Juvenile Animal Studies: When can they contribute to cardiovascular safety assessments?

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What is the concern

Are you more or less concerned about safety in a neonate or a child or an adolescent?

Better question

What is your confidence level to generalize existing data to a neonate a child or an adolescent?

Pediatric Drug Development -Toxicology

- Same expectations as for adults
- Integrated assessment of available data
  - Prior toxicology
  - Adult clinical studies

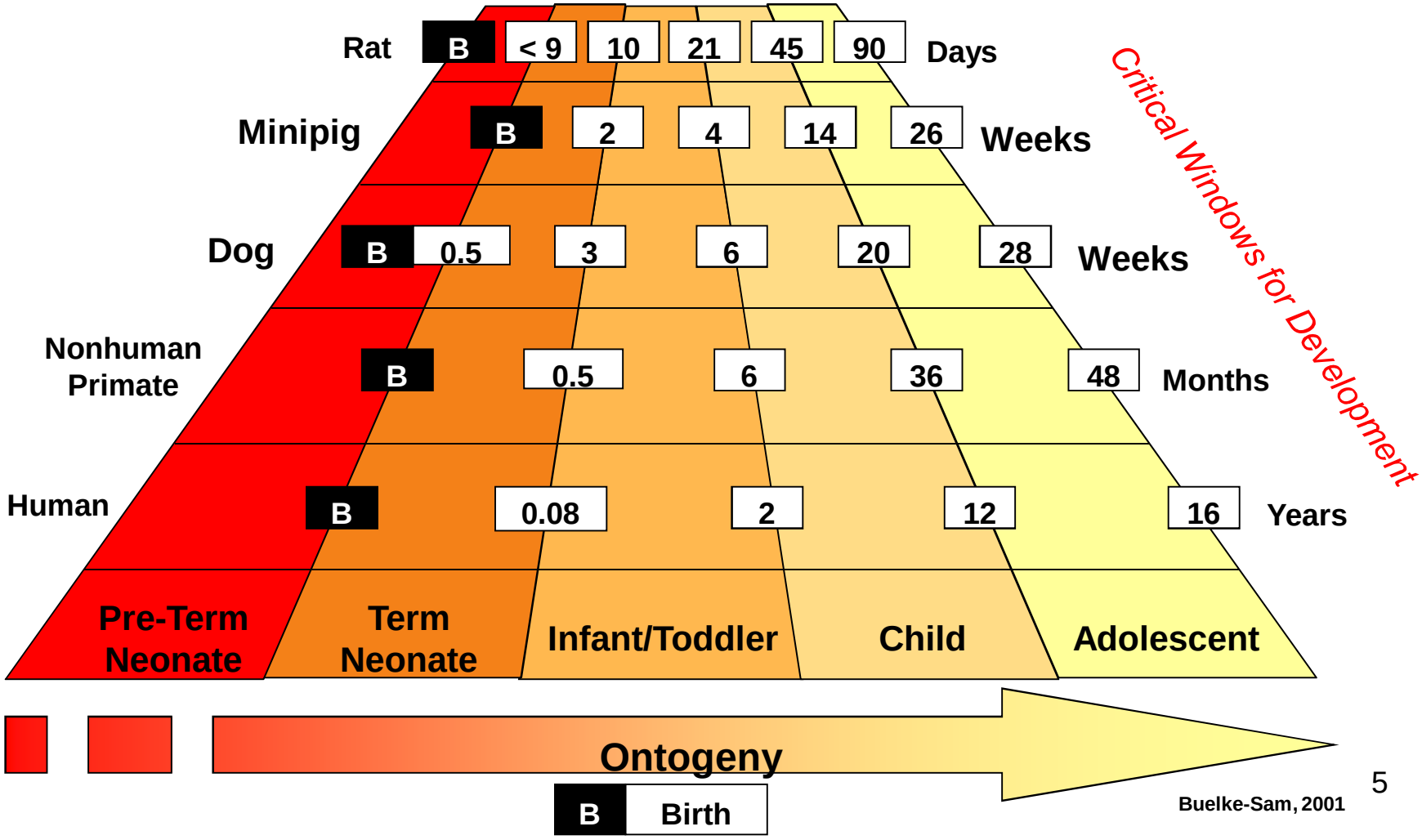
Juvenile animal studies are performed on a case-by-case basis

- Is there a signal of concern?
  - If yes, does the existing data characterize the signal sufficiently?
    - If no, what additional data are needed?

Juvenile Animal models for cardiac toxicity

- What do you want to know?
  - What aspect of cardiovascular toxicity?
- Choosing your model
  - Which species were used in the adult studies
  - Most relevant or sensitive species
- When to test
  - Comparative species development

Comparative Age Categories Based on Overall CNS & Reproductive Development



Buelke-Sam, 2001

Heart Parameters

	Age				
Human Infant	1 day	6 days	1 month	2 month	6–11 months
Heart rate (beats/min)	133	135	155	150	140
RV pre-ejection period (msec)	71	59	51	55	55
RV ejection time (msec)	199	203	193	204	232
LV pre-ejection period (msec)	65	59	55	59	59
LV ejection time (msec)	197	192	184	192	200

C57bl/6 Mouse	3 days	3 weeks	4 weeks	10 weeks	16 weeks
Heart rate (beats/min)	372	422	390	442	360
LV cardiac output (ml/min)	1.1	8.7	9.3	15.7	14.3
LV stroke volume (ml)	3.2	20.8	23.9	35.6	40.2

Sheep	Term fetus	Newborn	Adult
Heart rate (beats/min)	150	200	100
Ventricular output (ml/min/kg)			
Left	150	400	100
Right	300	400	100

Modified from Hew and Keller, BDR B 2003

What do the studies tell us

Value

- Increased sensitivity
  - Some helped to set age limits for use
- Unique toxicity
- Non specific study designs often replicated toxicities already characterized and were least likely to be of benefit

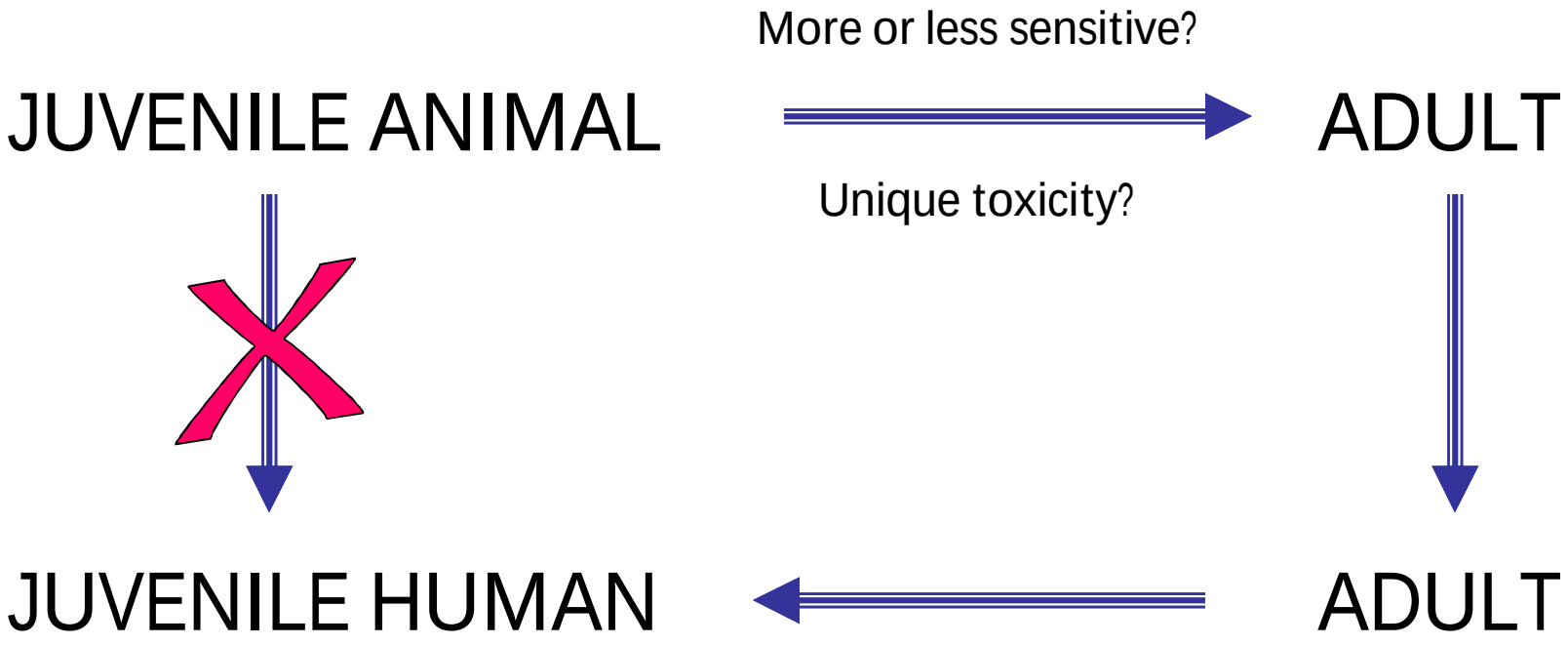
Case study

Drug A (treatment of 1° and 2° hyperparathyroidism)

- Species – rat and dog
- Rat: age at dosing PND 21 – 49; recovery to PND 67
  - No unexpected toxicity; adverse effects attributed to pharmacology
- Dog: age at dosing PND 70 – 98 recovery to PND 126
  - Cardiac toxicity
  - Findings drove request for an additional dog study for safety
  - Pediatric studies on hold until completed
- Dog: 6 month study; age at dosing PND 70 with 3 month recovery higher doses used
  - No cardiac toxicity; other findings consistent with excess pharmacology
  - Pediatric studies now underway

Value – unexpected finding in a study with a 'general toxicity' design had potential clinical consequence; a second, more directed, study supported resumption of pediatric program

Interpreting the data



When can Juvenile Animal Studies contribute to cardiovascular safety assessments?

- What would trigger an expectation for juvenile animal toxicity testing?
- For assessing potential cardiovascular toxicity what are the key parameters?
  - To measure routinely
  - To measure when there is a suggested cardiovascular toxicity signal