How Evolving Science is Improving Safety Assessment of Food Relevant Chemicals

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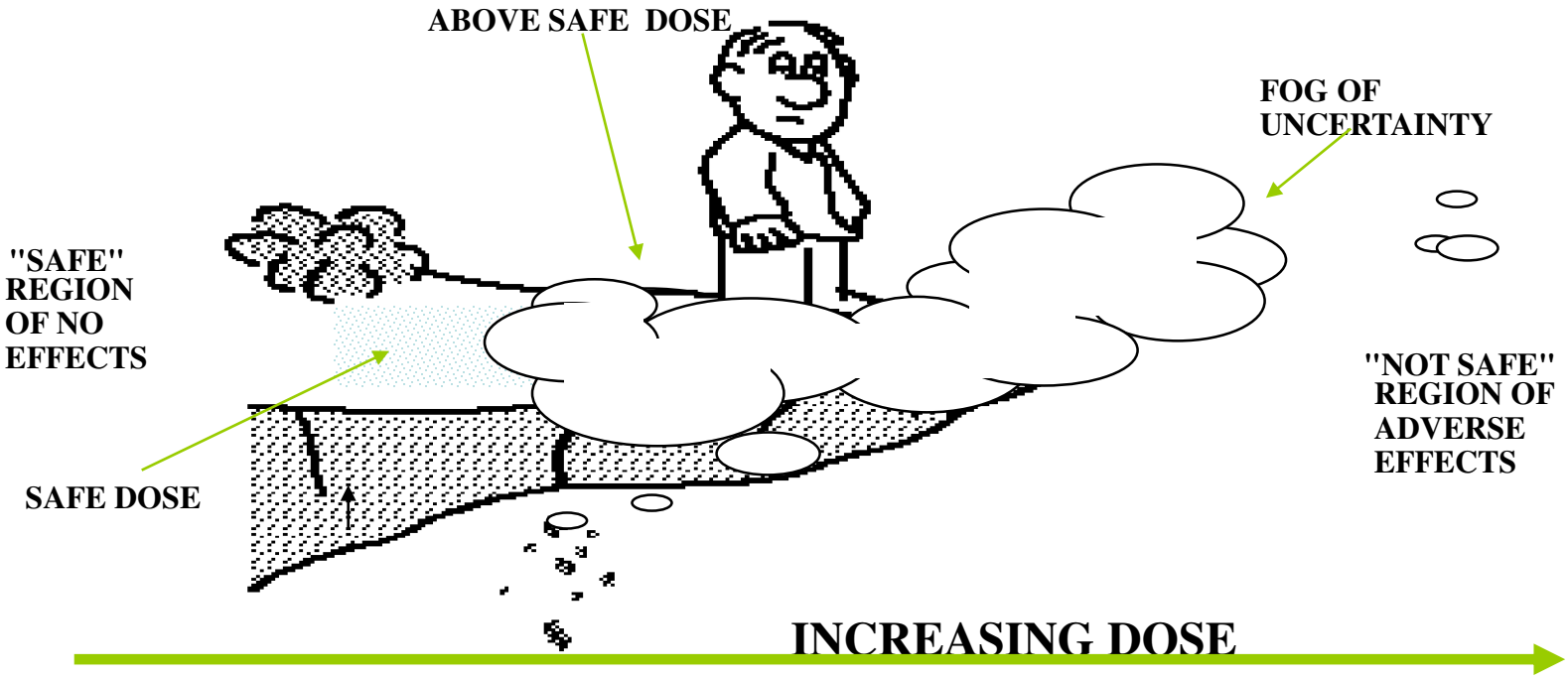
Presentation Objectives

- Identify elements of chemical safety assessment.
- Describe ways improved science is affecting our methods.
- Identify the impacts of these improvements.

The Safety Assessment Process



Assessing Chemical Safety

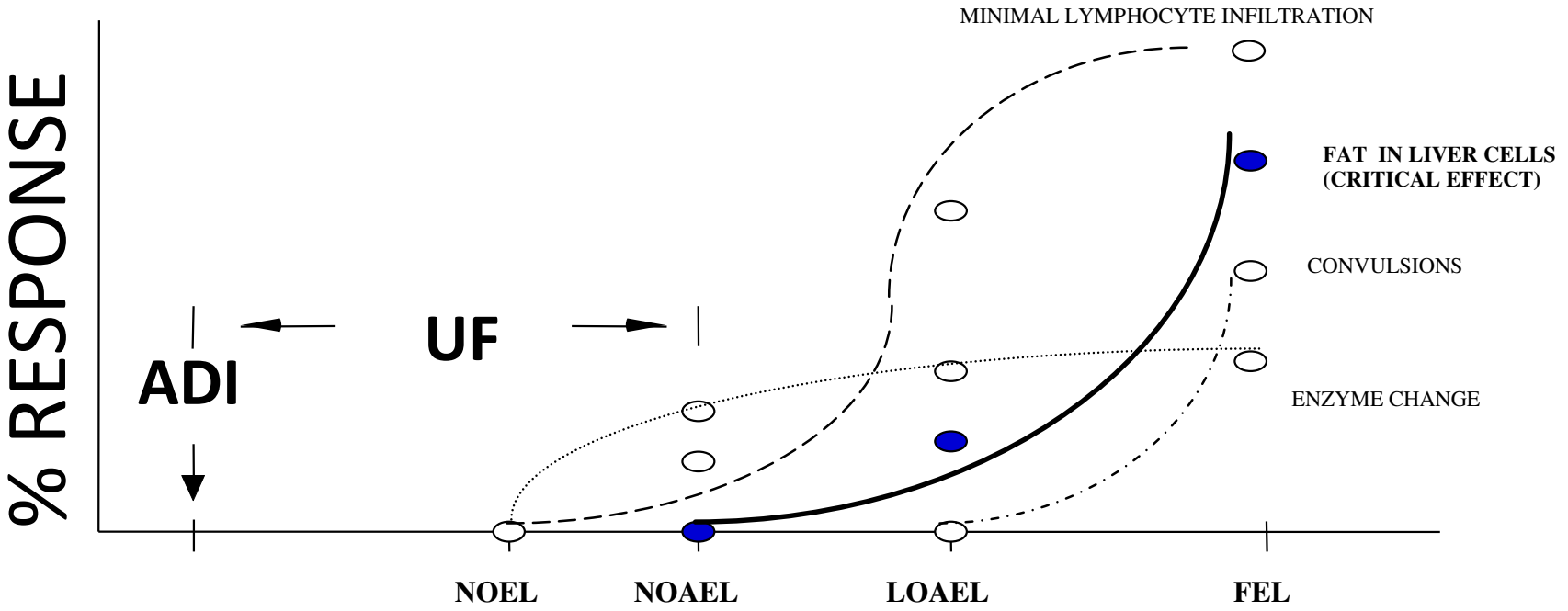
- Evaluate Toxicology data to derive a “safe dose” such as ADI, TDI, etc.

$$\text{Safe Dose (ADI)} = \frac{\text{Dose Response Measure (NOAEL)}}{\text{Uncertainty Factors } (U_A \times U_H \times U_D)}$$

- Characterize risk:

$$\text{Hazard Quotient (HQ)} = \frac{\text{Exposure}}{\text{ADI}}$$

Point of Departure ID



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Areas of Uncertainty

- Interspecies (UF_A) – Are humans more sensitive than the animals used to identify the POD?
- Human variability (UF_H) – Did the POD cover the sensitive population?
- LOAEL to NOAEL (UF_L) – Does the POD estimates a dose with no adverse effects?
- Subchronic to Chronic (UF_S) – Would a lower POD have been seen with a longer study?
- Database (UF_D) – Would additional studies identify a lower POD?

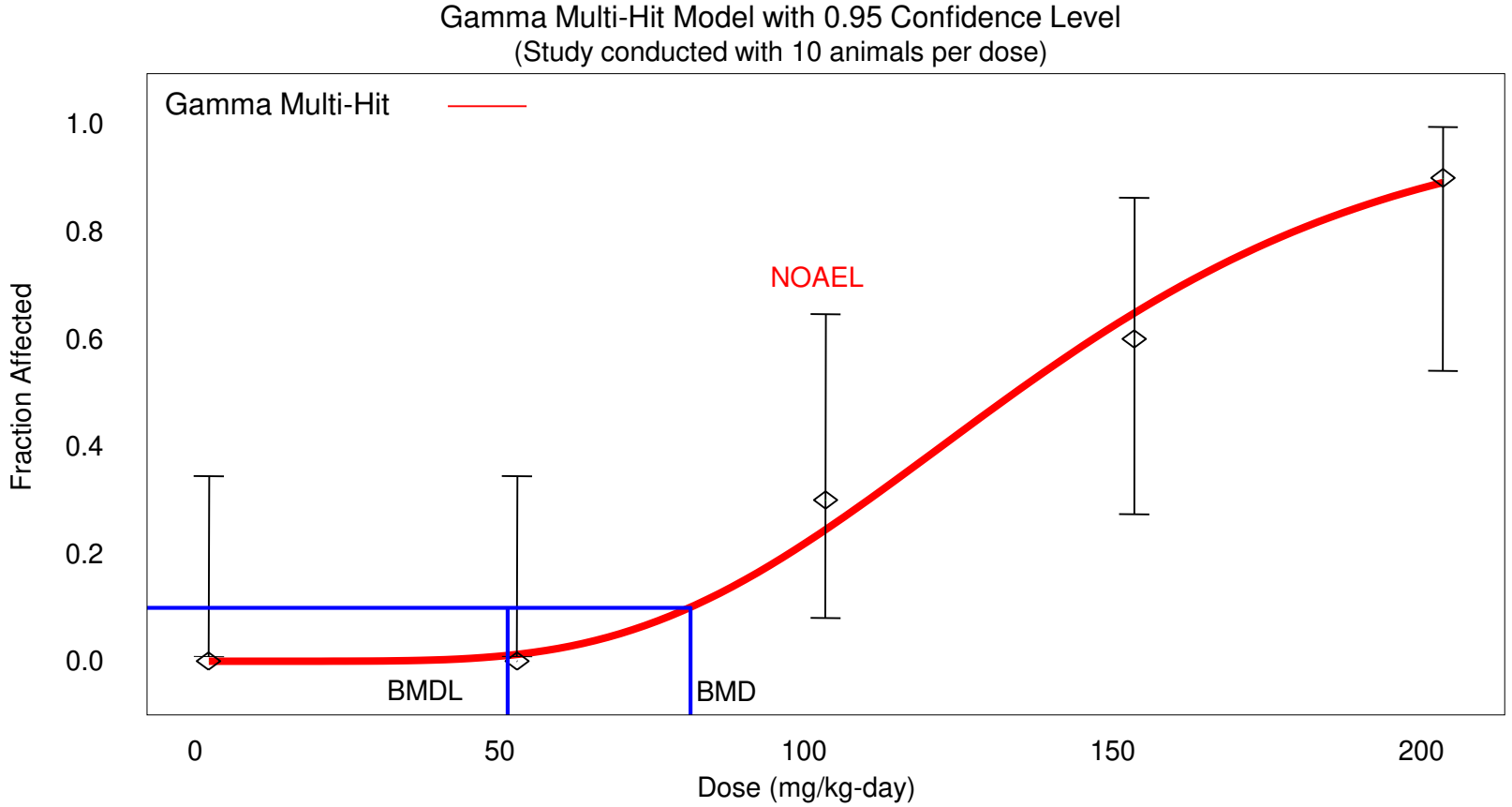
Evolved Safety Assessment

- Better statistical estimation of the PoD.
- Using biology understanding to address uncertainty in dose-response.
- Using chemistry to fill data gaps.

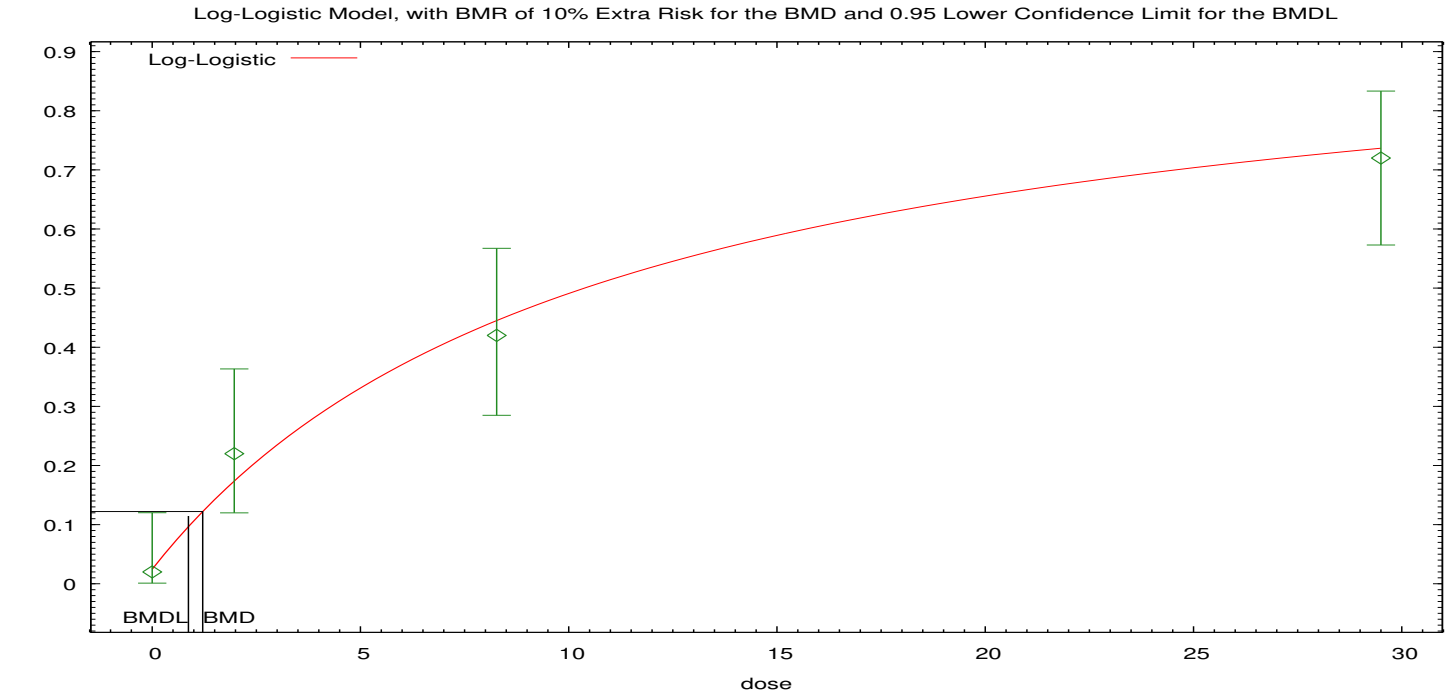
3-MCPD Assessment

- 3-Monochloropropane-1,2-diol is a contaminant formed primarily through the refining of edible oils.
- Five groups used the BMD approach to derive a Tolerable Daily Intake (TDI).
- All of these groups based their TDIs on the same study (Cho et al. 2008), which reported kidney hyperplasia.

Benchmark Dose Modeling



3-MCPD Renal Hyperplasia



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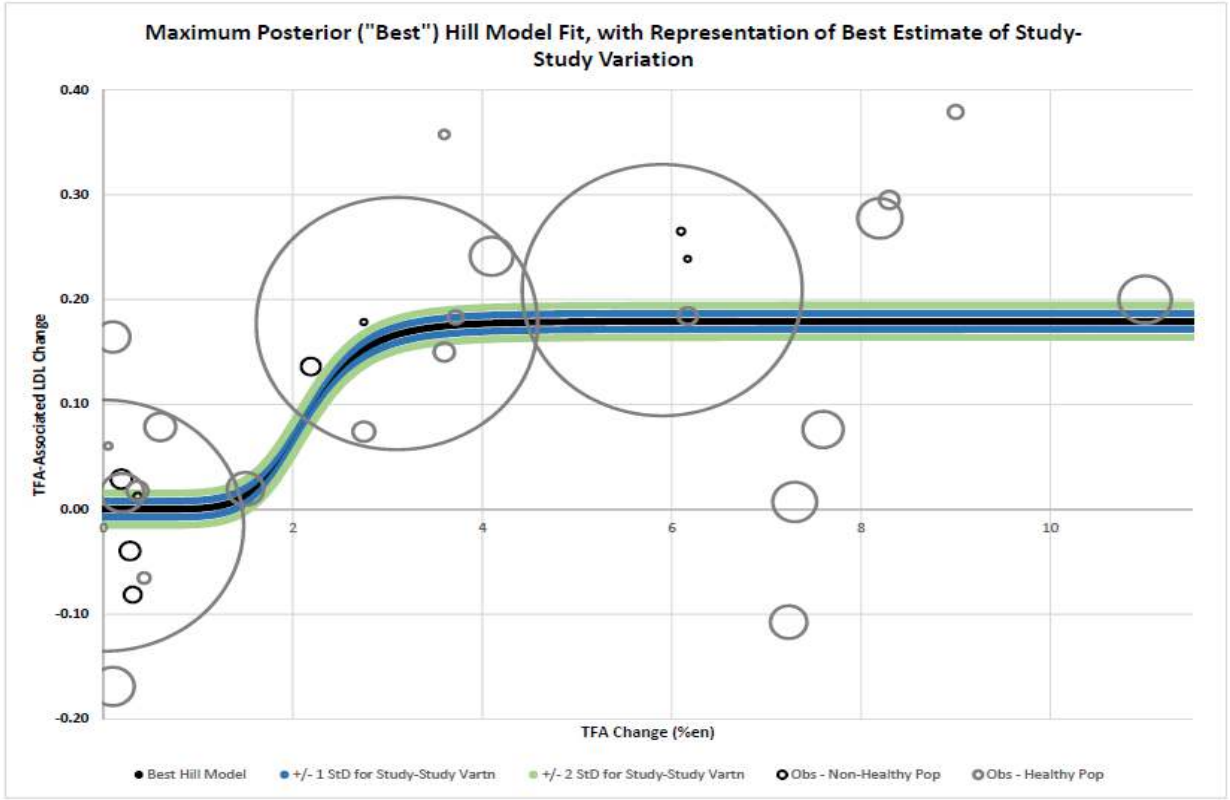
BMD and Resulting TDI

	Haber 2018	Haber 2018	EFSA 2016	EFSA 2018	JECFA 2016
BMD (mg/kg-day)	1.2		0.54		1.2
BMDL (Mg/kg-day)	0.87	0.74	0.077	0.2	0.87
TDI (ug/kg-day)	9.0	7.0	0.8	2.0	4.0
Model	Log-logistic (restricted)	Model averaging	Gamma (unrestricted)	Model averaging	Log-logistic (restricted)
Dose-response for renal effects reported in Cho et al. (2008).					

MCMC Analysis of Effect of Trans-fatty Acid on Serum LDL-C

- Markov Chain Monte Carlo Analysis – a probabilistic, Bayesian approach to fit the models
- Allows calculation of bounds.
- Allows consideration of a wide universe of combination of model parameters.
- Used the LDL-C values adjusted for predicted change in LDL-C, based on the fatty acid content of that diet (Yu et al., 1995).

Effect of TFA Intake on LDL-C



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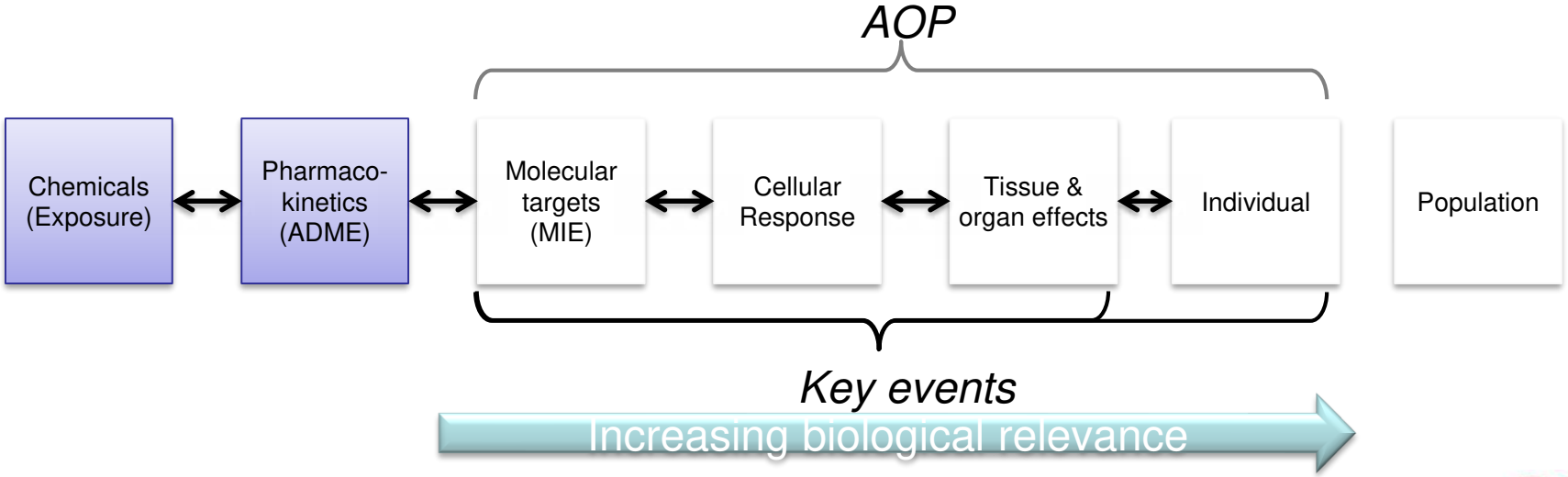
Adverse Outcome Pathway

OECD: AOP is a causal chain of biochemical and biological events that starts with a molecular initiating event (MIE), progresses though one or several key events, culminating in an adverse outcome at a biological level relevant for risk assessment.



EPA 2011; Ankley et al. 2010.

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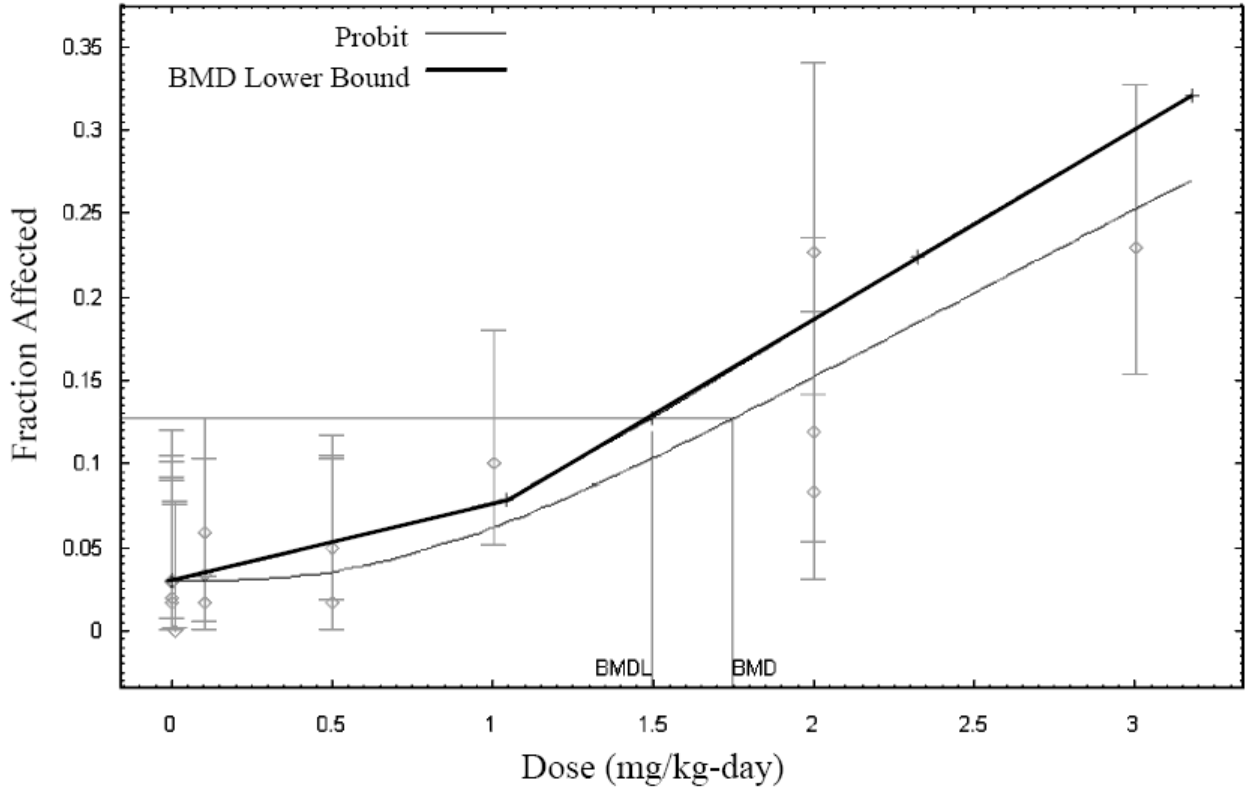
Acrylamide Assessment

- Acrylamide is present in heated carbohydrates.
- Demonstrated tumorigen in rodents, but the mode of action uncertain.
  - Direct reactivity of metabolite with DNA?
  - Oxidative stress by reducing cellular GSH?
  - Modified hormone metabolism?
- California Prop 65 limit for product labeling in debate.
- Mode of action concept improved addressing low dose – response prediction to include complex biology.

Probit model fitted to pooled-all thyroid tumor data, showing differing slopes between the low and high dose regions.



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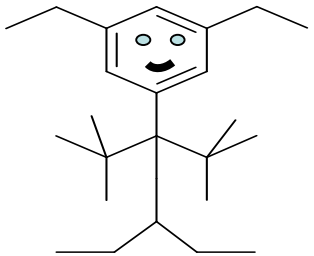
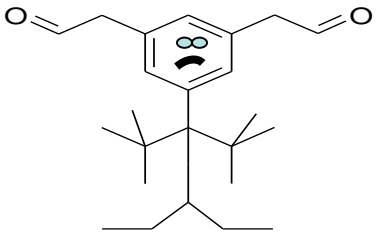
Distinguish between Safe and Toxic?





Many potential features

- Structural fragments
- Chemical/physical properties
  - Log Kow
- Molecular properties
  - Electronic States
  - Interatomic Distance

Many tools

- Statistical tools (OECD)
- Expert systems (DEREK)

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Handling Butter Flavors

- Not identified as a concern as a food ingredient – oral toxicity minimal.
- Workers respiratory disease –attributed to diacetyl.
- inhalation based limits for workers that range from 5 ppb to 200 ppb in air.
- Emphasis on diacetyl caused desire to *identify* substitutes with lower toxicity using read across approach.

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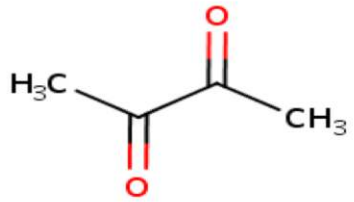
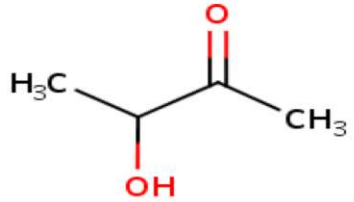
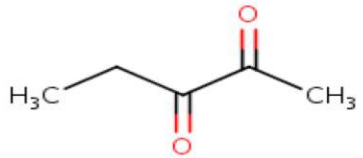
Equal Toxic Potency?

Substance Name	CAS	Structure/SMILES
2,3-butanedione	431-03-8	CC(=O)C(=O)C 
2-butanone, 3-hydroxy-	513-86-0	CC(O)C(=O)C 
2,3-pentanedione	600-14-6	C(C(C)=O)(CC)=O 

Conclusions

- Traditional approaches (NOAEL/UF) have served us well for an adaptable approach to assess food relevant chemical safety.
- New science and technology has allowed us the ability to refine the assessment methods.
- *Impact*: Reduced uncertainty and Increased confidence.

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Questions

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