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AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA)

Life Stages Task Force

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Life Stages Task Force

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Life Stages Task Force Objectives

- Reduce / refine/ replace animal usage
- Optimize study design / allow flexibility
- Exposure characteristics taken into account (route, level, frequency, duration)
- Facilitate risk assessments for relevant life-stages
- Tiered approach to testing

Conolly, R.B. et al., Stimulating research to improve the scientific basis of risk assessment. Toxicol Sci. 49: 1-4, 1999.

Goodman, J.I. The traditional toxicologic paradigm is correct: dose influences mechanism. Environ Health Perspect. 106, Suppl. 1: 285-288, 1998.

Food-use Pesticide: Current Testing

Required

- Prenatal developmental: 2 species
- 2-generation reproduction: 1 species

Conditional / Case-by-case

- Developmental neurotoxicity
- Endocrine modulation assessment
- Developmental immunotoxicity
- (for EU) TK at selected life stages

Problems with Current Testing

- 'Inevitable' progression to conditional / case-by-case studies
- High dose complications
- Relevance of route of administration
- Duplication of exposures
- Increasing use of animals
- Concern not addressing key life stages

Life Stages Review Tasks

- Reviewed existing tiered testing approaches
- Examined existing screens (including *in vitro)* and their value in risk assessment
- Considered ADME and TK needs and their integration into life stages evaluation
- Risk assessments for different life stages

Examples of Tiered Approach

Chemicals

- OECD SIDS and US EPA HPV
- NONS (92/32/EEC) or TSCA PMN

Pharmaceuticals

- ICH (human)
- VICH (veterinary drug residues)

Principle of tiered testing accepted by public/ regulators

Considerations of Life Stages Tiered Approach

Risk assessments *drive* the studies

Objectives of Tier 1

- Determine effects on reproduction
- Determine sensitivity of life stages (other than young adult) to major toxicities

Considerations of Life Stages Tiered Approach

Base set (Tier 1)

- Conduct exposure estimates (route, duration, amount)
- Consider life stages to be protected
- Use relevant group sizes for biological / statistical confidence in results
- Include key indicators (triggers) which, if negative, give a high level of confidence of no adverse effects ***If positive → Tier 2***
- Conduct risk assessment ***If low MOE → Tier 2***

Considerations of Life Stages Tiered Approach

Tier 2

- Exposure studies or refined estimates
- Focused second tier studies to quantify / characterize specific effect at biologically relevant doses
- Conduct risk assessment

Considerations of Life Stages Tiered Approach

Risk assessments involving life stages

- Dietary: acute and chronic
  - Infants, 1-6, 7-12, 13-19, >55 years
- Residential: short-term, intermediate, long-term
  - Toddlers, adults (females 13+ years)
- Occupational: short-term, intermediate, long-term
  - Females 13+ years, males 13+ years

Base Set (Tier 1) Life Stages Studies

- F1-'extended' one-generation reproduction study in one species

  (most probable = rat)

- Developmental toxicity study in second species

  (most probable = rabbit)

Considerations for Base Set (Tier 1) Testing

- Consider systemic toxicity, ADME, and other relevant data → refine toxicity endpoints for inclusion
- Administration by route of relevant human exposure (dietary preferred over gavage: adjust dosage to dietary intake)
- ADME to determine “internal dose” and kinetics
- Relate “internal dose” in risk assessment

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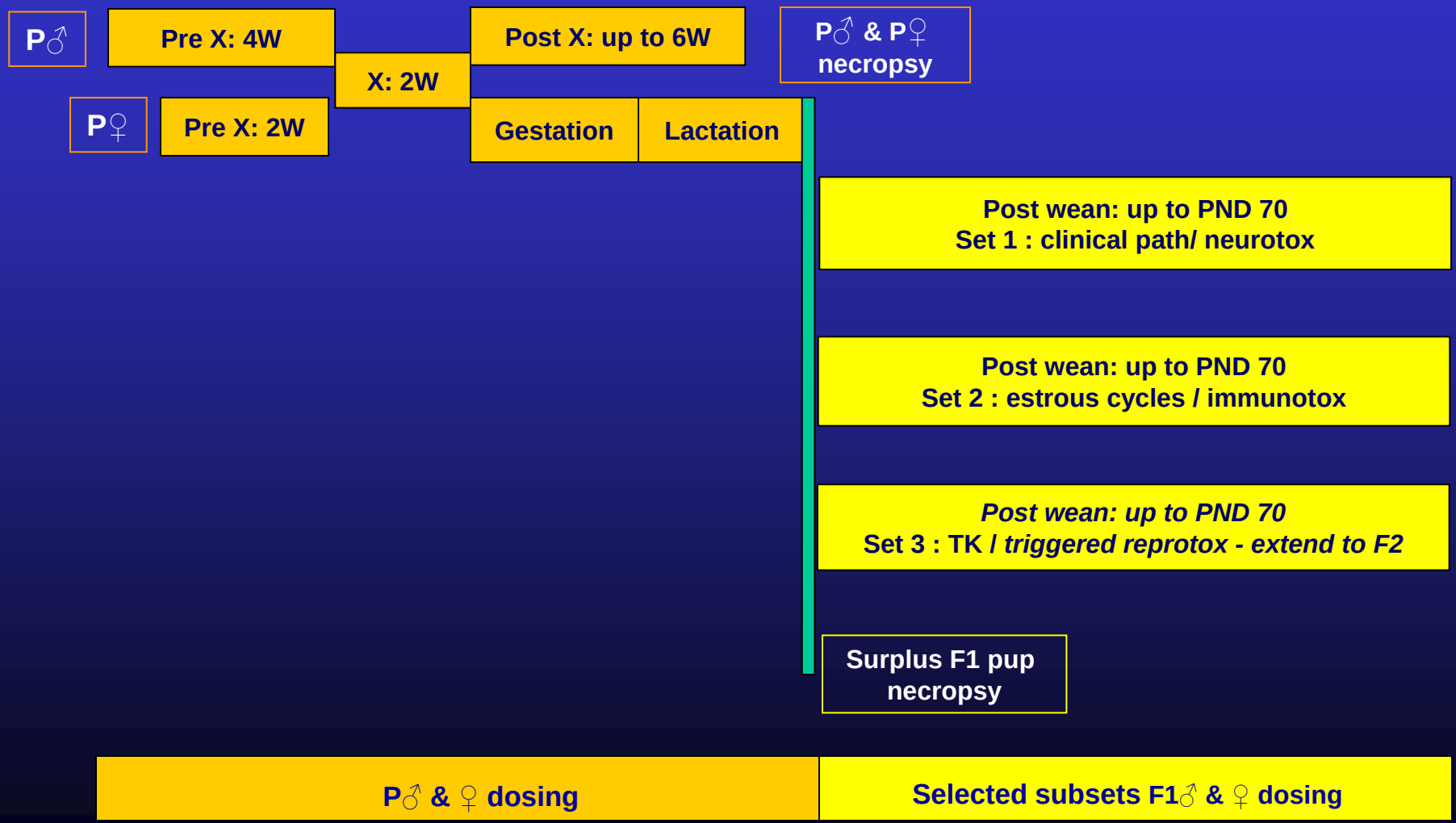
F1-'extended': 1-Gen Study



F1-'extended': 1-Gen Study

P generation

- N = sufficient for 20 litters / group
- Use ADME / TK in dose setting
- TK estimates at key stages of gestation / lactation
- Comprehensive repro evaluations
- Detailed histopathology on subset
- Use 'markers' for other toxicities identified from systemic toxicity studies
- Consider preliminary *in vitro* tests for potential mechanisms and refinement of endpoints

F1-'extended': 1-Gen Study

F1 generation (continues dosing to PND 70)

- Pre-wean (AG, sex, body weight, clinical observations)
- At PND 21, select **3 subsets** (each **1♂ and 1♀**)
- Surplus PND 21 pups (organ weight, histopathology, including neurological tissue)
- **Set 1**: Motor activity, FOB, neuropathology, clinical chemistry, hematology, thyroid hormones, detailed histopathology
- **Set 2**: estrous cycles, immunotox (SRBC antibody response; triggered phenotypic analysis of lymphocytes (if +) or natural killer cell assay (if -))
- **Set 3**: TK, endocrine, repro, and, *if triggered,* continue dosing beyond PND 70 and mate for F2 generation

Developmental Toxicity Study

Single developmental toxicity study in different species (likely rabbit)

- Design based on OPPTS 870.3700 / OECD 414
- Relevant human exposure route, but with **dietary** preferred over **gavage**
- Use ADME / TK in dose setting and measure TK
- Use ‘markers’ for toxicities identified from other studies, including histopathology
- Consider preliminary *in vitro* tests for potential mechanisms and refinement of endpoints

Potential Reduction in Animal Usage

Current testing guidelines

• 2 species developmental tox *(parental)*	160
• 2-gen reprotox *(parental and offspring)*	2600
• Developmental neurotox *(parental and offspring)*	1280
• Developmental immunotox *(parental and offspring)*	1280
	5320

Tier 1 testing only

• 1 species developmental tox *(parental)*	80
• Extended 1-gen reprotox *(parental & offspring)*	1400
	1480
(*If 2nd generation triggered*)	*(+1200)*

Considerations for Tier 2 Testing

Low MOE or triggers from Tier 1 testing lead to focused Tier 2 testing

- Case-by-case special studies to characterise effect(s)
- Conducted at relevant (*not MTD*) doses
- May include: further neurotox, immunotox, or endocrine tests, late-in-life sensitivity, fetal / neonatal ADME, detailed mode-of-action endpoints
- May include : 2-gen repro and/or second species developmental tox

Gains from Modified Approach

- Use of toxicokinetic and young adult systemic toxicity data in designing studies
- Assessment of systemic toxicity in young adults as a consequence of pre- and early postnatal exposure
- Developmental neurotoxicity assessment
- Developmental immunotoxicity assessments
- Assessment of multiple types of outcomes from the same population of animals
- Fewer numbers of animals used

Concessions under New Approach

- Shorter pre-mating exposures for males (4 weeks) and females (2 weeks) than the current 10-week period (although considered adequate for fertility assessment).
- Only mating F1 animals and producing an F2 generation *if triggered.*
- No prenatal developmental toxicity study in the rat.