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AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA)

Systemic Toxicity Task Force

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Syngenta

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The Comet

Are we stretching our technology too far?

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Are we stretching our technology too far?

The Nimrod

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The Airbus

Are we stretching our technology too far?

The Nimrod

The Risk Assessment Matrix: Duration of Exposure

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

The Risk Assessment Matrix: Life Stages

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

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The Risk Assessment Matrix: Life Stages

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult (~Systemic)			90d rat	24mth rat
Elderly				

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The Risk Assessment Matrix: Life Stages

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult (~Systemic)			90d dog 90d rat	1yr dog 24mth rat
Elderly				

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The Risk Assessment Matrix: Life Stages

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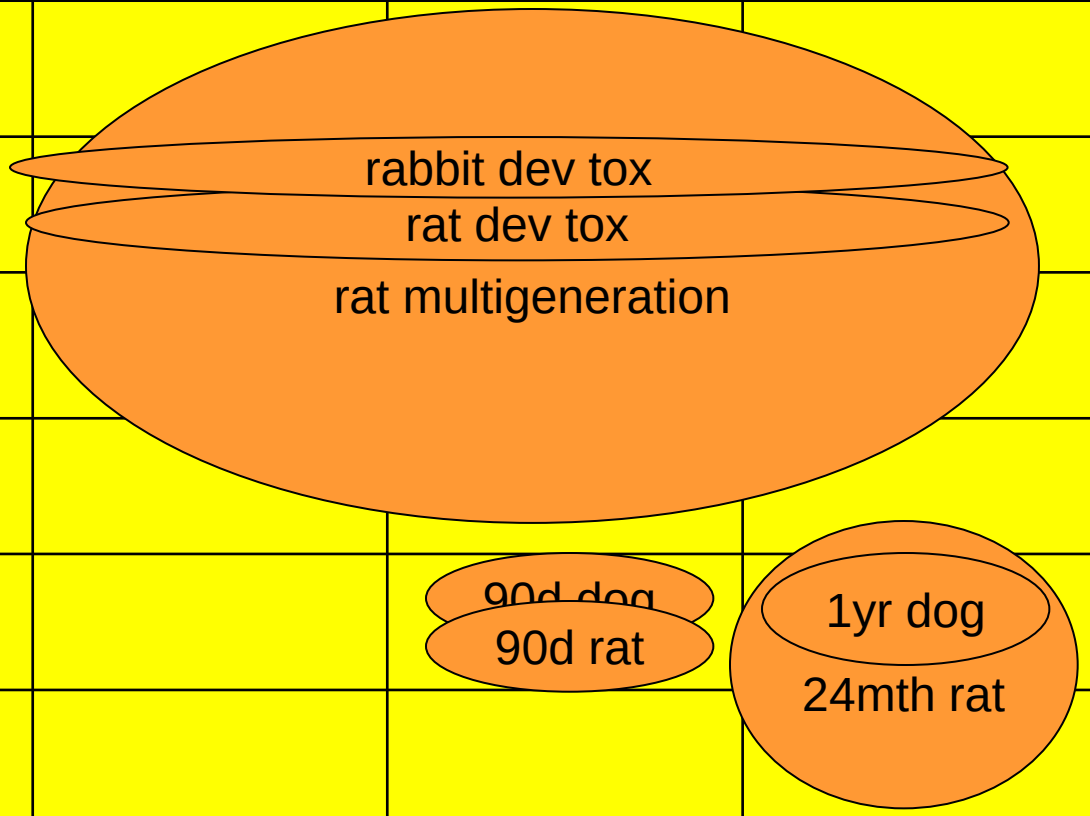

Concerns with Current Testing

- 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 the dog?
- Need more ADME and kinetic data to help with extrapolations

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

Using the Tiered Approach - Neurotoxicity

- Evidence of neurotoxicity from FOB, motor activity, pathology
- Tier 1 very similar to current neurotoxicity protocols

and

- Low margin of exposure

then

- Design appropriate study to get more information on effect and dose response

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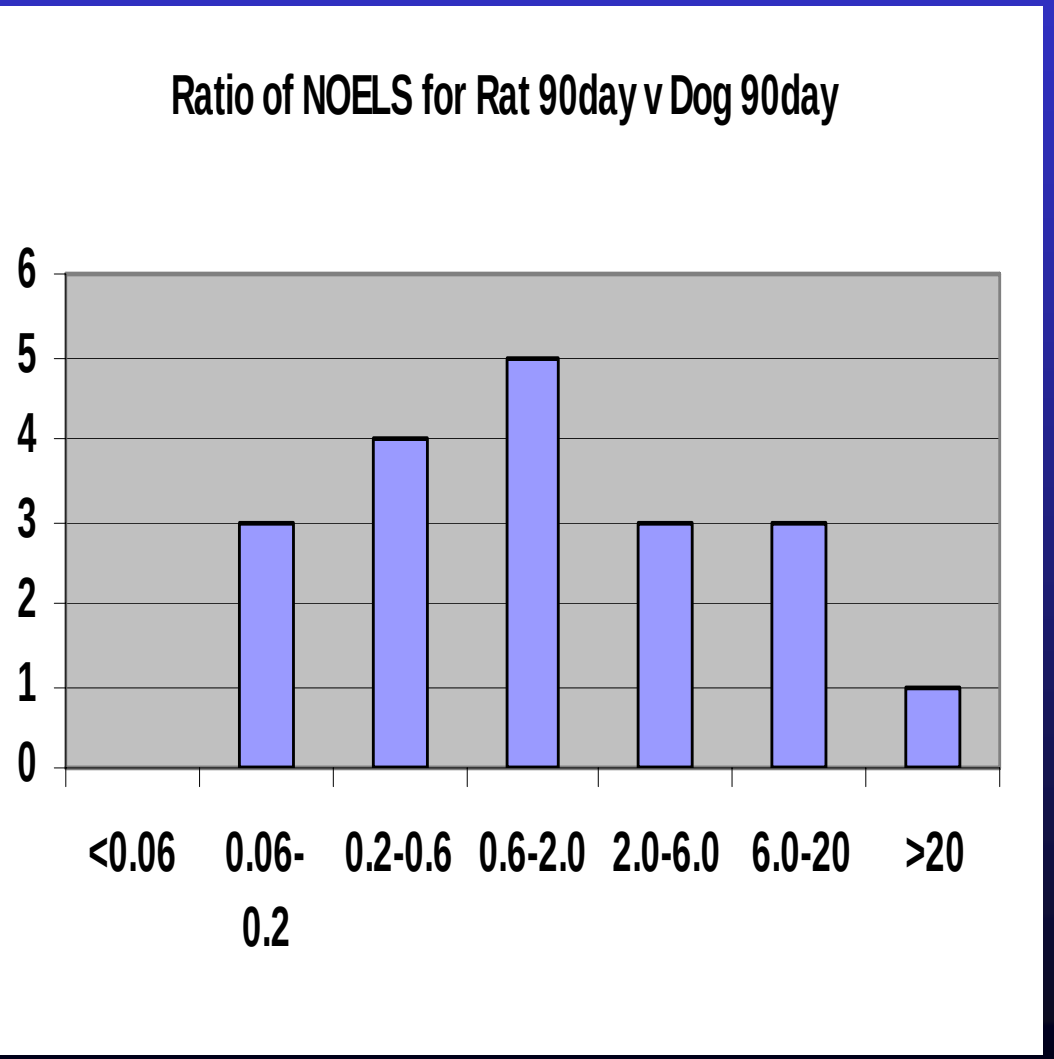
Is the dog necessary?

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



90-day dog study

Repeated ADME evaluation (e.g., on day 1, weeks 4 and 13)

- Repeated Clinical Chemistry and Haematology (e.g., pre-study, weeks 4 and 13)
- Physiological evaluation (e.g., cardiovascular, respiratory)
- Dermal dosing for ADME (during preliminary study for dose-setting)

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-day rat and 90-day dog
- Otherwise
  - refine exposure assessment
  - consider need for acute study in rat or dog

Exposure over 6 months

- 12-month study in rat as an interim kill in 24-month 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

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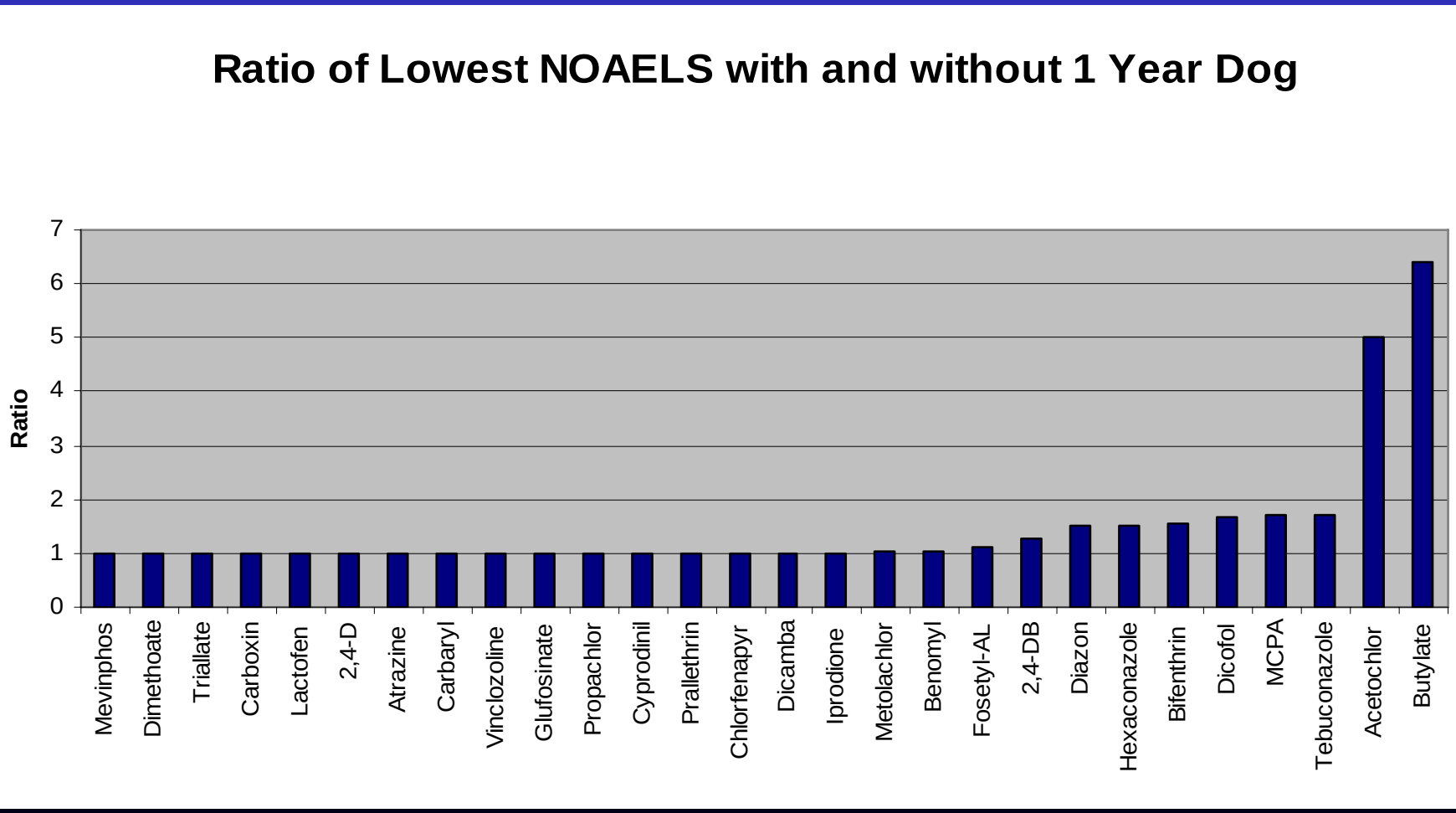
Is the 12-month dog study necessary?



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

The Risk Assessment Matrix: Systemic Toxicity

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Adult		28d rat		
Elderly				

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Childhood				
Adult		28d rat	90d dog	
Elderly				

The Risk Assessment Matrix: Systemic Toxicity

	1 Day	2-30 days	1-6 months	>6 months
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Childhood				
Adult	1d rat or dog	28d rat	90d dog	
Elderly				

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The Risk Assessment Matrix: Systemic Toxicity

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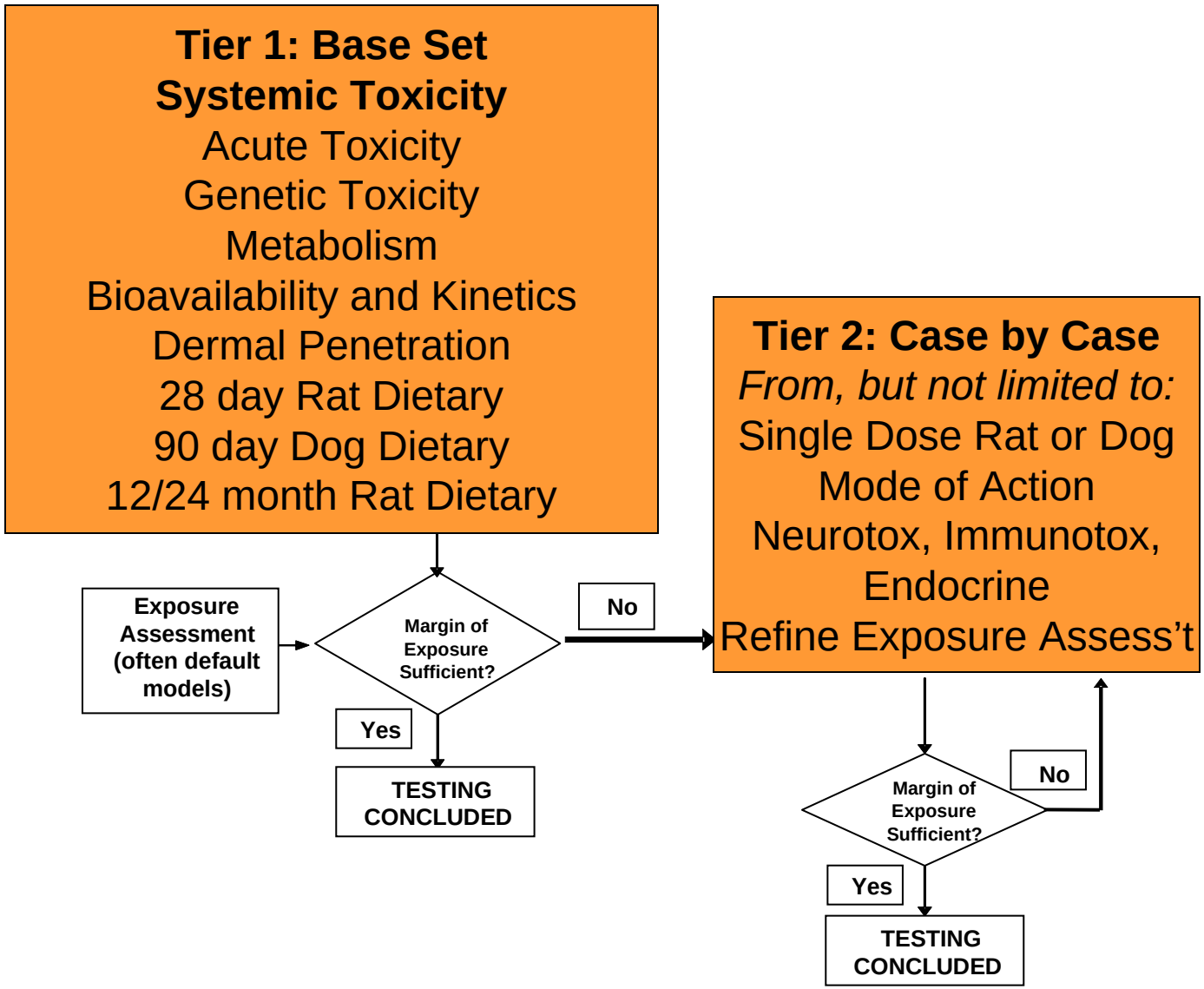
Tier 1: Base Set
Systemic Toxicity
Acute Toxicity
Genetic Toxicity
Metabolism
Bioavailability and Kinetics
Dermal Penetration
28 day Rat Dietary
90 day Dog Dietary
12/24 month Rat Dietary
Exposure Assessment (often default models)
Margin of Exposure Sufficient?
No
Yes
TESTING CONCLUDED
Tier 2: Case by Case
From, but not limited to:
Single Dose Rat or Dog
Mode of Action
Neurotox, Immunotox, Endocrine
Refine Exposure Assess't
Margin of Exposure Sufficient?
No
Yes
TESTING CONCLUDED

Comparison of Number of Animals Required for Systemic Toxicity

Animals	Current paradigm	New paradigm
rats	680	720
mice	520	0
dogs	72	48
Total	1272	768

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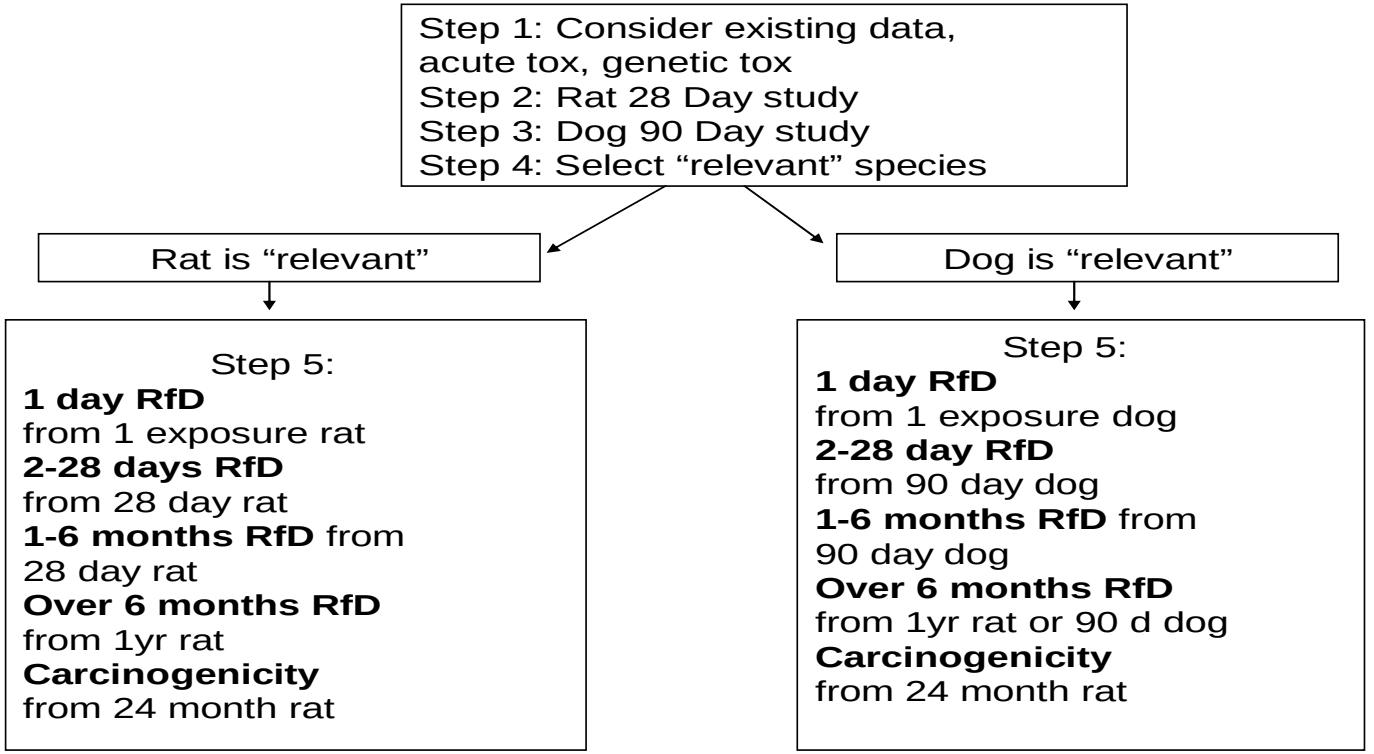
Stepwise approach



What is the output of the safety assessment?

- A qualitative and quantitative characterisation of the hazard potential of the compound
- A series of Reference Doses
- 1-day exposure
  - 28-day rat or 90-day dog or 1-day rat or dog
- 2-28 days exposure
  - 28-day rat or 90-day dog
- 1-6 months exposure
  - 90-day dog or 28-day rat
- Over 6 months exposure
  - 24-month rat or 90-day dog
- Assessment of carcinogenicity
  - Genetic toxicity and 24-month rat

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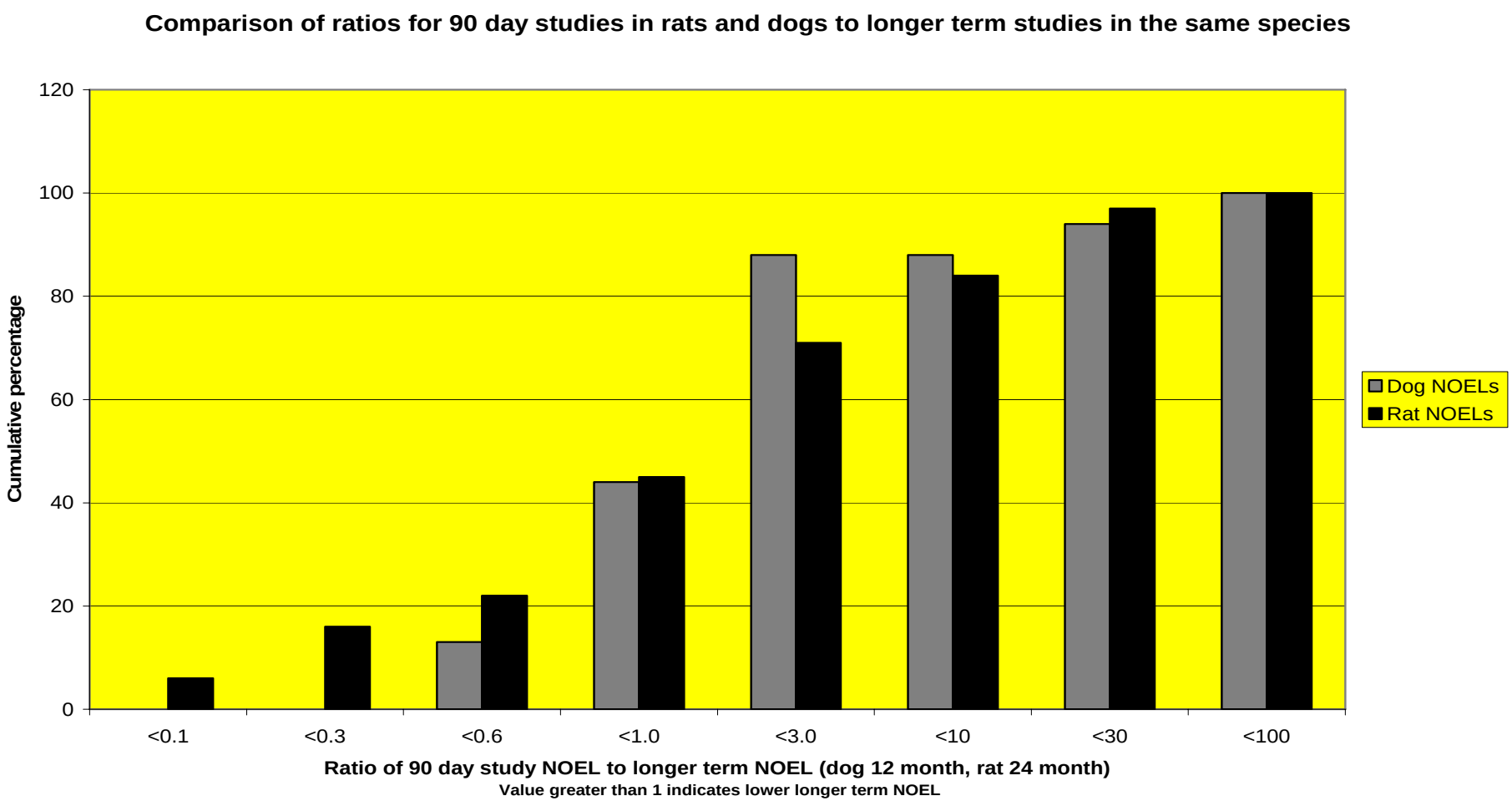
Why does the NOEL vary at different time points?



Rozman and Doull* identified the factors which underlie the toxicokinetics and toxicodynamics:

Toxicokinetics	Toxicodynamics
-Absorption	-Injury
-Elimination	-Recovery
-Distribution	-Adaptation
-Biotransformation	-Repair
-Excretion	-Reversibility

*Rozman, K.K. and Doull, J. (2000) Dose and time as a variable of toxicity. Toxicology: *144*, 169-178

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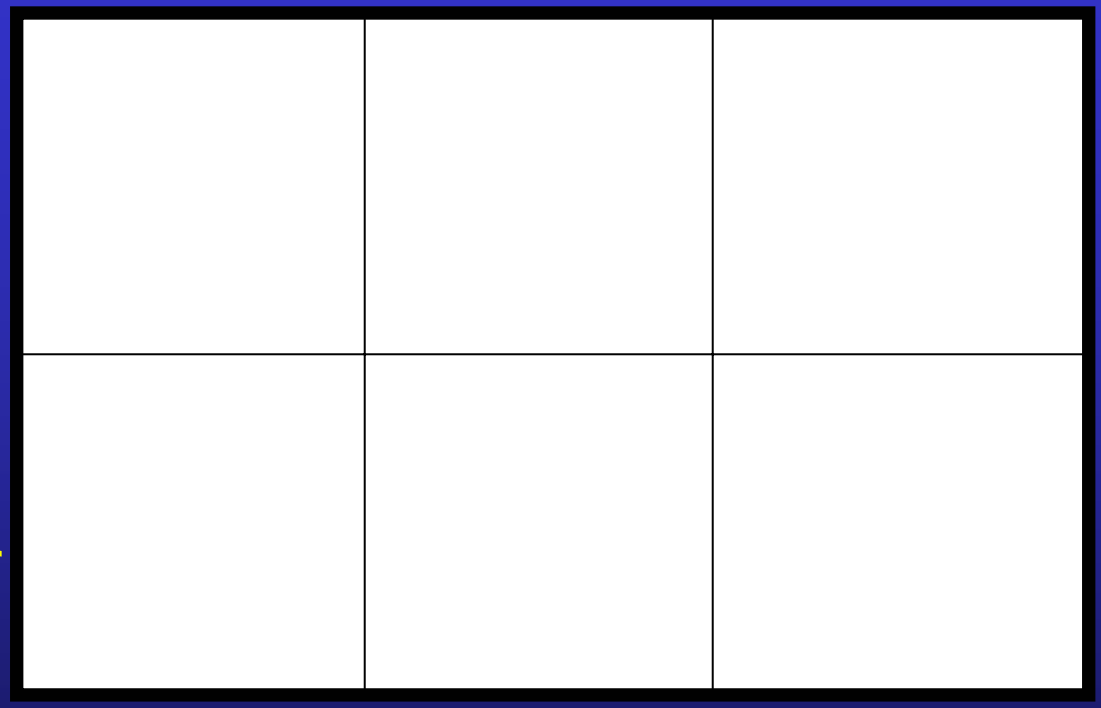
Effect depends only on current internal dose.

Resident effect

Dynamics

Effect depends on current and past internal dose -- "history" effect

Damage and repair



Rapid elimination

Slower elimination

Accumulation

Kinetics

What determines the relationship between NOELS for different exposure durations?

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		ADI <<< ARfD

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Kinetics

What determines the relationship between NOELS for different exposure durations?

Resident effect

Dynamics

Damage and repair

The highest spike	Highest total exposure within DT90 window (resulting in the max. internal dose).	Total exposure (AUC)
Frequent spikes above a threshold	Highest total within a time-window whose duration is a determined by DT90 and repair rate.	Total exposure (AUC)

Rapid elimination | Slower elimination | Accumulation

Kinetics

What exposures are of greatest concern?

How do we deal with varying or intermittent exposures?

The time weighted average daily dose (TWADD) for any given portion of the exposure should not exceed the relevant reference dose.

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To expand this:

- **No single day's exposure should be above the 1-day RfD, *and***
- **The TWADD for any period of 2-28 days should not exceed the 2-28 days RfD, *and***
- **The TWADD for any period of 1-6 months should not exceed the 1-6 months RfD, *and***
- **The TWADD for any period of 6 months should not exceed the over-6 months RfD.**

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- **The TWADD for any period of 6 months should not exceed the over-6 months RfD.**

Operates for compounds across the matrix as the relationship between the RfDs will reflect their properties.

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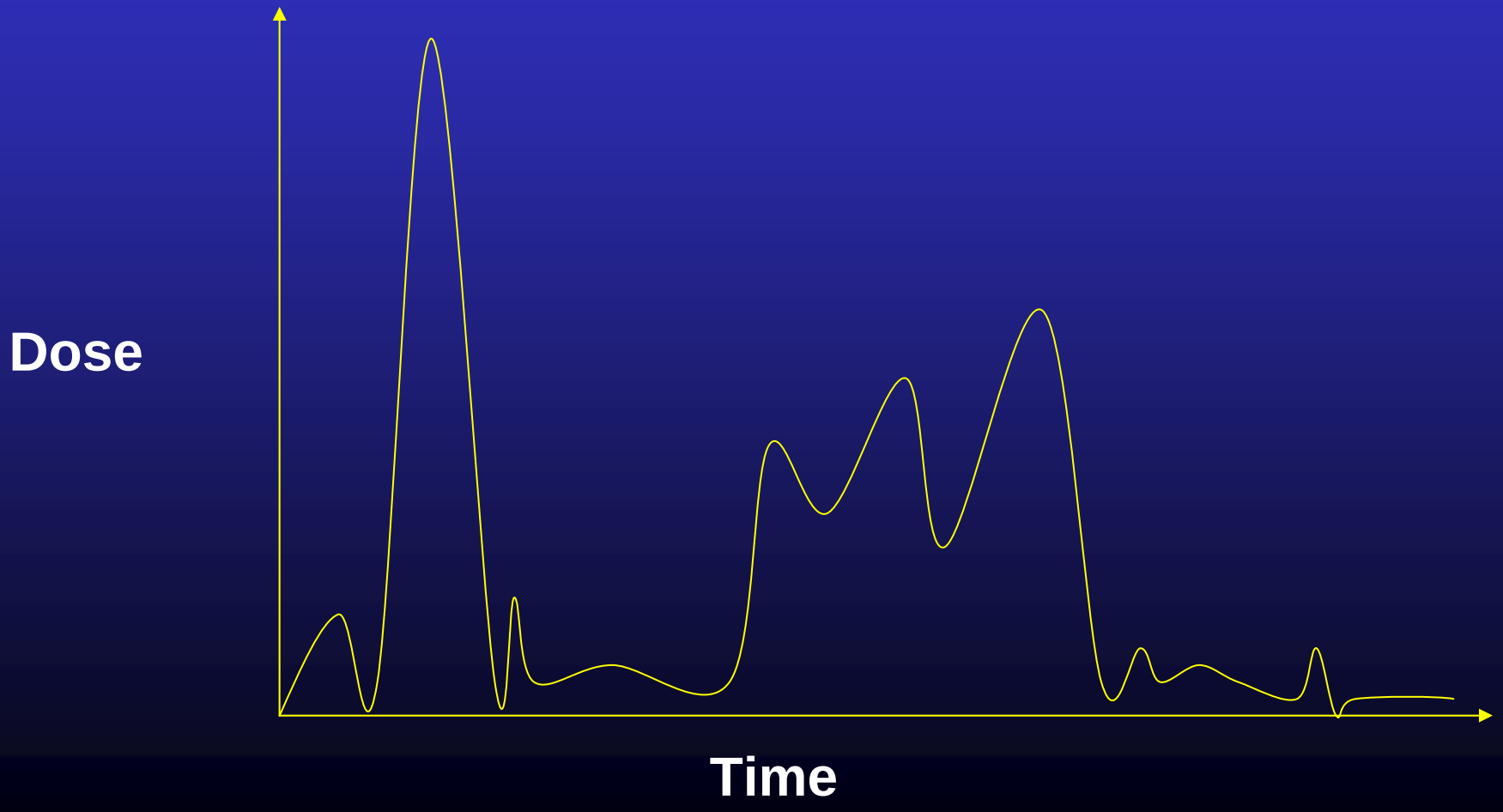
How do we deal with varying or intermittent exposures?



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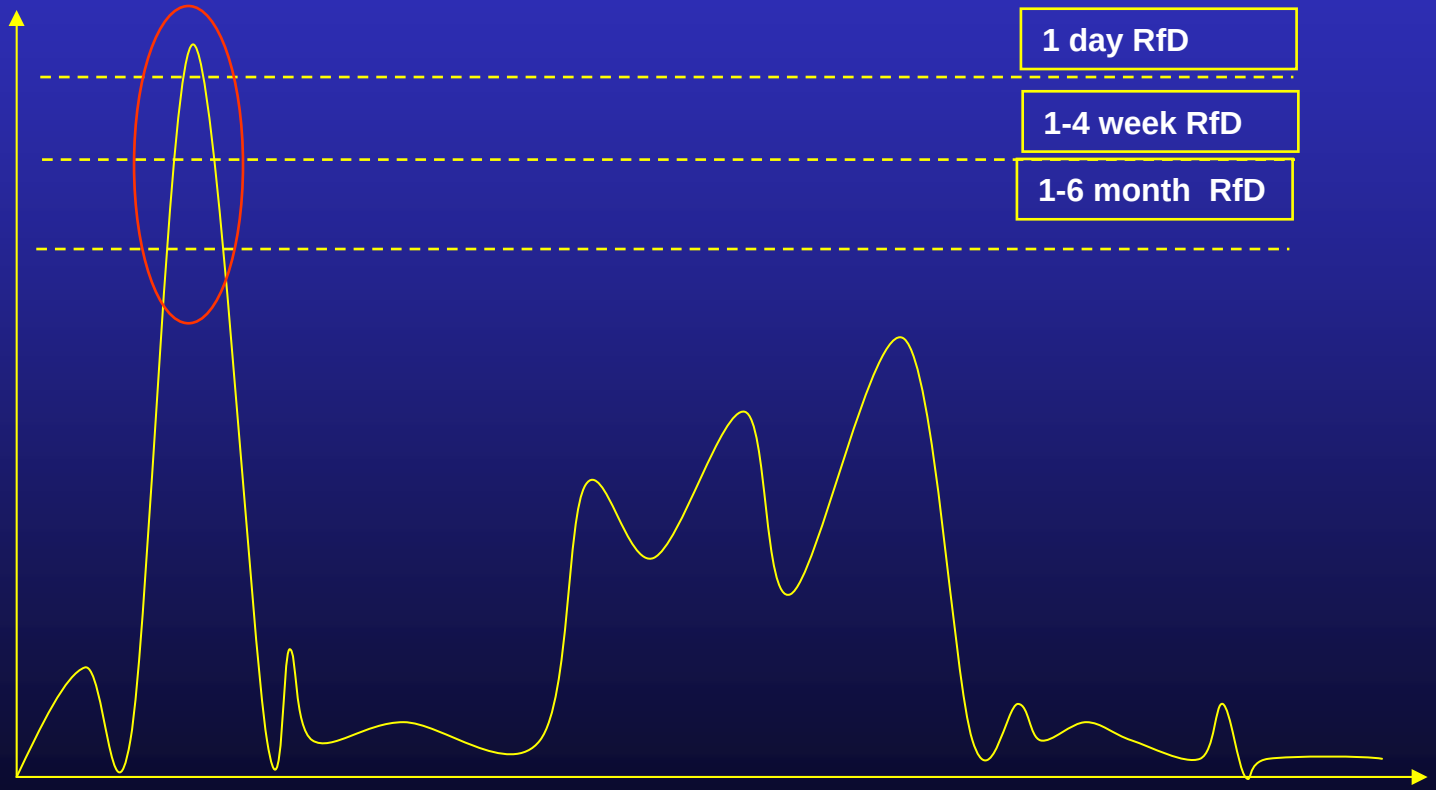

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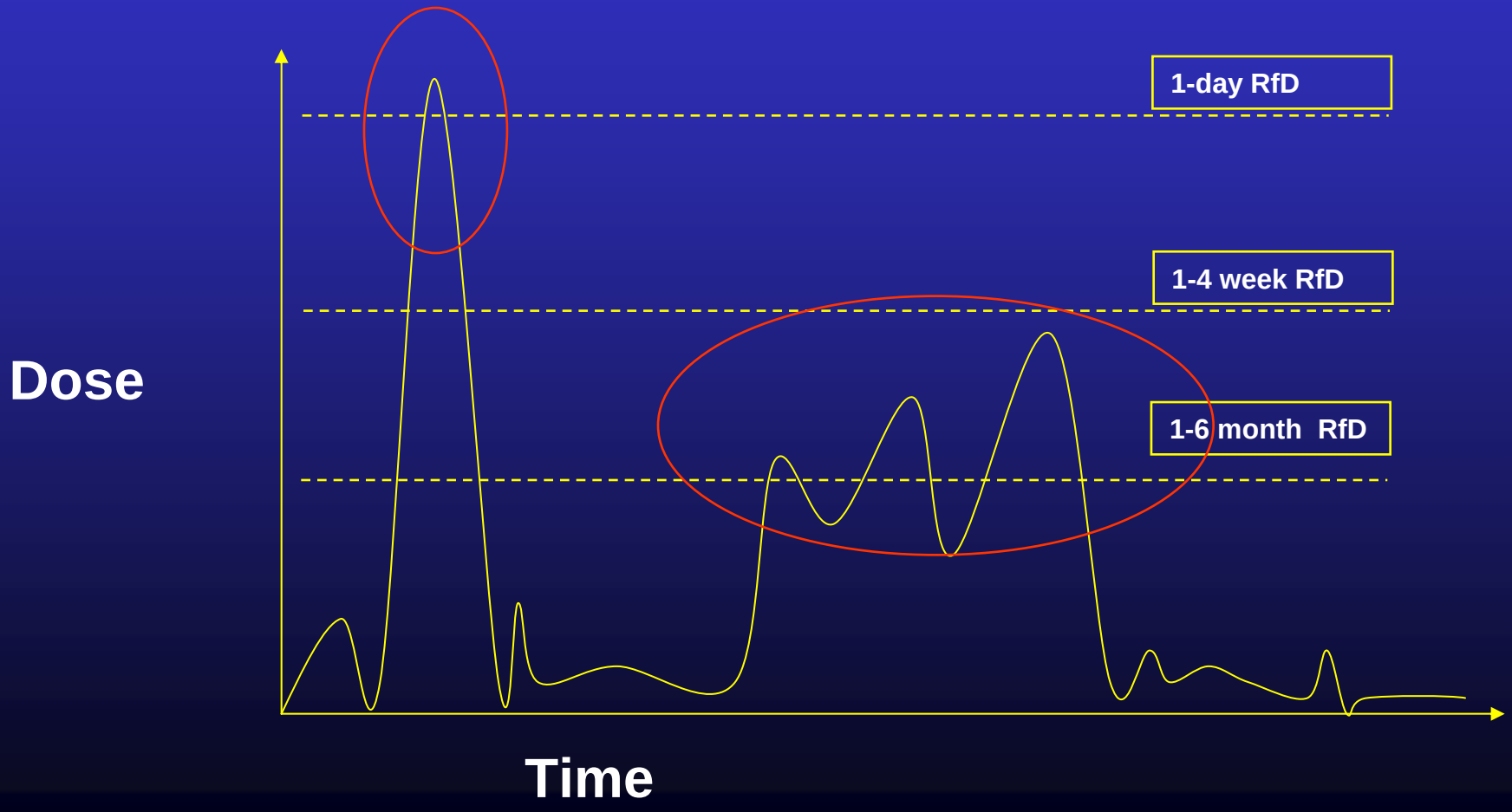

ACSA Proposal Addresses Concerns with Current Testing

- 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
- More ADME and kinetic data to help with extrapolations
- Reduced number of animals required
- Greater understanding of characteristics of chemical