit Risk

- "Acceptable" risk if ≤ Benchmark risk (e.g., 10^{-6}, 10^{-5}, or 10^{-4})
- "Unacceptable" risk > Benchmark risk

Risk Quotient [Ecological]

Risk Quotient = PEC/PNEC

- "Acceptable" risk if PEC/PNEC ≤ 1
- "Unacceptable" risk if PEC/PNEC > 1

Risk Assessments Supporting Socio-economic Analyses

Human epidemiology

Evidence of causal relationship?

Quantitative exposure-response relationship

Compare with expected exposures under different risk management scenarios

Input into policy analyses (including socio-economic analyses)

How do we bridge the gap?

How do we bridge the gap?

How do we bridge the gap?

How do we bridge the gap?

How do we bridge the gap?

Most Existing Risk Assessments

Experimental animal toxicology

Animal-to-human extrapolation (qualitative and quantitative)

"Safe" or "Protective" exposure level

Compare with conservative exposure estimates

Input into policy analyses (not including socio-economic analyses)

Outline

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- **Bridging the Gaps:**
  Challenges, Opportunities, and Recommendations

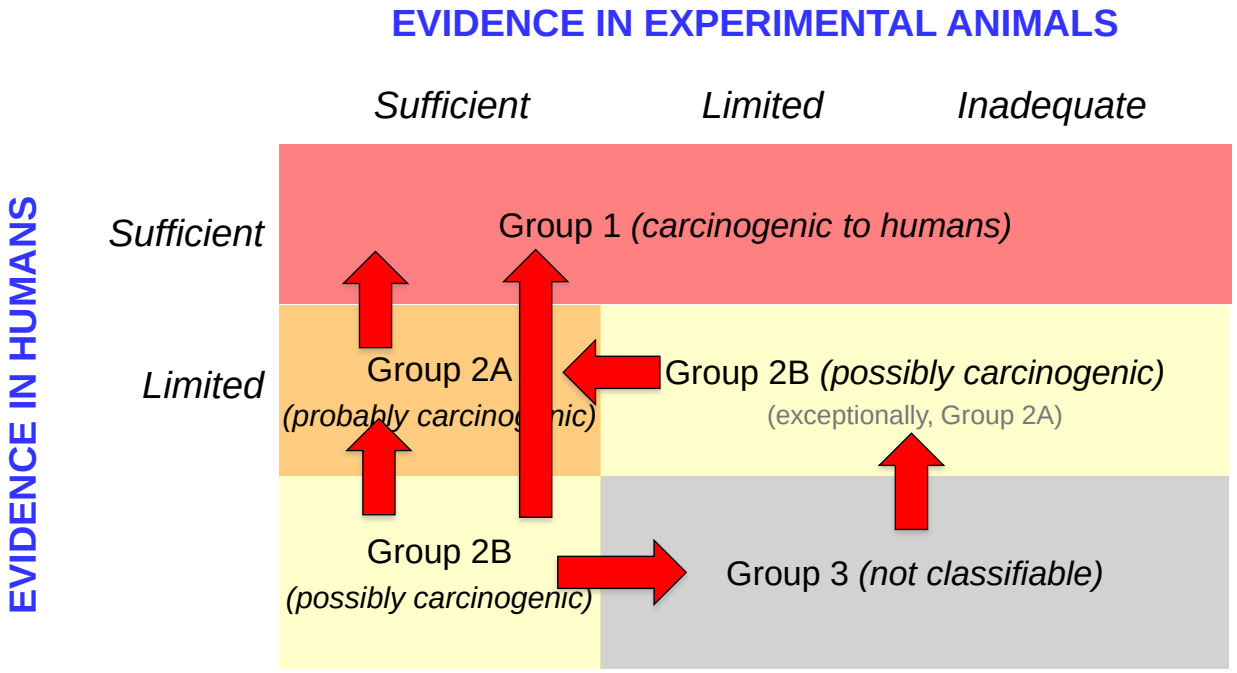
Feasibility of Adopting/Adapting Existing Exposure Assessments

- **Central tendency values: FEASIBLE**
  - Already exist for many risk assessments
  - Can derive using standard references for “central tendency” exposure parameters
  - Additional refinement: characterizing and distinguishing between uncertainty and variability
- **Impact of risk management alternatives: FEASIBLE**
  - Will always need to tailor the exposure assessment to the risk management alternatives being considered
  - Extensive experience already exists in the community

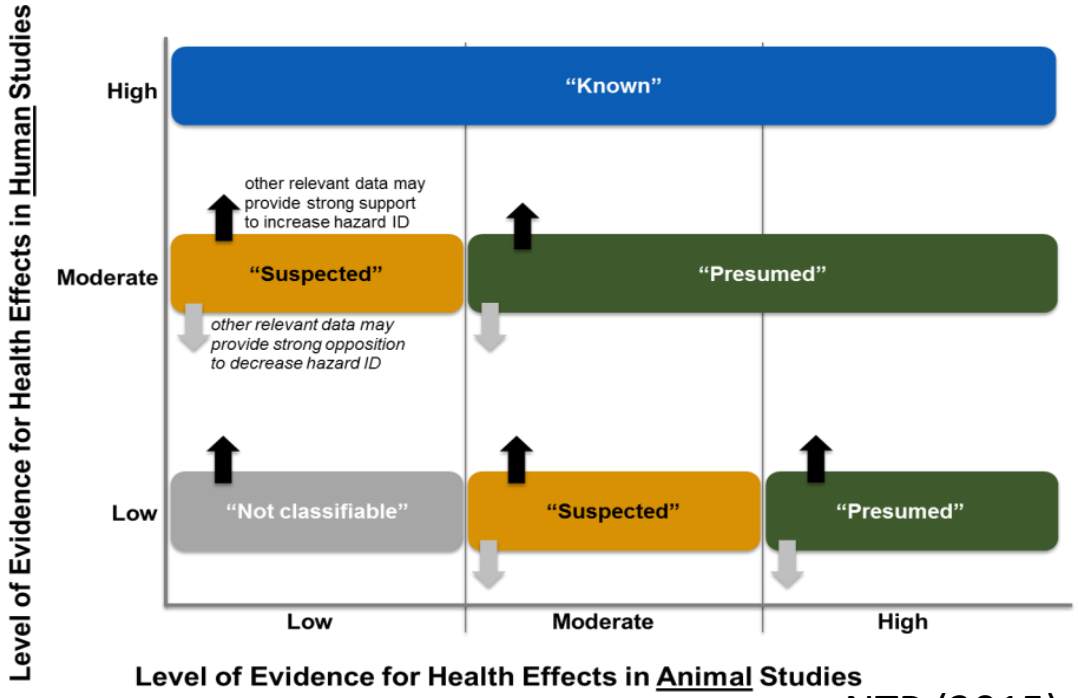
Feasibility of Adopting/Adapting Existing Hazard Identifications

- **Conclusion regarding causality:** **FEASIBLE** (see next slide)
  - Facilitated by trend towards adopting formal causal frameworks like those used at U.S. EPA, WHO/IARC, U.S. NTP.
  - Can assign probability (or range of probabilities) of causation, depending on the risk assessment conclusions (Trasande et al. 2015).
- **Economically-meaning endpoints:** **FEASIBLE SOMETIMES**
  - Facilitated by trend towards endpoint-by-endpoint causal determinations
  - Often challenged by uncertainty in animal-to-human concordance
  - Short term, focus on endpoints with unambiguous human counterpart
  - Medium-/longer-term, develop economic valuations for “sub-clinical” and more “ambiguous” endpoints.
- **Non-overlapping endpoints:** **FEASIBLE SOMETIMES**
  - Facilitated by trend towards using more mechanistic / Adverse Outcome Pathway data
  - Short term, not likely issue given limited economically meaningful endpoints.
  - Medium-/longer-term, develop quantitative models of endpoint relationships.

Convergence of causal frameworks … and probabilistic hazard identification?



IARC (2006)



NTP (2015)

TABLE 6-5 Example Conversion of Quantitative Output to Qualitative Categorical Judgments

Chance that Chemical X is a Carcinogen	Categorical Judgment
> 90%	Carcinogenic in humans
≤ 90% to > 75%	Likely to be carcinogenic in humans
≤ 75% to > 50%	Suggestive evidence of carcinogenicity
≤ 50% to > 5%	Inadequate information
≤ 5%	Not likely to be carcinogenic in humans

NAS (2014)

Table 1. Framework for Evaluating Probability of Causation

Epidemiological Evaluation	Toxicological Evaluation		
	Strong (Group 1)	Moderate (Group 2A)	Weak (Group 2B)
High	Very High (90–100%)	High (70–89%)	Medium (40–69%)
Moderate	High (70–89%)	Medium (40–69%)	Low (20–39%)
Low	Medium (40–69%)	Low (20–39%)	Very Low (0–19%)
Very Low	Low (20–39%)	Very Low (0–19%)	Very Low (0–19%)

Adapted from Ref. 32.

Trasande et al. (2015)

Feasibility of Adopting/Adapting Existing Dose-Response Assessments

- **Functional relationship with exposure and time:**
- **Effects expressed as incidence or severity:**
- **Expected or central tendency values:**

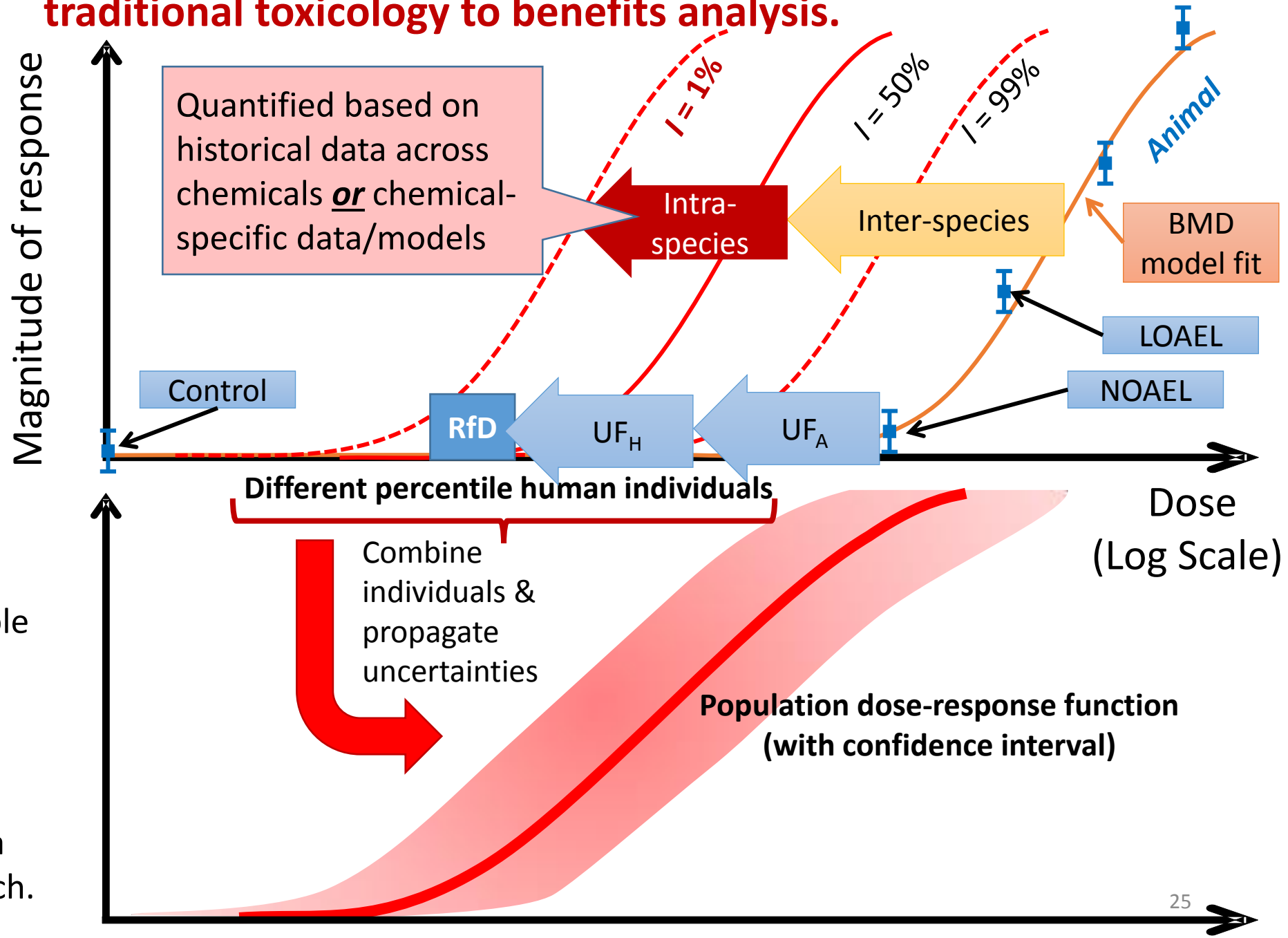
FEASIBLE AND INTER-RELATED

- **Replacing LOAEL/NOAEL/BMDL with a function describing the dose-response data**
  - Facilitated by trend towards using benchmark dose modeling (which requires a quantal or continuous endpoint) rather than LOAEL/NOAEL.
  - In short term, can extract the underlying model fits or re-analyze the data to fit a model curve
  - In longer term, can incorporate additional sources of uncertainty, such as model uncertainty
- **Prediction of extrapolated human population dose-response function**
  - Already done for cancer endpoints, assuming linearity.
  - For non-cancer effects, enabled by probabilistic approach to replace fixed uncertainty factors (recent Harmonized Guidance by WHO/IPCS includes probabilistic “default” distributions for immediate implementation).
  - In short term, will need to re-analyze data to derive predicted dose-response function, using default distributions.
  - In medium-/longer term, can utilize chemical-specific data and eventually quantitative biomarker-based models.

Using probabilistic approaches to bridge the gap from traditional toxicology to benefits analysis.

Economically-meaningful endpoints from hazard identification step

Quantified based on historical data across chemicals ***or*** chemical-specific data/models

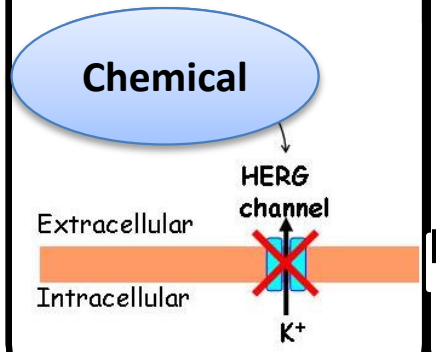


- Probabilistic approach recommended by multiple authorities (NAS 2009, 2014; WHO 2014).
- NAS (2009) specifically mentions economic benefit-cost analysis as a rationale for the approach.

In the future: using biomarkers to bridge the gap from "high throughput" toxicology to "high throughput" benefits analysis?

Molecular

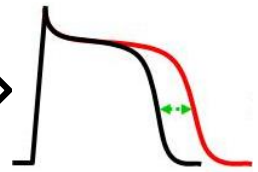
Chemical blocks ion channel



Source: hERGAPDbase

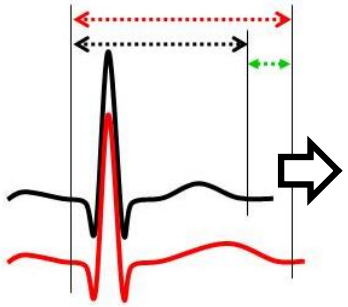
Cellular

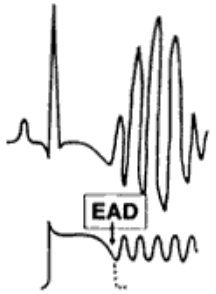
Action potential prolonged



Tissue

QT interval prolonged → Increased likelihood of toursades de pointes

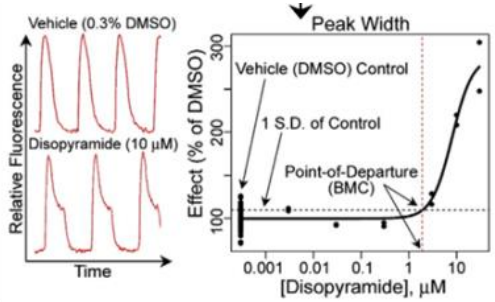




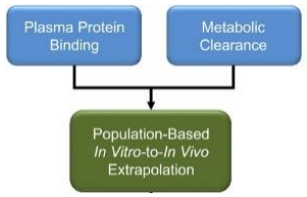
Organism

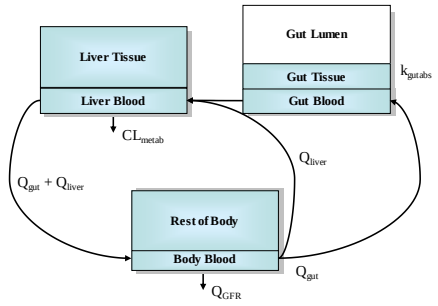
Increased likelihood of myocardial infarction → Increased likelihood of death

Human iPSC-derived cardiomyocyte OCM in 384-well format



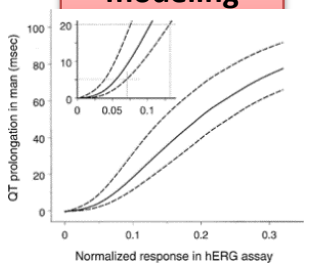
IVIVE



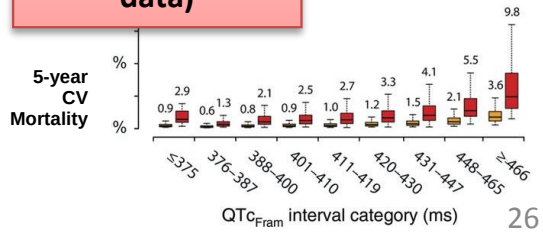


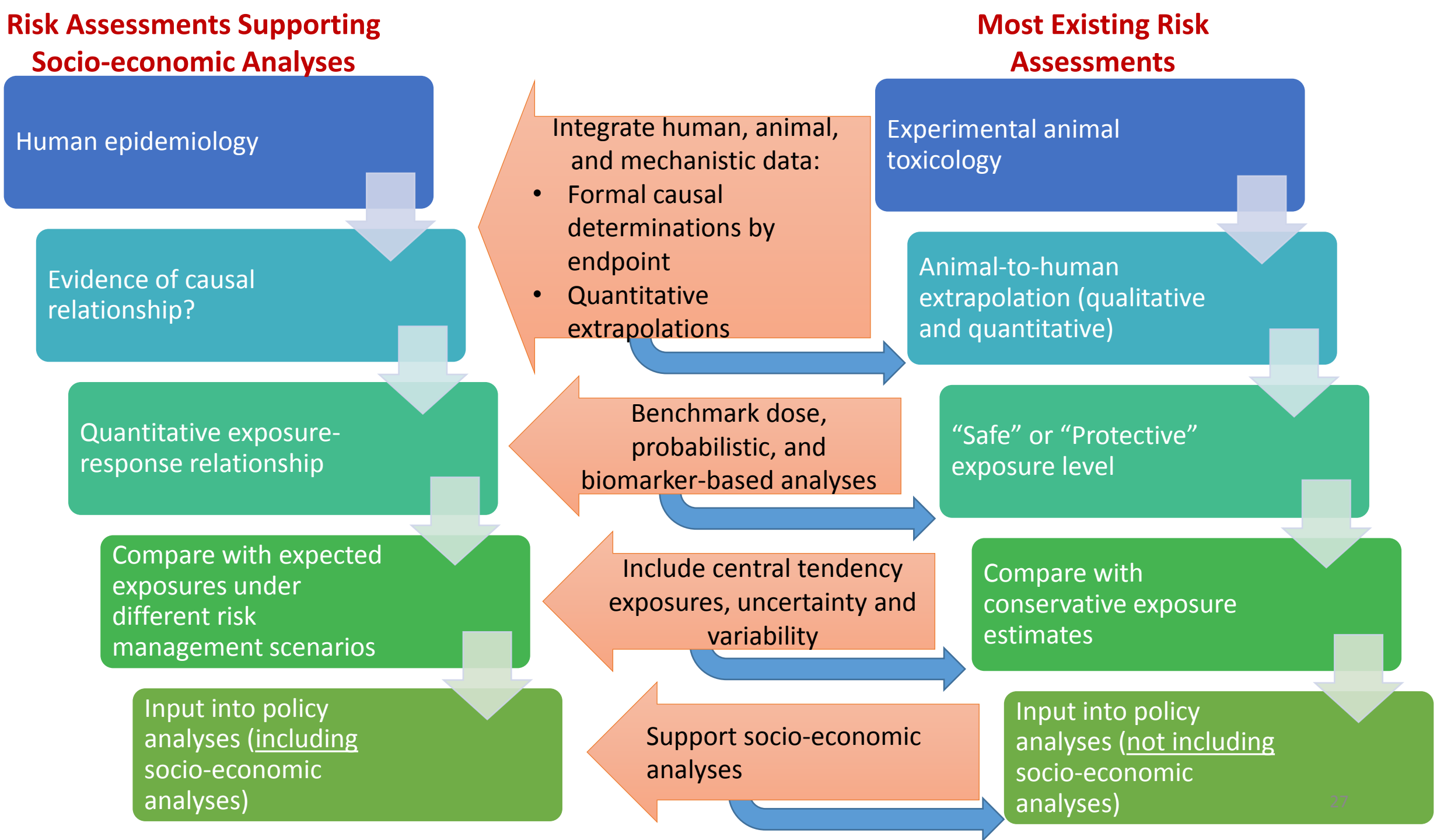
Calibration with published human concentration-response data QTc data → Predicted population dose-response for QTc → Dose-response of apical endpoints for broader risk assessment applications

Population PK/PD modeling



QTc and mortality models (clinical/ epidemiologic data)




Risk Assessments Supporting Socio-economic Analyses
Most Existing Risk Assessments
Human epidemiology
Experimental animal toxicology
Integrate human, animal, and mechanistic data:
• Formal causal determinations by endpoint
• Quantitative extrapolations
Evidence of causal relationship?
Animal-to-human extrapolation (qualitative and quantitative)
Quantitative exposure-response relationship
Benchmark dose, probabilistic, and biomarker-based analyses
"Safe" or "Protective" exposure level
Compare with expected exposures under different risk management scenarios
Include central tendency exposures, uncertainty and variability
Compare with conservative exposure estimates
Input into policy analyses (including socio-economic analyses)
Support socio-economic analyses
Input into policy analyses (not including socio-economic analyses)

Conclusions and Recommendations

- Existing “typical” risk assessments leave a number of critical gaps if they need to be “repurposed” for use in socio-economic analyses.

- Many current, recommended risk assessment methodologies facilitate better translation for socio-economic analyses.
  - Methods have not yet become “common” risk assessment practice.
  - “Bridging analyses” will be necessary in the short- and medium-term.
  - Need for multidisciplinary collaboration.

- Case studies demonstrating “bridging analyses” may provide valuable experience and facilitate uptake.

- Further progress possible with economic valuations of “subclinical” endpoints and “ambiguous” risks.