An Industry Perspective On Integrated Testing Strategies For REACH

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The Case For Integrated Testing Strategies

- Testing resources must be used efficiently and effectively
- Screening tools & predictive models are excellent for prioritizing and targeting information needs and guiding testing
- Annex XI of REACH acknowledges the ITS approach
- Guidance on information requirements encourages use of existing information and weight-of-evidence approach
- Many workshops, meetings held to identify the path forward and research to develop the tools and approaches

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Standard Information Requirements for REACH ... Human Health

Tonnage	Health
1-10 tpa	• In vitro skin & eye irritation • Skin senzitization • In vitro mutagenicity • Acute Toxicity
10-100 tpa	• In vivo skin irritation • Further in vitro mutagenicity • Acute toxicity • Sub acute toxicity • Reproductive tox screen
100-1000 tpa	• Further mutagenicity tests • Subchronic toxicity (90d) • Reproductive toxicity tests
> 1000 tpa	• Further mutagenicity tests • Further repro toxicity tests • Possible carcinogenicity • Possible chronic toxicity

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Annex XI General Rules For Adaptation Of The Standard Testing Regime

1. **Testing does not appear scientifically necessary**
   - Use of existing data: Phys/Chem; non-"standard" testing, human data/ experience
   - Structure Activity Relationships (QSAR)
   - Grouping of substance and read-across approvals
   - In vitro methods
   - Weight-of-evidence
2. **Testing is technically not possible**
3. **Substance - tailored exposure-driven testing**

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What Is An Integrated Testing Strategy?

- **Approaches that consider and use different types of data and information in the decision-making process**
- **Can include data from**
  - Individual assays
  - Test batteries
  - Tiered test schemes
- **Requires weight-of-evidence approach…"expert judgment"**
- **Exposure / population data inform the ITS for a risk assessment**
- **Encourages the use of multiple approaches for obtaining information necessary for a regulatory assessment avoiding an unnecessary laundry list of animal toxicity tests**

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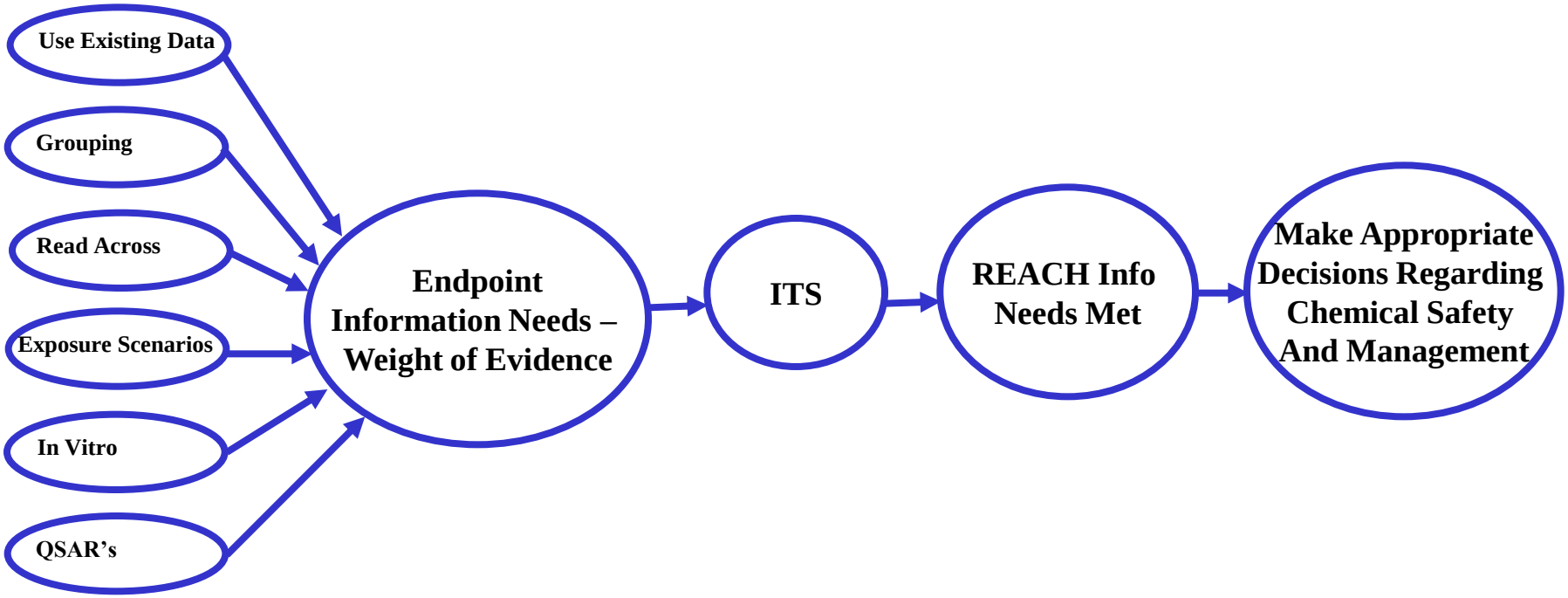
Approach To Develop ITS Requires Multi Expert Input



Use of Existing Data ... Human Data

- **Various types of human data exist**
  - Analytical epidemiology studies on exposed populations
  - Descriptive or correlation epidemiology studies
  - Case reports
  - Controlled studies on human volunteers
- **In general, these data are informative and need to be viewed in context**
  - Hill criteria
  - Exposure characterization
  - Statistically robust

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Use of Existing Data ... Exposure Based Waving

- **EBW is a decision based on lack of relevance for certain endpoints**
- **Can be driven by Phys/Chem properties... e.g. physical state and vapour pressure**
- **Can be informed by existing experience / knowledge regarding use**
  - No consumer exposure
  - No professional application
  - Used in closed system
- **Can be informed by existing experience / knowledge regarding hazard**
  - Threshold of Toxicological Concern
  - No absorption into target system
- **EBW requires adequate justification and is likely a function of the length of supply chain and complexity of the use pattern**

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Grouping And Read Across

- **A common practice for many years…key feature of HPV program**
- **A chemical category is a group of chemicals whose physico-chemical and human health / or environmental toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity**
- **Grouping approaches can be used to indicate either the presence or absence of an effect**
- **Grouping approaches avoid the need to test all members of a group for all endpoints of interest, thereby reducing costs and animal use**
- **Allows for data gaps to be filled by several general approaches**
  - Read-across... Efficient use of existing data
  - Trend analysis... SARs
  - Models... Such as QSARs

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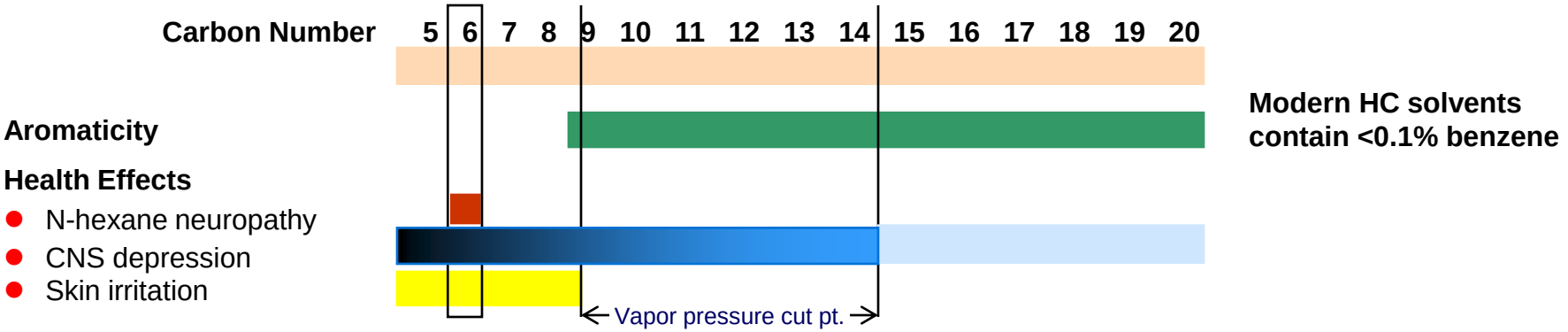
Chemical Category … Hydrocarbon Solvents

- **Numerous discrete products that vary by hydrocarbon type and boiling range**
- **Chemical categories developed for U.S. EPA HPV and OECD SIDS**
  - Hydrocarbon type
  - Human health effects
  - Physical chemical properties (carbon number)



Low aromatic aliphatics (<2% aromatics)

HC types

normal,iso-, cyclo-paraffins

Sub groups

C5 pentanes
C6 hexanes
C7-9 aliphatics
C9-14 aliphatics
C14-20 aliphatics

High aromatic (2-20% aromatics)

HC types

normal, iso-, cyclo-paraffins,
alkylated benzenes
alkylated naphthalenes

Sub groups

C9-14 hydrocarbons
C14-20 hydrocarbons

Fully aromatic

HC types

alkylated benzenes
alkylated naphthalenes,
naphthalene

Sub groups

C9 Aromatics (no naphthalene)
C10-C12 Aromatics

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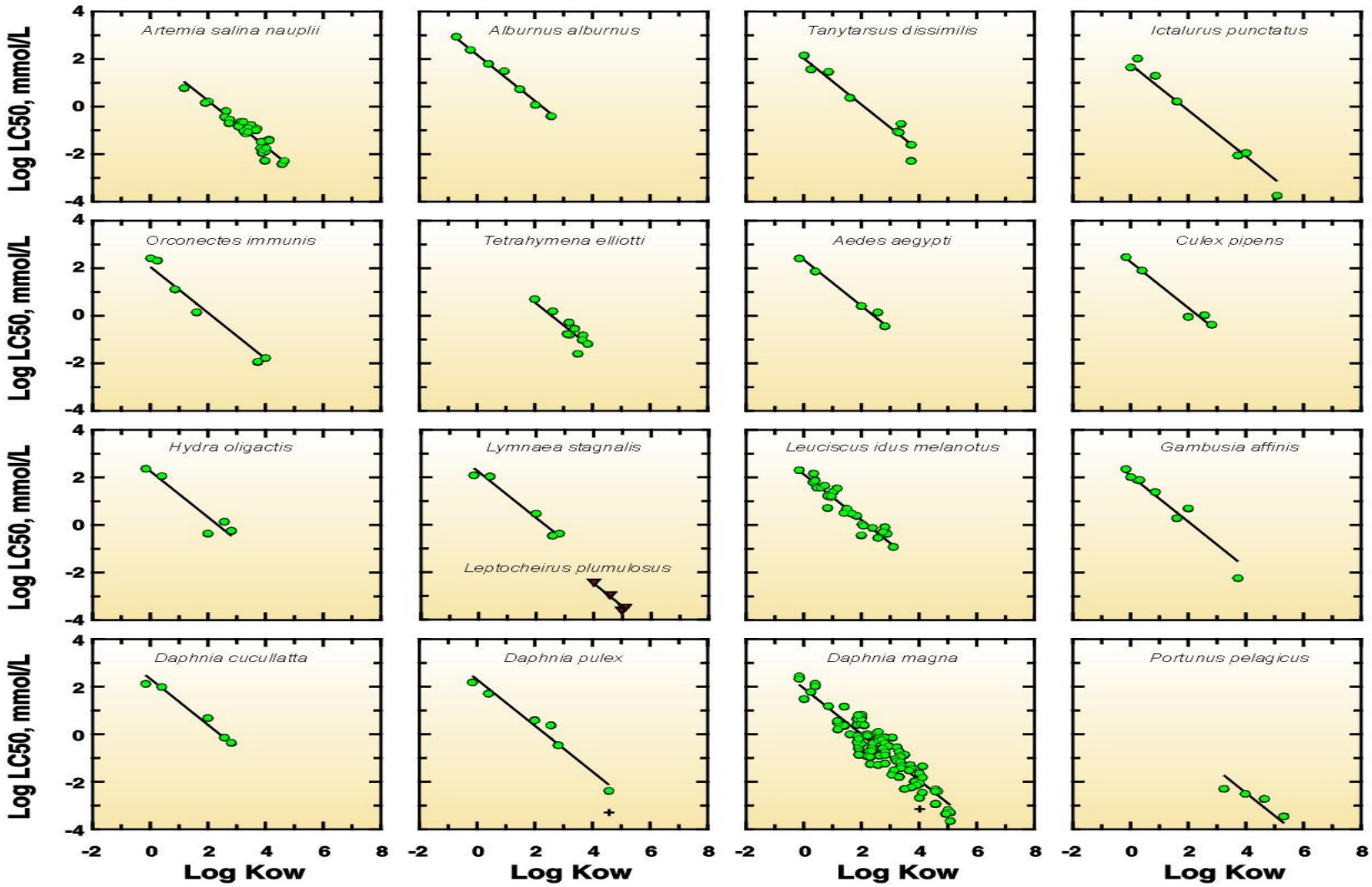
Calibration of TLM To Acute Toxicity Data Sets



(Di Toro et al., ETC, 2000)

Note: Each Plot Represents a Different Test Species

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Issues With In Vitro Tests / Data

- **Two categories of acceptable in vitro methods are referred to in REACH**
  - Validated methods
  - Test meeting internationally agreed pre-validation criteria
- **In vitro tests rarely totally replace an animal test but provide**
  - Predictive information about the likelihood of a certain endpoint
  - Information regarding mechanisms and mode of action
  - Insight to possible impacts on critical physiological pathways
- **In vitro tests can inform decision making relative to Hazard ID**

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Role of (Q)SARs – What Are The Benefits?

- **Optimize use of existing test data**
- **Minimize animal use / reduce costs**
- **Identify suspect data / strengthen weight of evidence**
- **Gain mechanistic insights**

But this will come only if we accept QSAR results and ...
Acceptability is related to transparency

- **Only possible if:**
  - QSAR is applicable for a chemical
  - QSAR was validated
  - QSAR prediction reliability and uncertainty is defined

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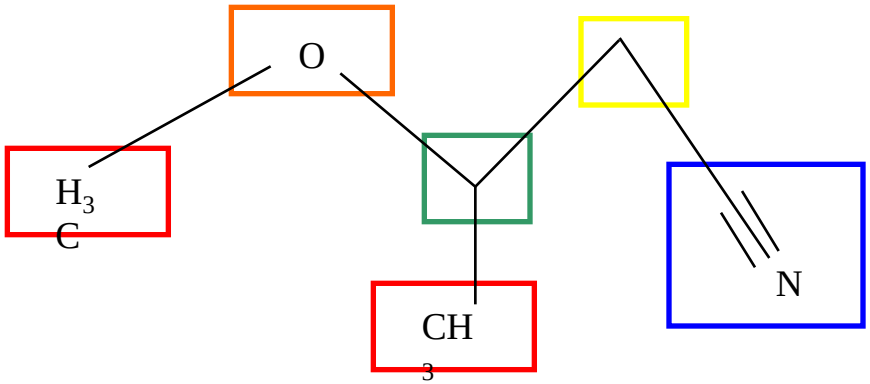
(Q)SAR Models Using Advanced Expert Systems Improve Utility

- **Advanced technical modeling of chemical structure relationships**
  - U.S. EPA Analogue Identification Model



- **Mechanistic determinates (e.g. TIMES Model)**
- **Toxicodynamic and Toxicokinetic determinates**

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Use of (Q)SARs in the Decision Making Process

- **What are the concerns**
  - False positives
  - False negatives
- **How to address these concerns?**
  - Develop transparent guidance on QSAR use, reliability & applicability
  - Focus on QSARs that are most pertinent in regulatory contexts
  - Gain external validation of the models and assessment of predictive power
  - Determine model applicability domain and use of part of decision-making
  - Use uncertainty assessment for model predictions

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Evaluation And Integration Of All Available Information ... Weight Of Evidence

- **The term "WOE" does neither constitute a well-defined term nor an agreed formalized process (Weed 2005)**
- **Reasoning, expert judgment and an element of common sense are components**
- **An evidence based approach involves an assessment of relative values / weights of different information**
  - Weights / value can be assigned in an objective or subjective way
  - Use of Klimisch scores as an example for toxicology data
  - Application of Hill criteria is an example for epidemiology studies
- **Application of WOE will be case dependent and needs to be transparent, inclusive of all data and clearly documented**

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New Developments To Incorporate Into ITS

- MOA framework
- Human Biomonitoring Data
- Toxicokinetic Models
- Tox Testing in 21st century
- FP6 / 7 Research

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IPCS / ILSI Mode Of Action / Human Relevance Framework

- **Systematic consideration of WOE for hypothesized mode of action, based on Bradford Hill criteria / guideline for causality**
- **Subsequent consideration of human relevance, based on concordance analysis for key events**
- **Objective is transparency, including delineation of uncertainties, as a basis for peer engagement in decision making**
- **Context is hazard characterization ... effort needed to incorporate / utilize for ITS**

Meek et al (2003) Crit. Rev. Toxicol. 33-591

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Human Biomonitoring Data Provides An Opportunity

- **Available biomonitoring data is increasing**
- **Provides opportunity to make better assessment of human exposure trends**
- **Can be used to more efficiently design tox studies by improving internal dose evaluation in animal toxicity studies**
  - Internal dose pharmacokinetics can be assessed under conditions in which toxicity data are used for risk assessment (i.e. diet / Drinking water)
  - Advances in analytical technologies facilitate sensitive and rapid quantitation of parent and / or metabolite levels
  - Reduce uncertainty in human risk assessments by developing better margin of exposure (MOE) comparisons
    - Internal dose (animal) / internal dose (human) ratios

(Saghir et al, Tox Appl. Pharm. 211:245-260, 2006)

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ILSI ACSA: Focus On Toxicokinetics In Study Design

- Incorporation of existing knowledge in area of operator exposure and dietary exposures should be given due consideration in selection of doses for toxicology studies
- Kinetic data allows the investigator to avoid use of high doses that are irrelevant due to saturation of metabolic processes
- Recommended that chemical levels in blood be measured as part of, or along with, each toxicity testing protocol ... purpose of such data is to understand the disposition of a compound in the body under the actual conditions of the toxicity study
- Understanding this relationship in short-term studies can be helpful in WOE to reduce the need for longer term studies

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The NRC Vision Of Toxicity Testing In The 21st Century

- **Envisions a not-so-distant future in which virtually all routine toxicity testing would be conducted in human cells or cell lines in vitro by evaluating cellular responses in a suite of toxicity[1] pathway assays using high throughput tests, implemented with robotic assistance**
- **Dose response modeling of perturbations of pathway function would be organised around computational system biology models of the circuitry underlying each toxicity pathway**
- **In vitro to in vivo extrapolations would rely on pharmacokinetic models that would predict human blood and tissue concentration under specific exposure conditions**

[1] or “normal physiological pathways perturbed by an insult

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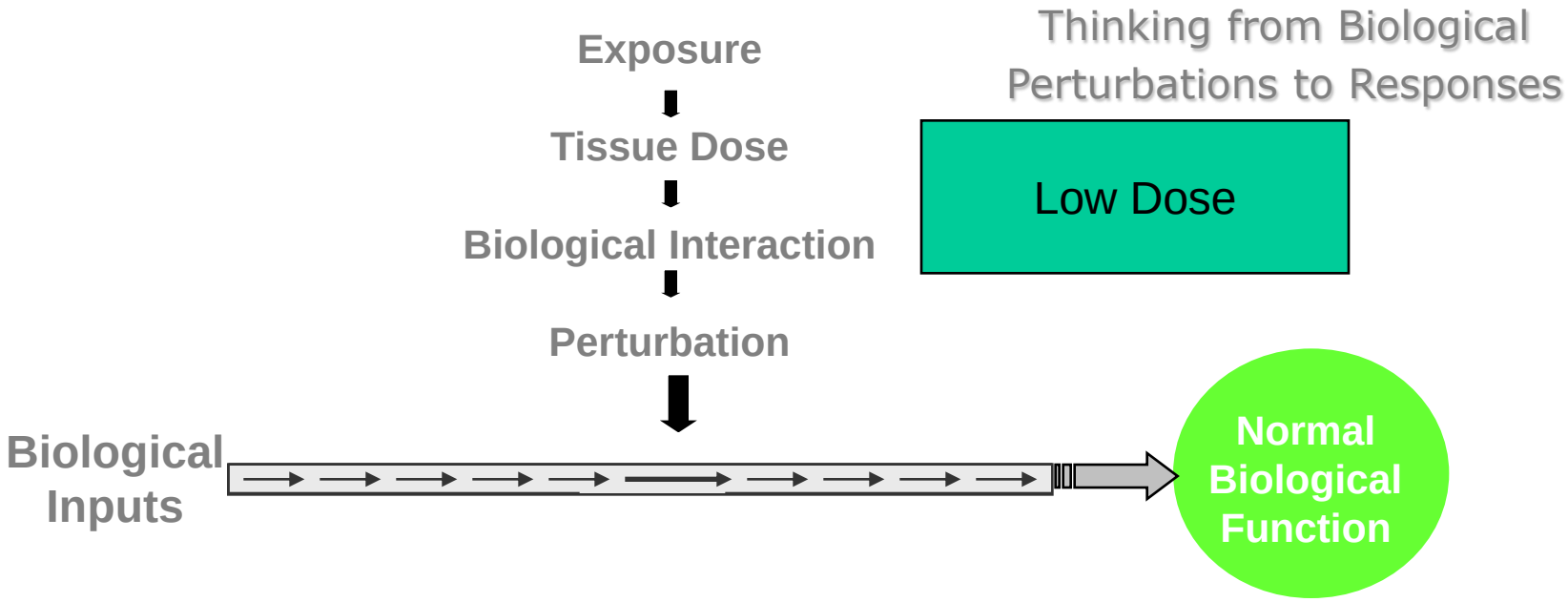
The Future Paradigm



Benefits: Reduce time, cost, animal use ... More relevant to low dose human risk

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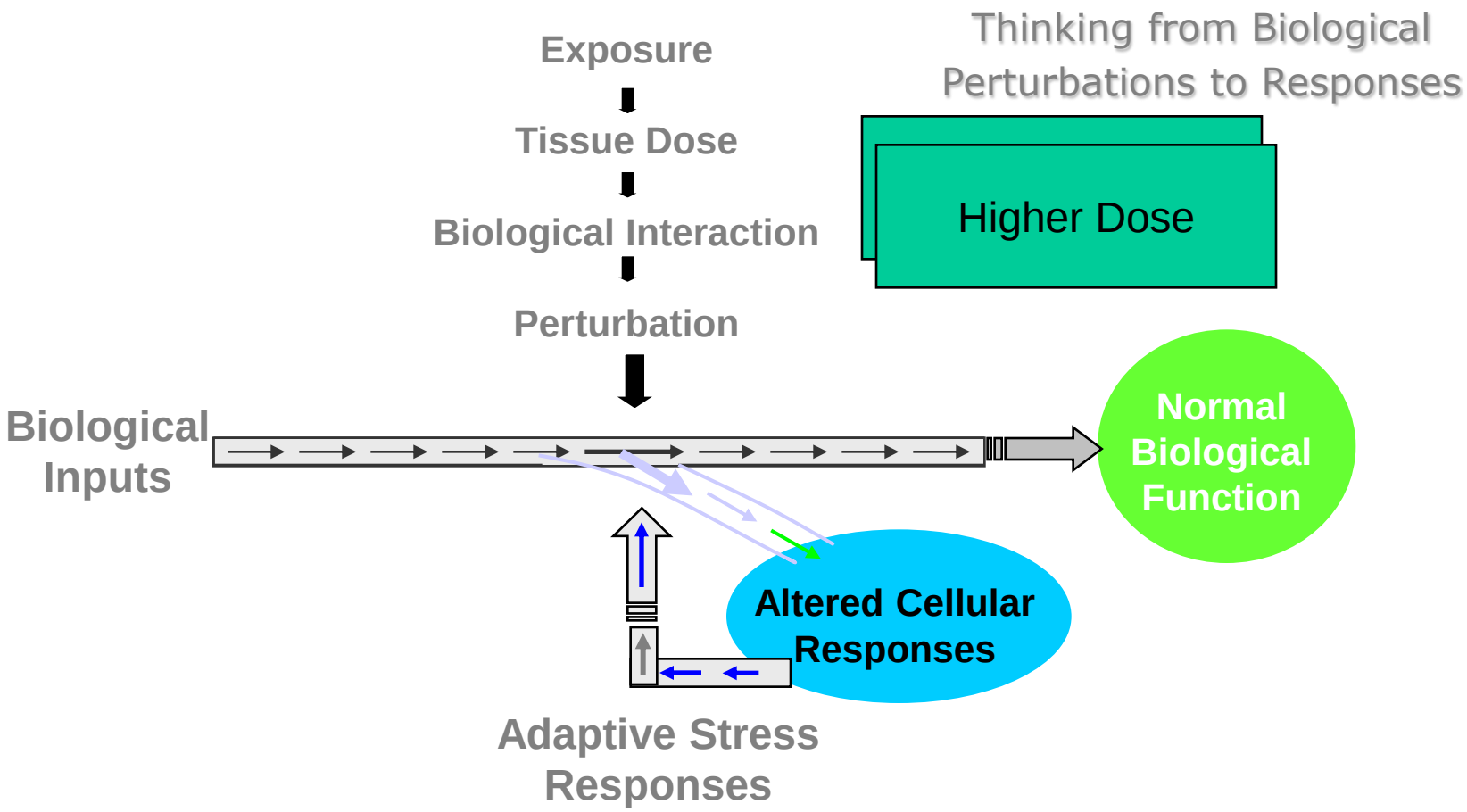
The Future Paradigm



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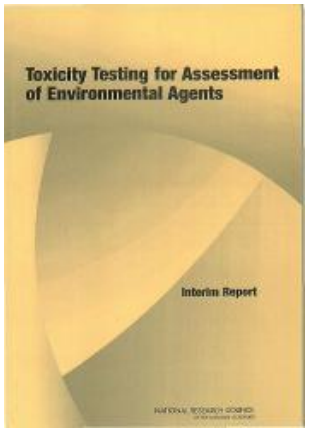
The Future Paradigm



Exposure

Tissue Dose

Biological Interaction

Perturbation

Thinking from Biological Perturbations to Responses

Higher yet

Biological Inputs

Normal Biological Function

Altered Cellular Responses

Adaptive Stress Responses

Cell Injury

Disease

Benefits: Reduce time, cost, animal use ... More relevant to low dose human risk

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What's Needed As We Go Forward

- Continue focus and support for incorporating new, improved technology in our assessments (e.g. FP 6 / 7 programs, CEFIC LRI)
- Develop tools to link chemistry and biology in the new paradigm
- Systems to manage, interpret, apply the explosion of data
- Education of the public to avoid policies that trade problems with no real benefit or possibly greater adverse consequences
- Policies supporting science and reasoned approaches to chemical management aided by:
  - A renewed commitment of research to follow the scientific method
  - Testing hypotheses and validating methods
  - Confirming data and results clearly
  - Communicating data and results clearly
  - Considering alternative, biologically plausible and reasonable explanation for observations

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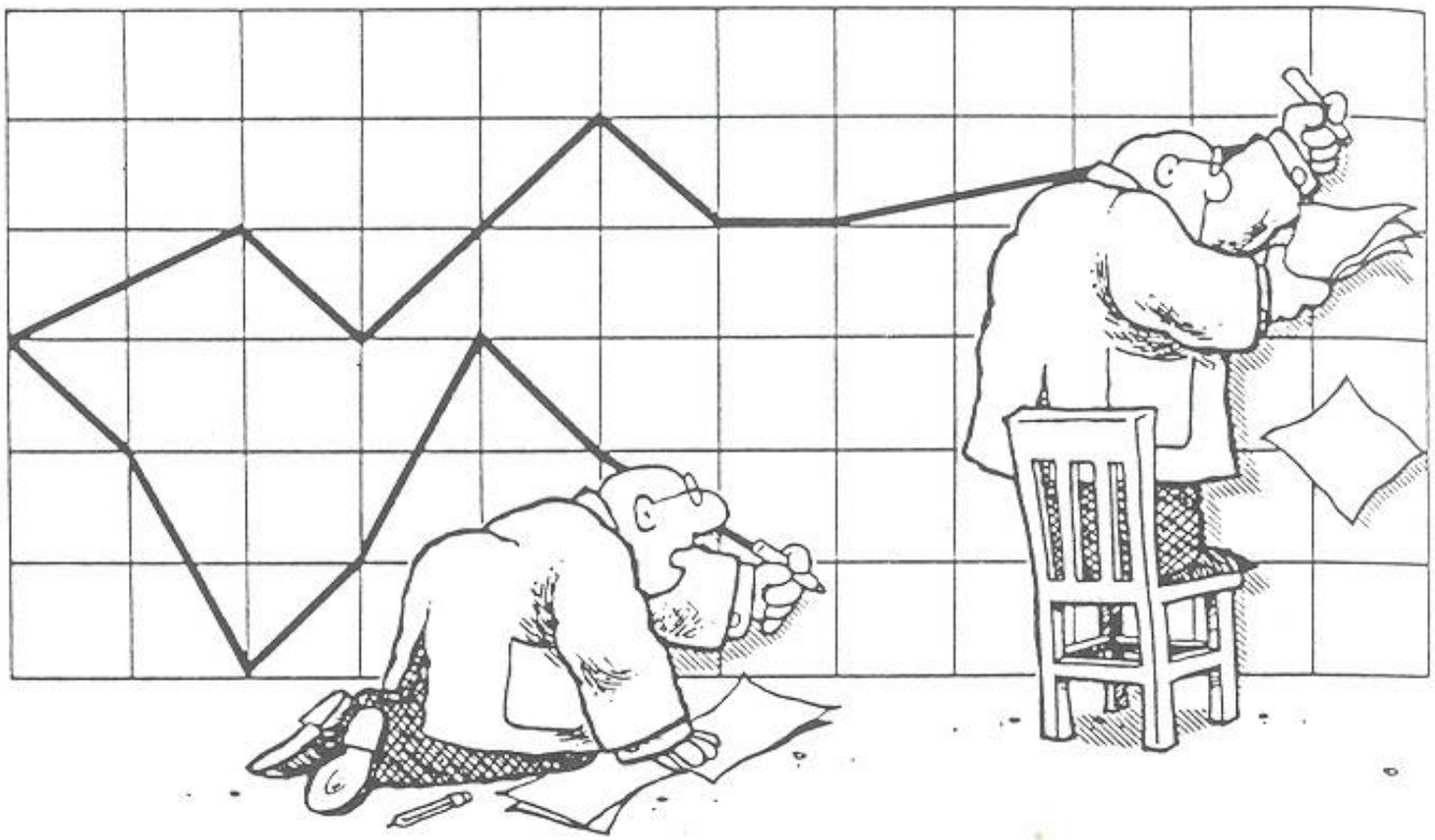

"HEY, I THOUGHT WE WERE WORKING WITH THE SAME DATA..."

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