Alternative Testing: Back to the Future

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Where We Are Headed

- Setting the Stage
  - The Problem and the Solution
- Beyond Science
  - Lines of Influence
- Looking Back
- Looking Around
- Looking Forward

The Problems

- Cost
- Time
- Impac

Test	Species	Number of Animals
Acute Toxicity (Inhalation)	Rat	40
90-Day Subchronic (inhalation)	Rat	80-120
Carcinogenicity	Mouse	400
Developmental Neurotoxicity	Rat	1280
2-Generation Reproductive	Rat	2600

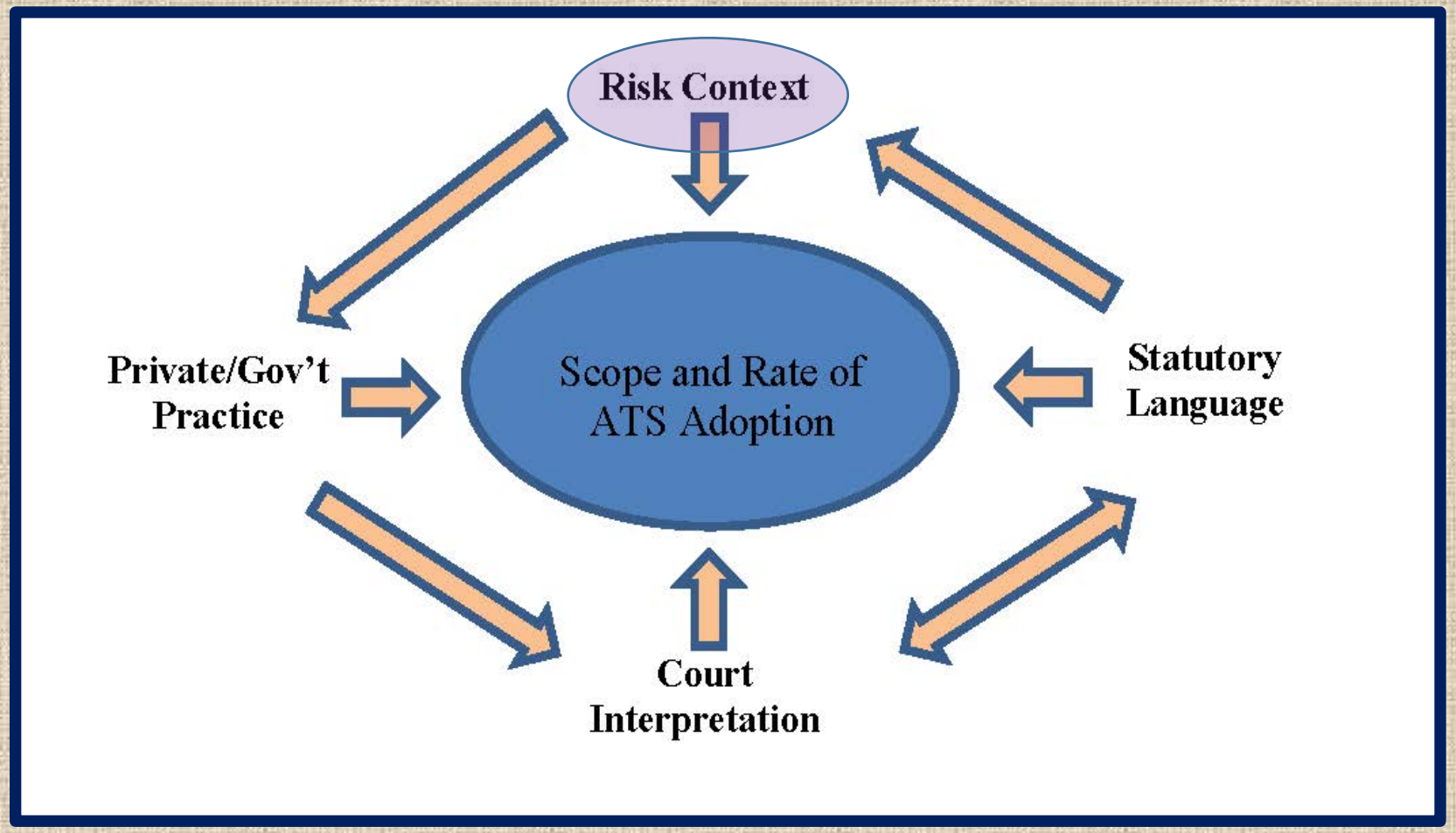
EPA, Economic Analysis of Expedited New Use Rule for Fifteen Chemical Substances (EPA Docket EPA-HQ-OPPT-2013-0100)

K Sullivan, *et al*, A discussion of the impact of us chemical regulation legislation on the field of toxicity testing, 25 *Tox. In Vitro* 1291 (2011)

The Solution?

- Alternative Testing Strategies (ATS)
  - Alternative testing strategies seek to reduce, refine or replace the use of animals, minimize cost and diminish uncertainty by placing greater reliance upon *in vitro* and *in silico* methods.
  - *Toxicity Testing in the 21st Century* (2007)
- ATS Categories
  - Mechanistically-Based (High Throughput) *In Vitro*
  - Mechanistically-Based (High Throughput) *In Vivo*
  - (Quantitative) Structure Activity Relationship models
  - Biomarkers

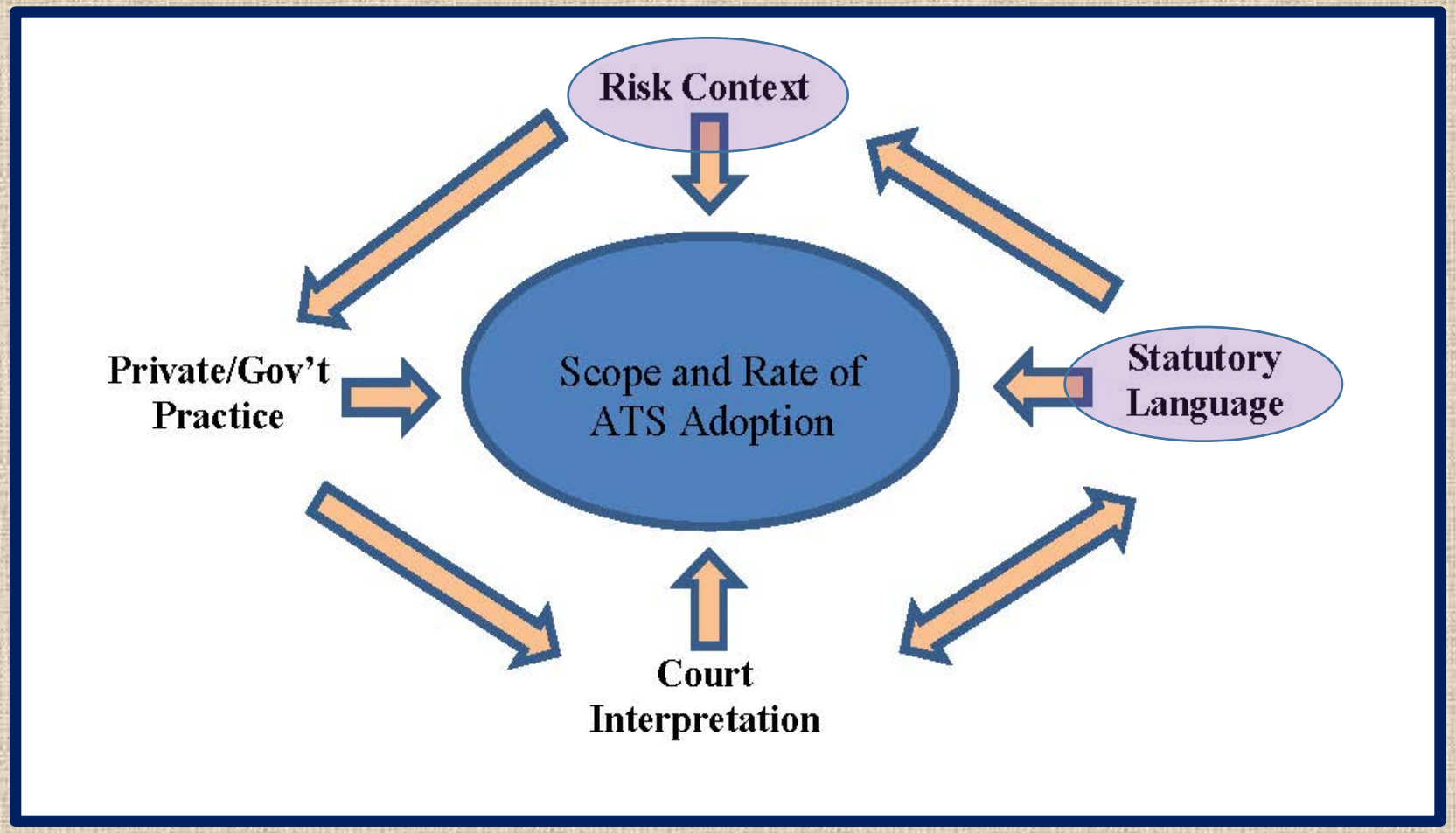
Lines of Influence



Risk Context

- Screening:
  - Identify chemicals for more extensive evaluation, including additional testing
- Risk Assessment:
  - Provide input to qualitative or quantitative risk assessment in developing acceptable exposure levels
- Alternatives Assessment:
  - Provide input to comparative evaluation of hazards/risks of different chemicals in support of safer product or process design

Lines of Influence



The Statutory Language and

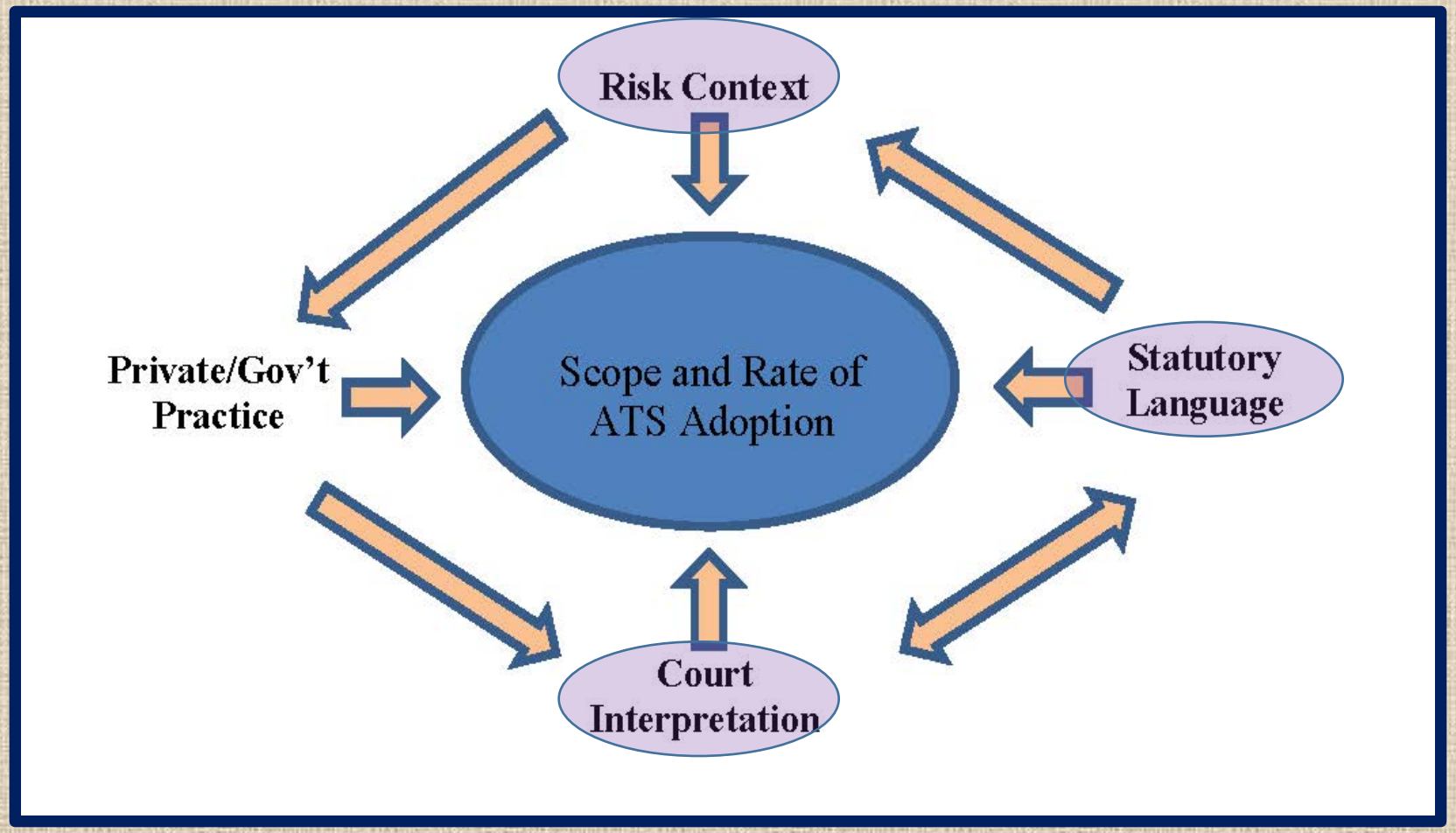
- "[T]he methodologies that … andards include epidemiolo… es, in vitro tests …

15 …

- "The Ad… ve test methods … n-animal tests for predicting … icals on health, the need for animal t… a substance or mixture causes or significan… an unreasonable risk will diminish."

House Inters… oreign Commerce Committee Report, Report of the House Intestate and …eign Commerce Committee, H.R. Rep. No. 94-1341, 5-6.

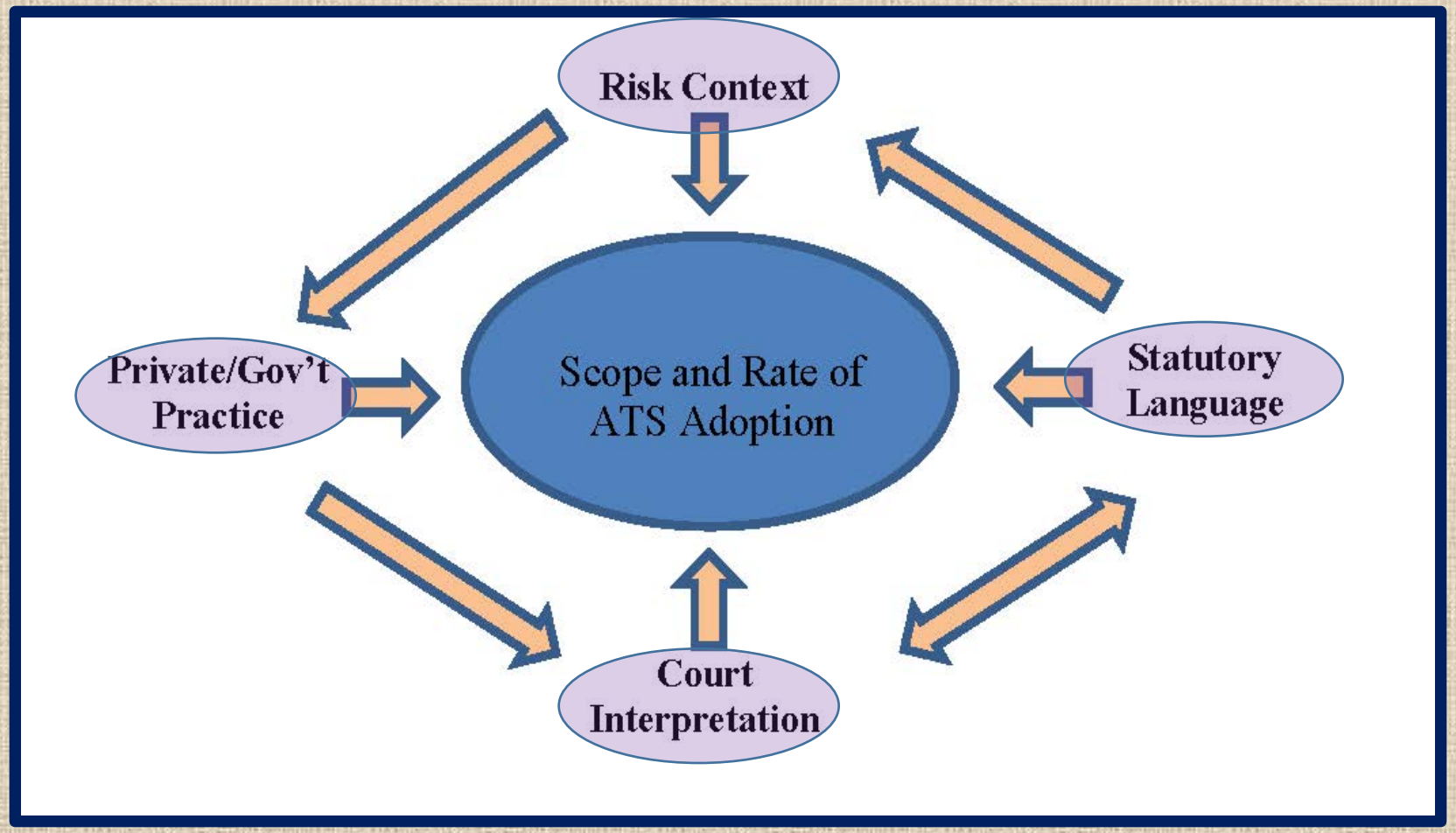
Lines of Influence



The Courts Speak

- **SAR**: "[W]e believe that the petitioners' attempt to transform EPA's concerns about the lack of scientific certainty into mere speculative scouting for data actually strengthens the government's position. These questions broaching the frontiers of scientific knowledge highlight the need for testing." *Ausimont U.S.A Inc. v. EPA, 838 F.2d 93,* 3d Cir. 1988.
- **SAR:** Observing that Congress expressly contemplated comparisons among structurally similar chemicals, the court went on to conclude that EPA's judgment was "supported by substantial evidence on the record viewed as a whole."*Chem. Mfrs. Ass'n v. EPA, 859 F.2d 977,* D.C. Cir. 1988.

Lines of Influence



EPA Alternative Testing Use
Under TSCA Section 4 for Screening

Type of Evidence/Number	Endpoints	Substance	Year
In Vitro/3 SAR/1	Mutagenicity Oncogenicity	Diethylenetriamine	1985
SAR	Mutagenicity Oncogenicity	Toxic Substances; Mesityl Oxide	1985
In Vitro/5	Oncogenicity	Hydroquinone	1985
In Vitro/6:	Mutagenicity Oncogenicity	Cresols	1986
In Vitro/1 SAR/3	Oncogenicity Reproductive Toxicity	Chlorinated Benzenes; Final Test Rule,	1986
SAR/7:	Oncogenicity Developmental toxicity Subchronic toxicity	2-Ethylhexanoic Acid	1986
SAR/2:	Ge		
In Vitro/4 SARs/2	M Or		
SAR/1	Ca		
SAR/2	Su		
In Vitro/1: **SAR**	M Or De Ne		
SAR	De Neurotoxicity	Monomethyl Ether	
In Vitro/1 SAR:	Mutagenicity Oncogenicity	Methyl Ethel Ketoxime	1989
In Vitro/2	Mutagenicity	Unsubstituted Phenylenediamines,	1989

ATS Practice for New Chemical Review

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- R
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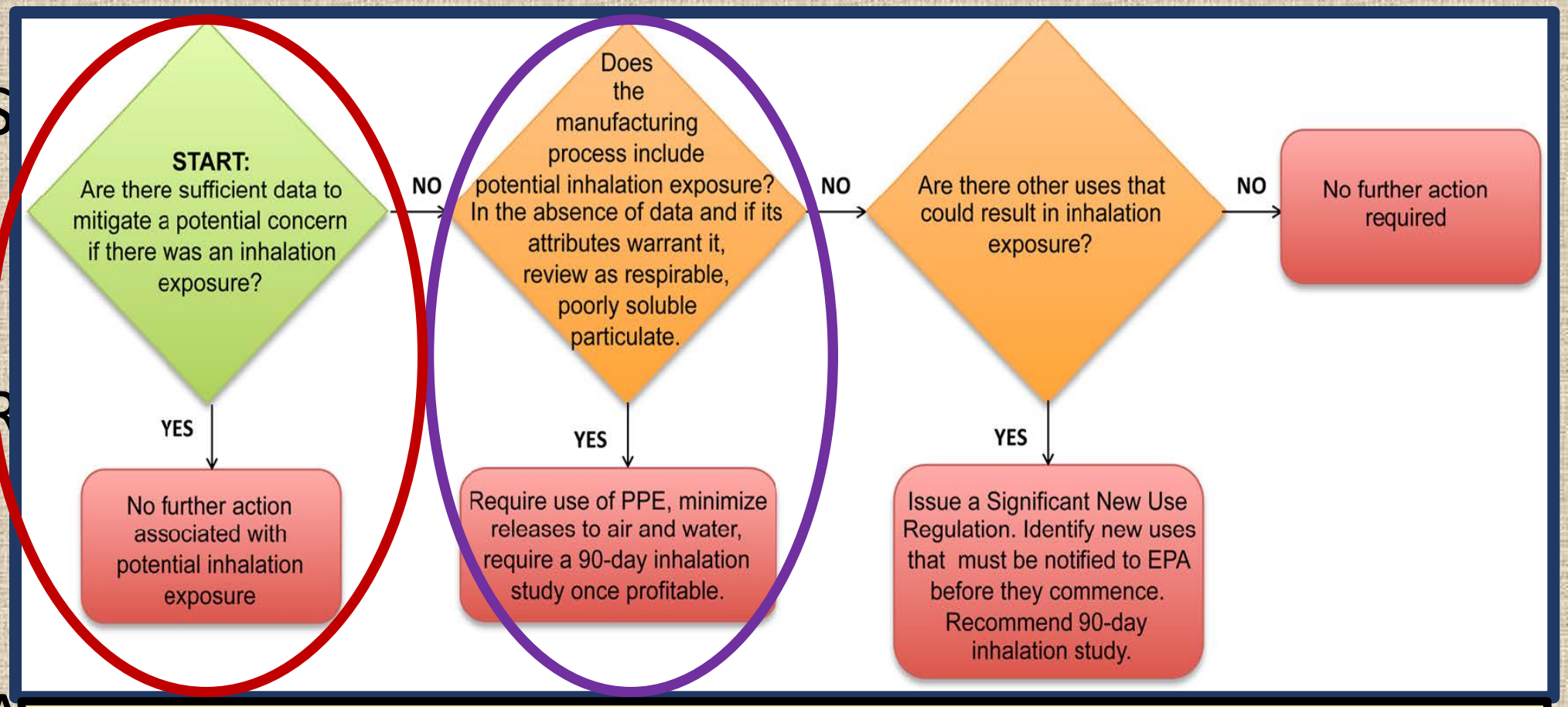
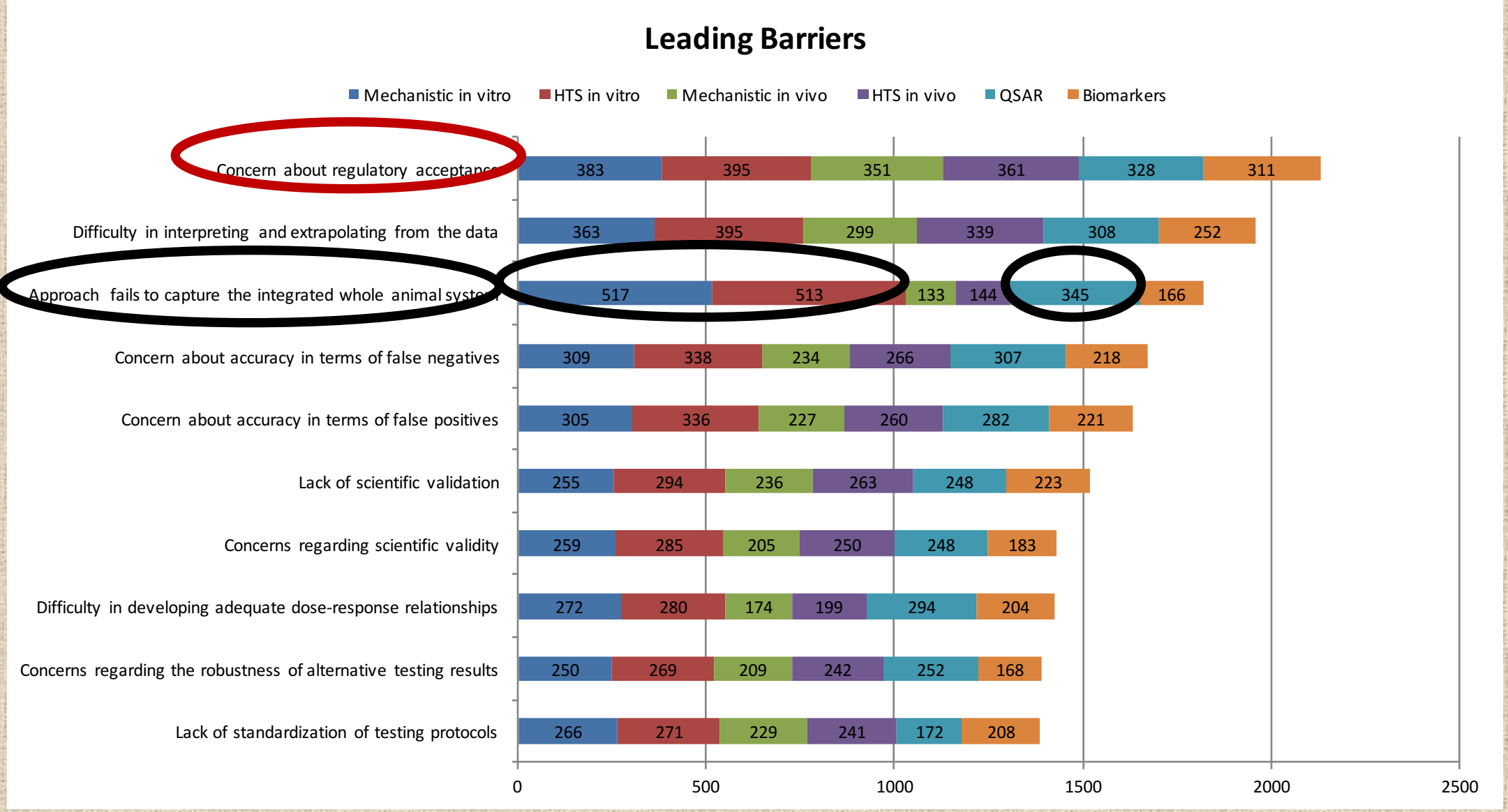


Godwin, *et al,* Nanomaterial Categorization for Assessing Risk Potential to Facilitate Regulatory Decision-Making, 9 *ACSNano* 3409 (2015)

Conclusions Regarding Current EPA Practice

- EPA has consistently relied upon alternative *in vitro* and *in silico* testing strategies for screening chemicals.
- The agency is more restrained in its use *in vitro* approaches for risk assessment and risk management, but more willing to rely upon *in silico.*
- EPA is reluctant to use *in vitro* tests for any purpose absent validation.
- EPA appears to be more flexible in its use of *in silico* methods such as chemical categories, SAR and QSAR without formal validation.

Current Practice



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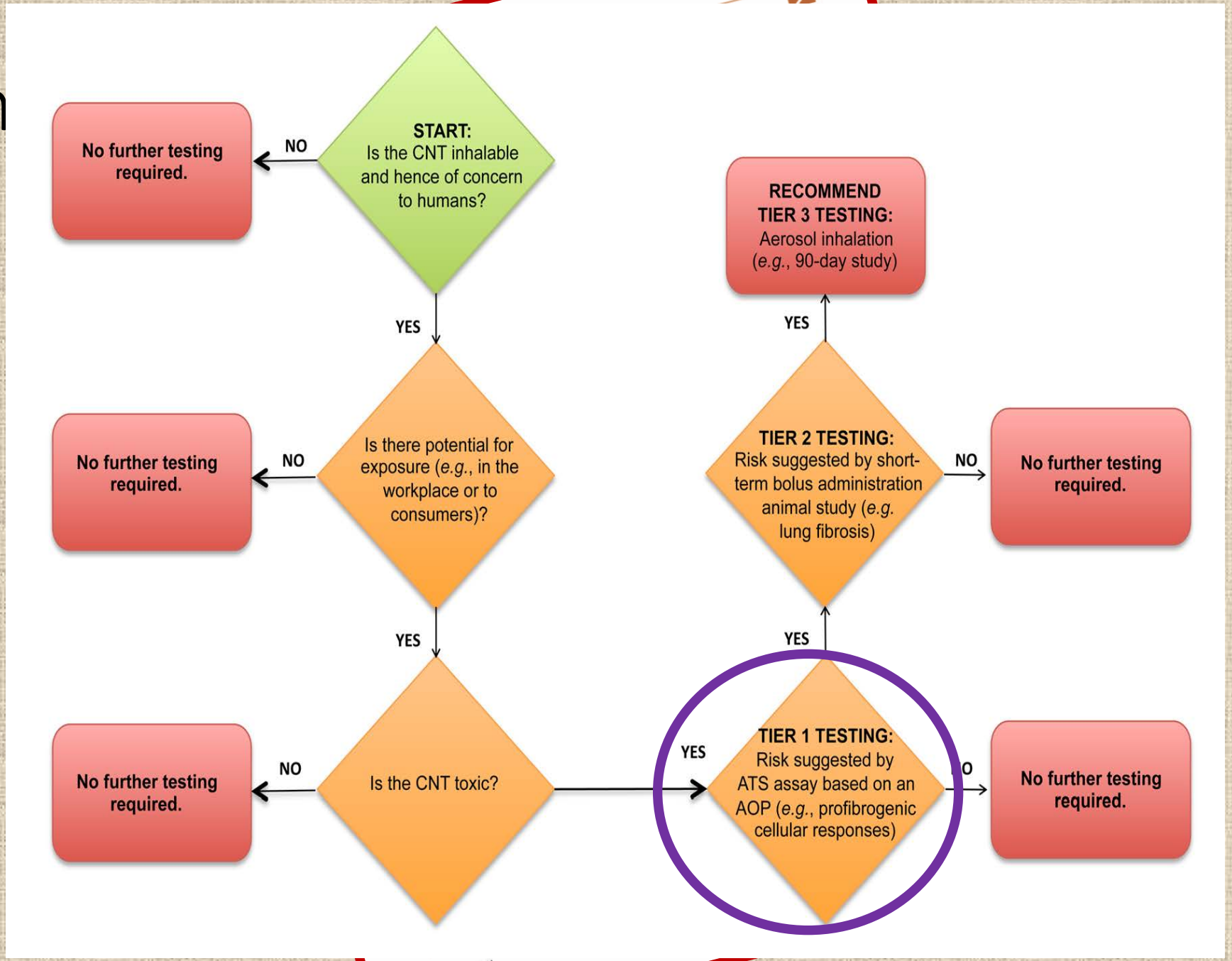

GODWIN ET AL.

Shifting Law

- **House**
  - "[R]eview the adequacy of the policies, procedures, and guidance . . . with respect to animal **nonanimal**
  - eliminate or reduce the use of animals while providing information of high scientific quality. . . .

"The Committee believes, however, that where scientifically reliable alternatives exist that will generate equivalent information, EPA can request, and in some cases should require, a non-animal test to first be used."