Tossicologia perinatale: lo stato dell'arte

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11.00-14.00 **CORSO PRE-CONGRESSUALE:**
TOSSICOLOGIA PERINATALE
Moderatore: Guido Mannaioni (Firenze)

11.00-11.30 Introduzione
Barbara Viviani (Milano)

11.30-12.00 Epilessia
Alessandra Pistelli (Firenze)

12.00-12.30 La gestione della paziente con disturbo da uso di sostanze in gravidanza e allattamento
Lorenzo Somaini (Biella)

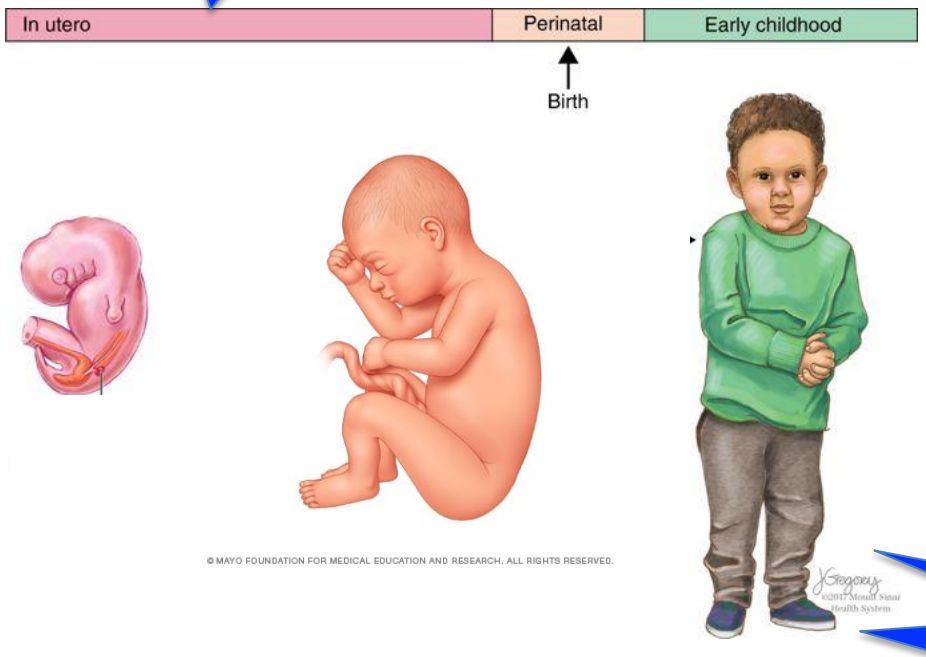
12.30-13.00 I farmaci psicoattivi in gravidanza e allattamento"
Georgios Eleftheriou (Bergamo)

13.00-13.30 Esposizione a radiazioni ionizzanti a scopo diagnostico in gravidanza, outcome fetale e neonatale
Andrea Missanelli (Firenze)

13.30-14.00 Depressione post partum
Cinzia Niolu (Roma)

Developmental toxicology

MEDICATIONS



Soil

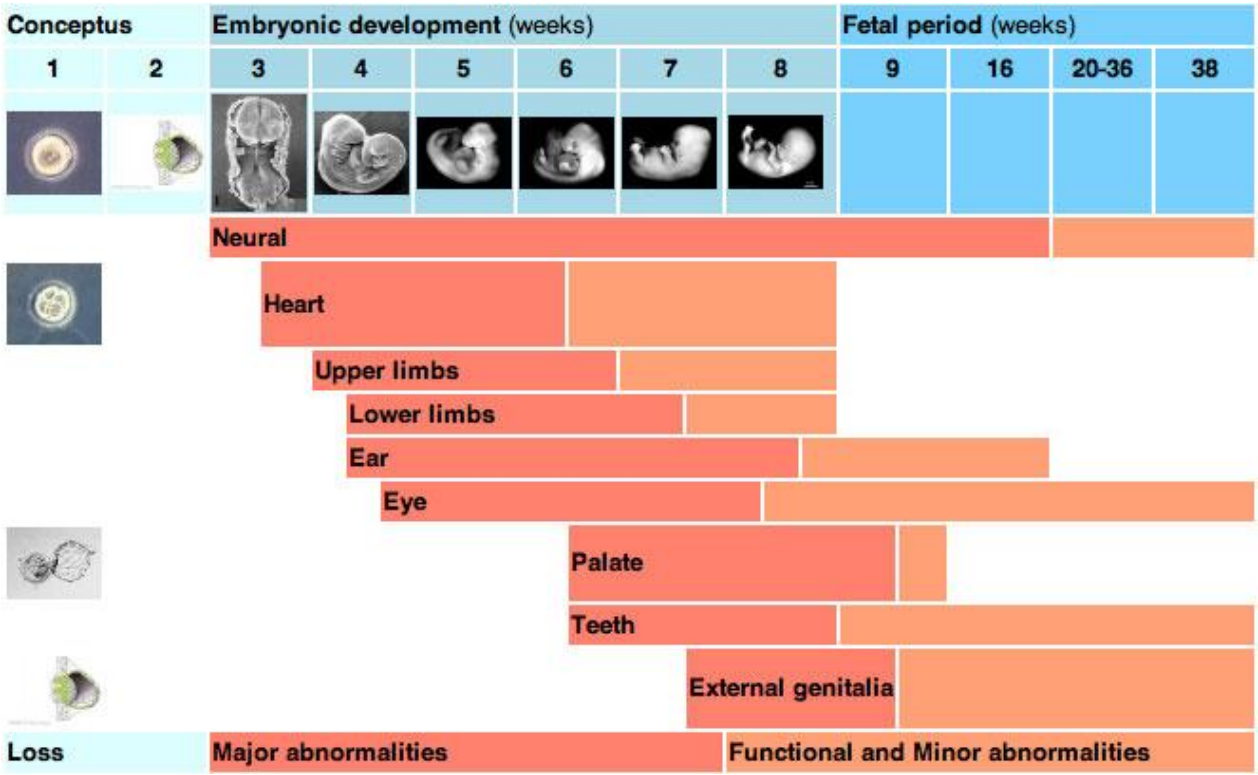
Diet

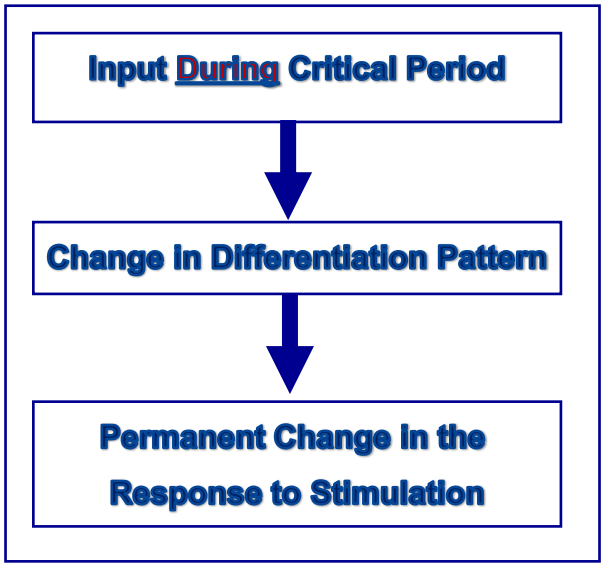
Air

CONTAMINANTS

Consumer products

Human critical period of development





Various organs develop at different times: *different windows of vulnerability*

Thalidomide (1961)

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

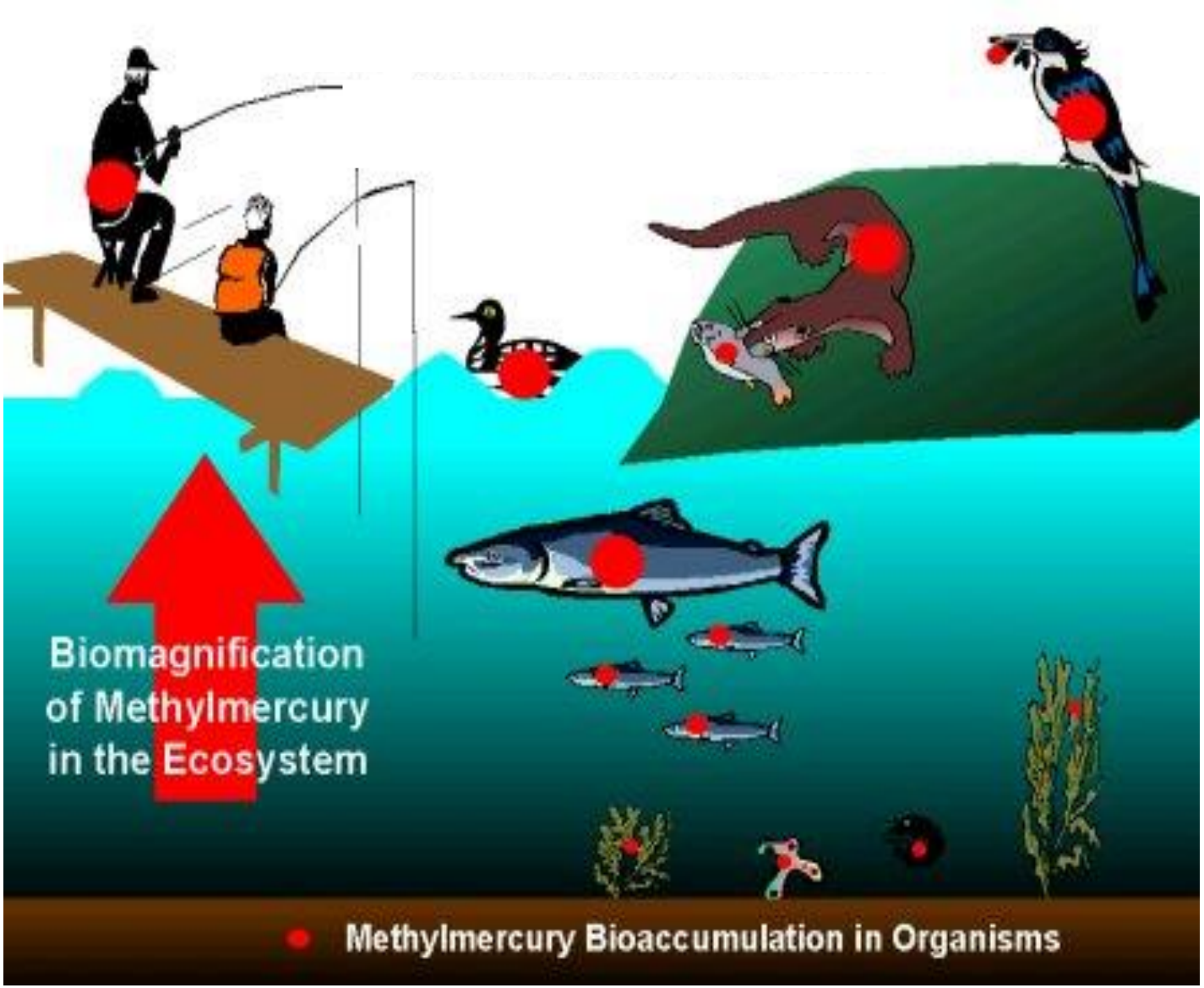
Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the fœtus in early pregnancy ". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

The Lancet, 1961

Minamata disease (1956): Methylmercury



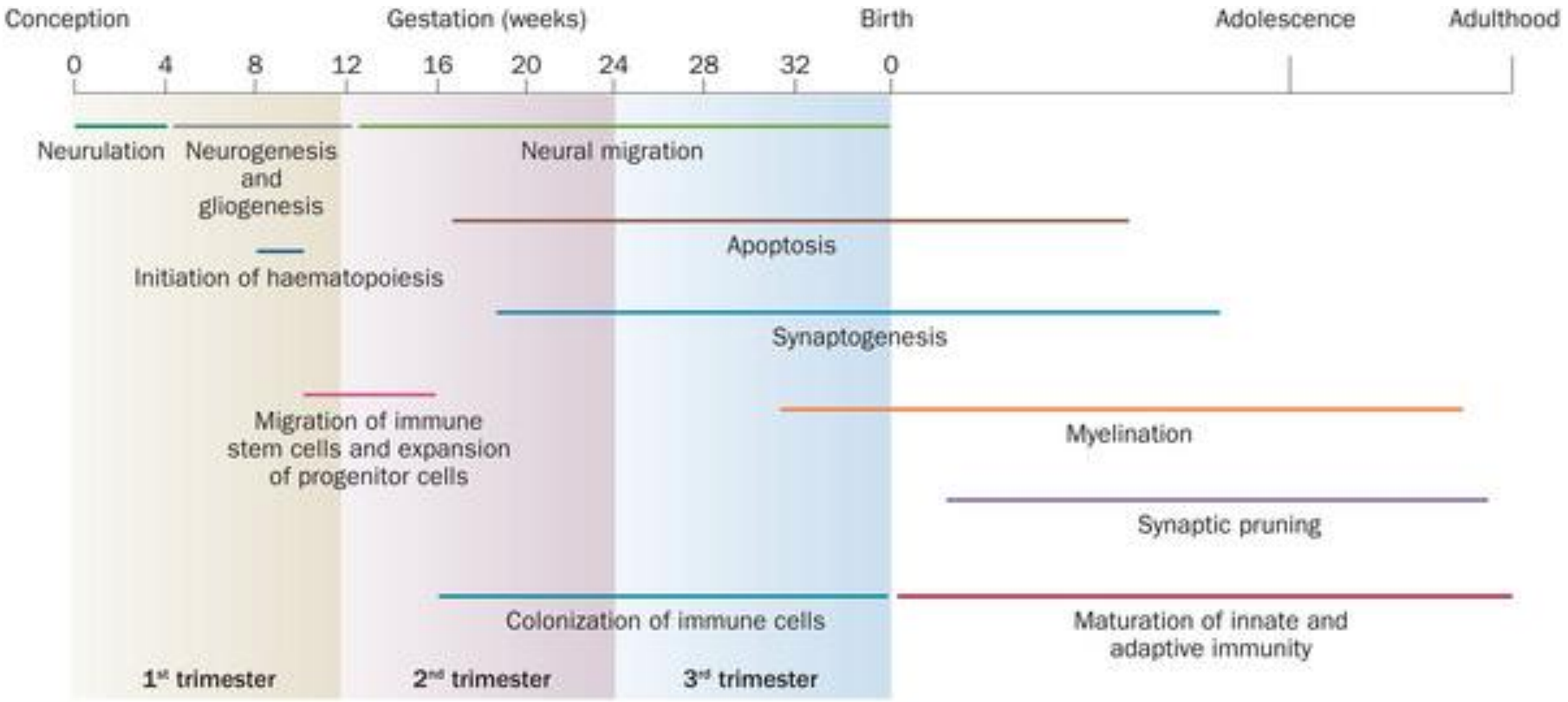
Birth does not represent the end of any developmental processes

System	General Considerations	Neonate (< 1 mths)	1st Solid Food (~ 6 mths)	Weaning Toddler (~ 2 years)	Puberty (~ 11-15 years)	Adulthood (> 18 years)
Integument	• Critical neonatal function (barrier, water and thermoregulation, conductance, sensation) • then progressive surface acidification, local microbiome and immune function					
CV	• Critical neonatal physiologic transitions (pulmonary and systemic vascular resistance) • Adaptive myocardial and vascular changes • Progressive increase in ion channels.					
GI	• Functional at birth, with adaptations especially over first year to accommodate shift in diet/complexity and populate microbiome					
Renal	• Nephrogenesis complete at term birth • Progressive increase in GFR and renal function over first year					
Hepato-biliary	• Structurally well developed at birth • Progressive increase in metabolic functionality, especially over first 6 months to 1 year of age					
Pulmonary	• Increased alveolization and surface area over first year					
Immune	• Progressive population of secondary immune tissues and development of memory as a function of time and environment					
Endocrine	• Most glands are well developed at birth and critical for growth • Zona reticularis of adrenal cortex and gonads undergo expansion in late childhood/early puberty					
Repro-ductive	• Testes descended at birth, populated by germ cells, Sertoli cells and Leydig cells • 'Mini puberty' at 2 to 4 months of age, adrenarche in late childhood • Subsequent reproductive changes occur at onset of puberty and continue until adulthood					
Nervous	• Defined sequential and progressive development into adulthood • Maximum neuron count and brain:body weight at birth, with postnatal apoptosis, pruning and migration • Myelin and glia present at birth • Neurotransmitter and conduction systems mature at variable rates (ie: opiate receptors/metabolism, GABA, serotonin & noradrenalin differ)					
Skeletal	• Growth plates present at birth • most rapid postnatal growth occurs prior to age of 4 years, with slower growth through childhood primarily mediated by GH and TH • pubertal growth spurt driven by sex hormones • growth plates close during adolescence/early adulthood					

	Major period of functional and structural growth and development
	Completion of structural development; active period of growth and/or functional maturation
	Slow continued growth or refinement of function; also can reflect a period of relative inactivity, as in prepubertal reproductive tissues
	Structurally and functionally fully mature

ICH guideline S11 on nonclinical safety testing in support of development of paediatric medicines
EMA/CHMP/ICH/616110/2018

The timeline of development processes in the nervous system



Knuesel, Nat. Rev. Neurol, 2014

Various part of the brain develop at different times: *different windows of vulnerability*

Birth does not represent the end of any developmental processes

Developmental Origins of Health and Disease (DOHaD)

DEVELOPMENT

LOW DOSE CHEMICALS

No teratogenic effect evident at birth

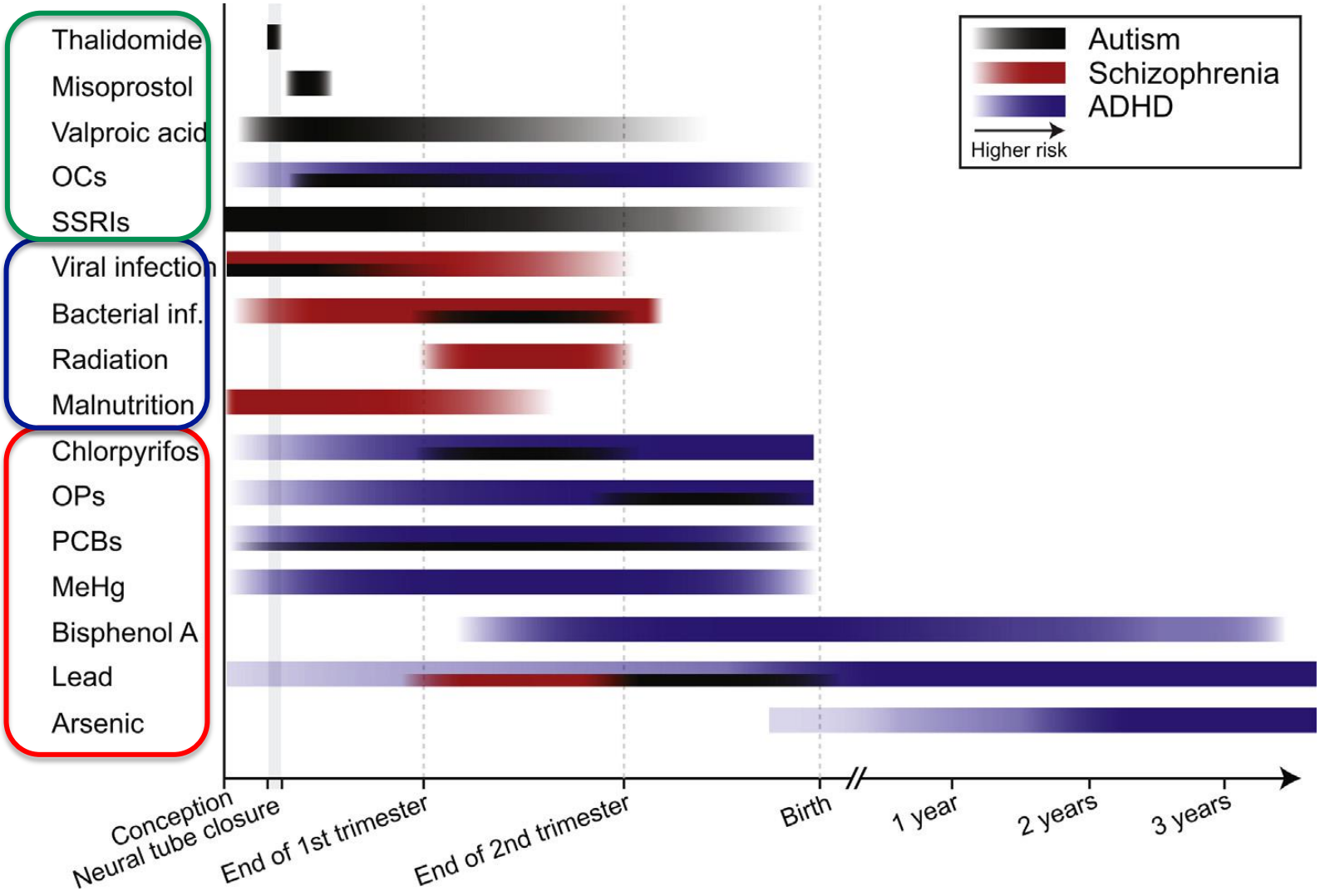
But

Subtle disruption in the absence of a phenotype at birth
(changes in cell signalling and gene expression)

ADULTHOOD

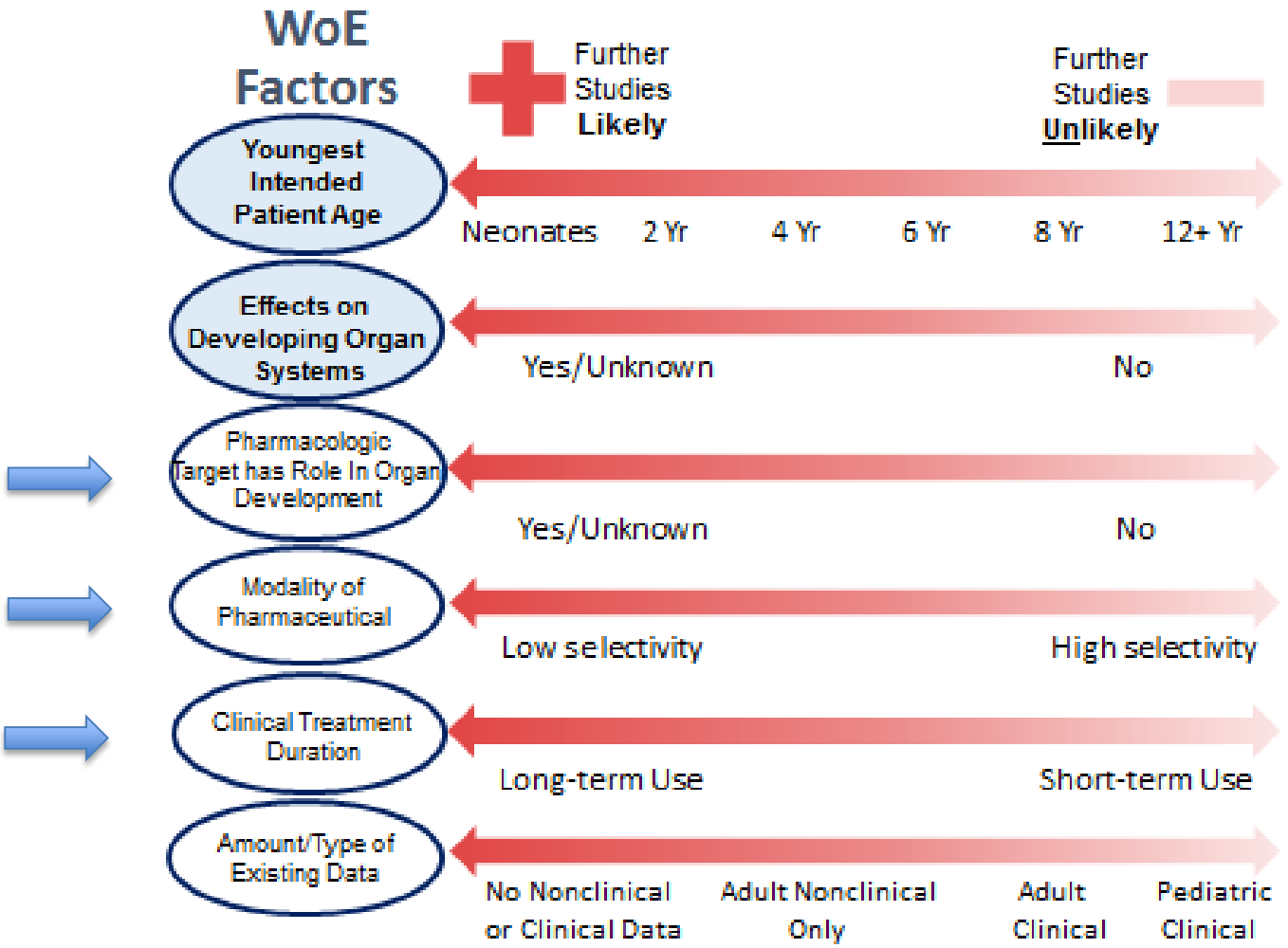
Long-term impact on later health and disease risk

Sensitive time windows for exposure to neurotoxicants and susceptibility to neurodevelopmental disorders



Heyer and Meredith, 2017

Key Weight of Evidence factors to be considered in determining if nonclinical studies are warranted



ICH guideline S11 on nonclinical safety testing in support of development of paediatric medicines
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Factors favouring toxicants exposure in developing organisms

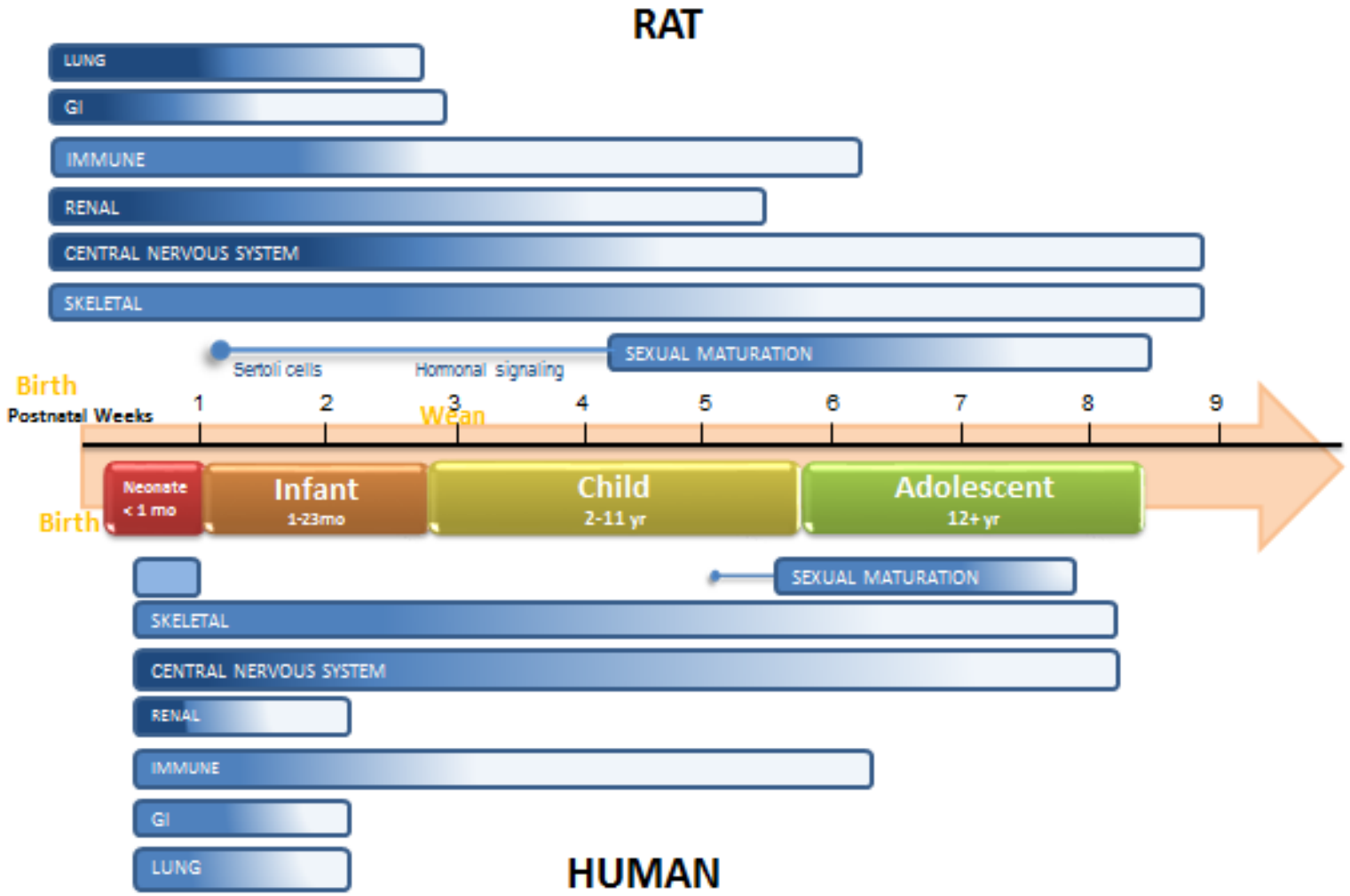
1. Some lipofilic substances are shown to accumulate in maternal adipose tissue and breast milk and can be transmitted by breast feeding (DDT)

2. Many substances easily cross the BBB (MeHg-methylmercuric-cysteinyl complexes)

3. A greater energy demand then adults due to development, thus relative to b.w., they breath air more rapidly and ingest a higher proportion of water, fruit, vegetables in their diet than adults

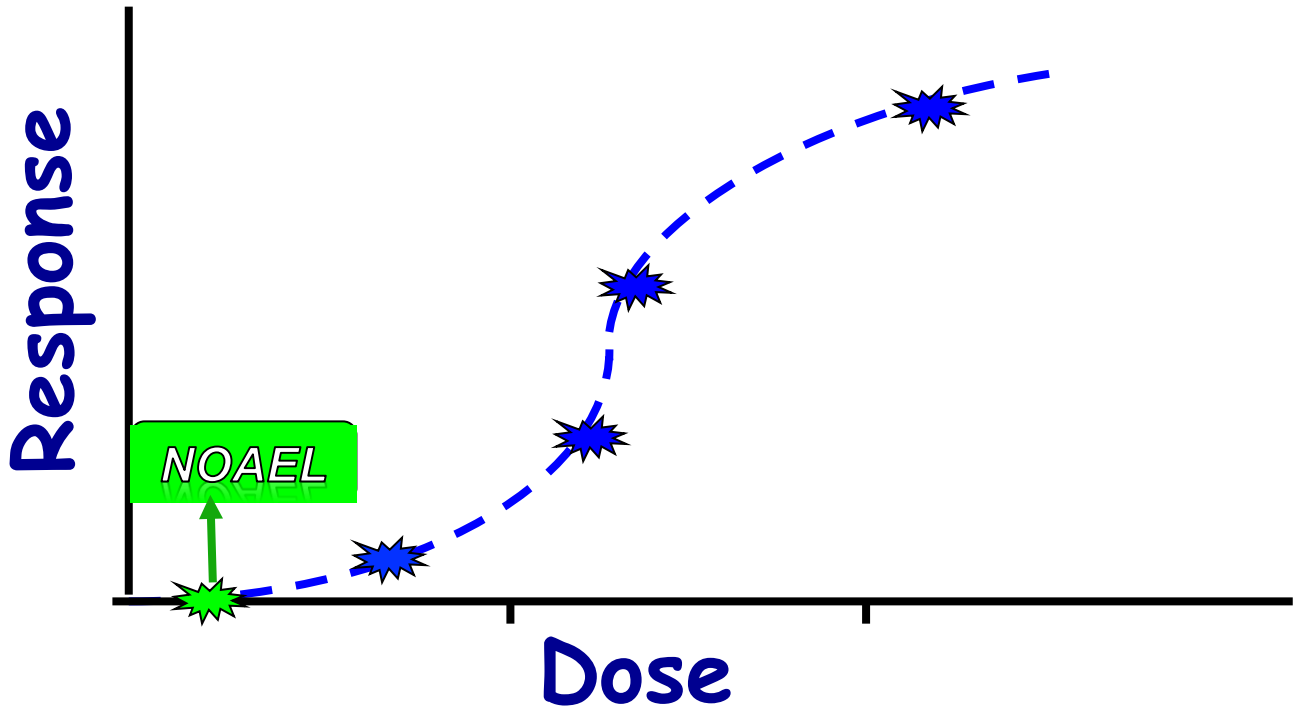
4. Natural behaviour and activity, in and outdoor crawling, sticking objects or soil to their mouths

Comparison of Rat and Human ontogeny



Dose-response for critical effect

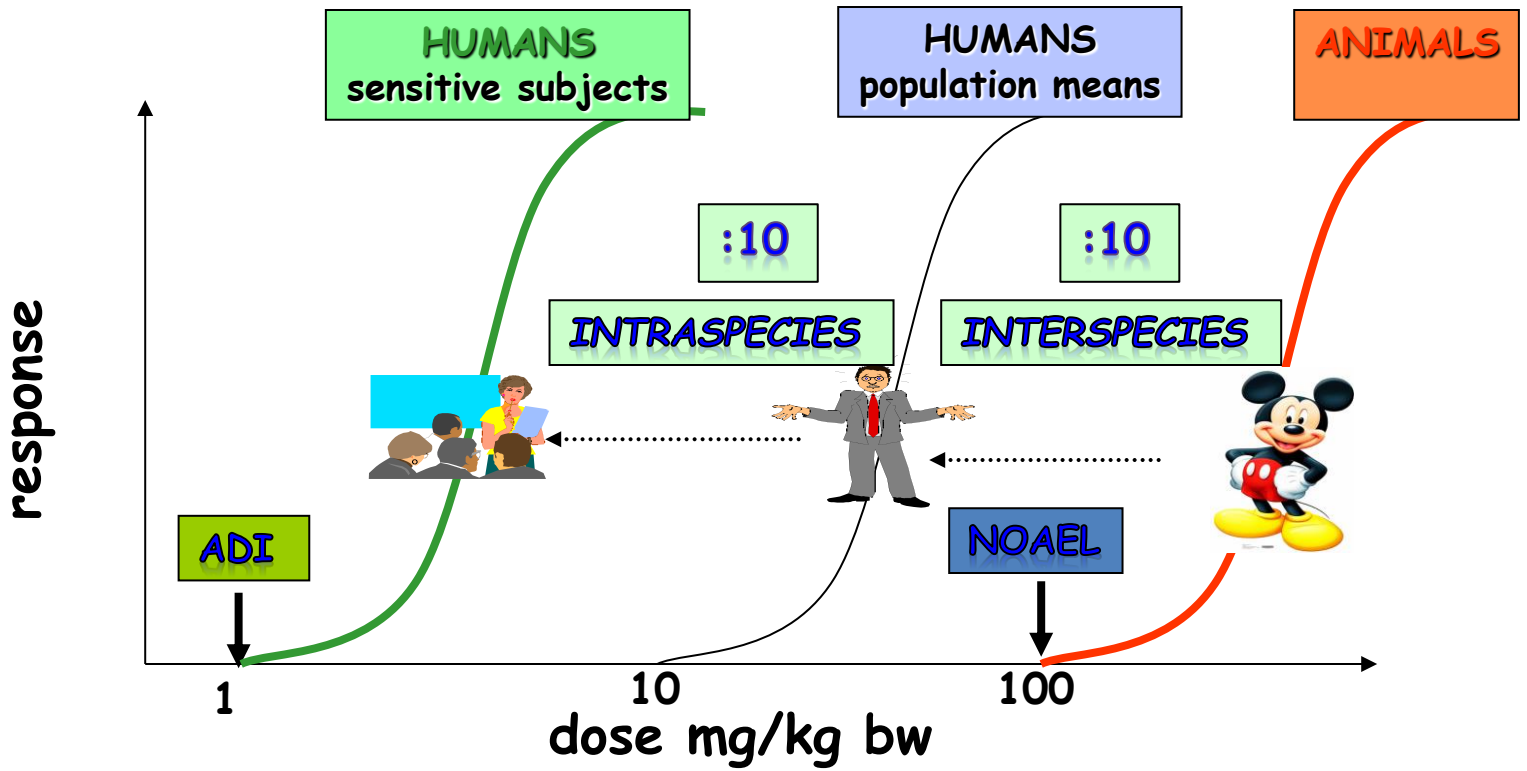
To establish a dose without adverse effect



NOAEL: No **O**bserved **A**dverse **E**ffect Level is the highest concentration or amount of an agent, found by study or observation that causes no detectable, usually adverse (or toxic?) alteration in morphology, functional capacity, growth, development or lifespan of the target

Animal based toxicological studies

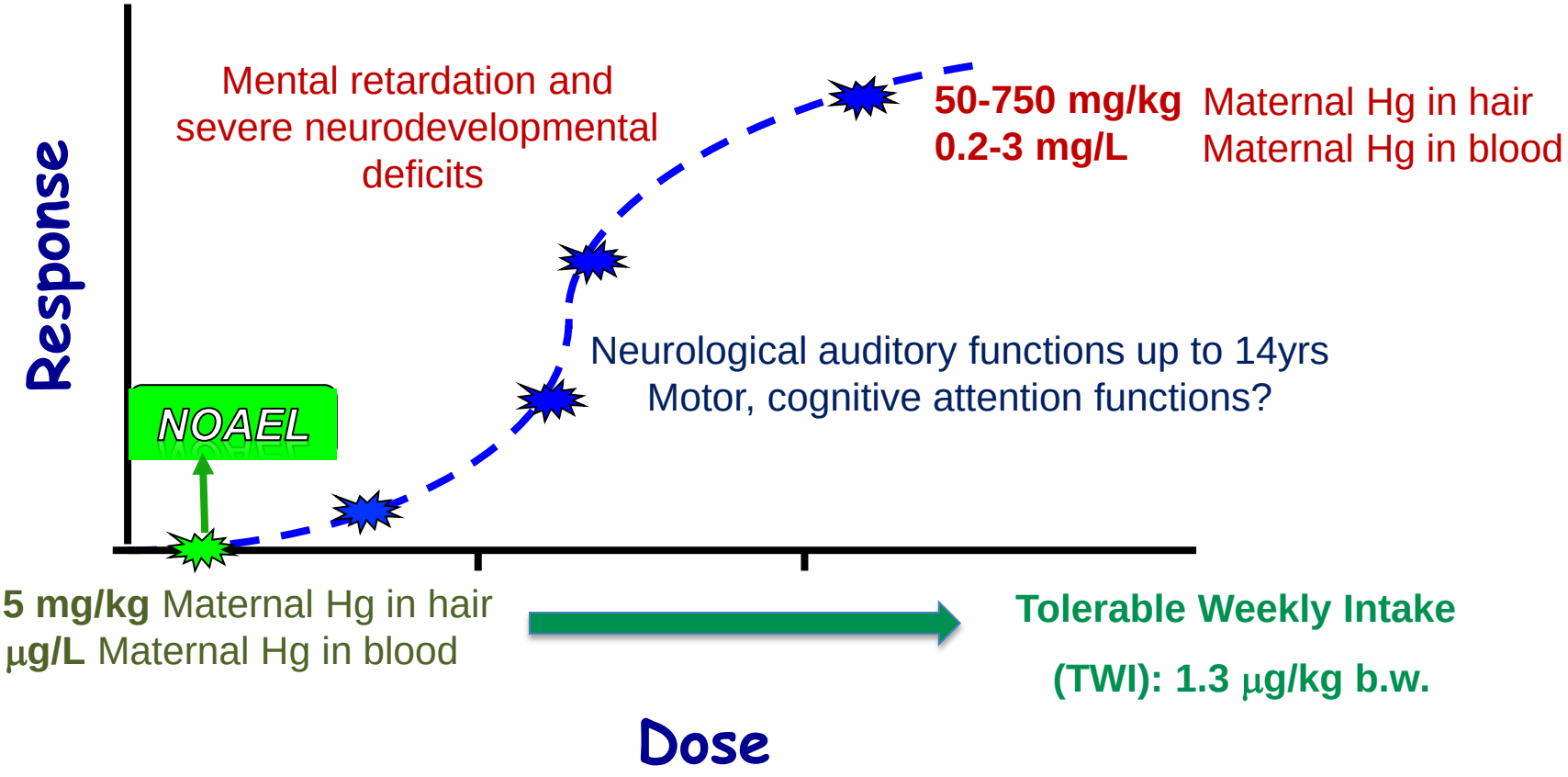
Quantification of adverse health effects



ADI: Admissible **D**aily **I**ntake represents the amount of a food additive, a pesticide or a veterinary drug residue, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.

Dose-response for critical effect

To establish a dose without adverse effect



EFSA Journal, 2012

Conclusions

NOAEL, ADI, TWI: allows to adopt preventive measure

The Seventh Environment Action Programme adopted by Decision No 1386/2013/EU of the European Parliament and of the Council (3) establishes the long-term objective of a non-toxic environment and, for that purpose**, stipulates that action is needed to ensure the minimisation of significant adverse effects of chemicals on human health** and the environment by 2020 (Official Journal of the European Union- 24.5.2017- *Legislative act*)

Dose-response for critical effect:

the lead (Pb) case