Use of Biomarkers in the Benchmark Dose Method

Beyond Science and Decisions: From Problem Formulation to Dose-Response

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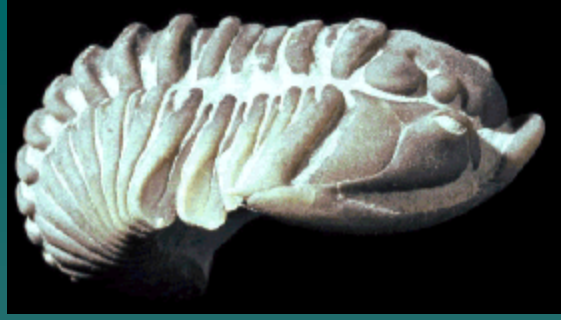
Disclaimer



- The views expressed in this presentation are those of the authors and do not represent the policy of the U.S. EPA.

These are the views of Robinan Gentry, Cynthia Van Landingham, Lesa Aylward, Sean Hays

MeHg Hazard Characterization

- Effects of adult exposure or during development range from mortality through subtle effects on ability to learn
- Not likely to be a human carcinogen
- Developing nervous system has been focused on as a sensitive target for low dose MeHg exposure
- Human and animal evidence of cardiovascular effects – from adult and *in utero* exposure
- Animal evidence of immune and reproductive effects
- Mode of action is not established

Three State-of-the-art Studies on Children, *in utero* exposure

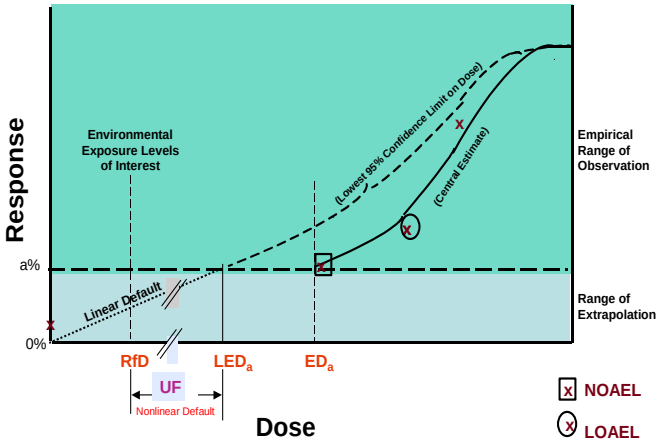
Faroes	Seychelles	New Zealand
Northern Caucasian	African	Multi-ethnic
900 mother child pairs	700 mother child pairs	200 mother child pairs
Cord blood, maternal hair	Maternal Hair	Maternal hair
Pilot whale	Variety of fish (mostly	Shark (fish and chips)
Effect meas		ests
Boston Na Continuou Test, Finge California Verbal Learning		Scales,

2006 publication on Seychelles --
BMD similar to Faroes for a few measures

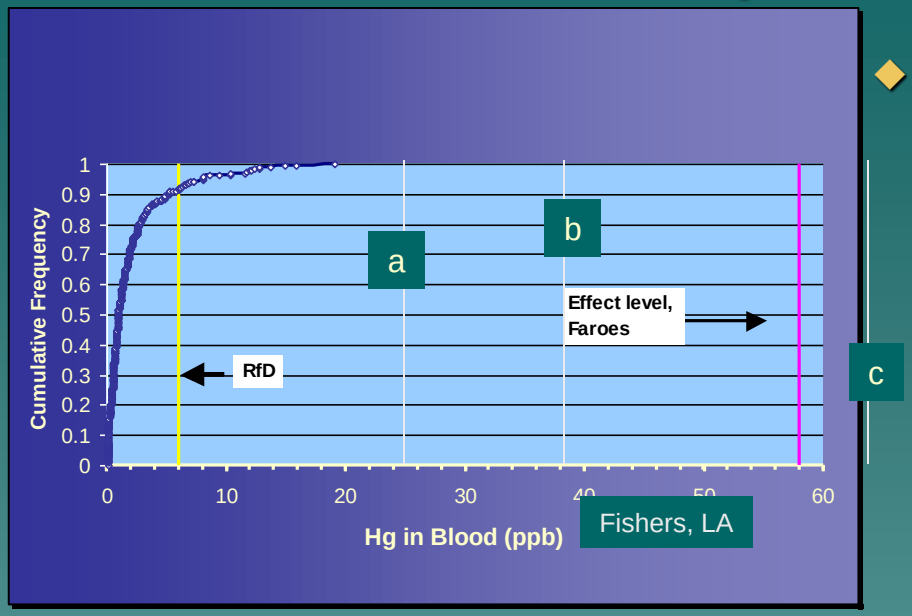
- CVLT Long Delay
- Finger Tapping Preferred Hand
- CPT Reaction Time
- Boston Naming Test With Cues

MeHg Dose Response '01

- RfD = 0.1µg/kg/day (about 1.1 ppm hair, 5.8 ug/L blood) neuropsychological effects (test scores) in children exposed *in utero* through maternal seafood consumption
- BMD set at level for doubling of the number of poor performers on tests (from 5% to 10% of the population)
- UF = 10
- Used Boston Naming Test as example BMDL = 58 ug mercury / L blood
- Cord blood = maternal blood



Most U.S. Exposure is from Fish



- Data from a large, continuing CDC study indicate distribution of MeHg blood levels
  - 7.8% (5.7%) women of childbearing age were above RfD
  - Blood mercury higher in some ethnic groups
  - Fish consumption was associated with increased blood Hg

–Data from smaller, localized surveys show higher blood mercury than NHANES

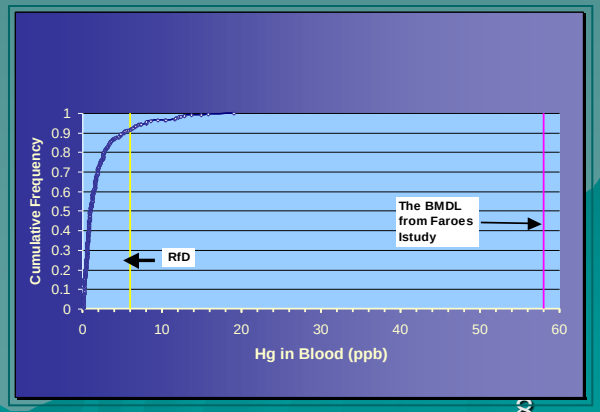
- Median blood mercury was 7.1 ppb, people eating fish from AR waters
- Median was 25 ppb in 6 commercial fishers and family in LA (a)
- Family in WI, 37- 38 ppb (ate sea bass twice/week) (b)
- High income fish-eaters had greater than 80 ppb (c)

Case Study Method

- Development of risk values at doses above the Reference Dose (RfD)
- Methylmercury
  - Dose-response information in humans
  - BMDs estimated using biomarkers (i.e., levels in hair and cord blood)
  - Multiple BMDs available
  - Sensitive human subpopulation (children exposed *in utero*)
- Extension of the Benchmark Dose (BMD) method

Biomonitoring Data

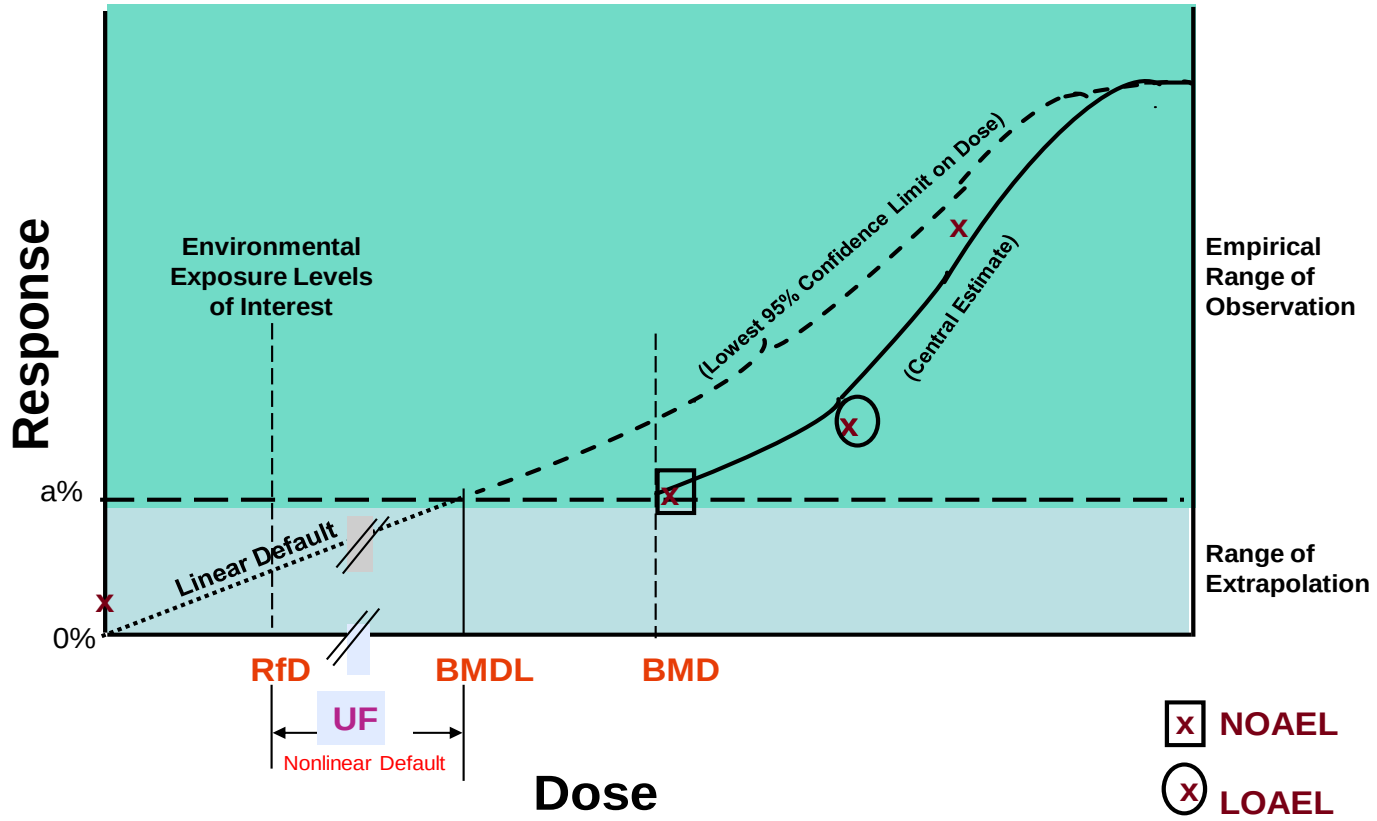
- National Health and Nutrition Examination Survey (NHANES)
  - Blood concentrations or total and inorganic mercury
  - Data available in children (1-19) and women of childbearing age (14-45)
  - Population estimates



4 Approaches

- *Approach 1* - Straight line is drawn from both the BMDL and BMD to the RfD, RfD is considered to be zero risk
- *Approach 2* - The appropriate BMD model is extrapolated to the RfD, risk at the RfD is zero
- *Approach 3* - The appropriate BMD model is extrapolated to the RfD and this risk is allowed to stand as an upper bound
- *Approach 4* - The appropriate BMD model is extrapolated using a threshold term, where the threshold value is judged to be the RfD, or some higher value.

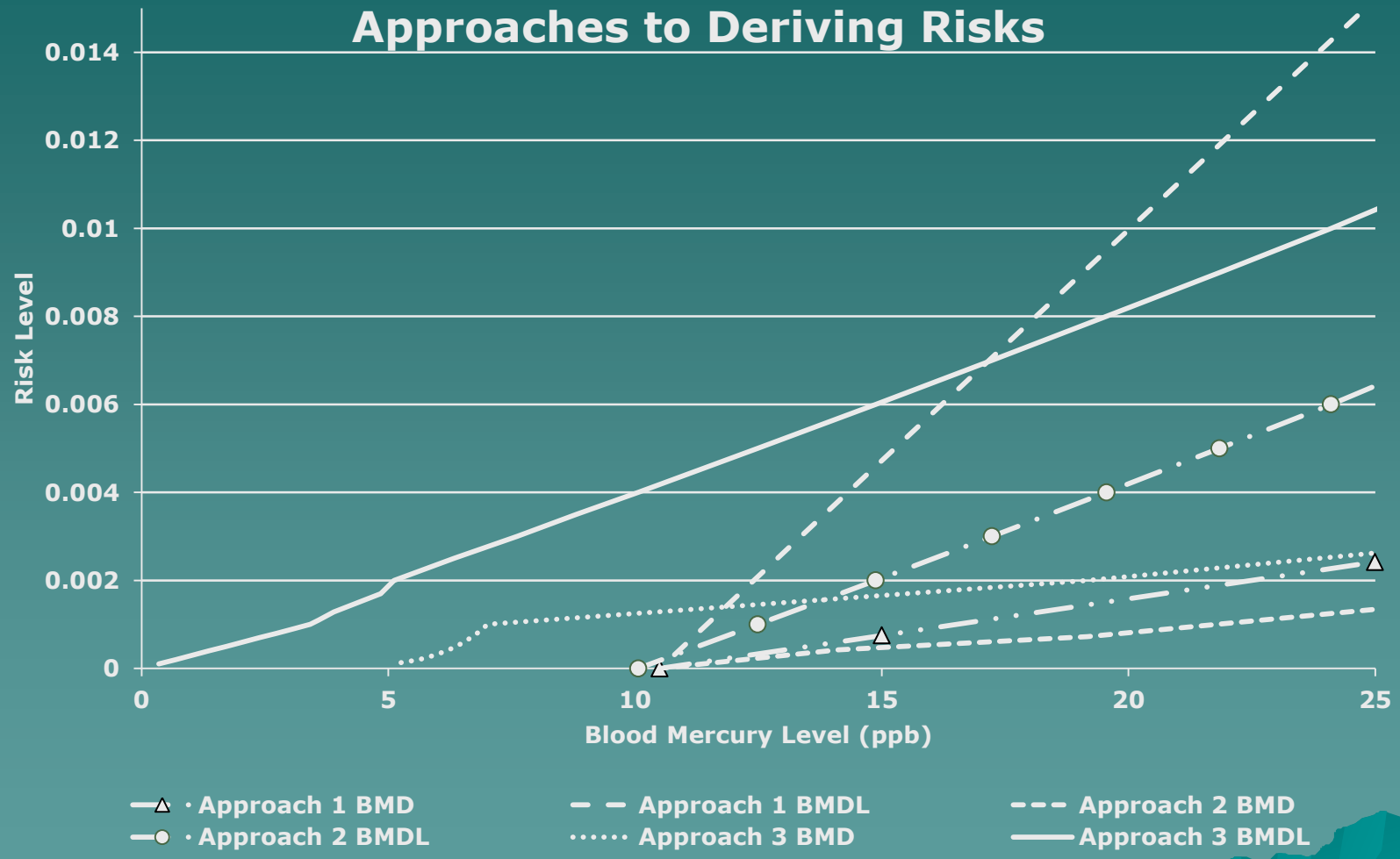
4 Approaches



Estimated Adverse Events

Approach	RfD (ppb)	Population	Range of organic Mercury Levels	Range of Associated Risks	Range of Associated Risks	Estimiated number of Adverse Events	
				Most Likely	Upper Bound	Most Likely	Upper Bound
1	5.8	Children (1 to 19 yrs)	6.3 - 9.9	3.2×10^{-4} to 2.6×10^{-3}	4.8×10^{-4} to 3.9×10^{-3}	256	389
	5.8	Women (14 -45 yrs)	6.0 - 10.8	1.3×10^{-4} to 3.2×10^{-3}	1.9×10^{-4} to 4.8×10^{-3}	1276	1936
	10.5	Children (1 to 19 yrs)	No Organic Blood Levels above 10.5 ppb				
	10.5	Women (14 -45 yrs)	10.8	5.0×10^{-5}	3.2×10^{-4}	1	9
2	10.5	Women (14 -45 yrs)	10.8	2.5×10^{-5}	3.0×10^{-4}	1	43
3	10.5	Women (14 -45 yrs)	10.8	1.3×10^{-3}	4.3×10^{-3}	37	122
	10.5	All US pop	10.6 - 42.9	1.3×10^{-3} to 4.5×10^{-3}	4.3×10^{-3} to 1.9×10^{-2}	3697	13275
4	10.5	Women (14 -45 yrs)	10.8	Estimated Threshold of 77.8 ppb			

Impact of Approach



Strengths

- Use of a biomarker, which is typically closer to the "target tissue" concentration than the use of external exposure concentration
- Ability to evaluate the potential fraction of people exposed above and below the RfD
  - Assess the likelihood of adverse noncancer effects at a specified internal concentration
  - May be extended to an exposure level if information are available.
- Ability to estimate potential risk at a specific dose or biomarker concentration above the RfD.

and Limitations

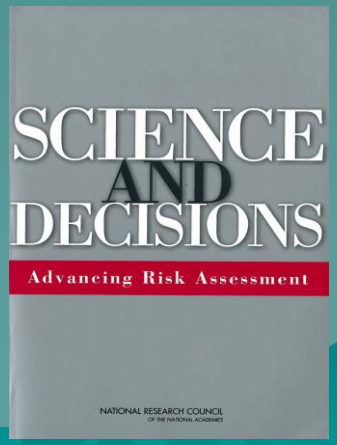
- Uncertainties (for other compounds) as to the relationship between biomarker and effects of concern.
- Information characterizing the potential shape of the dose-response curve below the BMD/BMDL

Science and Decisions

- Address human variability and sensitive populations?
  - Intraspecies variability and sensitive populations are usually addressed by the use of an intraspecies uncertainty factor of up to 10
  - this method can be used if measured biomarkers of exposure in sensitive subpopulations or selected populations, such as women of childbearing years, and evaluate the relationship to the RfD or the BMD/BMDL.
- Address background exposures and responses?
  - **C**onsideration of the NHANES data focuses on background levels of compounds in the general population. This method can be extended to biomarker information for specific populations as well, if data are available.

Science and Decisions 2

- Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?
  - The method allows for the estimation of risk, based on the biomarker information from individuals (if available) or subpopulations at or above the RfD.
- Work practically?
  - It is an easy method to apply, as long as the critical data are available.



What's Next?

- Consideration of the available information (if any) on the potential MOA for the effects that are the basis of the RfD to inform which approach would be preferred.
- Consideration of other compounds in NHANES which have been considered in the estimation of Chemical-Specific Biomonitoring Equivalents (BEs) and how this information can be used for additional application of the approaches demonstrated for methylmercury.