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Vanderbilt University School of Medicine Career Symposium

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Office of Research and Development
National Center for Environmental Assessment

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United States Environmental Protection Agency

The views expressed in this presentation are those of the author and do not necessarily reflect U.S. EPA policy.

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How does one get from here...

...to here?

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Academic Background

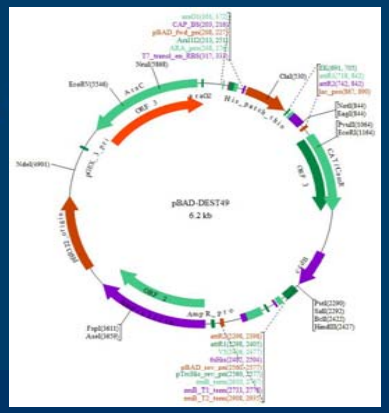
- Elizabethtown Community College (1993-1996)
  - Biology/Chemistry
  - Lab technician-Anatomy and Physiology
- Western Kentucky University, B.S. (1996-1998)
  - Double major: Recombinant Genetics/Chemistry
  - Lab technician in Molecular Biology lab
- University of Louisville (1998-2002)
  - M.S. (2001)
  - Ph.D. (2003)

Activities as a Graduate Student

Of course, classes…

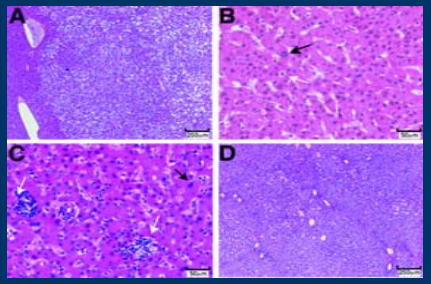
	Credit Hours earned
– Biochemistry I	4.0
– Biochemistry II	4.0
– Molecular Biology	4.0
– Systemic Physiology	6.0
– Topics in Pharmacology and Toxicology	3.0
– Principles of Drug Action	3.0
– Medical Pharmacology and Toxicology	7.0
– Research in Toxicology**	32.0
– Toxicology Seminar	4.0

- Pubs: Lambert et al., TAAP (2001); Lambert et al., Exp Biol Med (2003); Lambert et al., JPET (2003); Lambert et al., Am J Pathol (2003)
- OVSOT, SOT, Research Louisville, Cancer Center retreat
- Local seminar series (not just home department)



UofL

WKU



Post-Doc (2003-2004)

Phone call (Aug 2004)

U.S. EPA
ORISE Fellow
(2005-2006)

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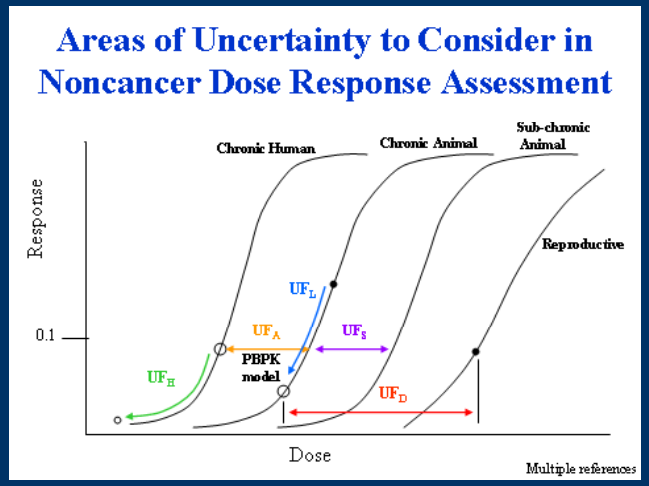

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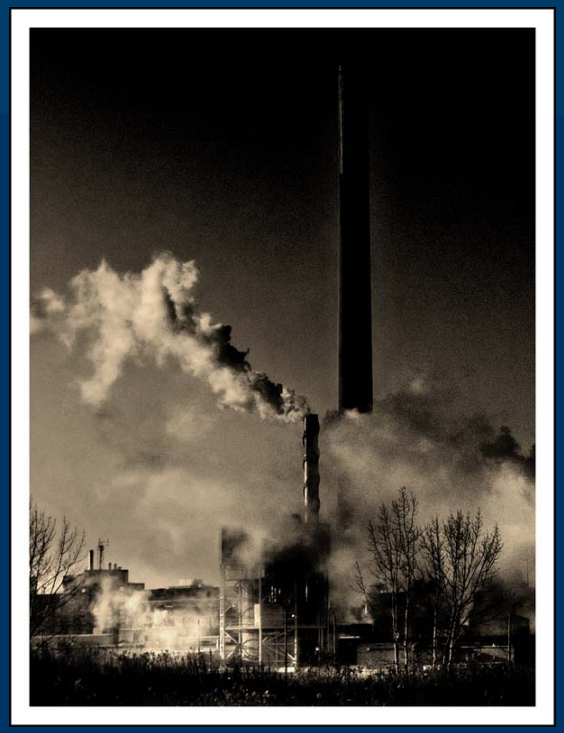

What in the world is human health risk assessment?

Where does my experience/skill set fit in?

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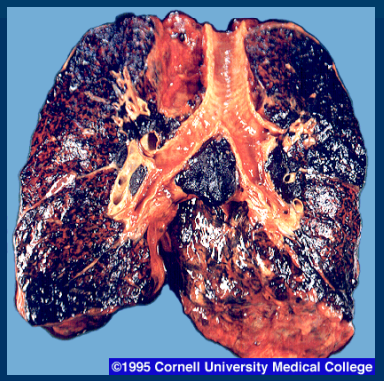
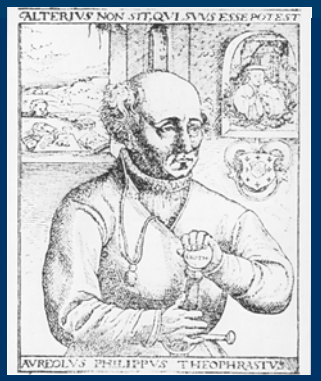
What should we be most worried about?

What is the dose-response for such an effect?





**"All things are poison
and nothing is without poison,
only the dose permits something not to be poisonous."**

Well then, what is the extent of our exposure?

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Hazard Identification

- Is the chemical a toxicant? What does it do?
- Under what conditions? Durations?
- By what routes of exposure?
- Data from various sources
- Quality of the data
- Weight-of-Evidence (WOE) Determination

- **Human**
  - Occupational epidemiology studies
  - Controlled clinical studies in volunteers
- **Animal**
  - Non-human primates, rabbits, rodents, etc.

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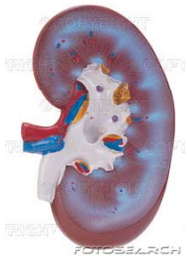
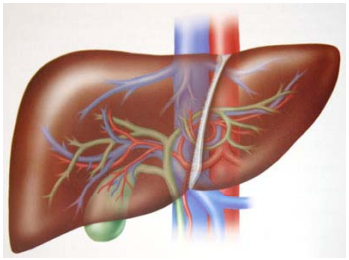
	No effects observed	proteinuria	proteinuria, ↑BUN, GFR decrements	↑↑proteinuria, hematuria, ↑↑BUN, GFR decrements, necrosis of proximal tubules, widespread droplet formation
	2% ↑ weight	↑ALT, AST, 5% ↑ weight, cytomegaly	↑↑ALT, AST, 11% ↑ weight, cytomegaly and necroinflammatory foci	↑↑↑ALT, AST, 16% ↑ weight, ↑↑ necroinflammatory foci and centrilobular hemorrhaging; 3/20 animals died

Dose

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Non-Cancer

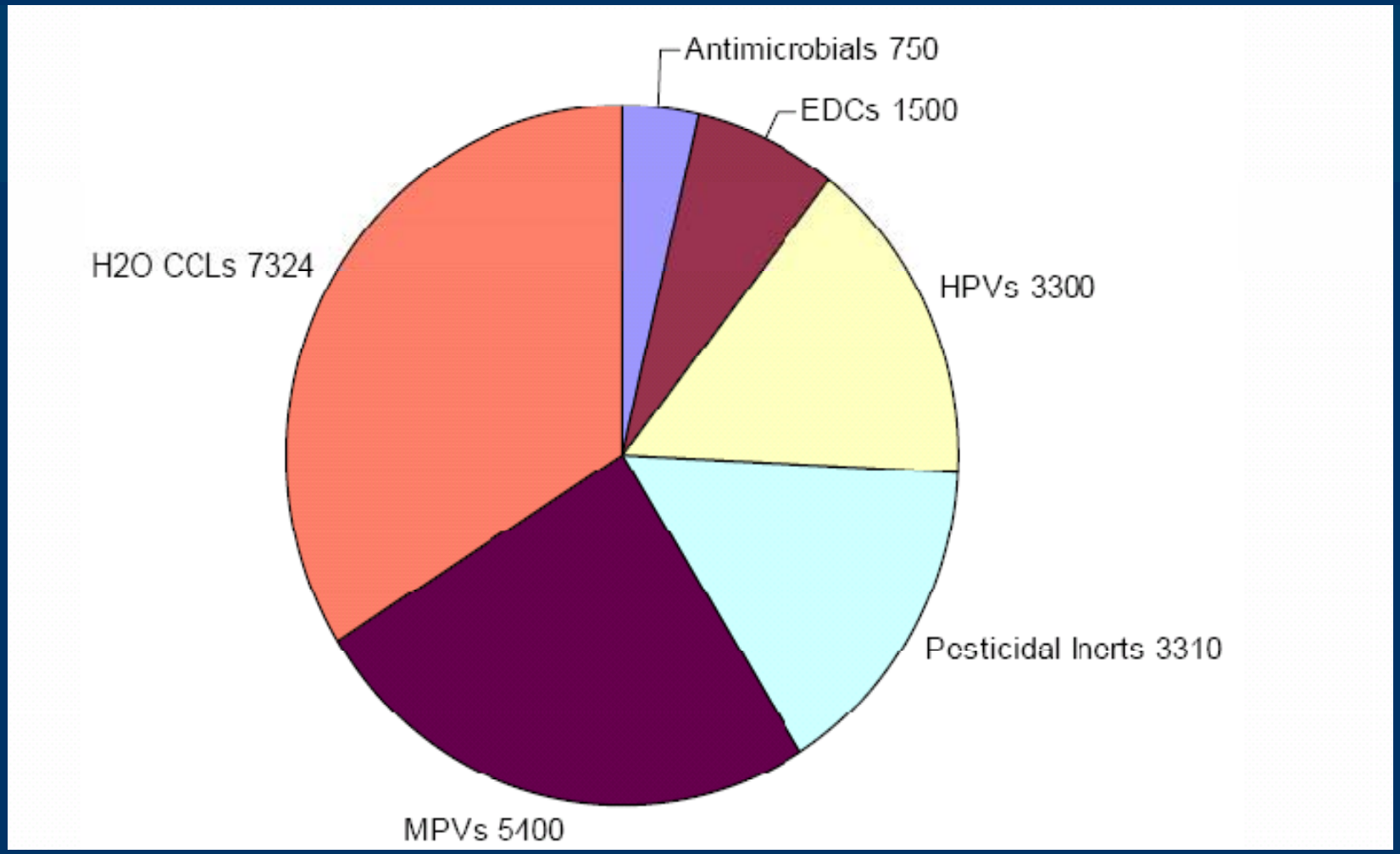
Reference Value (RfV): An estimate of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime.

Cancer

Slope Factor: An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent.

*Future considerations for the Risk Assessment paradigm

>10,000 Chemicals in Need of Evaluation



(Dix et al., *Tox Sci*, 2007)

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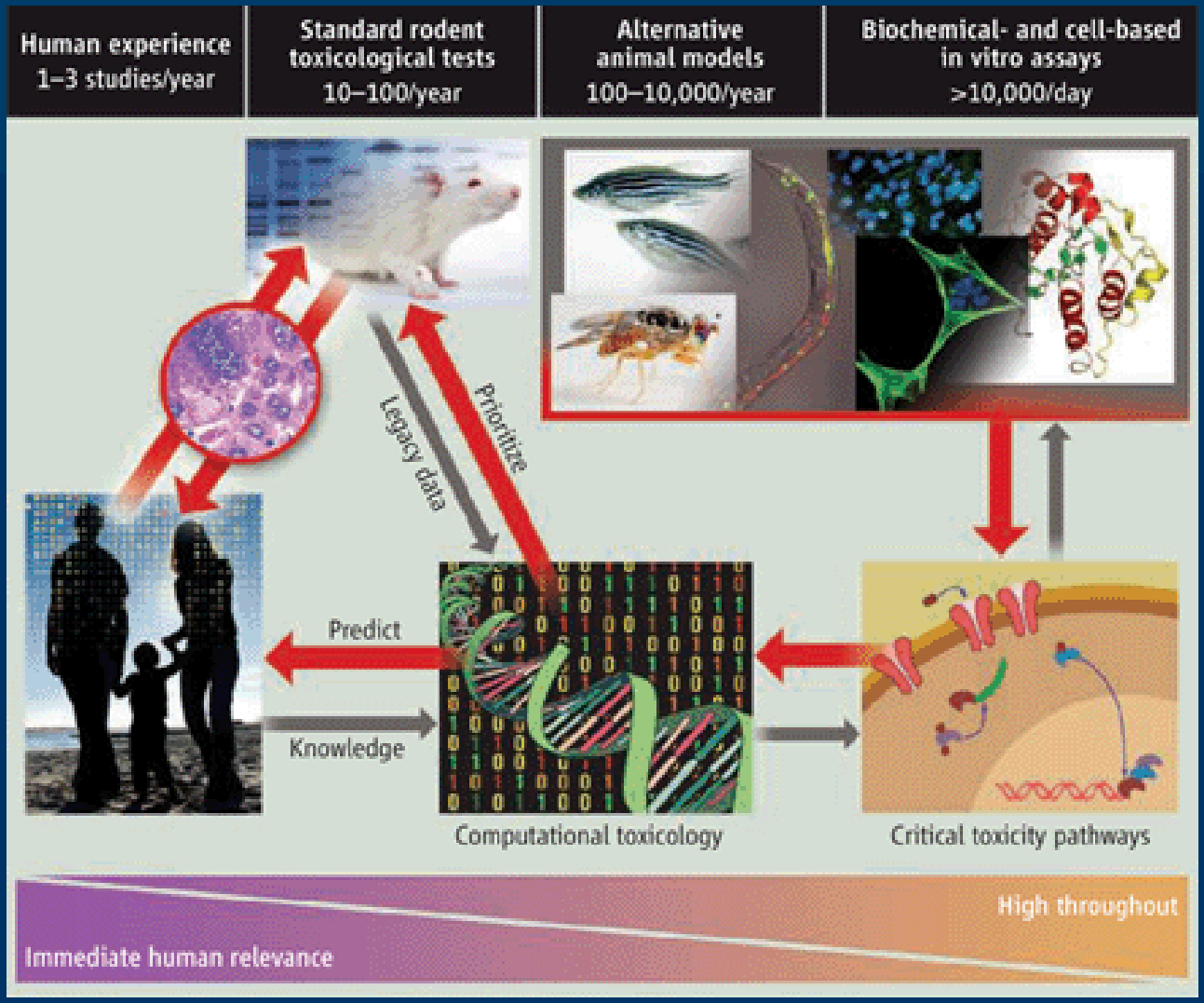
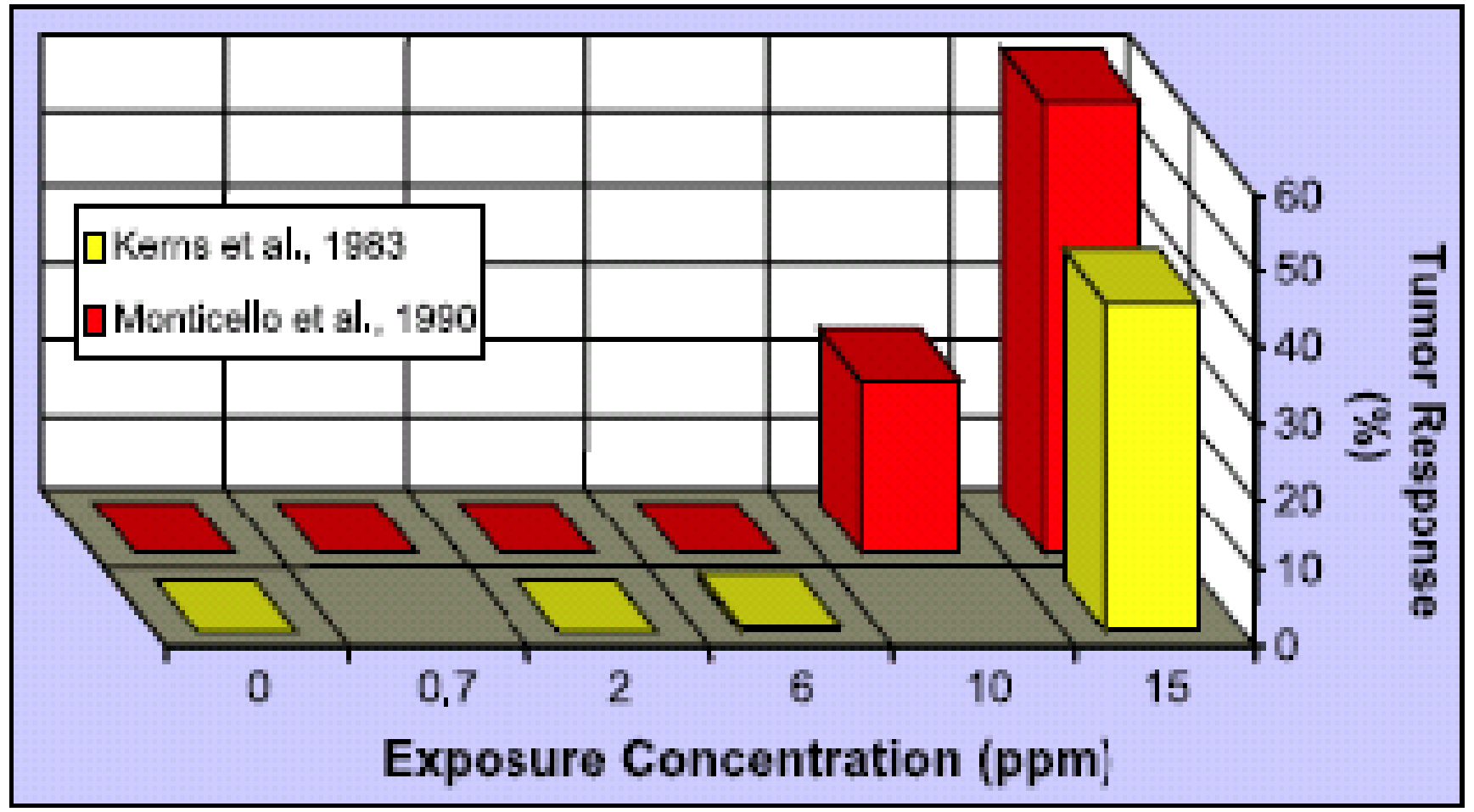


(Collins et al., *Science*, 2008)



Formaldehyde tumorigenicity in rats via the inhalation route

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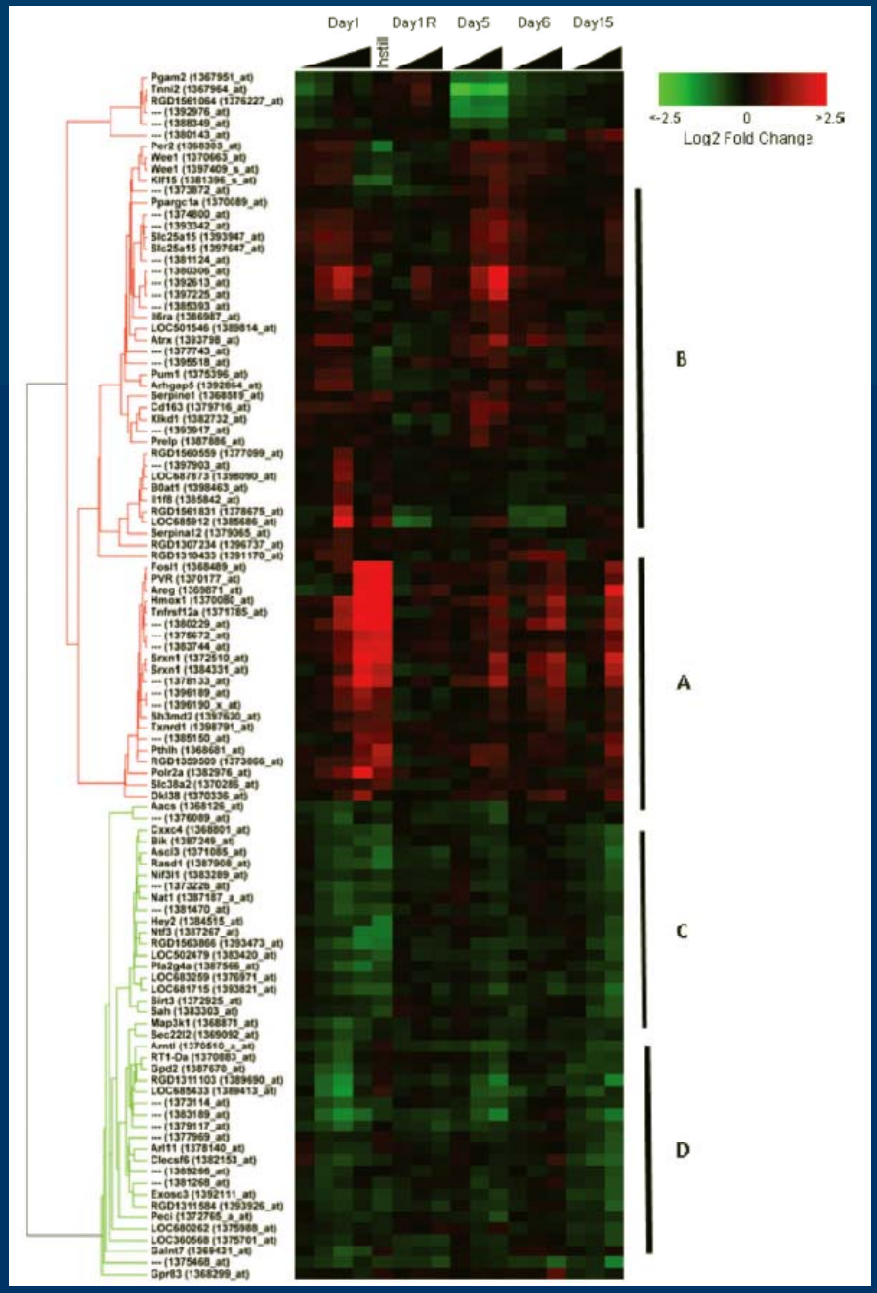
TABLE 6
Numbers of Genes in Level II Nasal Epithelial Tissues Significantly Altered by Formaldehyde Treatment Based on Microarray Analysis

Group	0.7 ppm	2 ppm	6 ppm	15 ppm	Instillation
Day 1	0	1	42	745	2553
Day1 recovery	0	0	0	—	—
Day 5	0	15	28	—	—
Day 6	0	0	9	—	—
Day 15	0	0	54	—	—



(Andersen et al., *Tox Sci*, 2008)

"The core of the committee's vision for the future involves the mapping of toxicity pathways in human tissues, and the identification of critical pathway perturbations responsible for toxic responses."

"Dose-response relationships for pathway perturbations can then be described quantitatively through biologically-based modeling of toxicity-pathway circuitry and human pharmacokinetics."

"When the vision is fully implemented, regulation will be based on avoidance of biologically significant perturbations of key human toxicity pathways, rather than on the current practice of assessing human health risks based on high-dose responses in animals and the use of questionable assumptions to extrapolate such findings to low-dose risks in people."

--NRC, 2007

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Hired on as full-time federal employee (Feb. 2007)

Challenges

- Balancing science with science policy
- Finding time to publish external to EPA
- Staying on top of newest developments in bench science/field(s)

Advantages

- Job Security!! If I do the work, I can stay as long as I like (what a concept)
- Exposure to sharp scientific professionals with skill sets very different from my own
- Work products have immediate impact (truly is applied toxicology)

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Setting yourself up for success

- Pro-active Academic and Research Collaborations
- Publish- not just prototypical original research articles; concepts/perspectives, reviews (demonstrate expertise)
- Get involved- don't just attend, but rather, "participate" in local, regional, and national meetings
- Serve the science: volunteer to review journal submissions, grant apps, etc.
- Students: The 4-5 year goal (earn PhD) is known; be smart about interim goals
- For post-docs: your interim goal is to not be a post-doc; make the hard choices (academia/industry/govt); identify a path forward (approx. 2-3 years) and network hard

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Knowing is half the battle

http://www.usajobs.opm.gov/

http://orise.orau.gov/science-education/internships-scholarships-fellowships/default.aspx