Dioxin MOA Update:

"Dose-Response Approaches for Nuclear Receptor-Mediated Modes of Action Workshop"

Bob Budinsky

Oct. 27, 2010 SAB Meeting

July 13 Comments on MOA

- EPA incorrectly rejected the MOA
- EPA failed to follow their own MOA Framework Guidance (2005 Cancer Guidelines)
- Dioxin-induced carcinogenicity in rodents is a biologically based, threshold phenomenon
- Clarification: MOA should not be confused with mechanism

Nuclear Receptor MOA Workshop

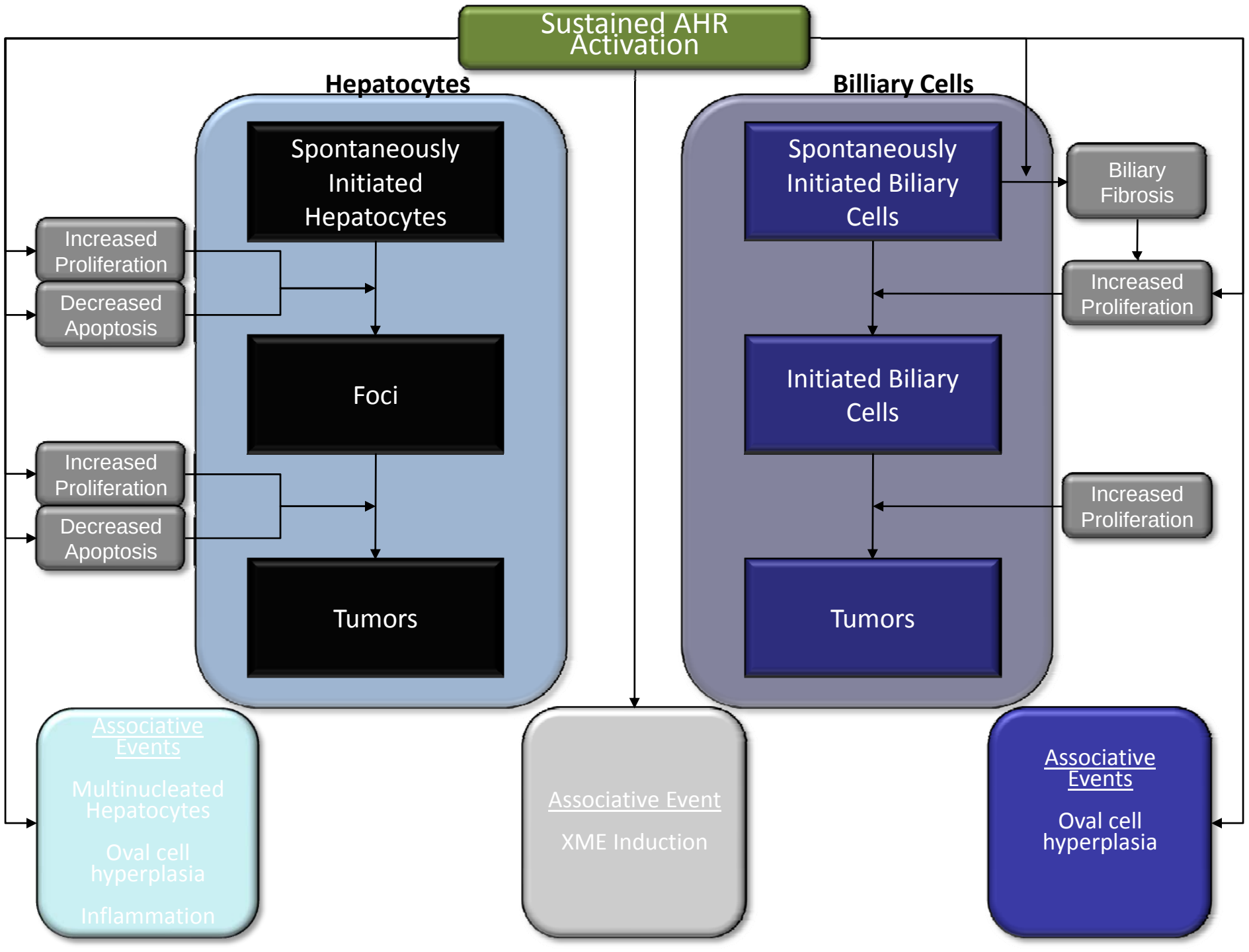
- Sept 27-29th at NIEHS
- Meeting Chairs: Julian Preston (EPA) and Mel Andersen (Hamner Institute)
- Purpose: To assess MOA and dose-response modeling of nuclear receptors
- 3 Case Studies: CAR/PXR, PPARα, and AHR

AHR Expert Panel Members

Chairs: Dieter Schrenk (*Univ. of Kaiserlautern*) and Bob Budinsky (*Dow Chemical*)

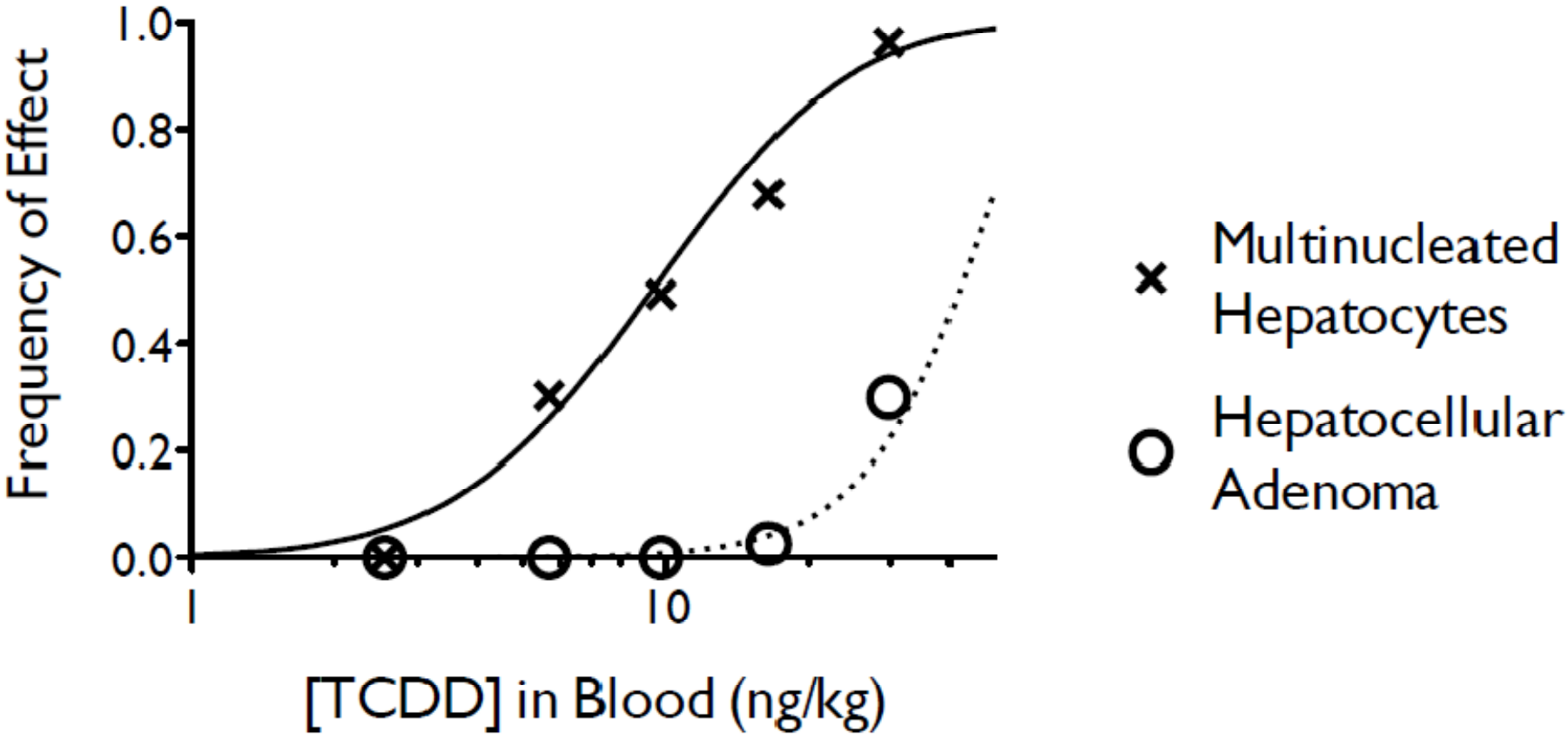
- Bruce Allen (Allen Consulting)
- Lesa Aylward *(SummitToxicology)*
- Amy Brix *(EPL)*
- Tom Gasiewicz *(Univ. of Rochester)*
- Norb Kaminski *(Mich State)*
- Gary Perdew *(Penn State)*
- Ted Simon *(Ted Simon, L.L.C.)*
- Tom Starr *(TBS)*
- Jay Silkworth *(General Electric)*
- Nigel Walker *(NIEHS)*
- Martin van den Berg *(Univ. of Uetrecht)*
- Presenters
  - Craig Rowlands *(Dow)*
  - Rusty Thomas *(Hamner)*
  - Mel Andersen *(Hamner)*

Andy Maier (TERA): Rapporteur


Sustained AHR Activation
Hepatocytes
Billiary Cells
Spontaneously Initiated Hepatocytes
Increased Proliferation
Decreased Apoptosis
Foci
Increased Proliferation
Decreased Apoptosis
Tumors
Spontaneously Initiated Biliary Cells
Biliary Fibrosis
Increased Proliferation
Initiated Biliary Cells
Increased Proliferation
Tumors
Associative Events
Multinucleated Hepatocytes
Oval cell hyperplasia
Inflammation
Associative Event
XME Induction
Associative Events
Oval cell hyperplasia

Dose Response Example: Hepatocellular Cancer Key Event

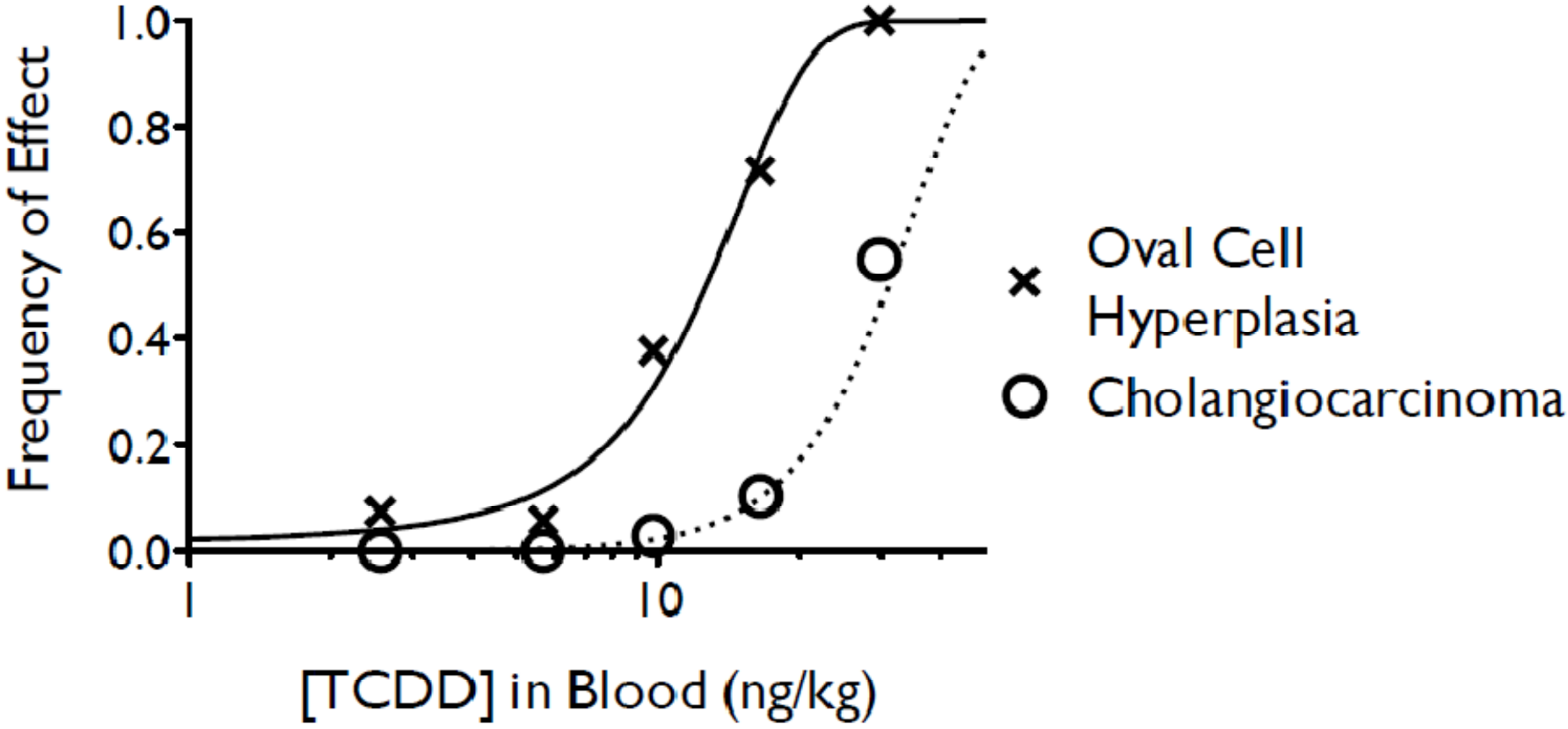
Multinucleated Hepatocyte RfD: 2 – 70 pg/kg/day (UFs: 1.0 – 30)
Hepatocellular Cancer RfD: 20 to 600 pg/kg/day (UFs: 1.0 – 30)



based on Simon et al., 2009

Dose Response Example: Biliary Cancer Key Event

Oval Cell Hyperplasia RfD: 0.8 to 20 pg/kg/day (UFs: 1.0 – 30)
Biliary Duct Cancer RfD: 10 to 300 pg/kg/day (UFs: 1.0 – 30)



based on Simon et al., 2009

Summary

- A MOA can be established for dioxin by applying the IPCS and 2005 EPA MOA Framework – this was done in the Nuclear Receptor-MOA workshop
- Significant number of dose-response studies for Key Events and Associative Events
- Threshold nature of sustained AHR-activation culminating in Key Events and Associative Events leading to liver tumors in rats and mice.