Using Animal Data to Communicate Human Risk

Labels without Categories: A Workshop on FDA's Pregnancy and Lactation Labeling Rule
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Outline

- **Terminology**
- **Animal Data Sources**
  - Study Designs
  - Types of Data collected
- **Hazard identification – treatment-related signals**
  - Data interpretation
- **Evaluating human risk**
  - Integrating study data – CDER Guidance
- **Conclusions**

Terminology Part 1

- Equivalent Terms:
  - Reproductive and Developmental Toxicology
  - Developmental and Reproductive Toxicology (DART)
  - Reproductive Toxicology
  - Reprotox

Reproductive Toxicity in Animals

- Animal reproductive toxicity data is frequently the only information available to assess reproductive risks in humans
  - Prescriber decisions; patient counseling

Testing Guidelines:

- ICH S5 Detection of toxicity to reproduction for medicinal products & toxicity to male fertility
  - Describes what needs to be tested and some general approaches for testing
  - Allows flexibility for alternative study designs

- ICH S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals - Addendum (R1): Step 4
  - Describes additional considerations for biologics

ICH S5: Reprotox Testing Strategy

A. **Premating to conception** - adult male and female reproductive functions, development and maturation of gametes, mating behavior, fertilization

B. **Conception to implantation** - adult female reproductive functions, preimplantation development, implantation

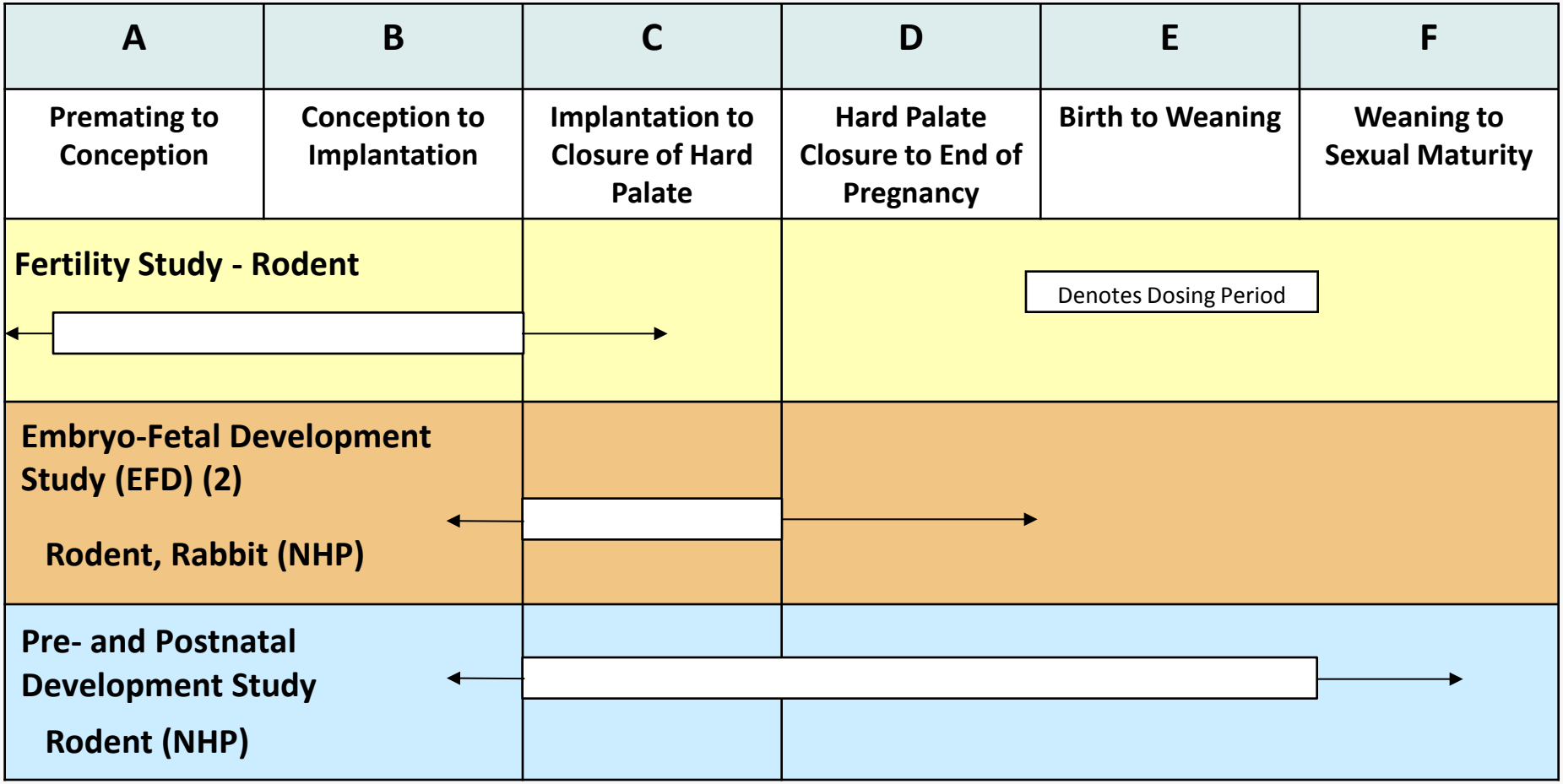
C. **Implantation to closure of the hard palate** - adult female reproductive functions, embryonic development, major organ formation

D. **Closure of the hard palate to the end of pregnancy** - adult female reproductive functions, fetal development and growth, organ development and growth

E. **Birth to weaning** - adult female reproductive functions, neonate adaptation to extrauterine life, preweaning development and growth

F. **Weaning to sexual maturity** - postweaning development & growth, adaptation to independent life, attainment of full sexual function

Standard Study Designs ICH S5(R2)



S. Campion, Pfizer

Types of Data by Study

- Fertility and Early Embryonic Development Study
  - Mating behavior; hormonal control
  - Fertility
  - Embryonic survival prior to implantation

Label Sections 13.1 and 8.3

- Embryo-fetal Development Study
  - Fetal morphology (external, visceral, skeletal)
  - Survival
  - Growth
- Pre-/postnatal Development Study
  - Morphology
  - Survival
  - Growth
  - Function – behavior, reproductive function
  - Parturition and Lactation

Label Sections 8.1, 8.2 and 8.3

Terminology Part 2 – Fetal Morphology

Term	Definition
Fetal Anomaly	Congenital change from normal in external, visceral (internal) or skeletal morphology Synonyms: Fetal Defect Fetal Abnormality Structural Abnormality Congenital Defect
Dysmorphogenesis	Production of a structural abnormality
Fetal Malformation	Anomaly that is serious, rare, often irreversible and could interfere with survival or normal function Example: cleft palate; cardiac atrial septal defect
Fetal Variation	Anomaly which is minor and would not be expected to be permanent or interfere with normal function; often seen in control animals Example: decreased bone ossification; dilated ureter
Teratogenic	Producing **Malformations**; NOT variations or other developmental toxicity

Terminology Part 2 - Mortality

Term	Definition
Preimplantation loss	% of ovulated eggs that do not implant into the uterus = embryo lethality OR effects on fertilization, etc.
Postimplantation loss	% of implanted embryos that do not survive until term = embryo or fetal lethality
Resorption (early or late)	Implantation site containing embryo or fetus that died during gestation and is being resorbed by the body = embryo or fetal lethality
Dead fetus	Dead at term but with full fetal form
Total litter loss	All implantation sites are dead or resorbed
Stillbirth	Born dead
Abortion	Delivery before term (miscarriage) - In rabbits – generally a sign of maternal toxicity
Neonatal death	Died after birth

Principles of Risk Assessment

- Using animal data to assess human risk is a two-part process!
- Step 1 – Identify the Hazard
- Step 2 – Assess the risk of the hazard occurring in humans under normal use conditions

Hazard Identification

- Hazard ID Requires Expert Interpretation
- Animal studies are large
  - N = 20-25 female animals/group; litter sizes = 8-15 per litter; 4 groups/study
  - Total fetuses/pups = 640 – 1500 per study
- Dysmorphogenesis and Mortality occur on every study (non-treatment related)
- Interpretation of treatment related effects depends on:
  - Dose Response
  - Statistical Significance
  - Outside of historical control ranges
  - Rare Event at high dose
- Sound Data Interpretation is first step in accurate label

RISK ASSESSMENT

How do we translate hazards (positive signals) identified in the animals to human risk?

Risk Assessment – CDER Guidance

- FDA-CDER Guidance for Industry:

Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns
September 2011

- PLLR Guidance – Use 2011 DART integration guidance to assess human risk

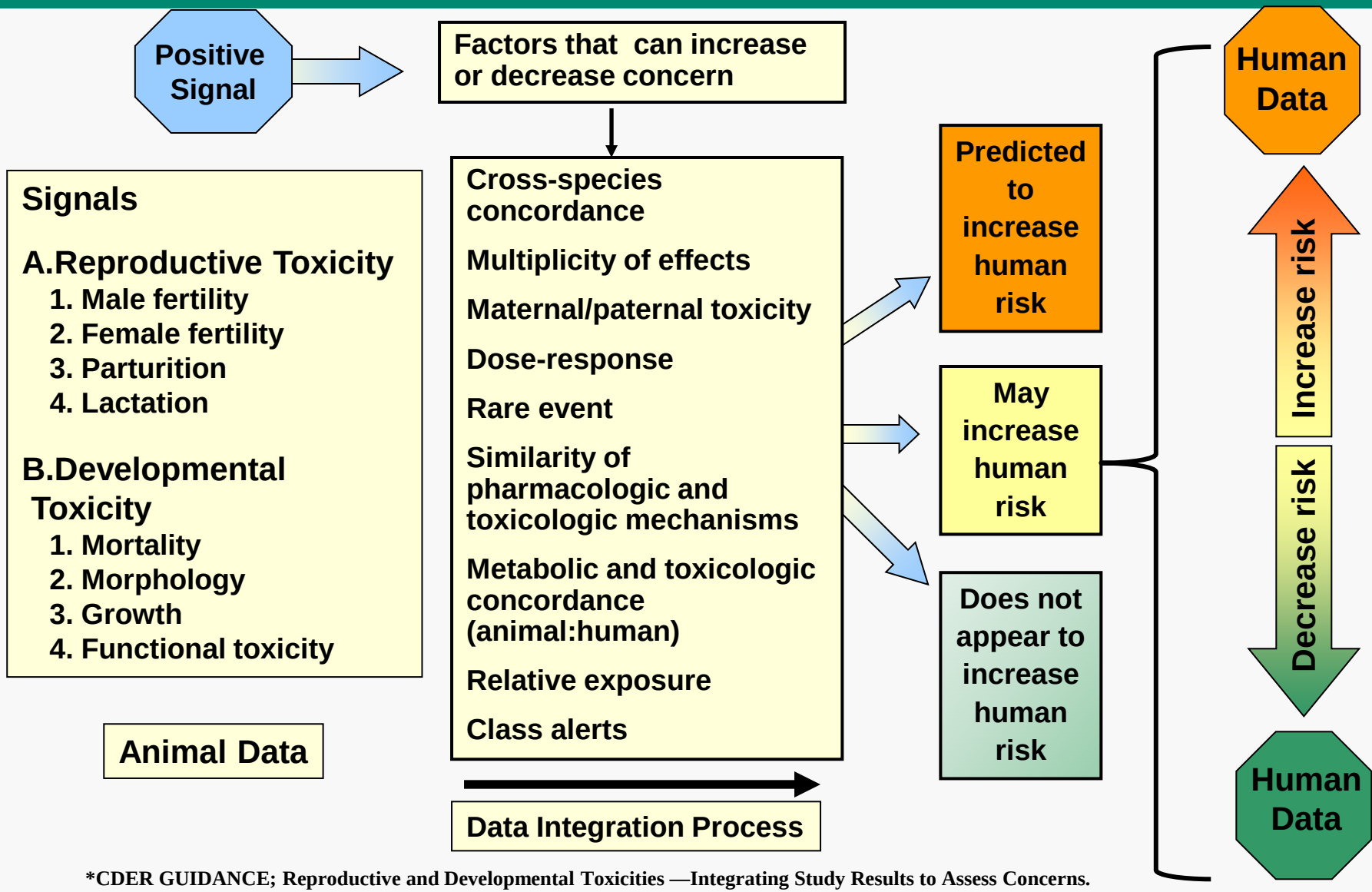
CDER Guidance - DART Risk Assessment

1. Consider these endpoints:

Reproductive Toxicity	Developmental Toxicity
Male fertility	Mortality
Female fertility	Dysmorphogenesis (structural abnormalities)
Parturition	Growth alterations
Lactation	Functional impairment

2. Determine positive signals (effects) for each endpoint among <u>all available studies</u>
3. Integrate all available data to assess risk

CDER Guidance – Integrating Results

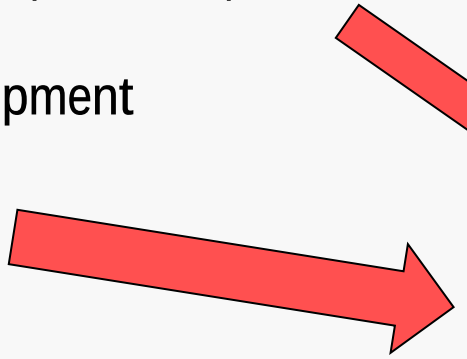


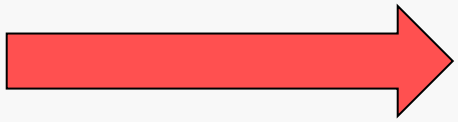
*CDER GUIDANCE; Reproductive and Developmental Toxicities —Integrating Study Results to Assess Concerns.

Types of Data by Study

- Fertility and Early Embryonic Development
  - Mating behavior; hormonal control
  - Fertility
  - Embryonic survival prior to implantation
- Embryo-fetal Development
  - Fetal morphology
  - Survival
  - Growth
- Pre-/postnatal Development
  - Morphology
  - Survival
  - Growth
  - Function – behavior, reproductive function
  - Parturition and Lactation

Reproductive Toxicity
Male fertility
Female fertility
Parturition
Lactation





Developmental Toxicity
Mortality
Dysmorphogenesis (structural abnormalities)
Growth alterations
Functional impairment

Integrated Risk Assessment

- CDER Guidance: Use the following factors to assess risk for a Positive Signal – for each endpoint:

Cross-species concordance - do all species show effects?	Pharmacodynamics (PD) - is effect related to PD?
Multiplicity of effects - are multiple endpoints affected?	Metabolic / Toxicity concordance - is metab/ tox similar across species?
Maternal/paternal toxicity - associated with severe toxicity?	Relative Exposure - high compared with MRHD?
Dose-response relationship	Class Alerts
Rare events	

- Concern may be increased, decreased or unchanged based on these factors.

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Example – Maternal Toxicity

- CDER Guidance: Positive signal only in presence of frank maternal toxicity can decrease concern if:
  - Causal relationship established or biologically plausible
- Desired maternal toxicity - ~15% reduced body weight gain
- Overt maternal toxicity = lethality, body weight loss, inappetance, convulsions, etc.
- Overt maternal toxicity can lead to*:
  - Abortion in rabbits
  - Decreased fetal/postnatal growth and developmental delays – decreased bone ossification
  - Possible increases in fetal lethality
  - Typically NOT fetal malformations (except cleft palate in mice)

***Beyer et al., Birth Defects Res, Part B, 92:36-51**

Example – Maternal Toxicity, Drug Z

- Rat EFD Study - 0, 10, 30, 100 mg/kg/day, N = 22/group

Maternal Toxicity (100 mg/kg/day):

- Mean decrease in body weight gain and food consumption
- 5 females at 100 mg/kg/day had severe toxicity
  - Body weight loss of 10 – 20% of starting body weight
  - Inappetance (5 – 10 days of little or no food consumption)
  - 2 females died prior to C-section; 3 females survived

Developmental Toxicity (100 mg/kg/day):

- Slight increase in unossified bones and resorptions
- Mean decrease in fetal weight (~5%)
- 3 highly affected females: 75% reduction fetal weight and higher % resorptions

- Concern Decreased – Dev Tox plausibly related to maternal toxicity

Example – Pharmacodynamics (PD)

- CDER Guidance:
  - Assess similarity between pharmacology mode of action (MOA) and mechanism of reproductive or developmental toxicity
  - Concern is increased if toxicity is related to MOA
  - Concern is decreased if MOA is animal-specific
- Examples:
  - Retinoids: Act through retinoic acid receptor, with important functions during development; Multiple species affected, including human
  - Vinca alkyloids (vinblastine, vincristine): Cytostatic drugs that inhibit cell division by interfering with the mitotic spindle; Multiple species affected

PD Example: α4 Integrin Inhibitor

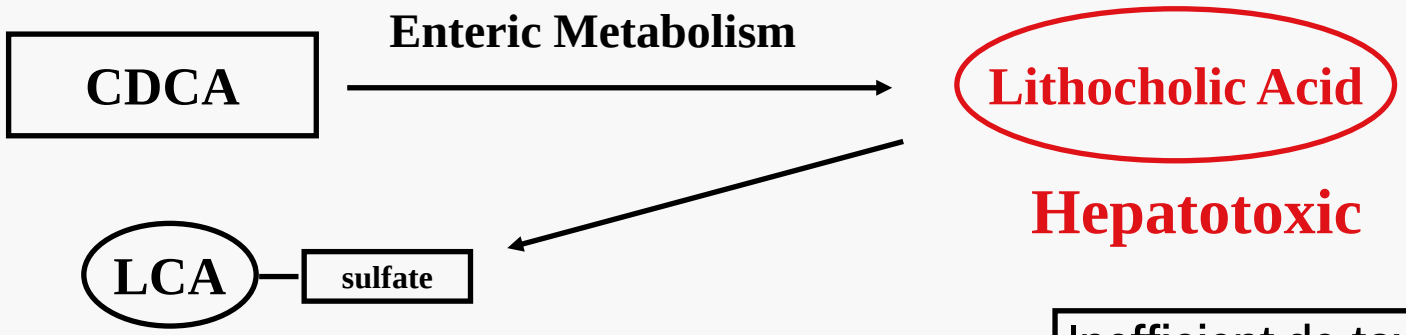
- α4 Integrins regulate cell-ECM and cell-cell adhesions by binding to fibronectin and VCAM-1
- α4 Knockout mouse (Yang et al., Development, 121:549-80, 1995)
  - Embryolethality (E9.5 - 11.5; E12.5 - 14.5)
  - Heart, cranial and facial malformations prior to death
- Crofts et al., 2004: Small molecule α4 integrin inhibitor:
  - Mouse: embryolethality, heart and skeletal defects
  - Rat: embryolethality, heart and skeletal defects, decreased fetal weight
  - Rabbit: embryolethality, heart and skeletal defects
  - Dose-dependent increases starting at low doses
- Concern increased: Developmental toxicity is likely related to PD mode of action

Example Metabolic / Toxicity Concordance

- CDER Guidance:
  - Evaluate concordance between species WRT metabolism and toxicity
  - Increased Concern if profiles are similar across species

Example – Metabolic/Toxic Concordance

- Bile Acids are used as a treatment for gall stones
- Chenodeoxycholic Acid (CDCA):
  - Hepatotoxicity in newborn monkeys after in utero exposure
  - Rodents: no fetal malformations or postnatal liver damage



Inefficient de-toxifiers:
Monkey, Rabbit

Efficient de-toxifiers:
Rat, Human

(McSherry et al., 1976)

Concern Decreased: Metabolic Discordance

Example: Relative Exposures

- CDER Guidance:
  - Comparison of systemic drug exposure at the DART NOEL to exposure at maximum recommended human dose (MRHD) is critical.
    - Compute animal:human ratio (A:H)
    - AUC is default (not mg/m^2), but use most relevant metric
    - Take into account other factors as appropriate (e.g., receptor occupancy, protein binding, biomarkers, etc.)
  - Concern is increased – A:H exposure < 10
  - Concern is decreased - A:H exposure > 25
- For PLLR:
  - Calculation needs to be explained, e.g., X-fold the human exposure (AUC) at the MRHD of X mg/day.
  - For label revisions – margins may need to be revised

Bringing it all together – Drug 123

- Drug 123:
  - Oral administration to women of childbearing potential
  - No pharmacologic (PD) mechanisms of concern
  - Metabolic / toxicity concordance
- DART Dataset for Drug 123
  - Male and Female Fertility Study – no effects
    - NOAEL = 100 mg/kg/day
  - Rabbit EFD Study – no effects
    - NOAEL = 175 mg/kg/day
  - Rat EFD Study – multiple effects
  - Rat pre/postnatal Study - multiple effects

Example, Drug 123, cont

- Rat Embryo-Fetal Development: 0, 10, 40, 100 mg/kg/day

Observation	**Dose (mg/kg/day)**	**Toxicity Endpoint**
Maternal Toxicity: • Mortality • Dehydration • Body weight loss (transient) • Decreased body weight gain	 100 40, 100 10, 40, 100 100	
Eye defects (an-/microphthalmia)	40, 100	Dysmorphogenesis
Paw and digit defects	100	Dysmorphogenesis
Decreased fetal weight	40, 100	Growth
Incompletely ossified bones	100	Dysmorphogenesis, Growth
Increased embryolethality	40, 100	Mortality
Total litter resorption	100	Mortality

Example, Drug 123, cont

- Rat Pre-/Postnatal Development: 0, 10, 40, 100 mg/kg/day

Observation	Dose (mg/kg/day)	Toxicity Endpoint
Maternal Toxicity: • Dehydration • Body weight loss (transient) • Decreased body weight gain	 40, 100 10, 40, 100 100	
Paw defects, reduced ear size	40, 100	Dysmorphogenesis
Postnatal mortality (week 1)	100	Mortality
Decreased live litter size at birth	100	Mortality
Decreased LD1 pup weight	40, 100	Growth
Decreased postnatal growth	10, 40, 100	Growth
No milk in stomach (normal nesting)	100	Lactation
Reduced Fertility in F1 offspring	100	Functional

Dysmorphogenesis – Factors to Consider

- Cross Species Concordance – Concern Decreased
  - Rabbit showed no effects
- Multiplicity of effects – Concern Increased
  - Multiple different malformations, plus mortality and growth
- Maternal Toxicity – no change
  - Maternal toxicity occurred but could not be plausibly related to malformations
- Dose Response – Concern Increased
- Rare Event – Concern Increased
  - Eye and paw malformations are rare
- Metabolic and tox concordance (animal-human) - Concern Increased
- Similarity of PD and tox mechanisms – no change

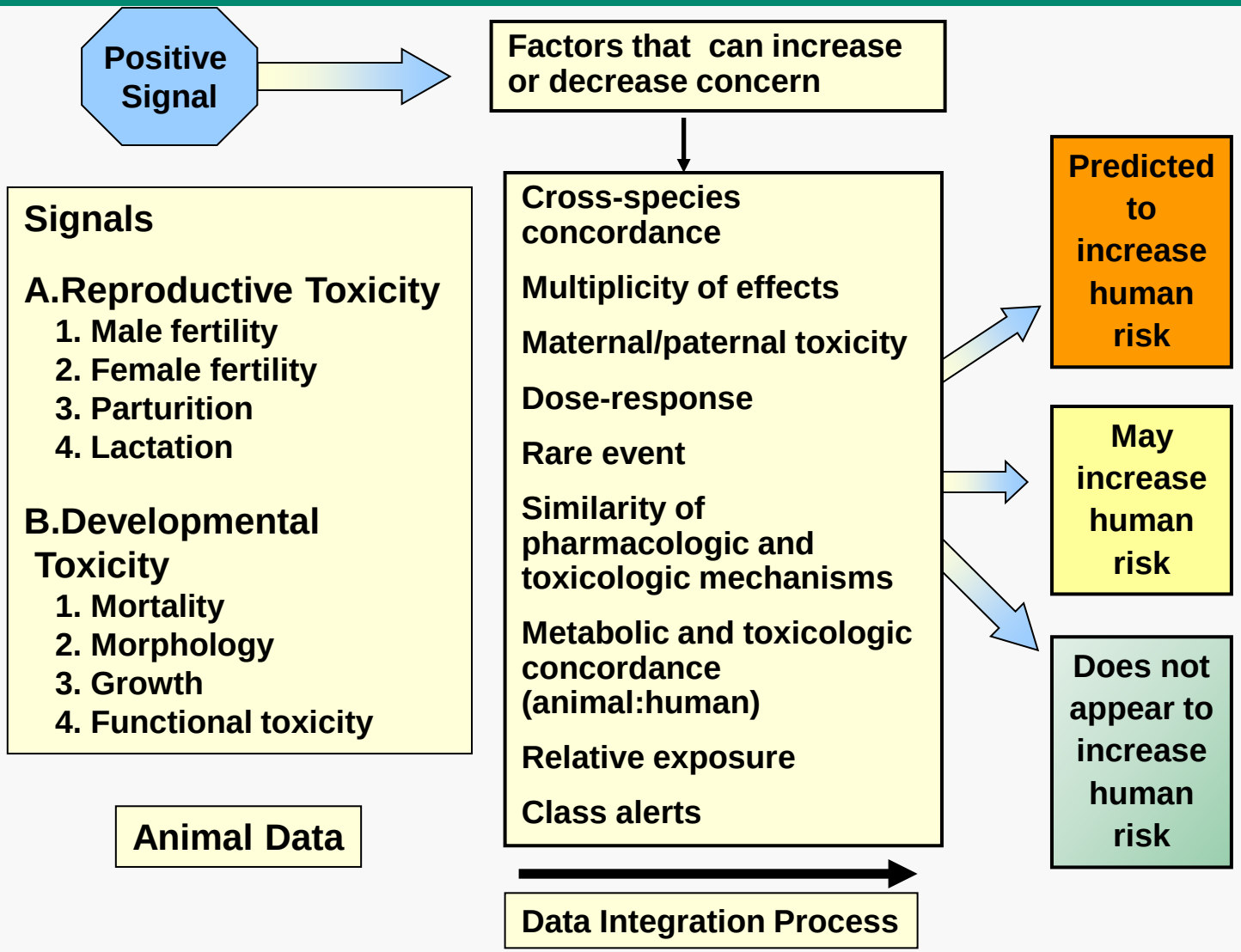
Dysmorphogenesis - Pharmacodynamics

- No apparent connection between PD and developmental toxicity
- In the rat: wide margin between toxic level and therapeutic level:
  - Therapeutic Index (TI) = Toxic dose$_{10\%}$ / Effective Dose$_{90\%}$
  - TI = 40 mg/kg/day / 0.3 mg/kg/day = 133
- No change in concern
  - No apparent relationship to pharmacology
  - If indirect relationship to pharmacology – large TI should be protective

Dysmorphogenesis – Relative Exposures

- Rat NOEL for Dysmorphogenesis = 10 mg/kg/day
  - Cmax = 458 ng/mL
  - AUC = 3360 ng.h/mL
- MRHD = 75 mg
  - Cmax = 19 ng/mL
  - AUC = 75.6 ng.h/mL
- Exposure Ratio = 3360 / 75.6 = 44
- Concern Decreased – Exposure Ratio > 25

Drug 123 – Integrating Results



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Risk Assessment, Dysmorphogenesis Drug 123

Factor	Concern
Species Concordance	↓
Multiplicity of Effects	↑
Maternal Toxicity	—
Dose-Response	↑
Rare Event	↑
Pharmacology	— ↓
Metab /Tox concordance	↑
Relative Exposure	↓
Class Alert	—

→ **May increase human risk**

- Multiplicity of rare events

<u>But</u> –

- Only in one species
- Large multiple of human exposure
- Unlikely to reach those doses in humans due to unacceptable toxicity

Conclusions – Animal DART Data

- Animal data are important!
- Frequently the only data to assess human risk!
- Obtain animal DART data from 3 main study types:
  - Fertility, embryo-fetal development, pre/postnatal development
- Identify DART hazards (positive signals) from all 3 studies for:
  - Developmental toxicity: Dysmorphogenesis, Growth, Mortality, Functional toxicity
  - Reproductive toxicity: Male / female fertility, parturition, lactation
- Assess human risk for DART effects by integrating information from all available data
  - e.g., maternal toxicity, strength of signal, exposure ratio, PD

Questions?