Optimized *in vivo* testing; uncertainties, reliability & use for regulatory testing - what lessons can we draw from experience in toxicology?

John Doe

Head of Product Safety

Why Reconsider the Agricultural Chemical Safety Assessment Process?

- Many studies and originated in the 1960s and 1970s.
- Knowledge increased in the last 40 years.
- More sophisticated and demanding health assessments
- Reducing the number of animals
- Can the process be more efficient and accurate?

- Problem Redefinition is a Key Step in Innovation

  - Looking at things in a different way

  - Working out what we are really trying to do

  - Finding ways to solve the redefined problem

Redefining the Question

We thought we were trying to improve the design of toxicology studies

but really

We needed to provide more relevant information for risk assessments

The Risk Assessment Matrix
Duration of Exposure

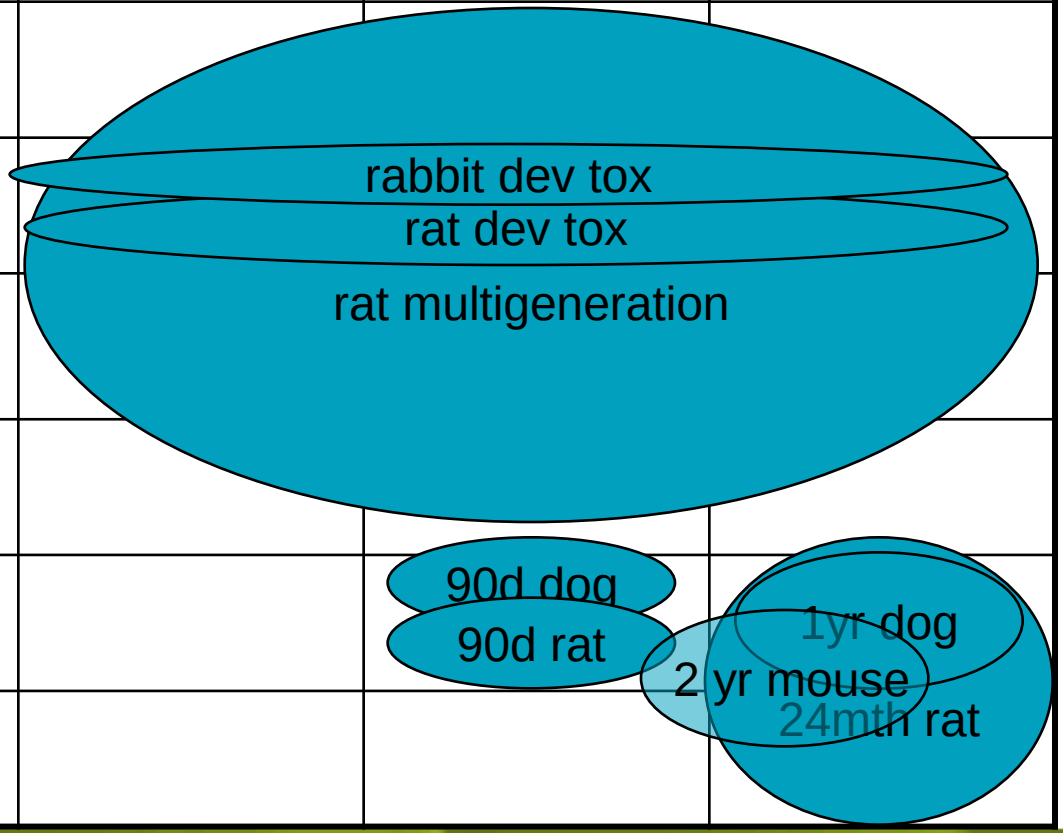
	1 Day	2-30 days	1-6 months	>6 months

The Risk Assessment Matrix
Life Stage

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult				
Elderly				

The Risk Assessment Matrix
Current Studies

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult				
Elderly				



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Concerns with Current Testing

- Shorter term durations of human exposure are not adequately covered
- Special endpoints such as neurotox and immunotox are not covered in the basic studies
- What is the value of studies in the dog and mouse?
- Although the multigeneration study covers most lifestages, the number of endpoints is limited
- Need more ADME and kinetic data to help with extrapolations

ILSI HESI ACSA Membership

Industry: BASF Corporation, Bayer CropScience, Dow AgroSciences, DuPont Crop Protection, Monsanto Company, Syngenta Ltd.

Government Participation: US EPA, DG Health and Consumer Protection (Belgium), European Commission, Federal Institute for Health Protection of Consumers and Vet. Medicine (Berlin), OECD, PMRA (Health Canada), RIVM (Netherlands)

Academic Participation: Imperial College School of Medicine & Technology, Johns Hopkins SPH Center for Alternatives to Animal Testing, Medical College of Wisconsin, Michigan State University, Mississippi State University, University of California (Riverside), University of Nottingham, University of Padua, University of Southampton

Other Participants: BBL Sciences, CIIT Centers for Health Research, Pacific Northwest National Laboratory, toXcel International Ltd., Tox Path Inc.

Systemic Toxicity Basic Principles

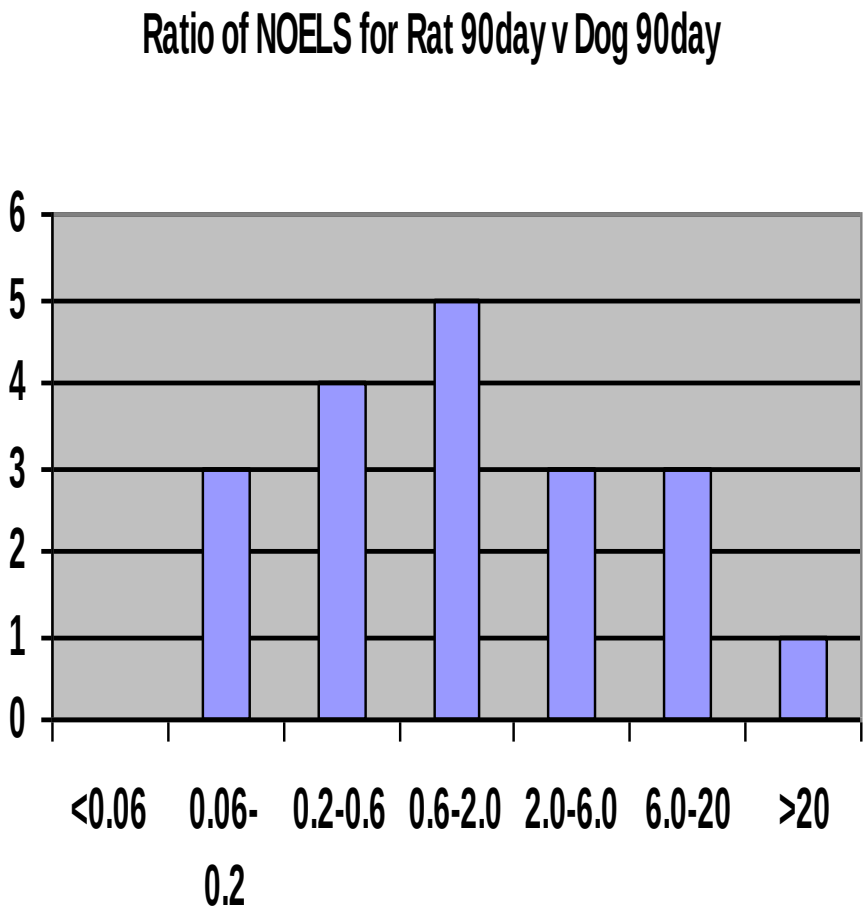
- Suite of studies designed to cover range of human exposure durations
- Indicators (trigger effects) in the basic studies which, if negative, give a high level of confidence of no relevant adverse effects
- Second tier studies to more precisely quantify such effects, if relevant for risk assessment

28 day study in rat

- ADME
- Clinical chemistry and hematology
- Triggers for neurotoxicity, immunotoxicity, endocrine effects
- Histopathology
- 14-day recovery group

Is the dog necessary?

- More sensitive species assumed to be relevant
- Distribution of relative sensitivities
- Dog more sensitive c.35% cases
- Need to include the dog



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90 day dog study

- Repeated ADME evaluation (e.g. on day 1, weeks 4 & 13)
- Repeated Clinical Chemistry & Haematology (e.g. pre-study, weeks 4 & 13)
- Physiological evaluation (e.g. cardiovascular, respiratory)

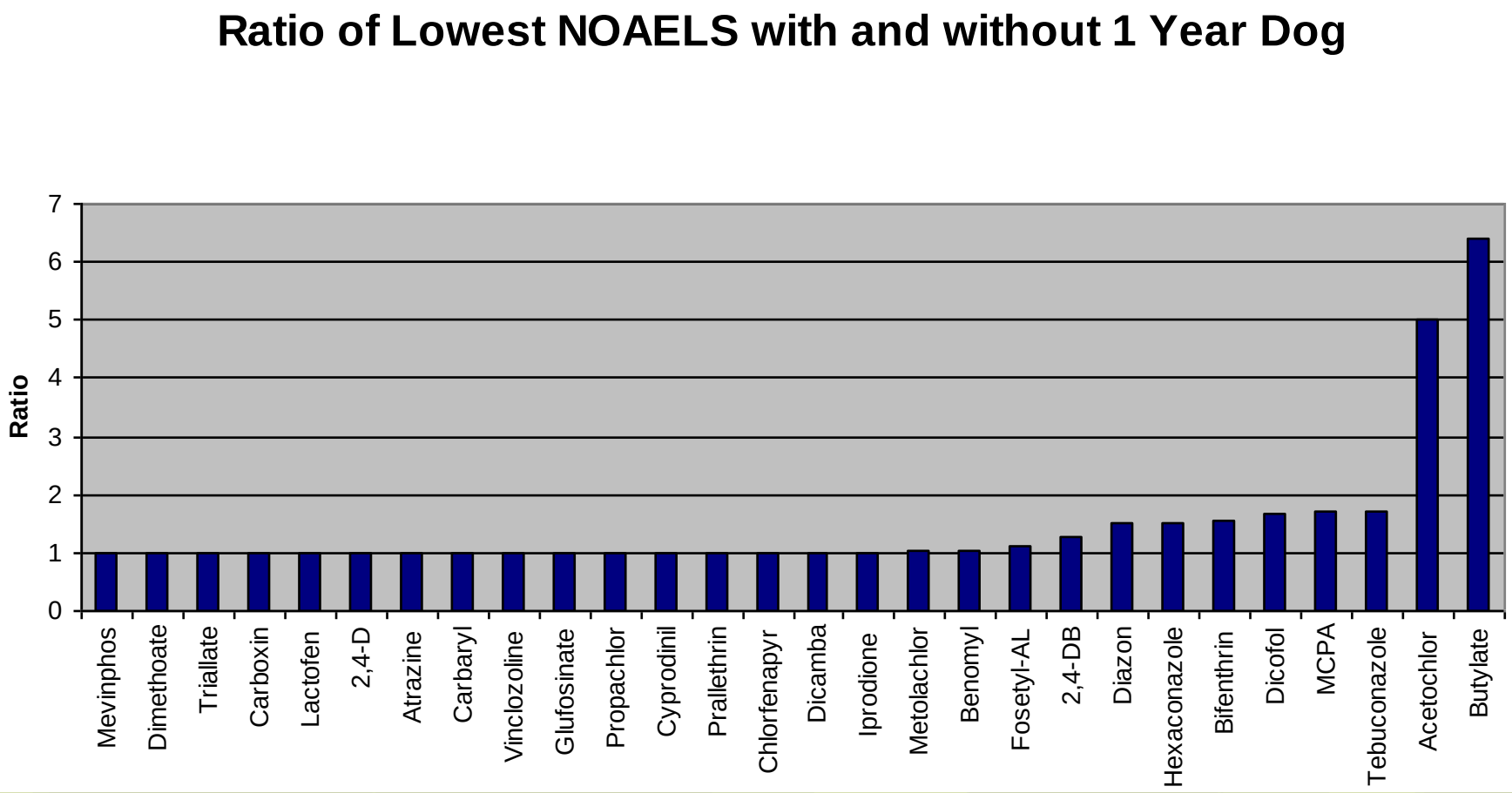
How to get data relevant for one day human exposure?

- No new study required if
  - in-life observations on day 1 in dog 90 day study from key effects
  - OR
  - adequate MoE from 28-d rat and 90-d dog
- Otherwise
  - refine exposure assessment
  - consider need for acute study in rat or dog

Data relevant to Exposure over 6 months

- 12 month study in rat as an interim kill in 24month carcinogenicity study
- 24 month study for carcinogenicity and for elderly life stage
- Mouse study shown to add no significant extra data apart from high dose liver tumours, usually discounted
- Compounds should be shown to be not genotoxic

Is the 12 month dog study necessary?



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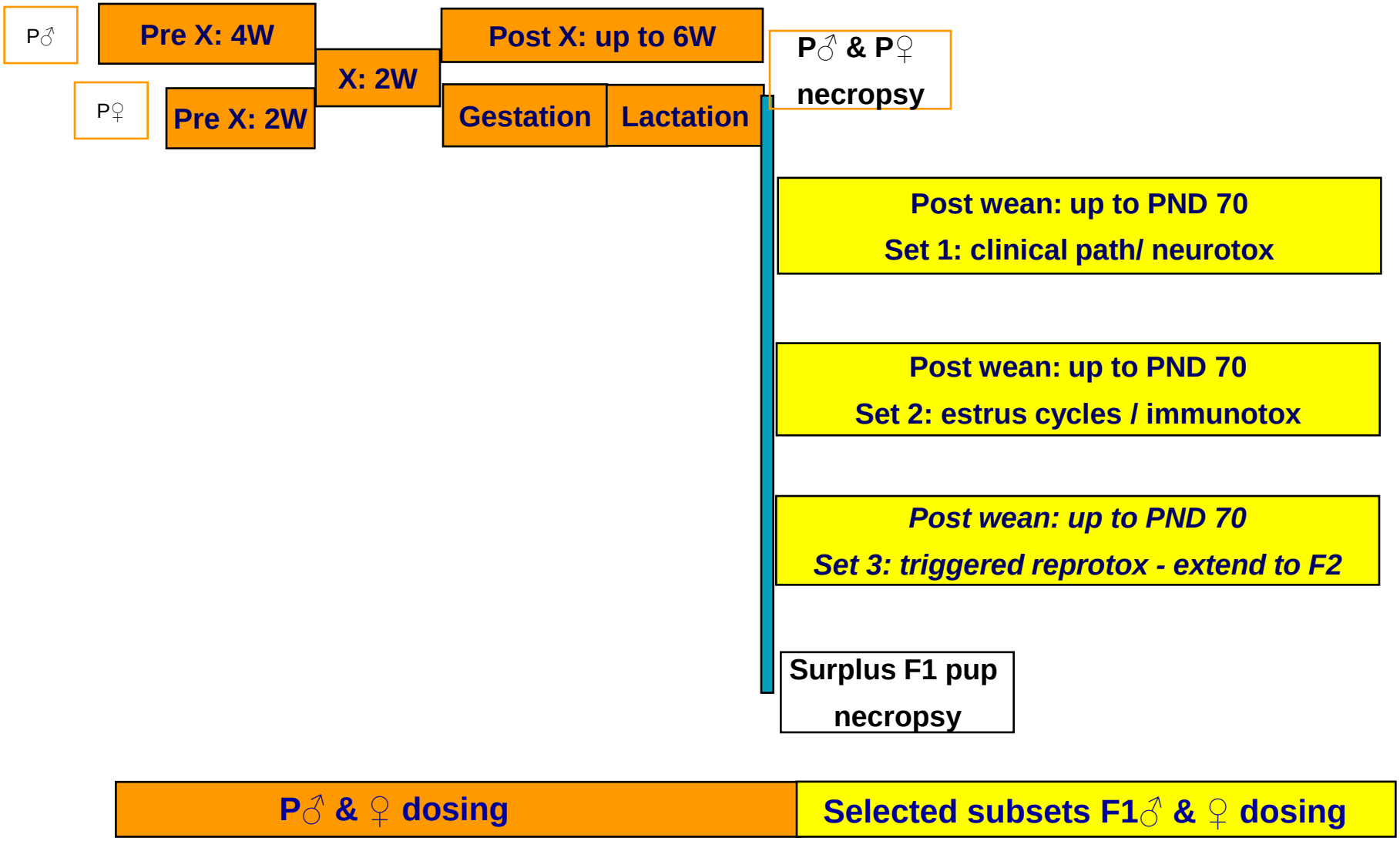
Route to Route

- Understanding of “internal dose” built in to all studies from ADME
- Dermal and inhalation absorption studies
- Dermal and inhalation local toxicity studies
- Repeat dose dermal toxicity studies have dosimetric and welfare concerns

Base Set (Tier I) Life Stages Studies

- F1-’extended’ one-generation reproduction study in rat
- Developmental toxicity study in second species (rabbit)

F1-'extended' : 1-Gen Study



The Risk Assessment Matrix
Tier 1 Studies

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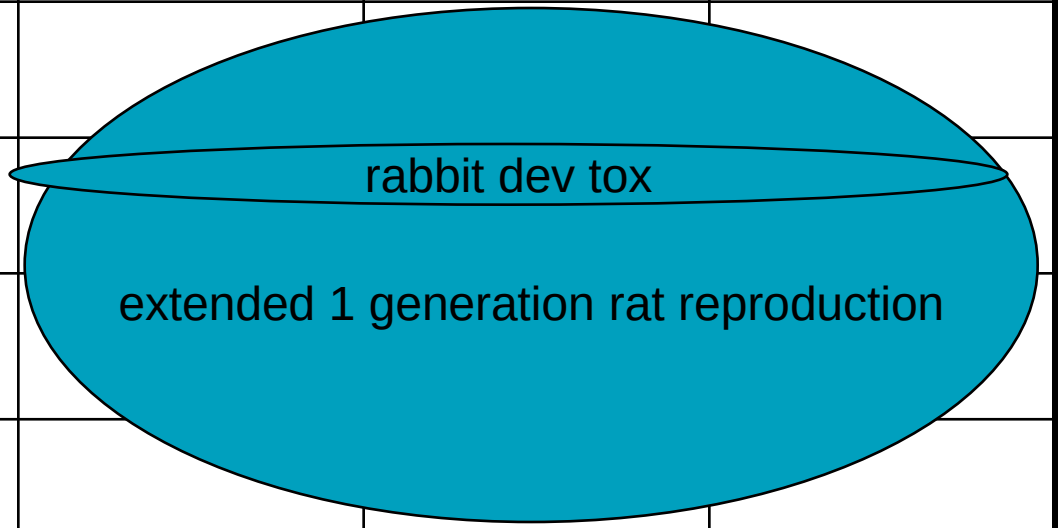
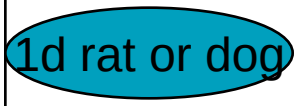
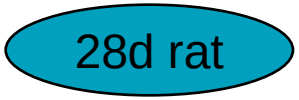
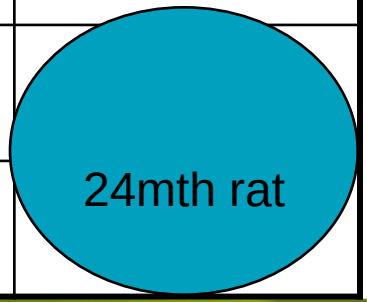
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult				
Elderly				









Comparison of Number of Animals Required

Animals	Current paradigm	New paradigm
rats	5920	2120
mice	520	0
rabbits	80	80
dogs	72	48
Total	6592	2248

ILSI ACSA Proposals address Concerns with Current Testing

- Shorter term durations of human exposure are adequately covered
- Special endpoints such as neurotox and immunotox are covered in the basic studies
- The value of the dog is to determine more sensitive species
- Increased endpoints in reproduction study covering lifestages
- More ADME and kinetic data to help with extrapolations
- Reduced number of animals required

WHAT'S OUR QUESTION?

Optimized *in vivo* testing; uncertainties, reliability & use for regulatory testing - what lessons can we draw from experience in toxicology?

Optimized

- What are we trying to optimise?

- What question are we trying to answer?

  - An accurate forecast of the effects and dose/time responses of a chemical in the human population or the environment
  - Optimise on what?
    - Accuracy
    - Time
    - Cost
    - Use of Animals

Uncertainty & Unreliability

- How much of the matrix of effects and dose/time responses of a chemical does the testing strategy cover?
- How much does it need to cover?
- Can you narrow the scope by bringing in exposure?
- How well does tonnage act as a surrogate for exposure potential?

Uncertainty & Unreliability

Data quality

- Test substance
- Study Design
- GLP
- Technical Competence

Data relevance

- Route
- Duration of Exposure
- Dose response
- Species extrapolation

What is evidence based toxicology?

- Recent offerings on the subject have rolled up several factors
  - Integrity of data
  - Relevance of animal studies
  - Weighing evidence from human studies
- It is trying to take out systematic bias, reduce controversy and increase levels of certainty over the toxicology of a chemical

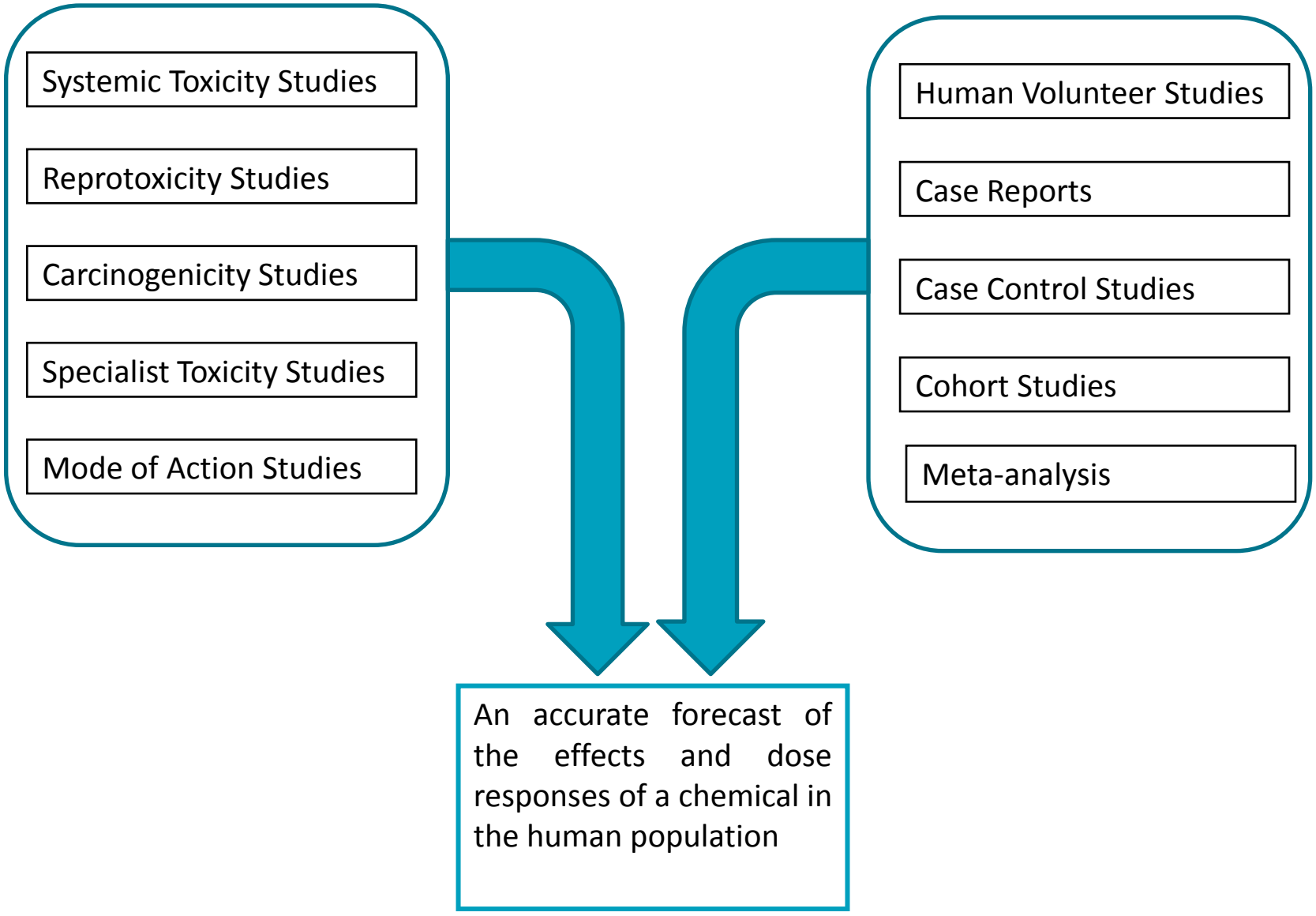
What do we mean by the toxicology of a chemical?

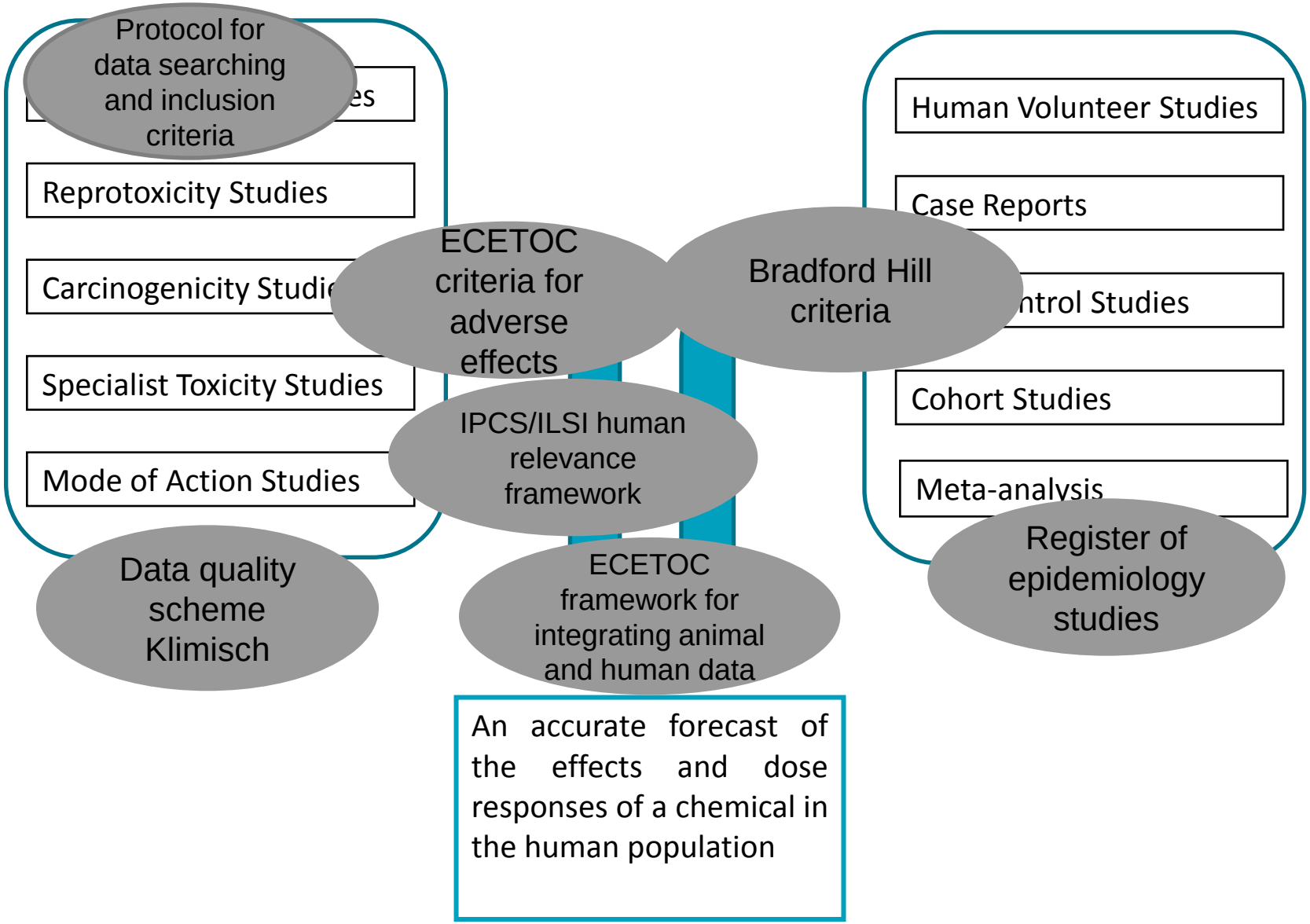
- An accurate forecast of the effects and dose responses of a chemical in the human population

- Based on evaluation of

  - Animal and laboratory data

  - Human data


Systemic Toxicity Studies
Reprotoxicity Studies
Carcinogenicity Studies
Specialist Toxicity Studies
Mode of Action Studies
Human Volunteer Studies
Case Reports
Case Control Studies
Cohort Studies
Meta-analysis
An accurate forecast of the effects and dose responses of a chemical in the human population


Protocol for data searching and inclusion criteria
Reprotoxicity Studies
Carcinogenicity Studie
Specialist Toxicity Studies
Mode of Action Studies
Data quality scheme Klimisch
ECETOC criteria for adverse effects
Bradford Hill criteria
IPCS/ILSI human relevance framework
ECETOC framework for integrating animal and human data
Human Volunteer Studies
Case Reports
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Cohort Studies
Meta-analysis
Register of epidemiology studies
An accurate forecast of the effects and dose responses of a chemical in the human population

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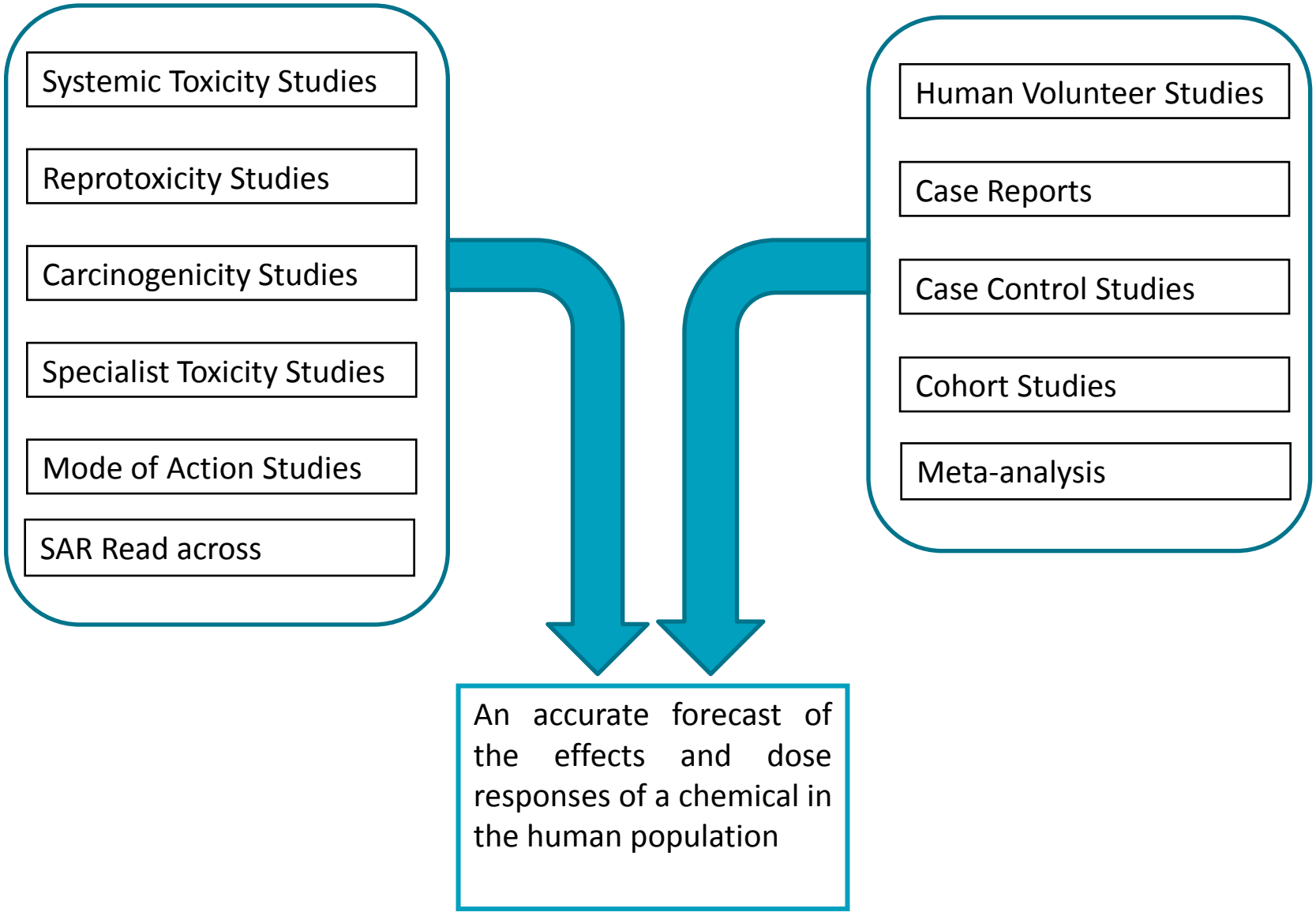
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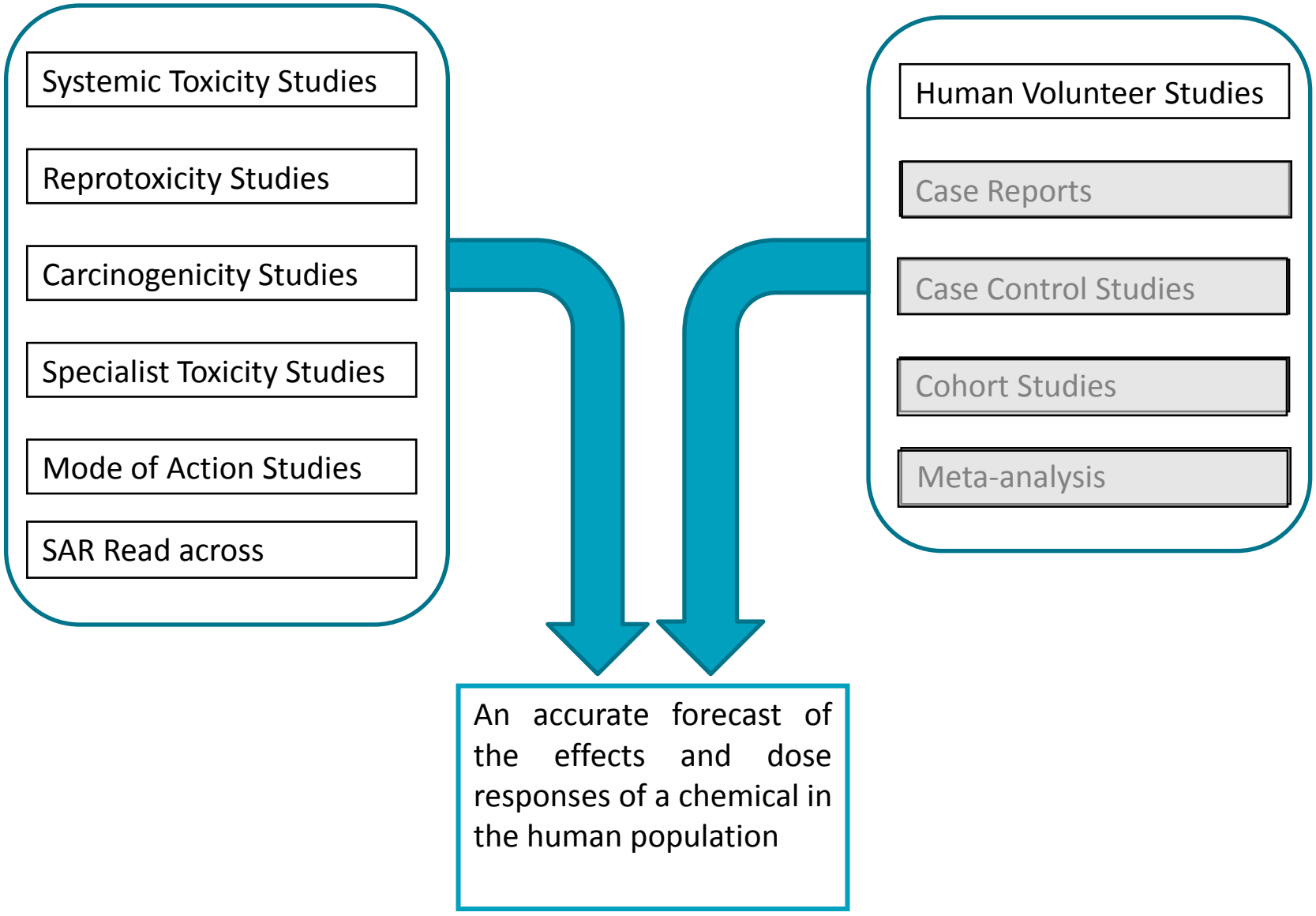
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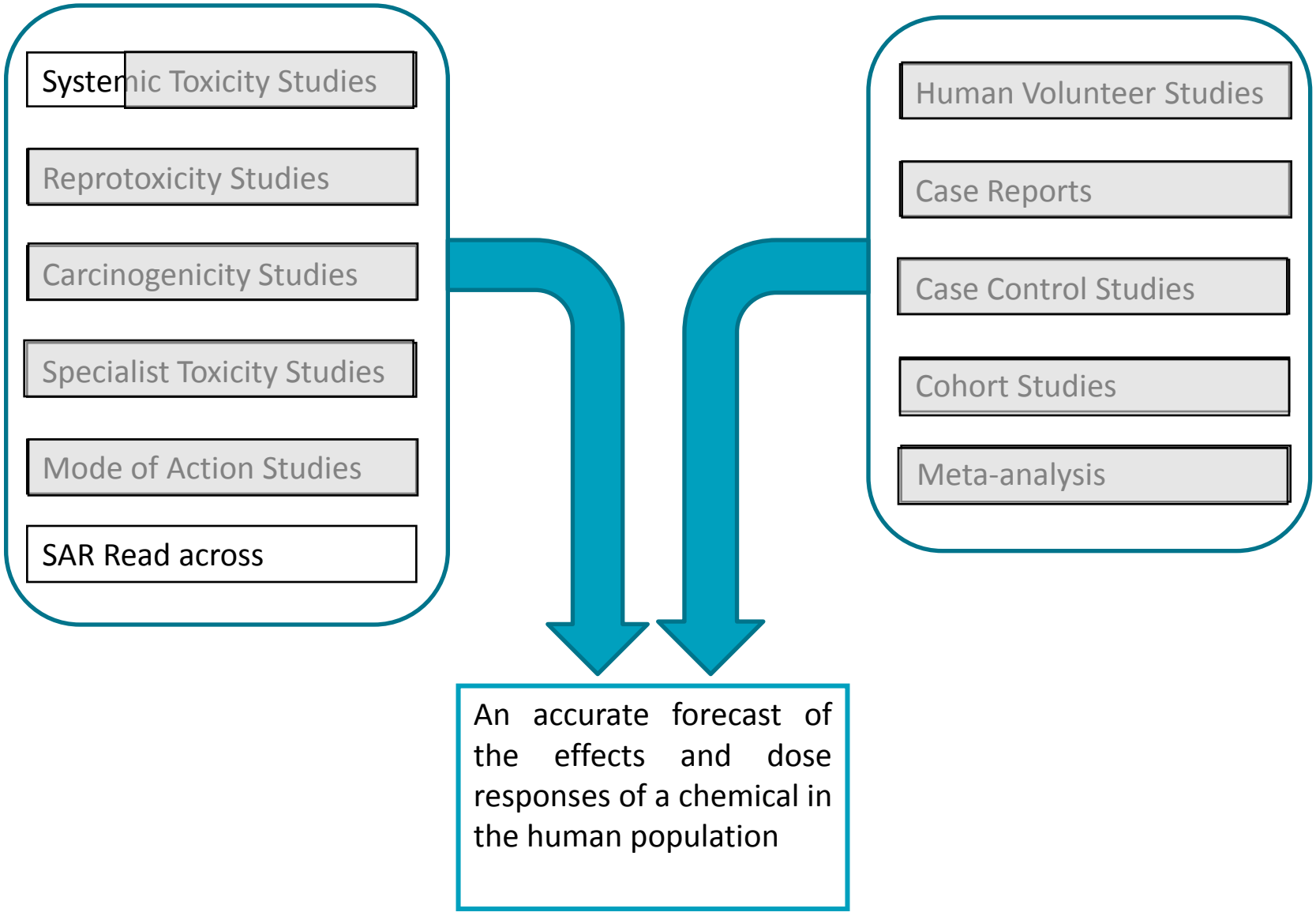
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