Mode of Action Analysis: Organizing Questions, Tabular and Graphical Tools

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Questions for Organizing MOA Consideration

- What is the MOA to be evaluated by the IPCS Human Relevance Framework and modified Bradford Hill considerations?
- Which events are truly causal or key events (KE)?
- Which events are associative events?
- What are the modulating factors?
- Is the proposed MOA relevant to humans?

Questions for Considering Dose-Response

- Are extant data sufficient for establishing dose response relationships for proposed KEs?
- Are extant data sufficient for DR modeling of proposed KEs? Are there data gaps?
- Does the current understanding support a threshold or non-threshold DR and low dose extrapolation approach?
- On either theoretical or practical grounds, is there a dose or AUC level insufficient for KEs or the AO?

KE, key event; DR, dose response; AUC, area under the curve; AO, adverse outcome

Questions for Considering the AO or precursor KEs

- Does the weight-of-evidence suggest an appropriate model or approach for the dose-response assessment?
- If so, what are the key data gaps? What data would have the highest value?

Three Proposed MOA Schemes

Table 4. Strawmen of PPARα mode of action key events.

Proposed mode of action of rodent liver tumors of PPARα activators			
	Strawman 1: taken from Corton (2010)	Strawman 2	Strawman 3: (taken from Klaunig et al., 2003)
KE #1	PPARα activation	PPARα activation	PPARα activation
KE #2	Increases in oxidative stress	Altered expression of genes involved in cell growth	a. Expression of peroxisomal genes b. PPARα mediated expression of cell cycle, growth and apoptosis c. Non-peroxisomal lipid gene expression
KE #3	NF-κB activation	Increased cell proliferation/decreased apoptosis	Increase in cell proliferation
KE #4	Increased cell proliferation/decreased apoptosis	Selective clonal expansion of preneoplastic foci cells	Clonal expansion of preneoplastic foci
KE #5	Increases in preneoplastic foci cells	Liver tumors	Liver tumors
KE #6	Liver tumors		

From Corton et al. 2013. Crit Rev Toxicol DOI: 10.3109/10408444.2013.835784

Table 5. Occurrence of key events in the mode of action after exposure to PPARα agonists in rats.

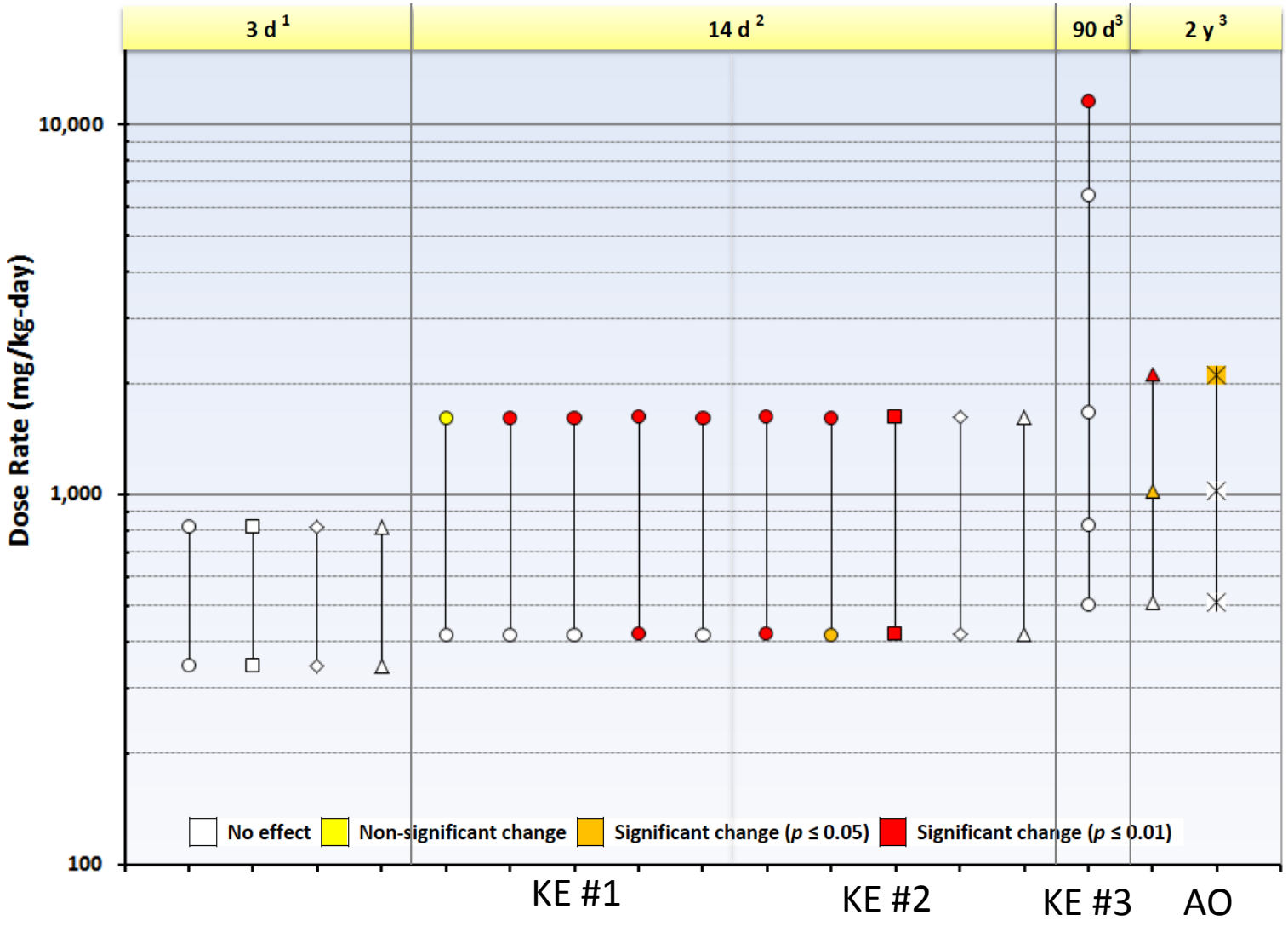
	Key events								
	KE#1	KE #3			KE#4	Modulating factors			Apical end point
Chemical	PPARα activation	Perturbation of cell growth and survival: Increases in transient acute cell proliferation	Perturbation of cell growth and survival: Decreases in acute apoptosis	Perturbation of cell growth and survival: Increases in chronic cell proliferation	Clonal expansion of preneoplastic foci	Oxidative stress	NF-κB activation	Alterations in gap junctions	Hepatic tumors
WY-14,643	+[1]	+[2]	+[3]	+[4]	+[5]	+/−[7,8]	+[9]	+[53]	+[6]
DEHP	+[10]	+[11]	+[12]	+/−[13]		+/−[14,15]		+[50]	+[14]
Clofibrate	+[16]	+[17]		+[18]		+/−[20,21]			+[19]
Nafenopin	+[22]	+[6]	+[23]	+/−[24,6]	+[25]	+/−[27,28]	−[29]	+[52]	+[26]
Ciprofibrate	+[22]	+[30]		+[31]	+[32]	+[34]	+[35]		+[33]
Methyl clofenapate		+[36]	+[37]	+[38]		+/−[39,40]			+[39]
Gemfibrozil (CI-718)	+[22]	+[57]			−[41]	+[42]	+[43]		+/−[41]
Di-n-butyl phthalate	−[10]					+[44]	+[43]		
Trichloroacetate	+/-[55]							+[54]	−[45]
Perfluorooctanoate	+[56]	+[46]				+/−[48,49]		+[51]	+[47]

Comments: In the table, (+) indicates that the chemical was found to lead to the event; (–) indicates that the chemical was found not to lead to the event; (+/–) indicates mixed results. PPARα activation was measured using transactivation assays. NF-κB activation refers to binding of NF-κB (p65:p50 heterodimer) to the NF-κB response element in electrophoretic mobility shift assays. Acute cell proliferation was measured in the livers of treated mice, usually with seven days or less of exposure. Apoptosis was mostly measured in primary hepatocytes, given the low background in intact livers. However, three studies have measured apoptosis in rodent livers after exposure to a PPARα agonist (Bursch et al., 1984; James et al., 1998a; Youssef et al., 2003). Chronic cell proliferation was measured in the livers of rats exposed to PPARα agonists, usually for more than three weeks.

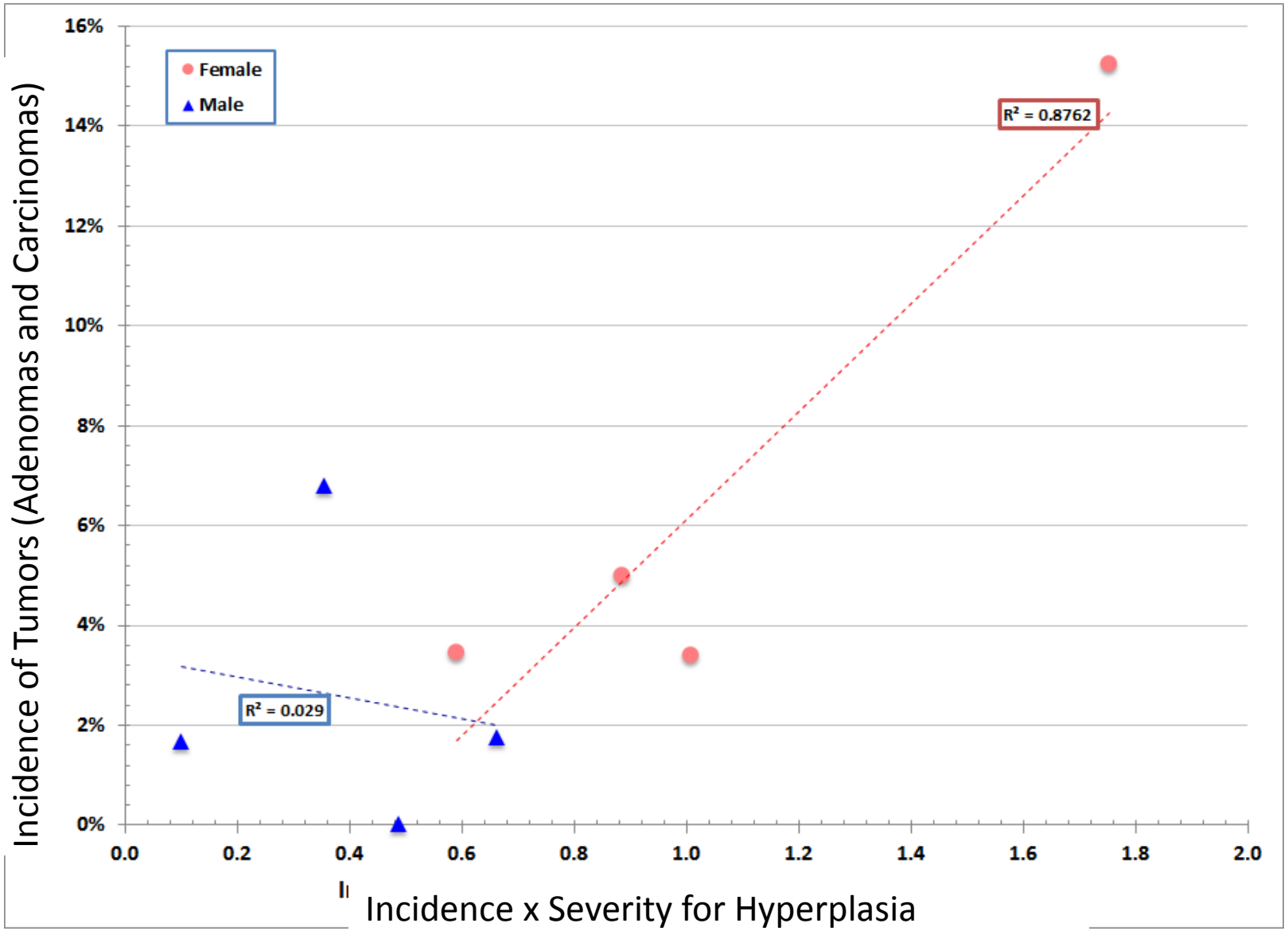
References:

1. Corton & Lapinskas, 2005; Gottlicher et al., 1992
2. Wada et al., 1992; Marsman et al., 1988, 1992; Lake et al., 1993
3. Youssef et al., 2003
4. Wada et al., 1992; Marsman et al., 1988, 1992; Lake et al., 1993
5. Marsman & Popp, 1994; Rose et al., 1999b
6. Lake et al., 1993

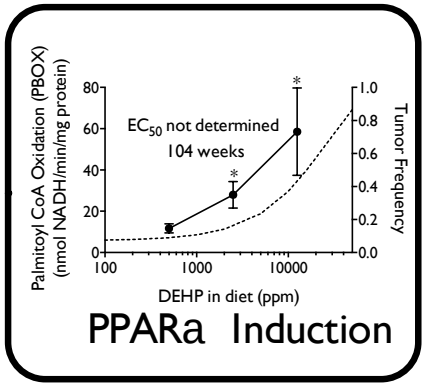
Dose Range Array

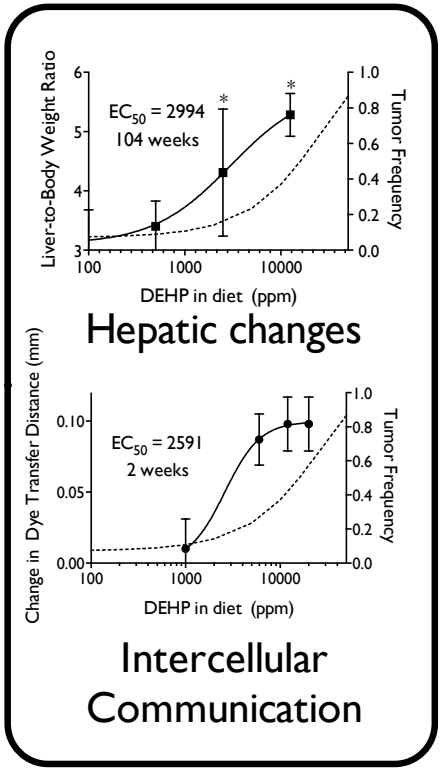


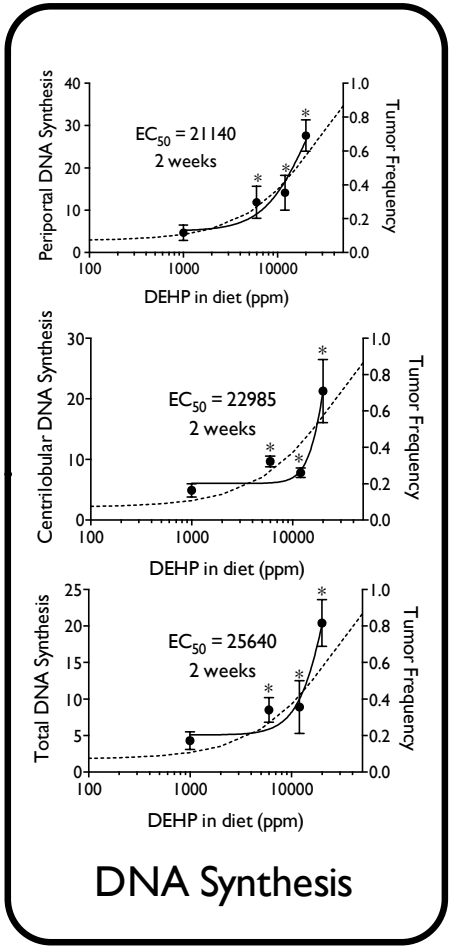
Correlation of KE with AO

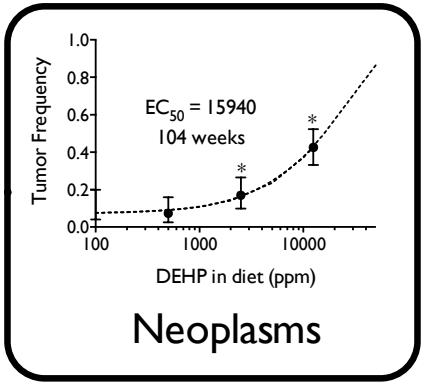


Comparison and Ordering of Dose-Response of KEs









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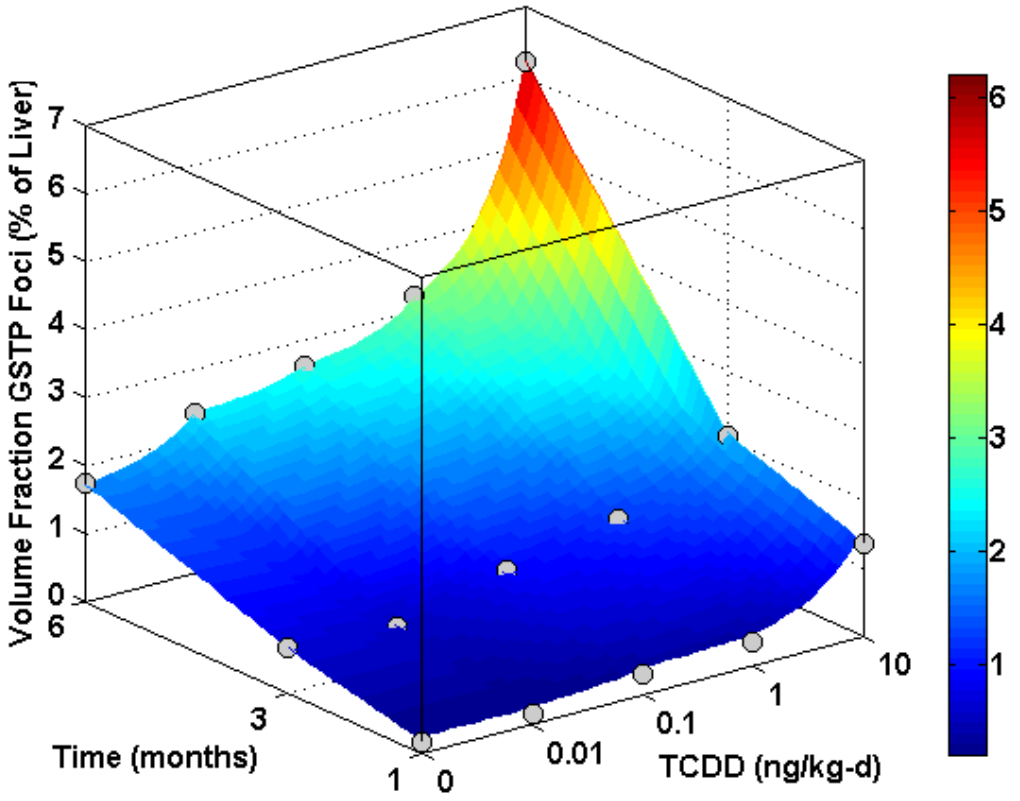
3D Graphs in Dose and Time



From Budinsky et al. 2013. Crit Rev Toxicol DOI: 10.3109/10408444.2013.835787

Summary

- Presenting MOA information in IRIS assessments in a credible fashion is important
- MOA is the central concept in the 2005 Cancer Guidelines
- Variety of ways to present data both in tables and in graphics
- The work of Edward Tufte may help conceiving effective data presentation methods
  - *The Visual Display of Quantitative Information*
  - *Visual and Statistical Thinking: Displays of Evidence for Making Decisions*