ESTIMATES OF RISK ABOVE/AROUND THE RFC FOR TCE USING EPA (2011) AND ALLIANCE FOR RISK ASSESSMENT *(ARA)* CASE STUDIES

Michael Dourson
Toxicology Excellence for Risk Assessment
dourson@tera.org

CASE STUDIES

- All case studies found at: http://www.allianceforrisk.org/Workshop/WS3/CaseStudiesWS3.html
- ARA Case Study:

1. **Use of biomarkers in the benchmark dose method**
   - Presented by R. Gentry. Coauthors: C. Van Landingham, S. Hays, L. Aylward
2. **Estimate Risk Above the RfD Using Uncertainty Factor Distributions**
   - Presented by Elizabeth Spalt (Indiana Department of Environmental Management) and Oliver Kroner (Toxicology Excellence for Risk Assessment,)

ARA Case Study #1: Use of biomarkers in the benchmark dose method

Note: The case study has been adapted to use with experimental animal data, and takes EPA (2011) determinations of BMD/BMDL for critical endpoints of TCE at face value.

RESULTS OF METHOD #1

SELECTION OF BMD

- The appropriate BMD is chosen in the usual fashion using existing EPA software and criteria, including p-values, AIC, residuals, BMD to BMDL ratios and visual inspection.
- The data are modeled to an appropriate point of departure (POPD) using the usual judgment
- Different procedures were investigated to extrapolate the potential risk

EXTRAPOLATING TO POTENTIAL RISK

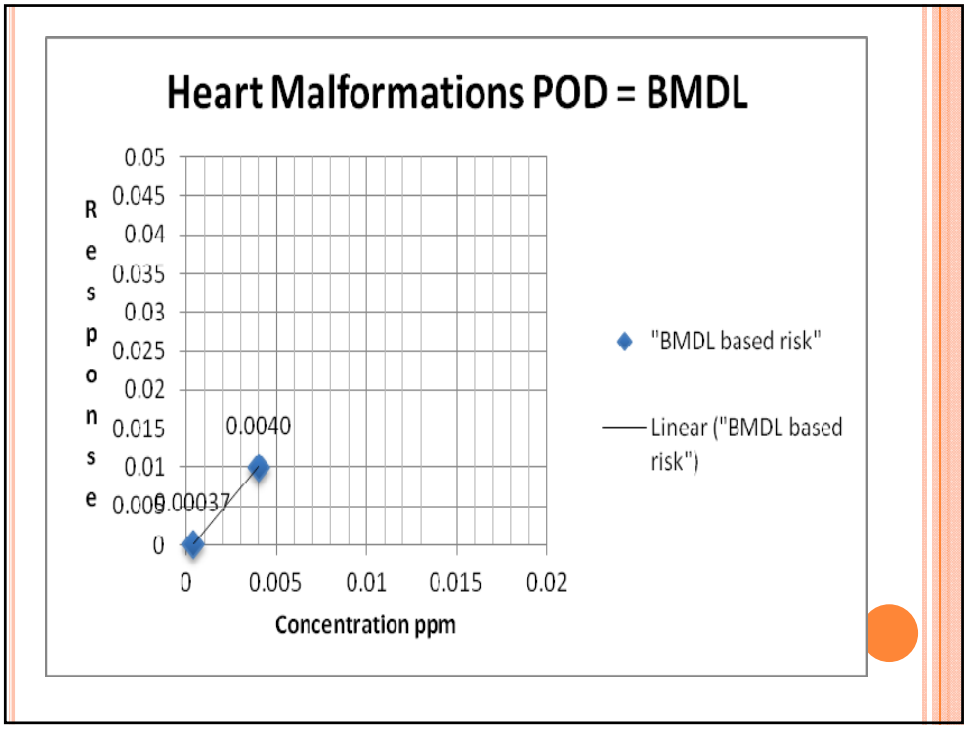
❖ **4 different procedures investigated to extrapolate the potential risk:**

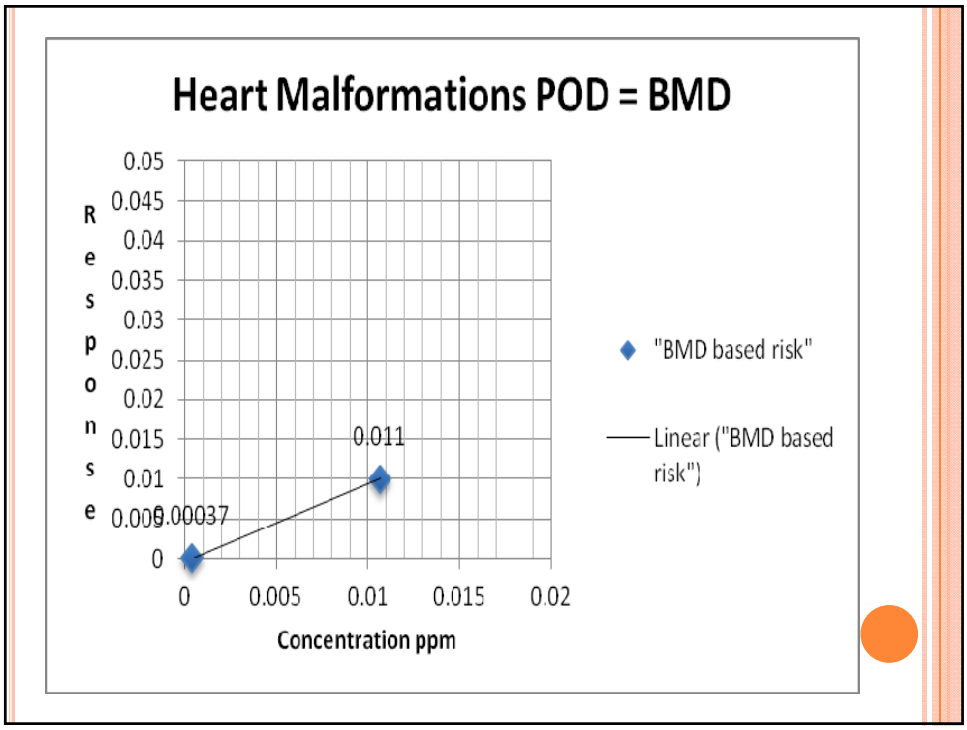
1. A straight line is drawn from both the BMDL and BMD to the RfD, where the RfD is considered to be zero risk;
2. The appropriate BMD model is extrapolated to the RfD and then the risk at the RfD is truncated to zero;
3. The appropriate BMD model is extrapolated to the RfD and this risk is allowed to stand as an upper bound;
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.*

JOHNSON ET AL. (2003) FETAL HEART MALFORMATIONS

	Concentration	Response
RfC	0.00037	0
HEC, BMDL/3UFad	0.0040	0.01
EPA, 2011,Figure F-15, page F-35)		
RfC	0.00037	0
HEC, BMD/3UFad	0.011	0.01
EPA, 2011, Table F-7 (page F-12) and EPA, 2011,Figure F-15, page F-35)		

Notes with the cardiac analysis:
- erudite developmental toxicologists think that effect is spurious
- assessment is based on pup statistics, against EPA guidelines
- BMDL01 is used; not typical choice and several models failed
- high dose dropped


Heart Malformations POD = BMDL
Response
0.05
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
0.0040
0.00037
0
0.005
0.01
0.015
0.02
Concentration ppm
"BMDL based risk"
Linear ("BMDL based risk")

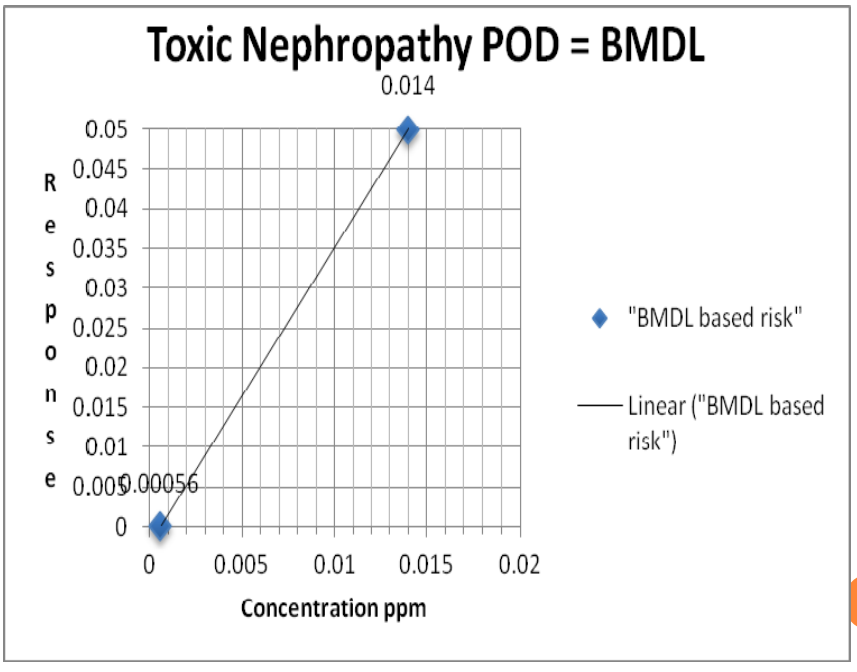

Heart Malformations POD = BMD
Response
0.05
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
0.011
0.00037
0
0.005
0.01
0.015
0.02
Concentration ppm
"BMD based risk"
Linear ("BMD based risk")

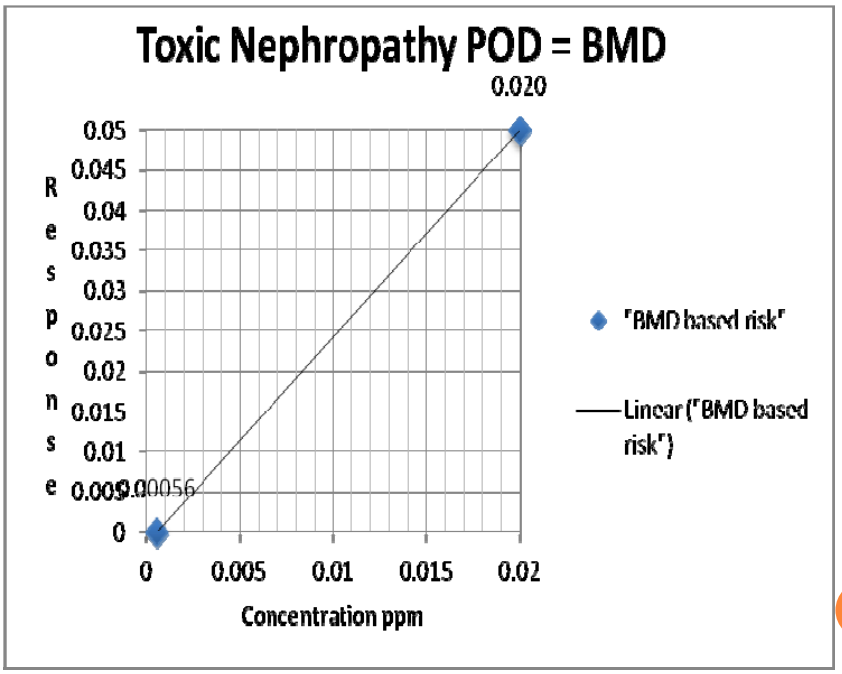
NTP (1988): TOXIC NEPHROPATHY

	Concentration	Response
RfC	0.00056	0
HEC, BMDL/3UFad	0.014	0.05
(EPA, 2011,Figure F-11, page F-30)		
RfC	0.00056	0
HEC, BMD/3UFad	0.020	0.05
EPA, 2011,Figure F-10, page F-29) and EPA, 2011,Figure F-11, page F-30)		

Notes with nephropathy analysis:

- BMDL05 is used; what would BMDL/BMD10 show?
- Risks above the RfC are more severe with nephropathy





ARA Case Study #2: Estimating Risk Above the RfD Using Uncertainty Factor Distributions

- Note: The method does not develop a dose response relationship in humans for the range of interest, because it uses theoretical distributions of uncertainty factors, 3 of which are based on dose groups, and not population response.
- Rather the probabilities are interpreted as the likelihood that the stated RfD is a sensitive human NOAEL, which is the intent of the RfD's definition.
- The probabilities developed have applicability in comparisons among RfDs and/or for determining different RfDs based on different

RESULTS OF METHOD FOR THE RFCS FOR TCE

Calculated 50th, 95th, and 99th Percentile for TCE RfCs in IRIS with Uncertainty Factors of 10 and 100.						
Study	**IRIS UF**	**Confidence**	**IRIS RfC**	**50th %**	**95th %**	**99th %**
Johnson et al. (2003)	10	Medium	**4E-04**	1E-03	**4E-04**	2E-04
NTP (1988)	10	High	**6E-04**	2E-03	**6E-04**	4E-04
Keil et al. 2009	100	Medium	**3E-04**	3E-03	6E-04	**3E-04**

- **BOLD printed entries, either black or red text,** show matches to the appropriate RfC
- Red printed entries show consistency in 95% probability.