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Near Term Case Study

Integrated Approach to Testing and Assessment to Inform Regulatory Decisions

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Case Study Overview

- Role: How to use available predictive tools now to evaluate hazard and exposure
- Goal: Make current risk assessment process more effective & efficient
- Benefits:
  - Save resources
  - Save time
  - Draw on all existing data
  - Incorporate new technologies

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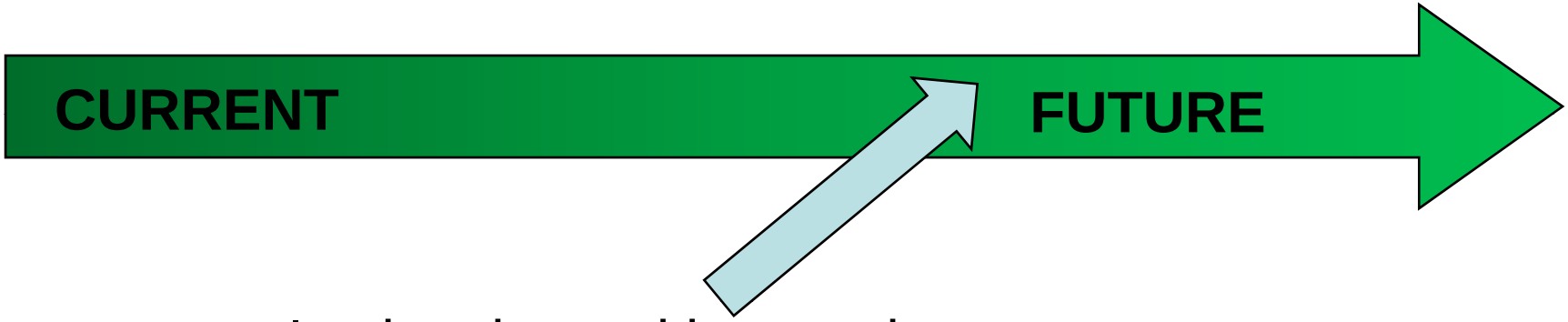
Paradigm Shift: Increasing Effectiveness & Efficiency



- In situations with poor data:
  - Maximize use of non-animal predictive methods to fill data gaps
- In situations with rich data:
  - Maximize any use of animal testing
  - Enhance interpretation of existing information

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Goal: Evaluate Inherent Chemical Properties More Efficiently & Effectively

- Chemical-specific properties that determine

- How it is used (exposure potential)

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How do we get there? Screening & Knowledgebases

- Screening requires relational, integrated and interactive knowledgebases – not just databases
- Goal:
  - Use screening as a predictive tool
  - Develop and expand knowledgebases that describe inherent chemical properties based on known molecular structure, and chemical and biological interactions

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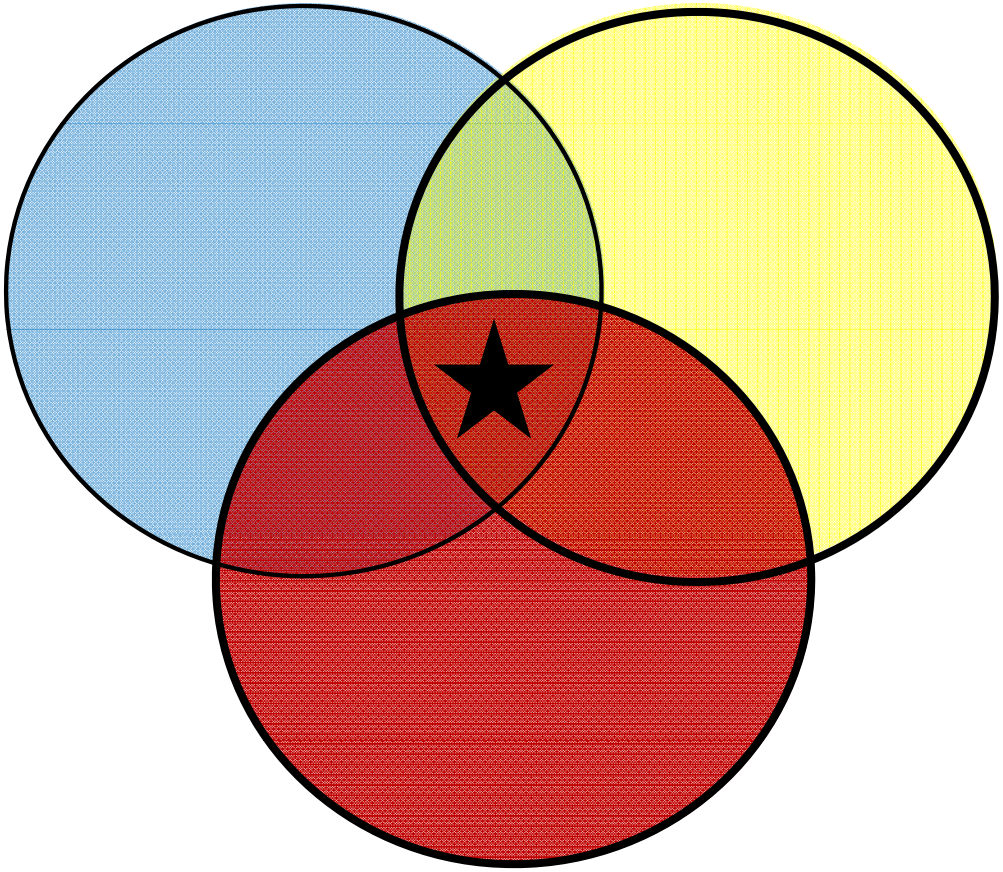
Goal: Clustering Chemicals Using Inherent Properties



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Data-Limited Chemicals

Today's Tool Box

Existing information + some use of:

ToxRefDb
ECOTOX
ACToR
ToxCast
QSAR Models
DSSTox
…. And more

Chemical grouping or categories & read-across

Improved Tool Box Using Newer Approaches

Integrating these in a way that makes sense

ToxRefDb
ECOTOX
ACToR
MetaPath
ToxCast
QSAR
DSSTox
…. And more

Relational Databases (links knowledge)

Inherent Properties of Chemicals
(chemical, biological & toxicity characteristics)

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Goal: More Effective Animal Usage

- Address quickly & accurately susceptible populations (Food Quality Protection Act) and reduce animal usage
- Integrate approaches to evaluate reproductive & other life stage effects
  - Full usage of animals in each study
  - Focus on effects of concern
  - Promote flexibility to use existing knowledge
  - Reduce/refine animal usage

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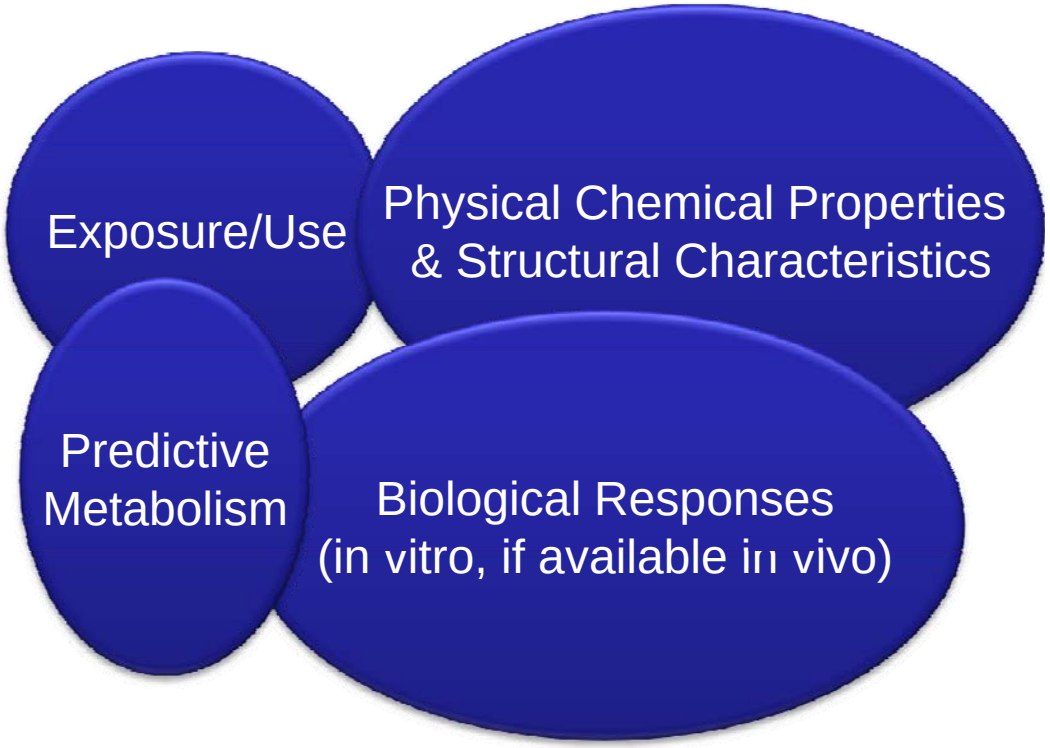
Example

Unknown or Data Poor Chemical (e.g., pesticide inert ingredients, industrial chemicals, metabolites of a pesticide active ingredient)

→

Are we concerned about this chemical?
If so, for which effects?
What information do we need?



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Example

Unknown or Data Poor Chemical (e.g., pesticide inert ingredients, industrial chemicals, metabolites of a pesticide active ingredient)

→ Are we concerned about this chemical? YES
If so, for which effects?
What information do we need?

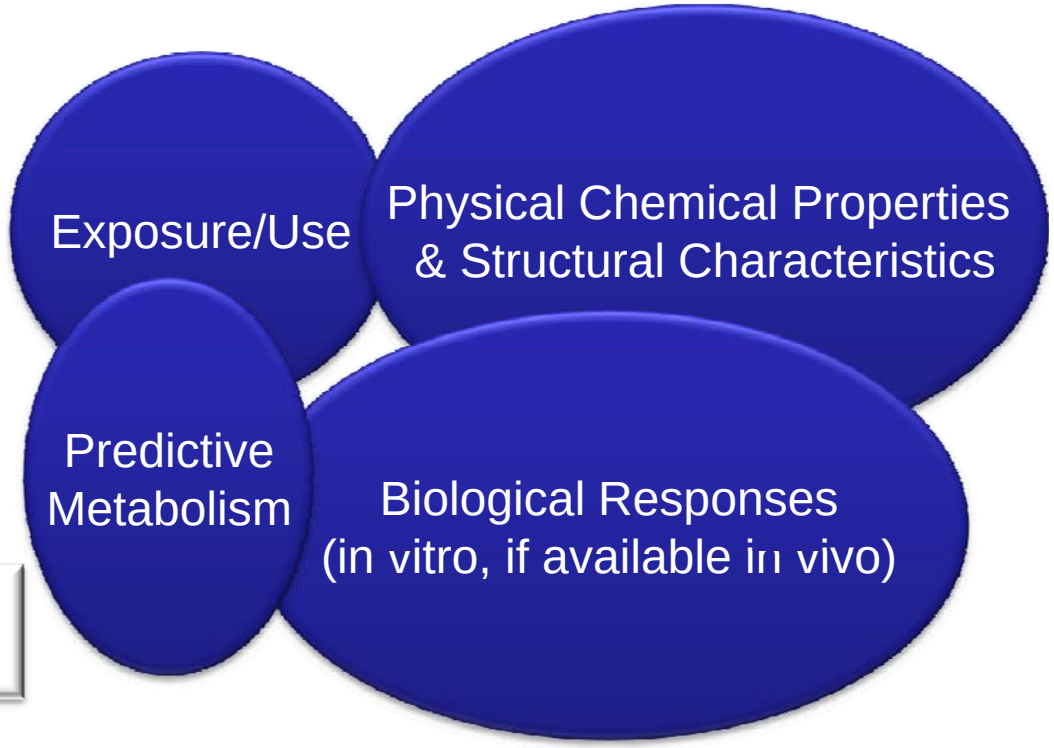
Carcinogenicity - NO

-No structural analog alerts
-Negative mutagenicity
-No high-throughput screening signaling Profile Alerts

Estrogen receptor binding - YES

↓

Screening level developmental & reproductive assays



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Example: Pesticide with Traditional Database

- Herbicide A: Agriculture & residential uses
- Issues were raised from existing information
  - Developmental neurotoxicity
  - Reproductive, thyroid & endocrine toxicity
- Currently, guidelines call for 2-generation reproductive test & DNT test (extensive use of animals)
- Revising current guidelines to reduce animal use from conventional study protocols by using alternative test: the extended F1

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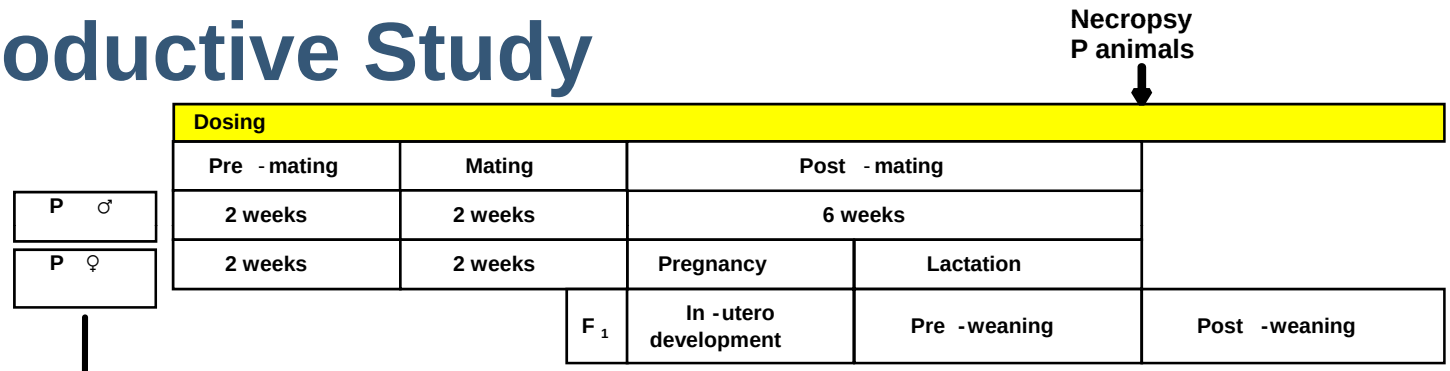
New: Extended 1-Generation Reproductive Study



Parental generation	Cohort	Designation	Animals/Cohort	Sexual Maturation	Approximate age at necropsy (weeks)
Target is 20 litters per group	1A	Reproductive	20 M +20 F	Yes	13
	1B	Reproductive	20 M +20 F	Yes	14 or 20 if triggered
	2A	Neurotoxicity	10 M +10 F@	Yes	9
	2B	Neurotoxicity	10 M +10 F@	No	3
	3	Immunotoxicity	10 M +10 F@	Yes	8
	Surplus	Spares		No	3

@ one per litter and representative of 20 litters in total where possible

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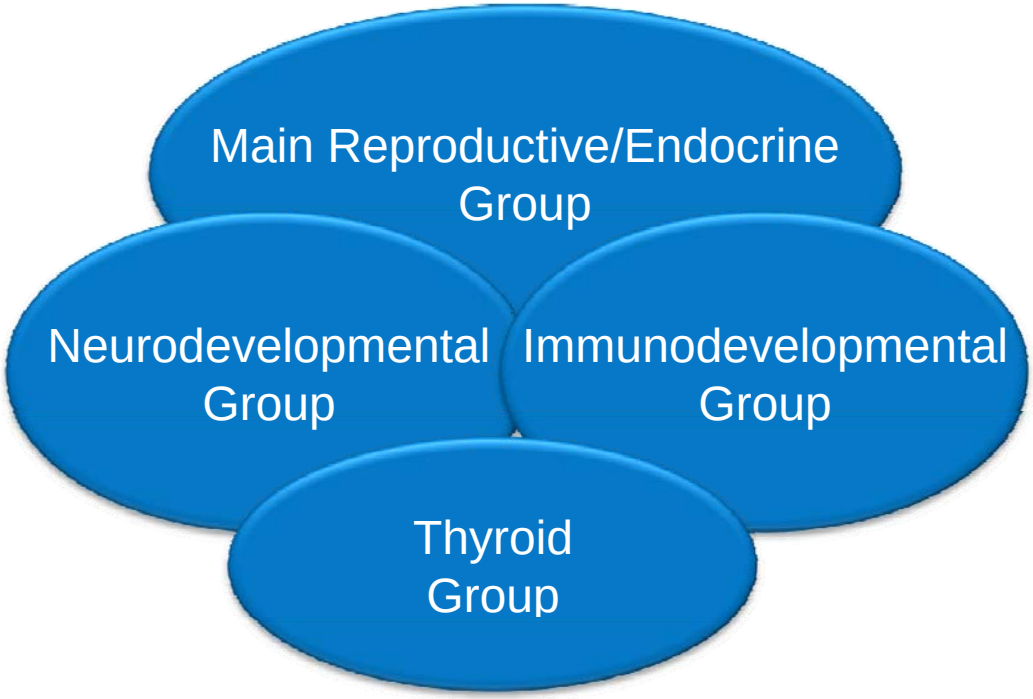
New: Extended 1-Generation Reproductive Study



Satellite Group:
Mechanism of chemical absorption data: fetus, dams, lactation.

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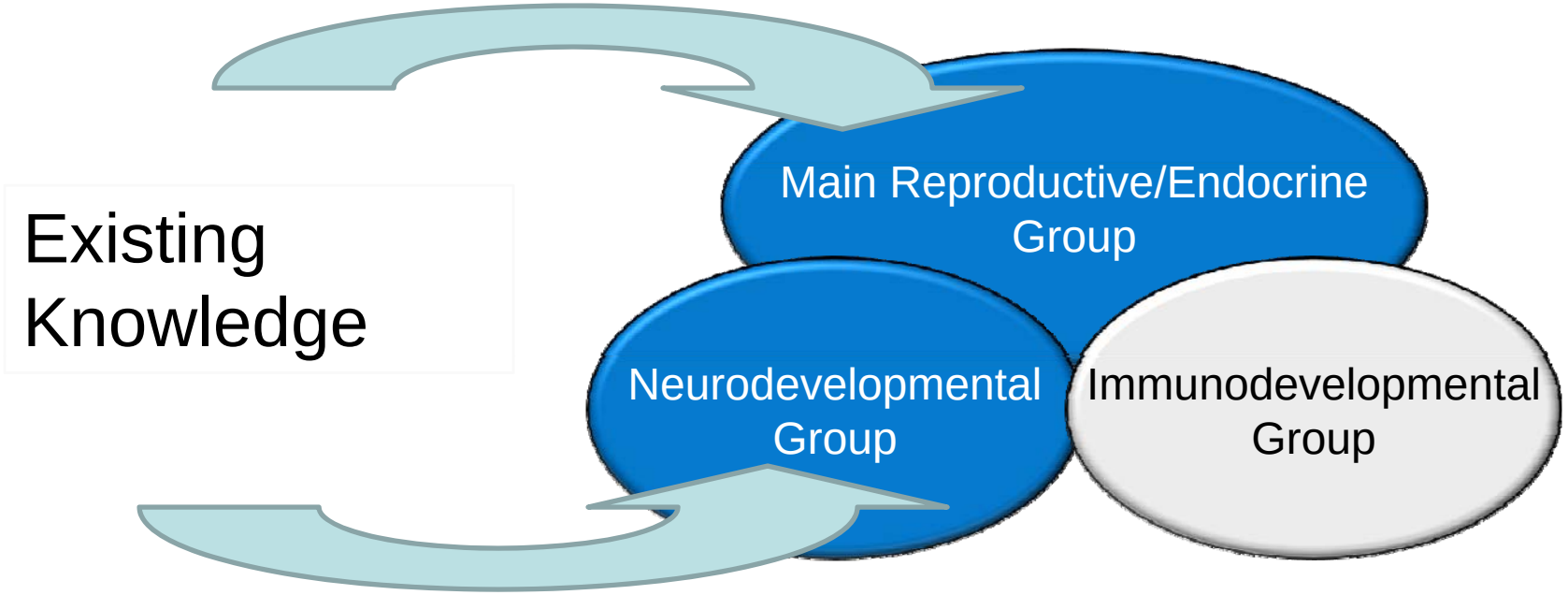
Herbicide A: New Extended 1-Generation Reproductive Study



Traditional Approach:
2-gen, developmental neurotoxicity & immunotoxicity = **~7,000 animals**

New Extended 1-Generation Approach = **~1,400 animals**

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Summary

- Integrated testing approaches evolves as new tools emerge
- Near term efforts:
  - Prioritization screening for data poor chemicals
  - Enhance interpretation of existing information & maximize animal testing information for data rich chemicals
- Holistic considerations of manufacture, use, exposure, hazard and risk