



Evidence on the Developmental Toxicity of Bisphenol S (BPS)

Developmental and Reproductive Toxicant Identification Committee

October 9, 2025

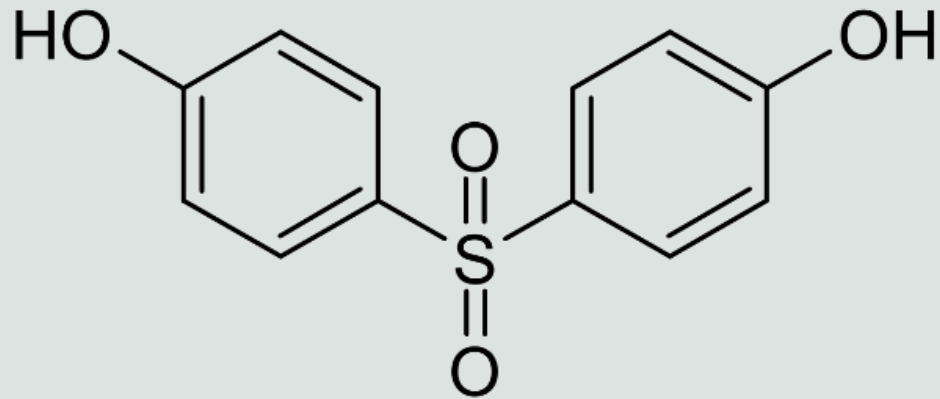
Reproductive Toxicology and Epidemiology Section
Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment, CalEPA

Outline

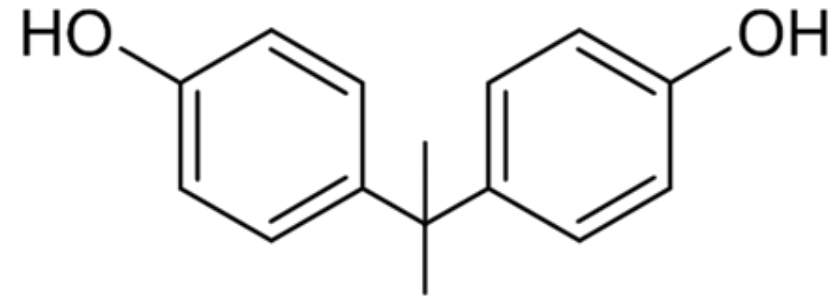
- Introduction
- Pharmacokinetics of BPS
- Animal studies
 - *in vivo* mammalian and non-mammalian
- Mechanistic data
- Human studies
- Summary across evidence streams



Bisphenol S (BPS)



Synonym:
4,4'-Sulfonyldiphenol



BPS is an analog of
Bisphenol A (BPA)

BPS uses, occurrence, and exposure

- Use
 - Thermal paper, hard plastic items, synthetic fibers for clothing and textiles
- Production
 - As of 2019, 1 to 10 million pounds per year in the US
- Exposure
 - BPS has been detected in cash register receipts, food, personal care products, and environmental samples of dust and sediment
 - Detection frequency in Biomonitoring California studies (2018 – 2020): 64.4% – 76.7% in California residents



Literature search and screening

- Conducted literature searches on the developmental and reproductive toxicity of BPS
- Used HAWC (Health Assessment Workspace Collaborative) as a tool for multi-level screening of literature search results
 - Level 1: Title and abstract
 - Level 2: Full text
- **For this review we focused on literature relevant to developmental toxicity**



Pharmacokinetics of BPS

- Absorbed rapidly after oral exposure
- Distribution throughout the human body:
 - Cord blood (*Liu et al., 2017*)
 - Amniotic fluid (*Tuzimski et al., 2023*)
 - Placental tissue (*Pan et al. 2020*)
- Metabolized via glucuronidation, sulfation, and hydroxylation
- Excreted in urine, bile, feces, and breastmilk
- Physiological changes during pregnancy:
 - Increased blood volume, basal metabolic rate, renal function, ventilation, etc.

Estimated half-life	Hours
Humans	7 – 9
Mice	3 – 4
Rats	4 – 8



Animal BPS treatment

Animal	Dose/Concentration
Rodents	0.025 µg/kg to 300 mg/kg [3.33 to 50 µg/L in drinking water]
Sheep	0.004 to 0.5 mg/kg
Zebrafish	0.001 to 400 mg/L
Chinese medaka fish	250 to 1000 mg/L
Chick embryos	0.27 to 207 µg/g egg, or 0.00075 to 7.5 mg/L
<i>C. elegans</i>	0.6 µg/L to 125 mg/L
<i>Drosophila</i>	62.6 to 250.27 mg/L

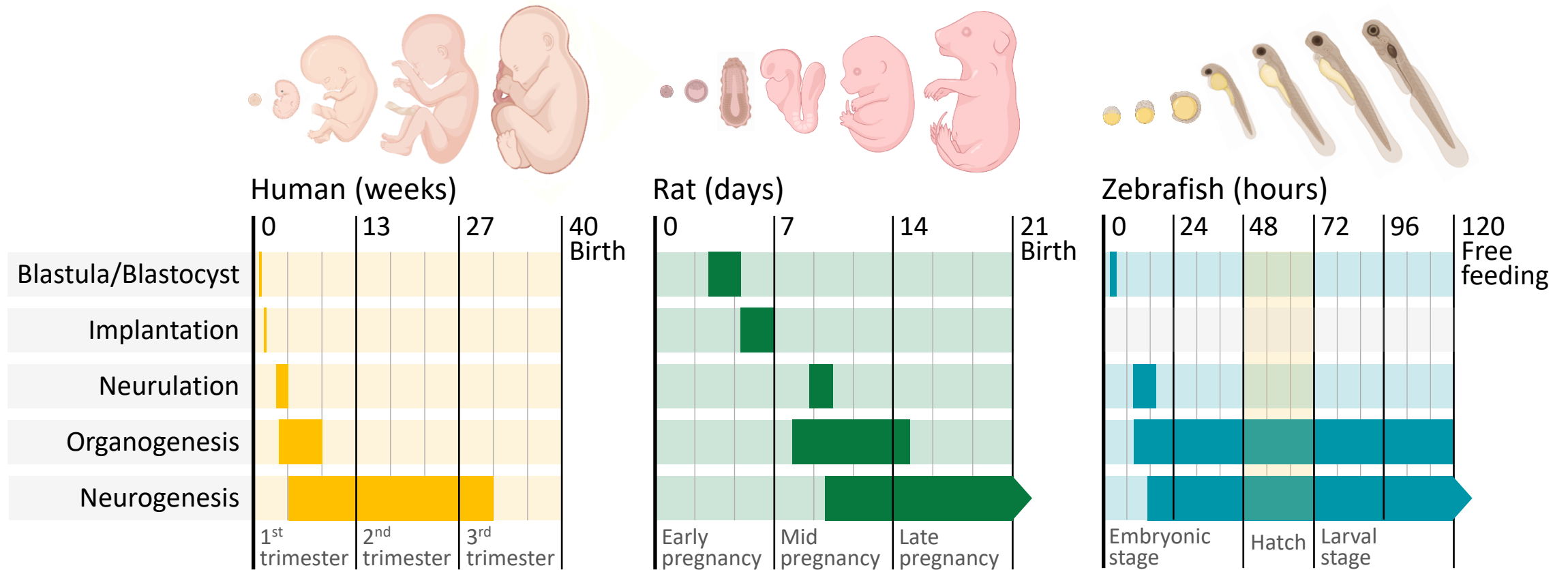


Animal Studies

Effects of BPS on Developmental Toxicity

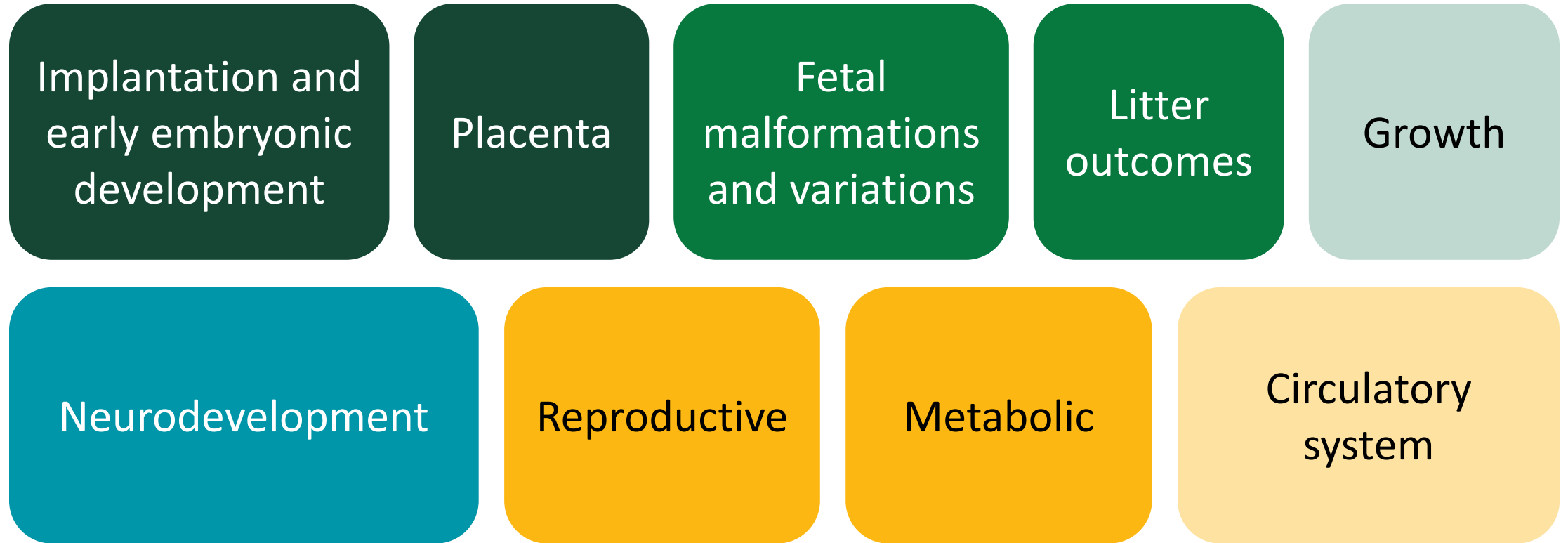


Critical windows of development



Adapted from Chahardehi et al. 2020, Figure 1. Images from www.biorender.com.

Toxicity of BPS on developing organisms



Implantation and early embryo development

**BPS diminished implantation
and early embryonic
development in animals.**

Rats

4 of 4 studies reported effects.

↓ Implantation

↑ Post-implantation loss

60 – 300 mg/kg-day

(BASF 2014 & 2019; ECHA 2019, Anon. 12 & 14)

Mice and Sheep

3 of 3 studies:

- Inhibited embryo development

2 – 100 µg/kg-day

(Desmarchais 2022; Nourian 2017; Zhang 2020)

Chicken embryos

1 study:

↓ Decreased growth

↓ Embryo mass and tarsus length

- Developmental delays

0.03 – 30 µM

(Harnett 2021)



Implantation and early embryo development



Mechanistic evidence supports BPS-induced effects on implantation and early embryonic development.

Human *in vitro* model

3 of 3 studies reported effects.

Δ Pluripotency markers

↓ Blastocyst attachment rate

Δ Gastrulation markers

0.1 – 100 μM

(Di Credico 2023; Fan 2021; Liang 2020)

Bovine blastocysts

1 of 2 studies:

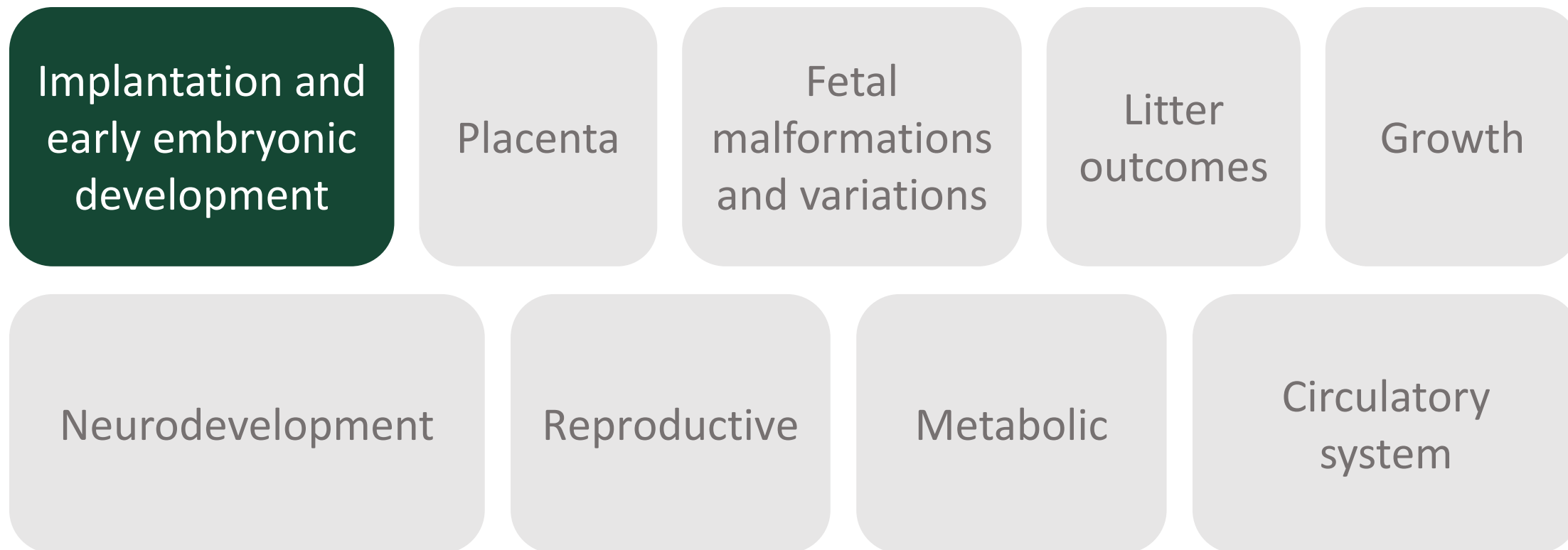
- Accelerated embryo development

0.05 mg/mL

(Sabry 2021a)



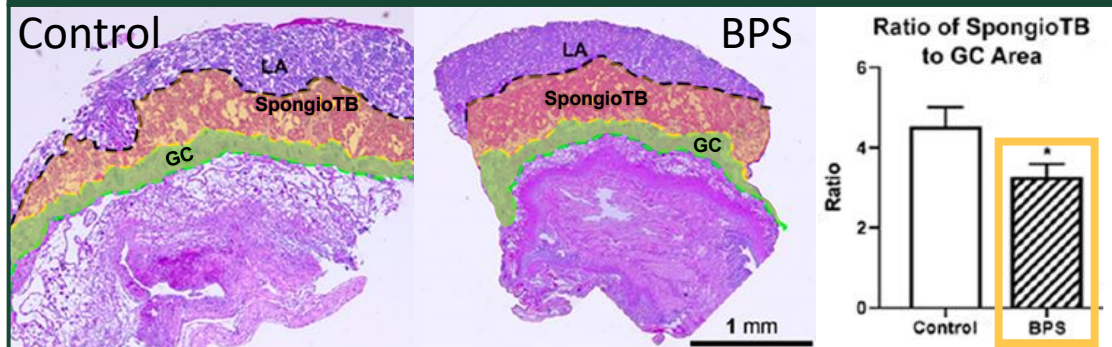
Toxicity of BPS on developing organisms



Placenta effects

BPS induced adverse effects on placental tissue.

Spongiotrophoblast and giant cell staining
(Mao et al. 2020, adapted from Fig. 4)



Rats and Sheep

2 of 2 studies:

↑ Placenta weight

4 μ g – 0.5 mg/kg-day

(Fudvoye 2025; Gingrich 2018)

Mice and Sheep

2 of 2 studies:

- Histopathological findings

200 μ g – 0.5 mg/kg-day

(Gingrich 2018; Mao 2020)

Placenta effects



Mechanistic evidence supports BPS-induced placental disruption.

Rodent and Sheep placenta

3 of 3 studies reported effects:

- ↓ Fatty acids
- ↓ Glycoproteins and E-cadherin
- ↓ DNA methylation
- Δ Relevant genes

0.025 µg – 0.5 mg/kg-day

(Fudvoye 2025; Gingrich 2018; Mao 2020)

Human and Mouse cells

4 of 4 studies reported effects:

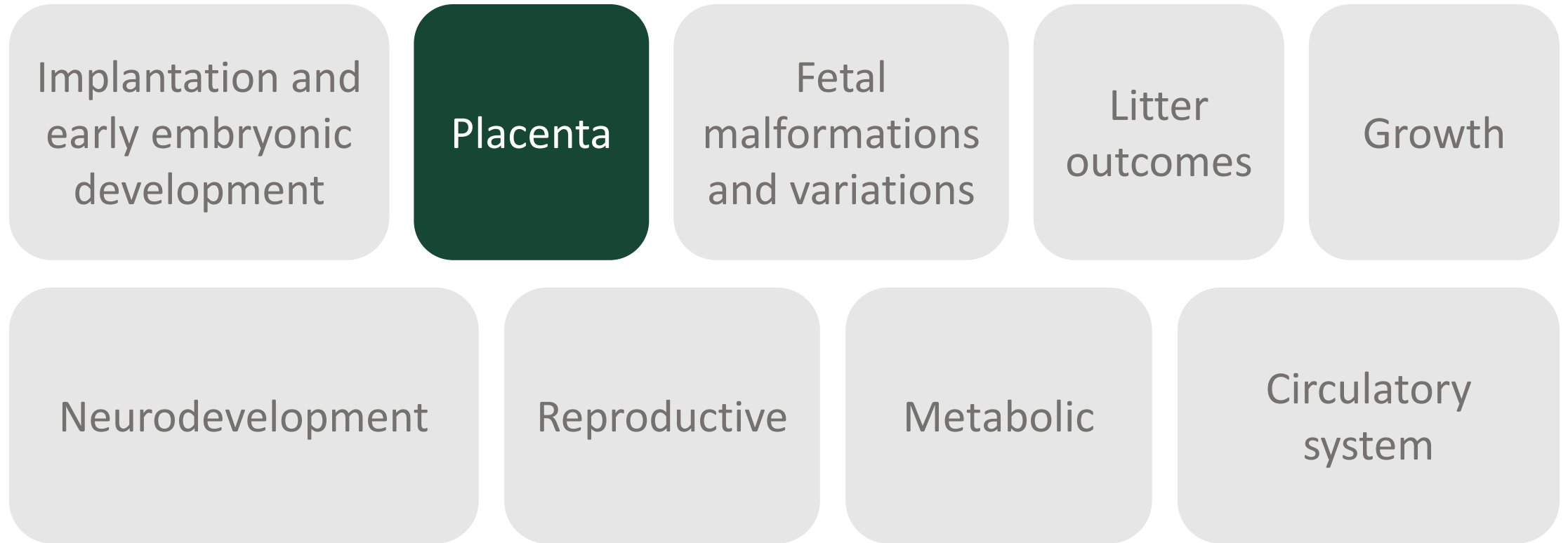
- ↑ Apoptosis
- Δ Hormone levels
 - Immunotoxicity
- Δ Trophoblast signaling and function

200 µg/kg-day, 0.15 – 10 µg/mL

(Mao 2020; Ticiani 2021 & 2022; Vidal 2024)



Toxicity of BPS on developing organisms



Malformations and variations

Variation

A change that is unlikely to negatively impact the survival or health of the animal and may or may not also occur in control animals.

Malformation

A permanent structural change that is likely to negatively impact the survival or health of the animal.



Malformations and variations

BPS treatment increased physiological abnormalities

Rats and Sheep

2 of 2 studies reported effects.

Malformations

↑ Total skeletal malformations

Variations

↑ Total and individual visceral variations

↑ Skeletal variation

0.5 – 300 mg/kg-day

(BASF 2014; Pu 2017)

Fish and Chicken embryos

9 of 14 studies reported effects.

Malformations

↑ Malformation/defect rates

Morphological effects observed

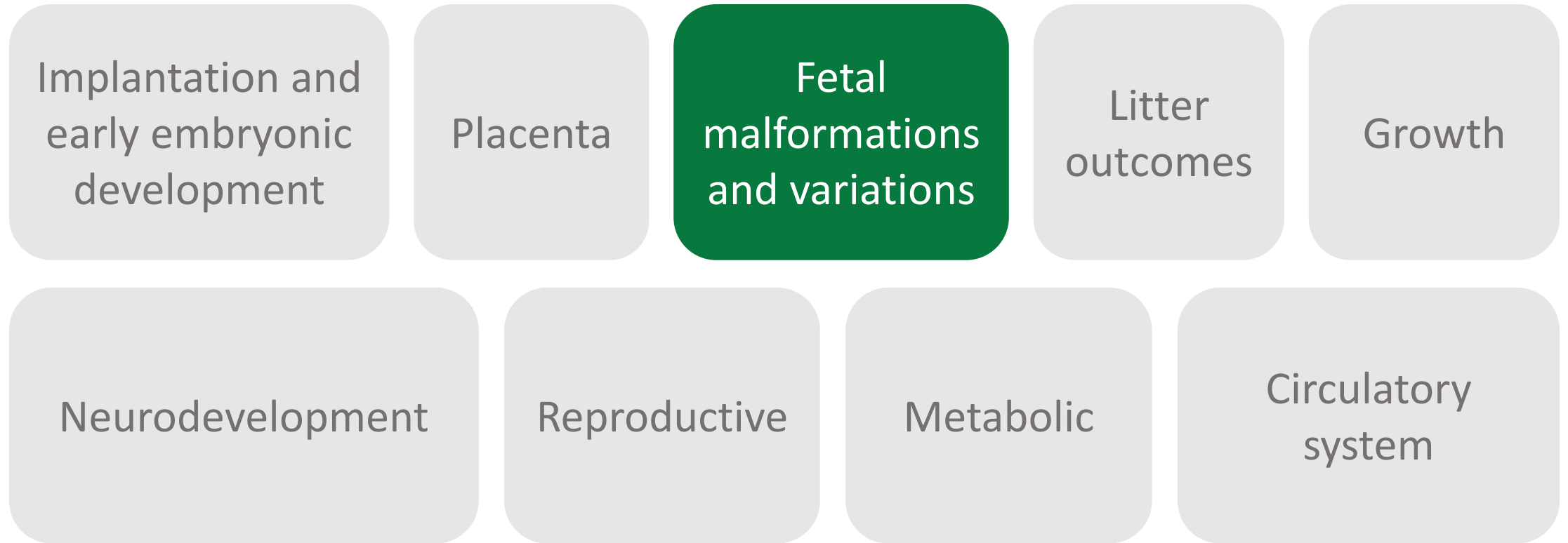
- Craniofacial, spinal, tail, yolk sac, heart, eye, limb, gonads, swim bladder, and/or pigment defects

0.2 µg – 400 mg/L, 0.03 – 50 µM, 210 nmol/g egg

(Bai 2023; Christophe 2023; Harnett 2021; Huang 2023; Ji 2013; Li 2024; Mentor 2020; Moreman 2017; Wei 2018)



Toxicity of BPS on developing organisms



Litter effects

BPS affected several litter outcomes in treated animals.

Mice and Rats

5 of 10 studies reported effects.

- ↑ Total litter loss and stillborn pups
- ↓ Litter size and liveborn pup number
- ↑ Parturition distress, nursing issues
- ↑ Early postnatal pup mortality

0.5 µg – 300 mg/kg-day

(BASF 2019; ECHA 2019, Anon. 12 & 14; Naderi 2014; Shi 2019a)

Fish, Nematodes, and Fruit flies

19 of 27 studies reported effects.

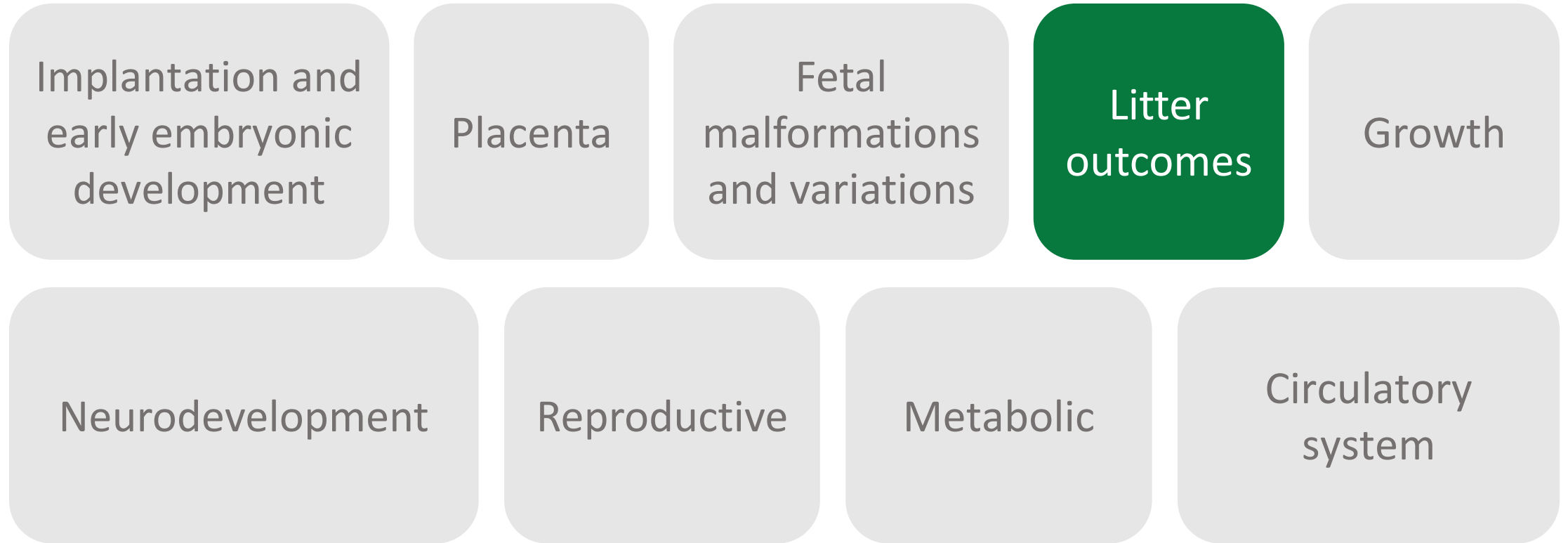
- Δ Hatching
- ↓ Number of pupae
- ↓ Brood size
- ↑ Embryonic lethality

20 ng – 300 mg/L, 0.1 µM – 10 mM

(Bonaldo 2022; Chen 2016; Coumailleau 2020; Dong 2018; Hao 2022; He 2024; Hyun 2021; Ji 2013; Kucharíková 2023; Lee 2019; Li 2024; McDonough 2021a; Moreman 2017; Neighmond 2023; Santos Musachio 2023; Qiu 2018 & 2021; Wei 2018; Xiao 2019)



Toxicity of BPS on developing organisms



Growth effects

BPS altered the growth of developing organisms.

Mice and Rats

2 of 7 studies reported effects.

↓ Body length

Δ Fetal weight

3.33 µg/L, 0.025 – 4 µg/kg-day

(Fudvoye 2025; Gao 2024)

Fish and Nematodes

13 of 17 studies reported effects.

Δ Body or segment length/width

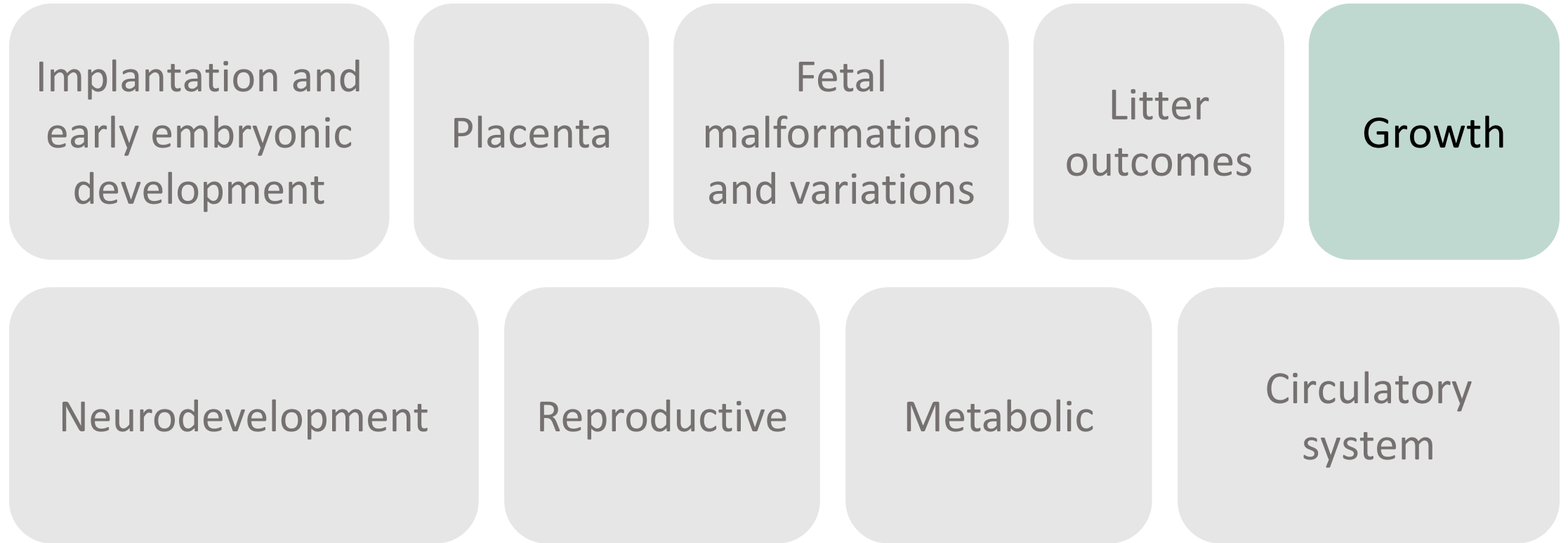
Δ Weight/mass

1 µg – 25 mg/L, 0.1 µM – 1 mM, 207 µg/g

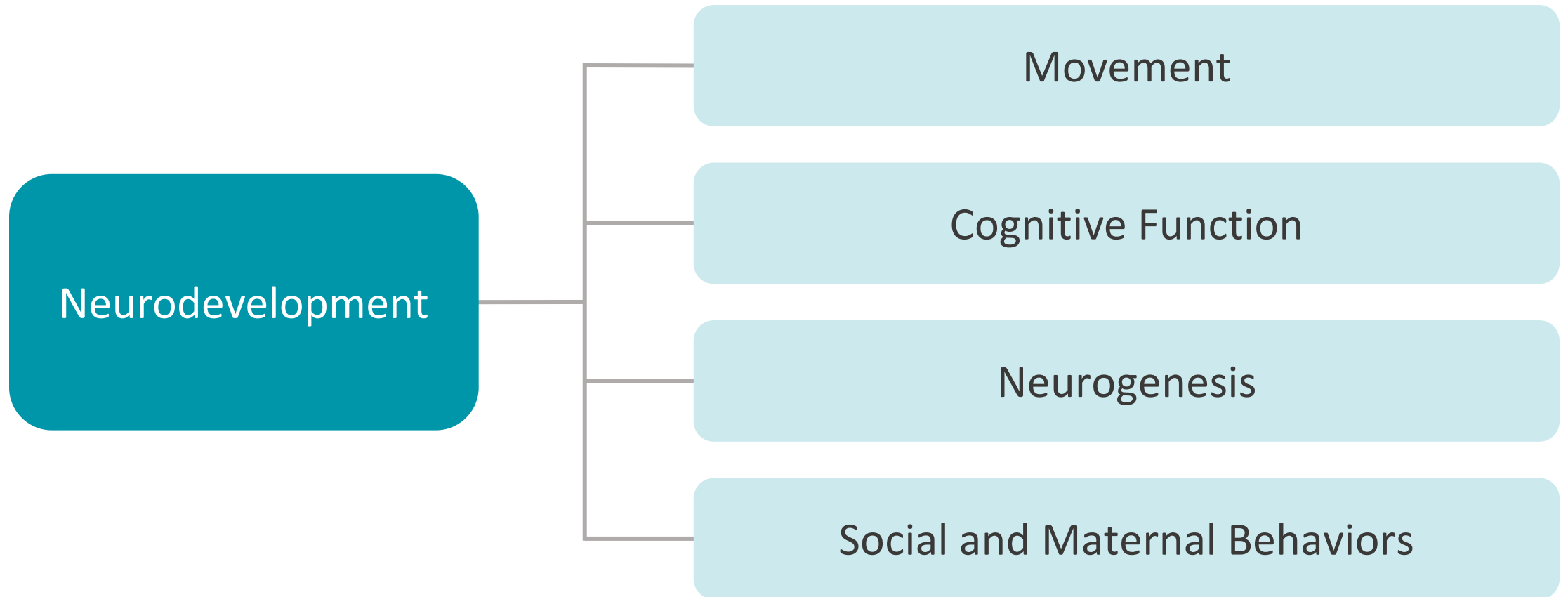
(Gao 2024; Gyimah 2021b; Hyun 2021; Kucharíková 2023; Li 2024; Mentor 2020; Qin 2023; Qiu 2018 & 2021; Wang 2019, 2020, & 2023; Xiao 2019; Yang 2018)



Toxicity of BPS on developing organisms



Toxicity of BPS on developing organisms



Neurodevelopment: Movement

Zebrafish

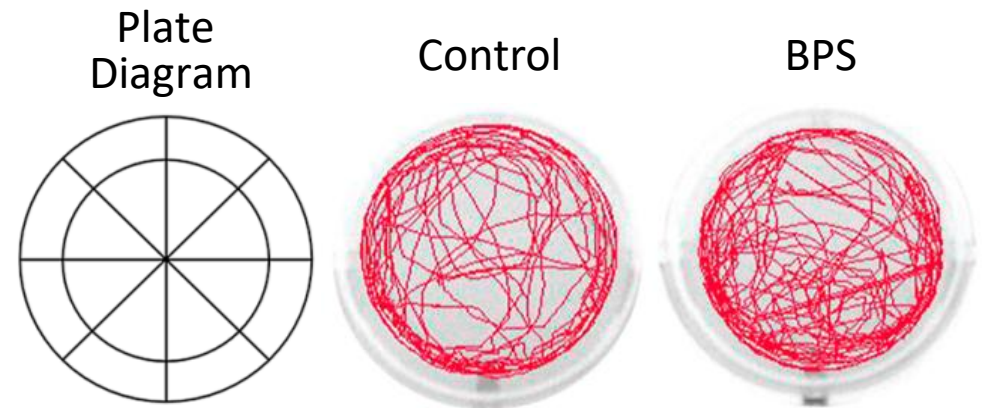
7 of 14 studies reported effects

- Δ Spontaneous movement
- ↓ Touch-evoked response
- ↓ Swirl escape rate
- Δ Swimming speed
- Δ Distance traveled
- ↑ Activity frequency

Exposures: 1 µg/L – 25.03 mg/L; 0 – 6 dpf

(Bai 2023; Fraser 2017; Gu 2019; Gyimah 2021b; Kinch 2015; Wang 2023; Wei 2018)

Example zebrafish trajectories over a 5-minute period using motion tracking
(Wang et al. 2023, adapted from Fig. 1)



Neurodevelopment: Movement

C. elegans

4 of 4 studies reported effects

↓ Body bend frequency

↓ Pharyngeal pumping

Δ Head thrashing

Exposure: 2.50 µg/L – 250.27 mg/L; egg – adult

(He 2024; Hyun 2021; McDonough 2021a; Xiao 2019)

Drosophila

1 study reported effects

↑ Distance traveled

↓ Vertical climbing time

Exposure: 250.27 mg/L; egg – pupation

(Santos Musachio 2024)



Neurodevelopment: Cognitive function

Mice

1 of 2 studies reported effects

↓ Working and short-term memory;
adult female offspring

Dose: 3 µg/kg-day, breeding – birth
(McDonough 2021a)

C. elegans

1 study reported effects

↑ Touches for habituation

Exposure: 125.14 µg/L – 1.25 mg/L; 0 – 4h
(Kucharíková 2023)

Rats

1 of 2 studies reported effects

↓ Learning and memory function;
juvenile offspring

Dose: 40 µg/kg-day, GD 6 – LD 21
(Tiwari 2024)

Drosophila

1 study reported effects

↓ Associative learning

Exposure: 250.27 mg/L; egg – pupation
(Santos Musachio 2024)



Neurodevelopment: Cognitive function

Juvenile rat hippocampus imaging

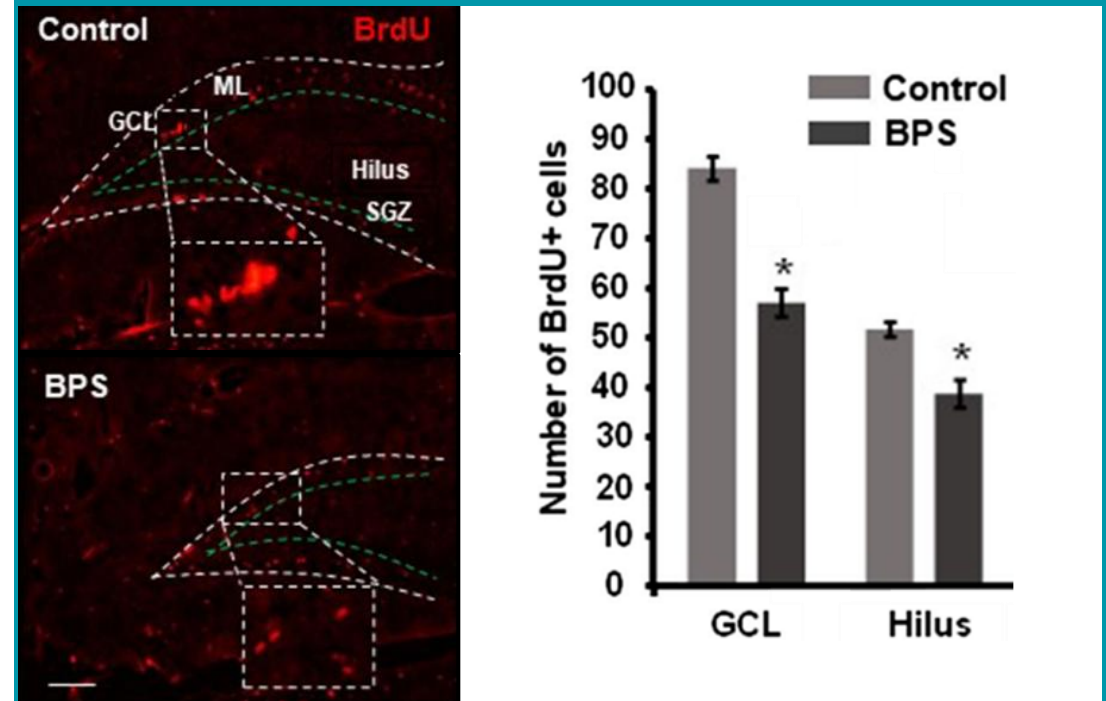
- ↓ Proliferation in granular cell layer and hilus
- ↓ Stemness and self-renewal in neural stem cells [NSCs]
- ↓ NSC differentiation into neurons
- ↑ Myelin sheath decompaction
- ↑ Damaged synapses

Dose: 40 µg/kg-day; GD 6 – LD 21

(Tiwari 2024)

Proliferation in rat hippocampus

(Tiwari et al. 2024, adapted from Fig. 6)



Neurodevelopment: Cognitive function

Juvenile rat hippocampus imaging

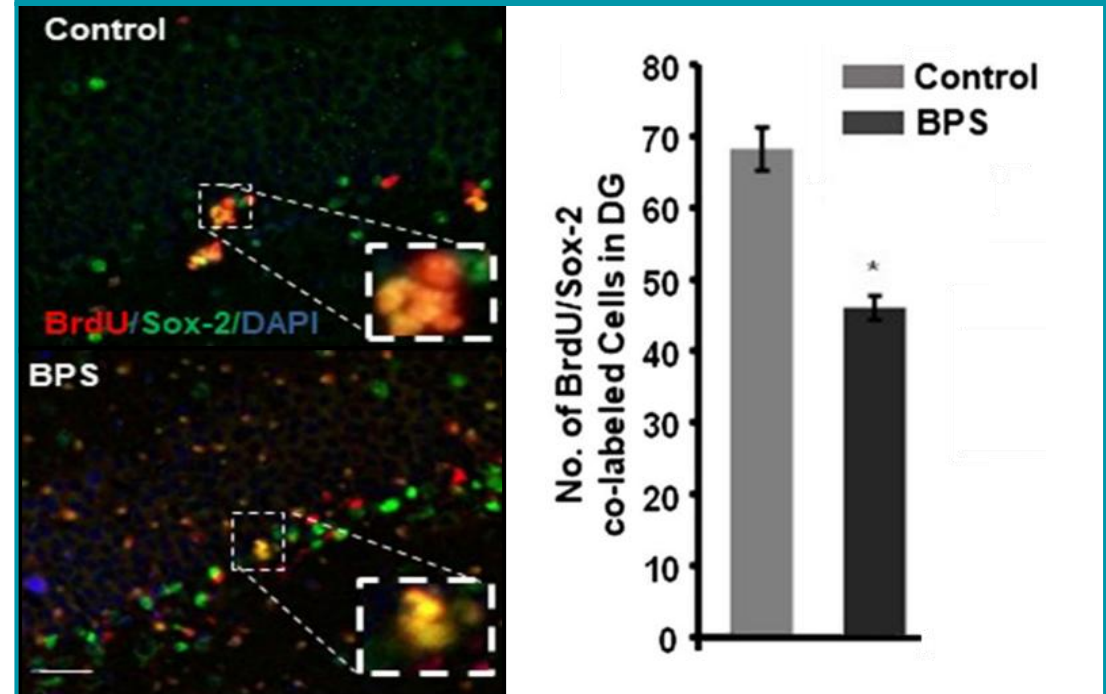
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- ↑ Damaged synapses

Dose: 40 µg/kg-day; GD 6 – LD 21

(Tiwari 2024)

NSC proliferation in rat dentate gyrus

(Tiwari et al. 2024, adapted from Fig. 7)



Neurodevelopment: Cognitive function

Juvenile rat hippocampus imaging

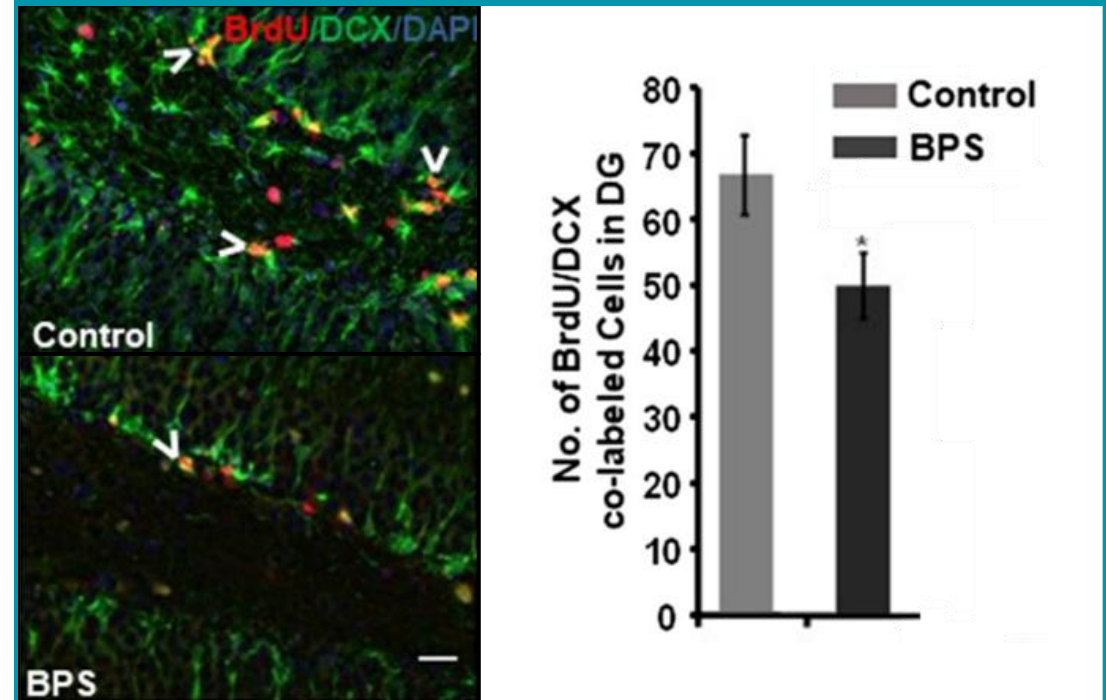
- ↓ Proliferation in granular cell layer and hilus
- ↓ Stemness and self-renewal in neural stem cells [NSCs]
- ↓ NSC differentiation into neurons
- ↑ Myelin sheath decompaction
- ↑ Damaged synapses

Dose: 40 µg/kg-day; GD 6 – LD 21

(Tiwari 2024)

NSC differentiation in rat dentate gyrus

(Tiwari et al. 2024, adapted from Fig. 8)



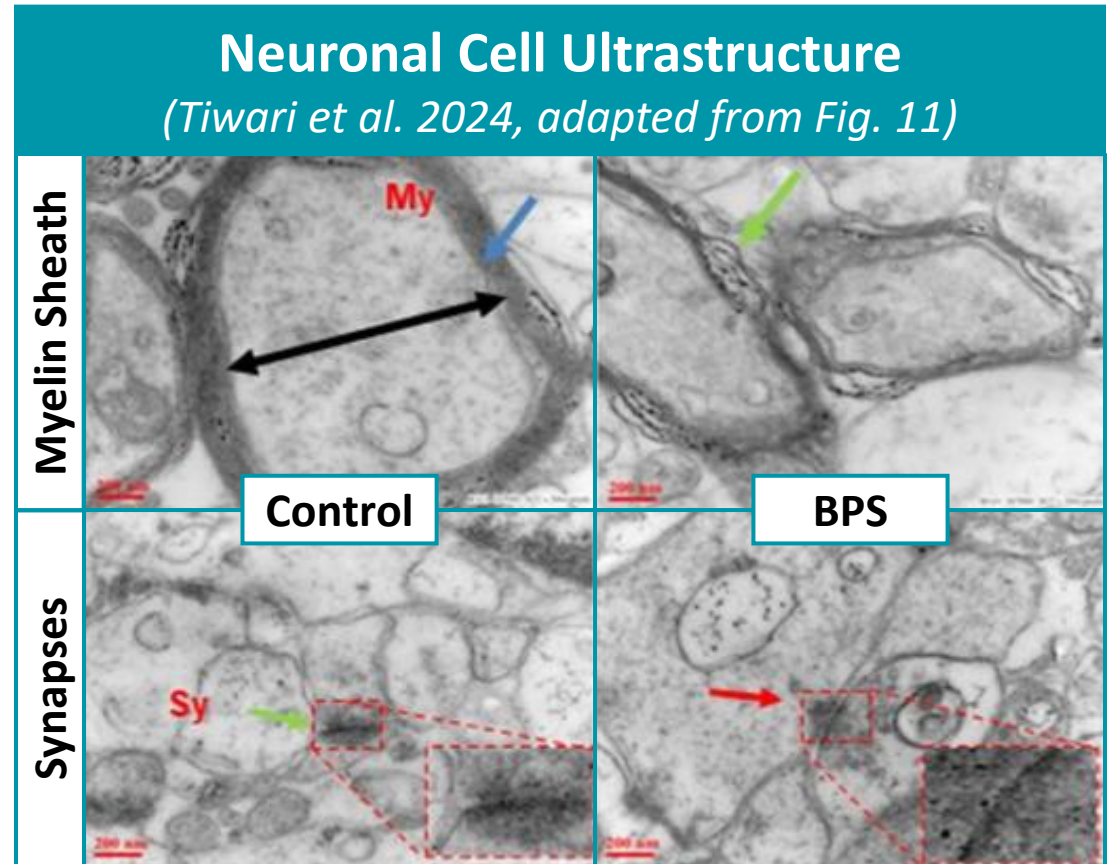
Neurodevelopment: Cognitive function

Juvenile rat hippocampus imaging

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- ↑ Damaged synapses

Dose: 40 µg/kg-day; GD 6 – LD 21

(Tiwari 2024)



Neurodevelopment: Neurogenesis

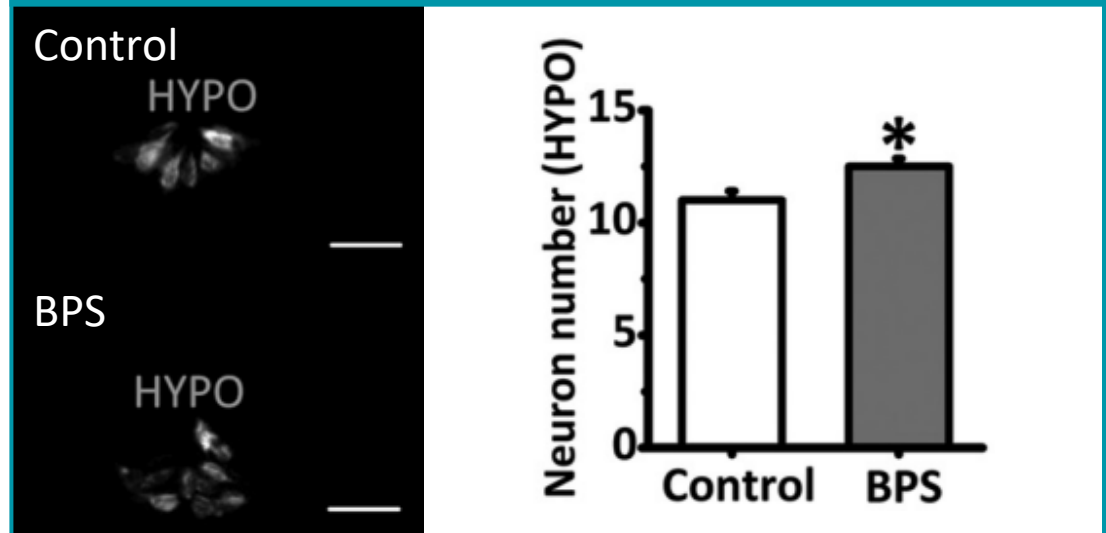
Zebrafish

- ↑ GnRH3-positive neurons in the hypothalamus
- ↑ Neurogenesis and proliferation (NS) in the hypothalamus
- ↓ CNS neurogenesis and motor neuron axon length
- ↑ Neurogenesis in the anterior telencephalon

Exposures: 1.7 – 250.27 µg/L; 0 – 6 dpf

(Bai 2023; Coumailleau 2020; Gu 2022; Kinch 2015; Qiu 2016)

GnRH3-positive neurons in the hypothalamus (Qiu et al. 2016, adapted from Fig. 1)



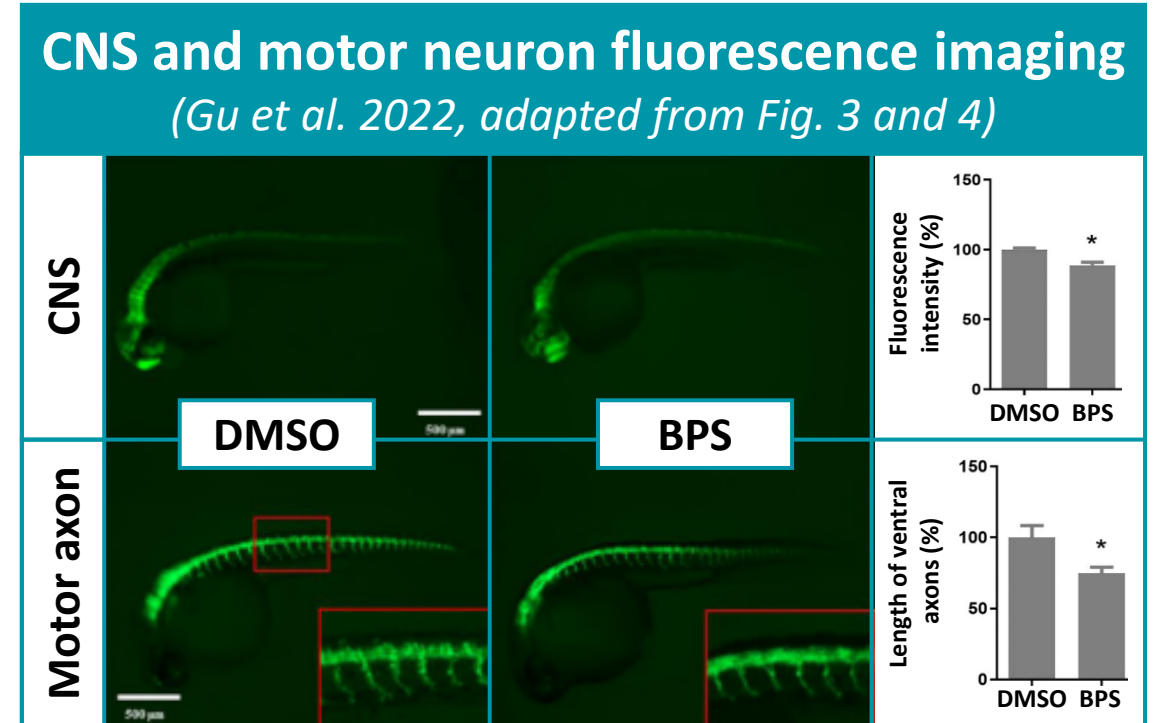
Neurodevelopment: Neurogenesis

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Neurodevelopment: Neurogenesis

Zebrafish

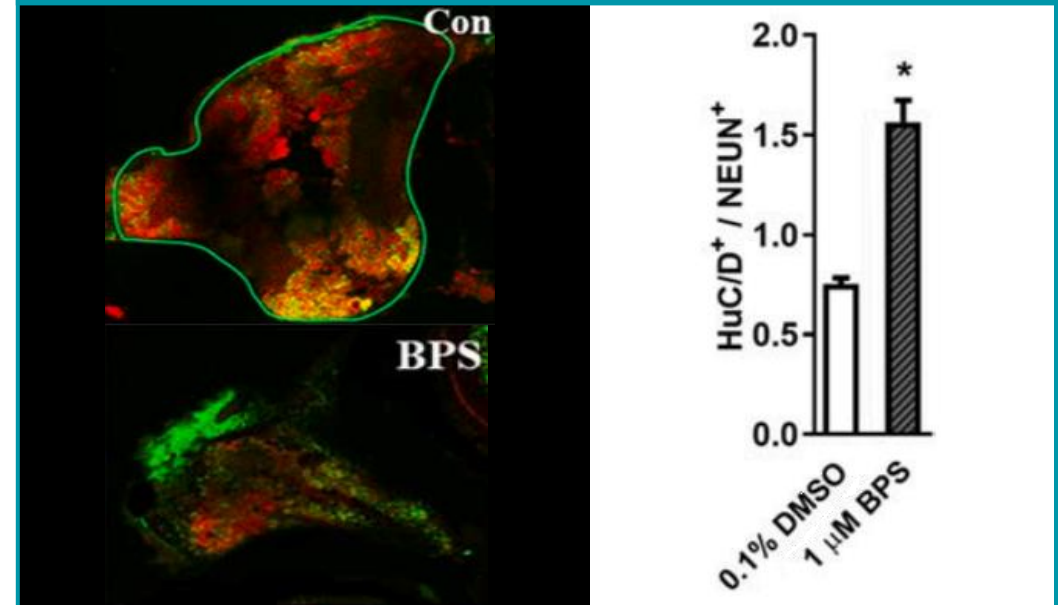
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Exposures: 1.7 – 250.27 $\mu\text{g/L}$; 0 – 6 dpf

(Bai 2023; Coumailleau 2020; Gu 2022; Kinch 2015; Qiu 2016)

Newborn (green) and mature neurons (red) in the anterior telencephalon

(Bai et al. 2023, adapted from Fig. 5)



Altered neurodevelopment-related gene expression in zebrafish

Gene	Description	Citations
<i>elavl3</i>	Neuron specific RNA-binding protein	Gu 2019; Gyimah 2021b
<i>gap43</i>	Axon growth, pathfinding, regeneration	Gu 2019; Gyimah 2021b; Wei 2018
<i>gfap</i>	Astrocyte intermediate filament; astrocyte-neuron interactions	Gu 2019; Gyimah 2021b; Wei 2018
<i>mbp</i>	Myelin formation, structure, stability	Gu 2019; Gyimah 2021b; Wei 2018
<i>mstn1</i>	TGFβ superfamily member	Gyimah 2021b
<i>neurog1</i>	Neuronal development, growth, differentiation	Gyimah 2021b
<i>vegfaa</i>	Early development; angiogenesis	Gyimah 2021b
<i>wnt8a</i>	Early development; dorsal axis formation	Gyimah 2021b



Neurodevelopment: Social and maternal behaviors

Mice

4 of 4 studies reported effects

- ↓ Social novelty preference;
juvenile offspring
- ↑ Anxiety; adult male offspring
- ↑ Depression; adult male offspring
- ↓ Social interaction interest;
adult offspring
- Δ F1 maternal behaviors

Doses: 2 – 200 µg/kg-day; GD 0 – PND 28

*(Catanese and Vandenberg 2017; Kim 2015;
McDonough 2021a; Moon 2023)*

Zebrafish

2 of 2 studies reported effects

- ↑ Novel tank stress; adult males
- ↓ Shoal cohesion; larvae, adult males

*Exposure: 1 µg/L – 25.03 mg/L; parental, 0 – 5 dpf
(Bai 2023; Salahinejad 2022)*

Drosophila

1 study reported effects

- ↓ Same-sex social interactions, adult stage
- ↑ Male combats, adult stage

*Exposure: 125.14 – 250.27 mg/L; egg – pupation
(Santos Musachio 2024)*

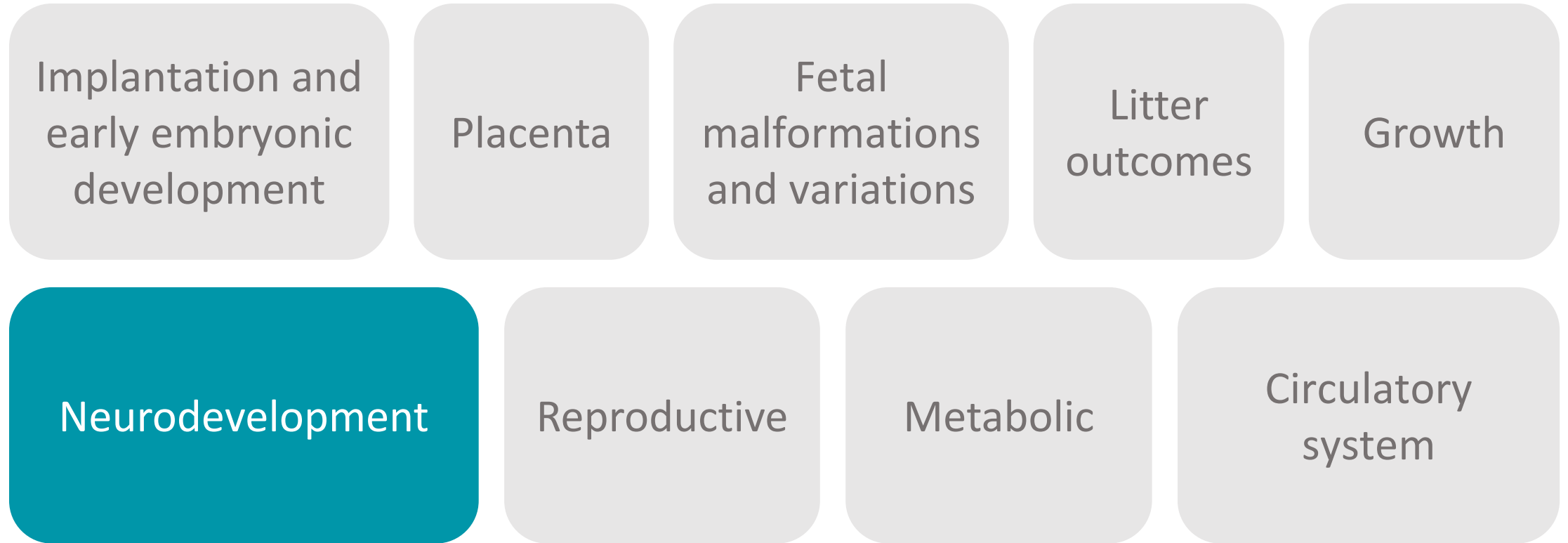


Altered neurotransmitter-related gene expression

Gene	Description	System	Citations
<i>chrna1</i>	nicotinic acetylcholine receptor	Zebrafish	Bai 2023
<i>Cyp2d4</i>	dopamine biosynthesis	Rat	Castro 2015
<i>Drd1 (NS)</i>	dopamine receptor	Rat	Castro 2015
<i>Drd3 (NS)</i>	dopamine receptor	Rat	Castro 2015
<i>htr1aa</i>	serotonin receptor	Zebrafish	Salahinejad 2023
<i>htr1ab</i>	serotonin receptor	Zebrafish	Salahinejad 2023
<i>mao</i>	neurotransmitter breakdown	Zebrafish	Salahinejad 2023
<i>syn2a</i>	neurotransmitter release at synapses	Zebrafish	Gu 2019; Wei 2018



Toxicity of BPS on developing organisms



Developmental reproductive effects

Female (OEHHA 2023)

- Δ Oocyte and follicle development
- Δ Mammary gland development
- Δ Reproductive function
 - ↓ Mating and pregnancy rates
 - ↑ Post-implantation loss
- Δ Reproductive hormones and other molecular markers

Male (OEHHA 2024)

- Δ Spermatogenesis
- Δ Sperm parameters
 - ↓ Sperm count
 - ↓ Sperm motility
 - ↓ Daily sperm production
- Δ Reproductive hormones and other molecular markers

Additional studies in OEHHA 2025

Female: 4

Male: 1



Developmental reproductive effects: Female

Mice

Ovarian effects

- ↓ Germ cell nests, ovarian reserves
- ↑ Primordial follicles

Pubertal onset

- ↓ Days to vaginal opening

Estrous cycle effects

- ↓ Days to first estrus
- ↑ Average cycle length

3.33 µg/L; from GD 8.5 – PND 3

(Gao 2024)

Reproductive function

- ↓ Litter size by third mating
- ↑ Infertility by fifth mating

Hormone & other molecular effects

- ↓ Serum Anti-Müllerian hormone
- ↓ Antioxidant and ovarian markers
- ↑ ROS and apoptosis



Developmental reproductive effects: Female

Rats

Pubertal onset & estrous effects

- ↑ Days to vaginal opening (NS)
- ↑ Estrous cycle regularity (NS)

0.025 µg/kg-day; pre mating – GD 18
(Fudvoye 2025)

Chick embryos

Ovarian effects

- Thinner left ovary (NS)

210 nmol/g egg; E4 – E19
(Mentor 2020)

Zebrafish

Oocyte effects

- Δ Oocyte development in offspring and grand-offspring

Reproductive function

- ↓ Egg numbers in offspring

Hormone & other molecular effects

- ↑ E2/T ratio in offspring
- Δ Sex hormone synthesis-related and DNA methyltransferase gene expression in offspring and grand-offspring

F0 exposure: 1 or 100 µg/L; 3 hpf – 120 dpf
(Hao 2022)



Developmental reproductive effects: Male

Rats

Pubertal onset

- No effects

0.025 µg/kg-day; premating – GD 18

(Fudvoye 2025)

Zebrafish

Sperm parameters

↓ Sperm concentration in untreated offspring and grand-offspring

F0 exposure: 1 and 100 µg/L; 3 hpf – 120 dpf

(Hao 2022)



Developmental reproductive effects: Worms

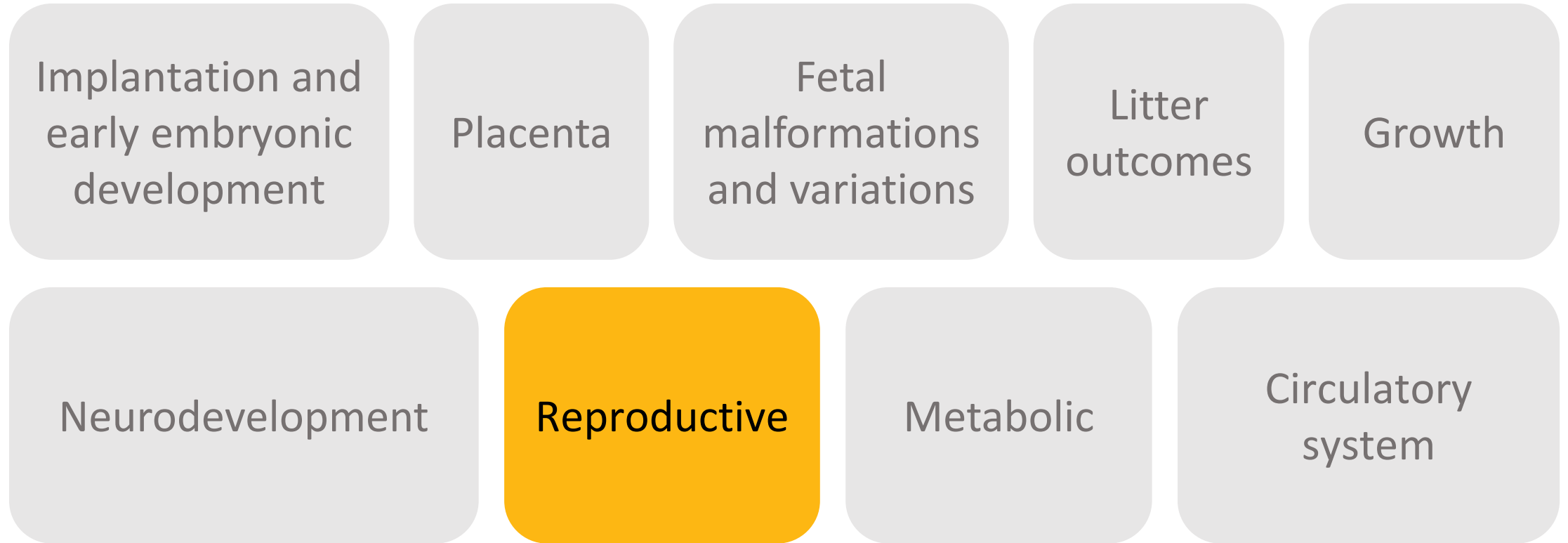
C. elegans

5 of 5 studies reported effects including:

- ↓ Egg-laying days; 1 – 10 μM (*McDonough 2021a*)
- ↓ Number of eggs laid; 60 $\mu\text{g/L}$ (*He W 2024*)
- ↓ Brood size; 0.01 μM – 1 mM (*Chen 2016; Hyun 2021; Xiao 2019*)
- ↑ Protruded vulval structures; 1 mM (*Hyun 2021*)



Toxicity of BPS on developing organisms



Metabolic alterations: Fat

Male mice

2 of 2 studies reported effects.

↑ White adipose tissue weight
(Ahn 2020*; Zhang 2023)

- Adipocyte hypertrophy (Ahn 2020*)

↑ Lipid accumulation in liver (Zhang 2023)

0.05 – 50 mg/kg-day

**Ahn 2020 observed effects in mice fed a high-fat diet.*

Mouse adipocytes

↑ Lipid accumulation; 200 nM (Kulsange 2024)

Male rats

2 of 3 studies reported effects.

↓ White adipose tissue weight
(Kaimal 2021)

↑ Fat mass, liver steatosis, and
• Adipocyte hypertrophy
(Molangiri 2023)

0.4 – 5 µg/kg-day

Male sheep

1 study reported effects.

↓ Adipocyte size; GD 120

0.5 mg/kg-day

(Pu 2017)



Metabolic alterations: Glucose and Lipids

Mice

2 of 2 studies reported effects.

- ↓ Non-fasted glucose in juvenile and adult male offspring (*McDonough 2021b*)
- ↑ Triglycerides in adult male offspring (*Zhang 2023*)

3 or 50 µg/kg-day

Rats

1 study reported no effects on:

- Fasting glucose, triacylglycerol, or cholesterol (*Molangiri 2023*)

0.4 µg/kg-day

Zebrafish

4 of 4 studies reported effects.

- ↓ Brain glucose uptake (*Wang 2024*)
- ↑ Glucose (*Gyimah 2021a*)
- ↓ Triacylglycerol levels and brain lipid distribution; and
- Δ Total cholesterol (*Wang 2023*)
- ↓ Total and LDL cholesterol; untreated offspring (*Wang 2019*)

1 – 100 µg/L; 0.3 and 1 µM



Altered expression of hepatic and/or lipid metabolism-related genes

System	Tissue/cell type	Description	Citations
Mice	Adipose tissue	Gestationally-exposed adult males fed a high-fat diet	Ahn 2020
Rats	Adipose and liver tissue	Gestationally-exposed adult males	Molangiri 2023
Sheep	Adipose tissue, adipocytes	GD 120 males	Pu 2017
Zebrafish	Whole body	Offspring of treated F0 & embryo/larvae	Wang 2019 & 2023
Chickens	Liver tissue; hepatocytes	Embryonic tissue and cells	Crump 2016; Ma 2015
Human cells	Embryoid bodies, hepatocyte-like cells	Embryonic stem cells	X Liang 2021



Metabolic alterations: Fatty acids

Humans

- ↑ Prenatal urinary BPS associated with altered cord blood concentrations of fatty acid metabolites (*Blaauwendraad 2021*)

Mice

- Δ Female GD 12.5 placentae (*Mao 2020*)
- ↑ Serum non-esterified fatty acids in male offspring (*Zhang 2023*)

50 or 200 µg/kg-day

Proteomics analysis in adipocytes (Kulsange 2024)

- Biosynthesis of unsaturated fatty acids & Fatty acid metabolism pathways

Rats

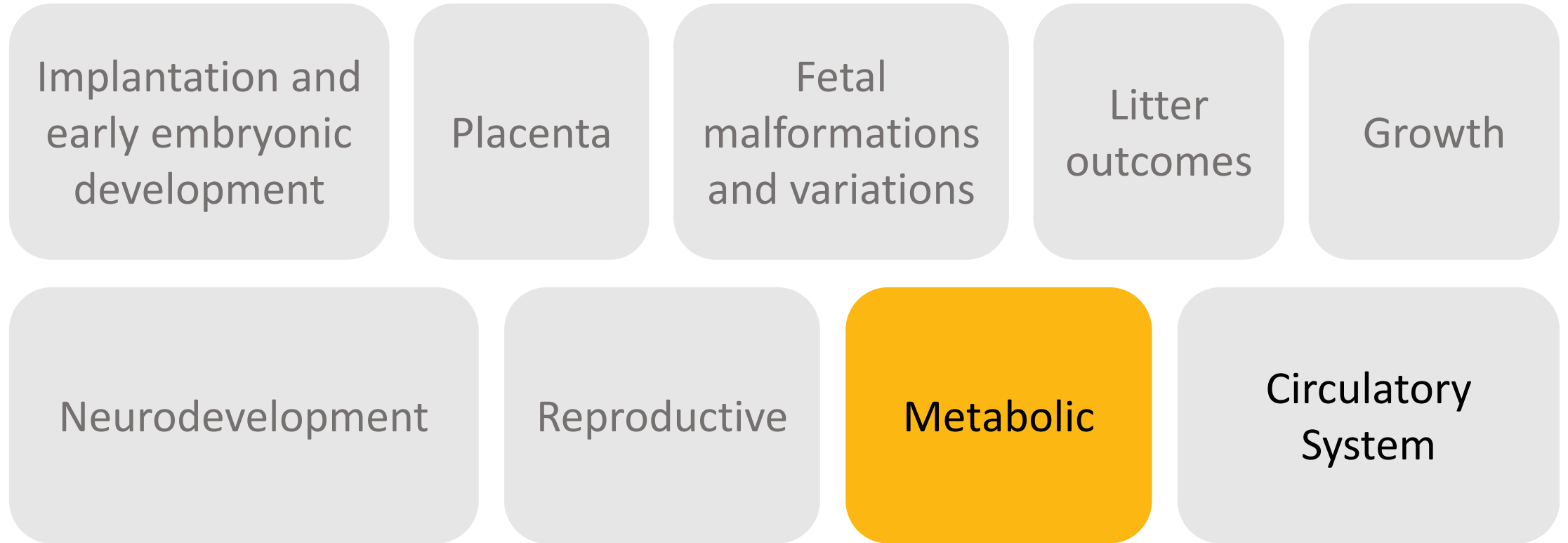
- ↑ Plasma docosahexaenoic acid (*Varma 2023*)
0.4 µg/kg-day

Zebrafish

- ↓ Long chain fatty acid and Δ gene expression; embryo/larvae (*Wang 2023*)
- Δ Gene expression related to cellular energy metabolism; 5 dpf (*Huang 2023*)
1 – 100 µg/L; 50 µM



Toxicity of BPS on developing organisms



Circulatory system effects

Zebrafish

7 of 11 studies reported effects.

- ↑ Cardiac edema
(*Ji 2013; Moreman 2017*)
- Δ Heart rate; 1.5 – 5 dpf
(*Huang 2023; Qin 2023; Qiu 2020; Zhang 2022*)
- Δ Heart rate; 2 – 5 dpf untreated grand-offspring, and
- ↑ Heart rate; 2 – 3 dpf untreated great-grand-offspring (*Hao 2022*)

1 µg/L – 200 mg/L; 10 or 50 µM

Chinese medaka

1 study reported effects.

- ↑ Cardiac edema (NS); 15 dpf
0.2 and 2 µg/L; from blastocyst
(*B Li 2024*)



Circulatory system effects: Blood vessels

Zebrafish

5 of 5 studies reported effects including:

- ↓ Endothelial cells in common cardinal vein; 1 dpf (*Zhang 2022*)
- ↓ Sinus venous-bulb arteriosus size; 3 dpf (*Qin 2023*)
- ↓ Blood flow velocity; 3 and 4 dpf (*Wang 2020*)
- ↑ Common cardinal vein growth rate; 1 and 2 dpf (*Zhang 2022*)
- ↑ Common cardinal vein area; 2 dpf (*Ji 2022; Wang 2020*)
- ↑ Ectopic sprouting; 3 dpf (*Wang 2020*)
- ↑ Red blood cells in caudal vein; 3 dpf (*J Li 2023*)
- ↑ Lipid accumulation; 4 dpf (*Wang 2020*)

1 µg/L – 30 mg/L; 2 hpf – assessment



Circulatory system: Molecular effects

Mice

Δ Cardiac muscle-related gene *Actn2*

(Mao 2020)

HUVECs & rat embryonic heart cells

↑ ROS

↑ Apoptotic cells

↑ NFκB phosphorylation

Δ Apoptosis-related protein expression

(Luo 2023; Ji 2022*)

**Ji 2022 only assessed ROS and HUVECs.*

Zebrafish

Transcriptomic analyses:

- Cardiac hypertrophy signaling
(Qiu 2020)
- Endothelial cell growth &
- Cardiac muscle contraction
(Zhang 2022)

Human embryonic stem cells

Transcriptomic analysis:

- Role of NFAT in Cardiac hypertrophy

(Peshdary 2021)



Nitric oxide effects

Zebrafish

3 of 3 studies reported effects.

- ↑ Nitric oxide levels
(*Qiu 2018; Yang 2018*)
- ↑ Nitric oxide synthase activity
(*Qiu 2018 & 2020*)
- ↑ Nitric oxide synthase gene expression
(*Qiu 2018*)

1 – 1000 $\mu\text{g/L}$

HUVECs

1 study reported effects.

- ↑ Nitric oxide levels
- ↑ Nitric oxide synthase
(endothelial) activity
- ↑ Nitric oxide gene expression

0.01 – 1 μM
(*Hu 2024*)



Epidemiologic Studies

Effects of BPS on Developmental Toxicity



Measures of BPS exposure varied across studies

Sample matrices

- Urine (58 studies)
- Serum (5 studies)
- Cord blood (1 study)
- Placenta (1 study)

Limits of detection (LOD)

- 0.003 – 0.5 ng/mL
- Mode: 0.1 ng/mL

Distribution of detection rates (%)

- Range: 14 – 99%
- Median (25th, 75th):
68% (40%, 86%)



Study samples represented different settings

Birth years of study participants

- 1998 to 2023

Countries represented

- China (n = 26)
- U.S. (n = 16)
- Netherlands (n = 8)
- France (n = 6)
- Korea (n = 2)
- Canada (n = 2)
- Sweden (n = 2)
- Other (n = 3)

U.S. cohort studies

- ECHO (n = 3)
- EARTH (n = 3)
- LIFECODES (n = 3)
- PROTECT (n = 2)
- TIDES (n = 1)
- NYU CHES (n = 1)
- IKIDS (n = 1)
- Healthy Start (n = 1)
- Michigan Mother Infant Pairs (n = 1)



Developmental outcomes examined in epidemiologic studies of BPS

Birth outcomes

Infant growth

Neurodevelopment

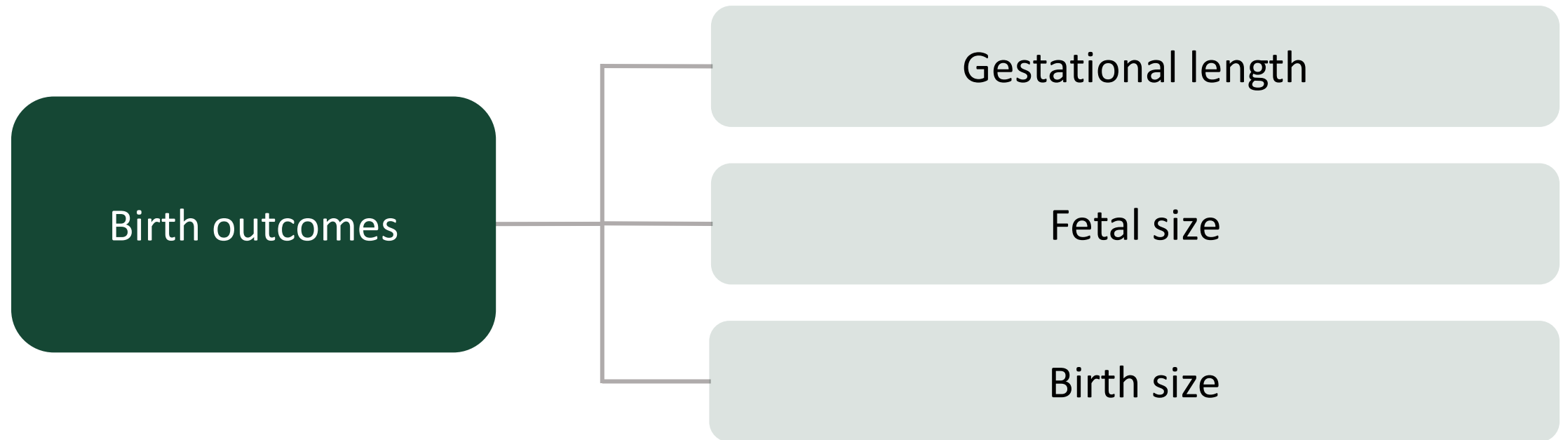
Immune function and
related outcomes

Endocrine and
metabolic outcomes

Other outcomes



Developmental outcomes examined in epidemiologic studies of BPS



Gestational length

Preterm birth

Binary variable representing birth before 37 weeks gestation

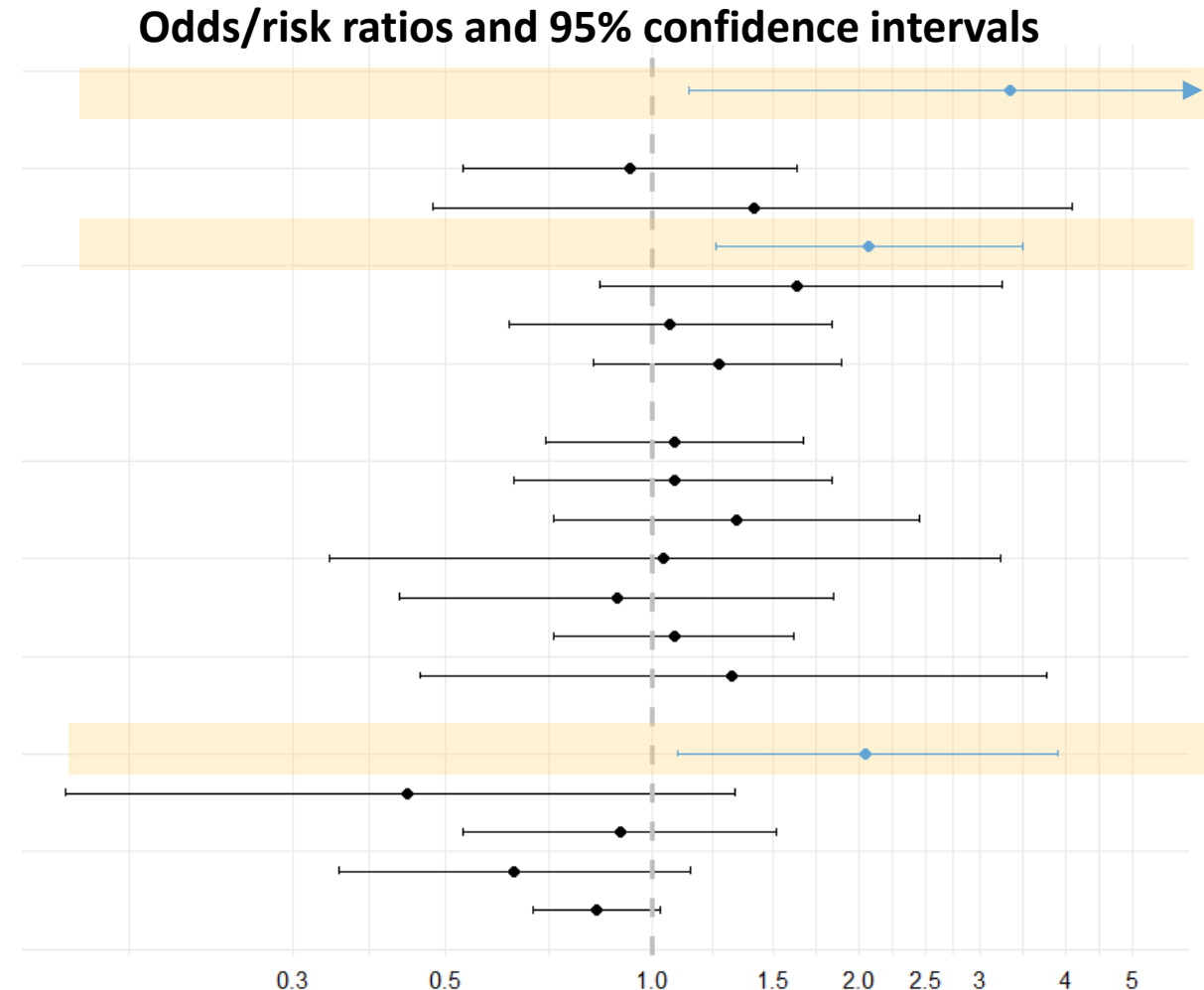
Gestation duration

Continuous variable measured in days or weeks

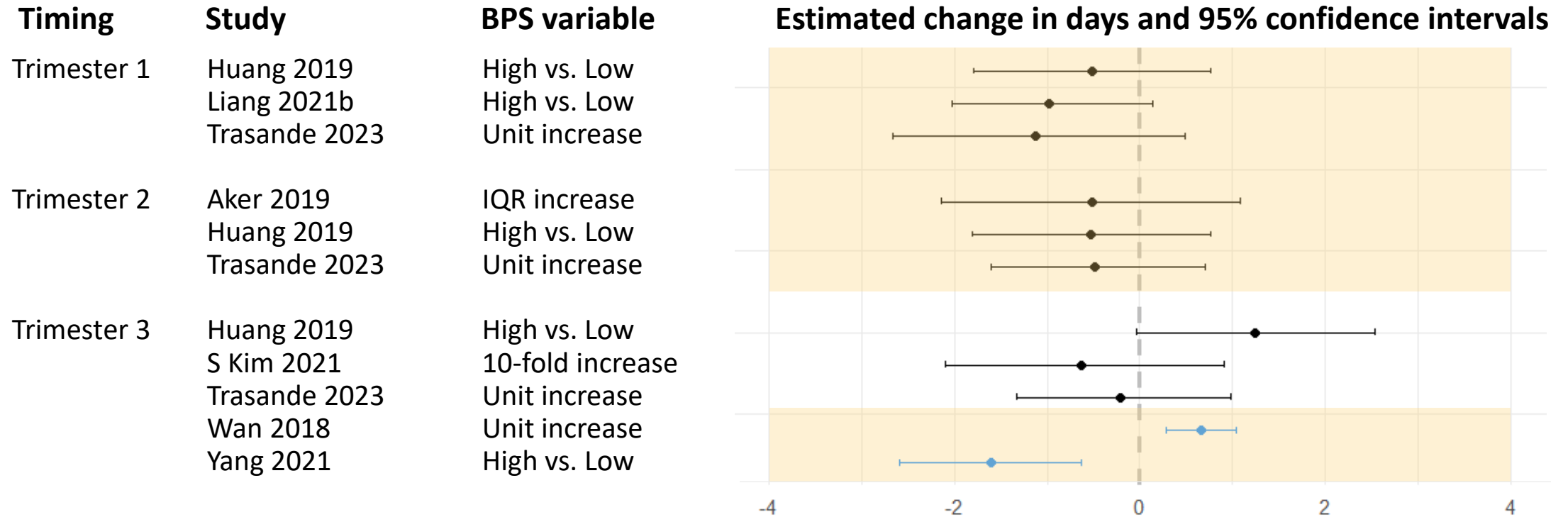


BPS and preterm birth

Timing	Study	BPS variable
Preconception	Mustieles 2020	Unit increase
Trimester 1	Aung 2019	Detect
	Huang 2019	High vs. Low
	Liang 2021b	High vs. Low
	Sol 2021	Detect
	Trasande 2023	Unit increase
Trimester 2	Zhang 2021	Unit increase
	Aker 2019	IQR increase
	Aung 2019 (18 wks)	Detect
	Aung 2019 (26 wks)	Detect
	Huang 2019	High vs. Low
	Sol 2021	Detect
	Trasande 2023	Unit increase
	Zhang 2021	Unit increase
Trimester 3	Aung 2019	Detect
	Huang 2019	High vs. Low
	Trasande 2023	Unit increase
	Zhang 2021	Unit increase
	Wan 2018	Unit increase



BPS and gestation duration



BPS and gestation duration

Three studies reported significant associations between BPS and shorter gestation duration among specific subgroups only:

- Among women reporting **negative life events** (*Aker 2020*)
- Among **non-Hispanic White women** (*Trasande 2023*)
- Among pregnancies with **female fetuses** (*Trasande 2023*)
- Among pregnancies with **male fetuses** (*Liang 2021b*)



Fetal size and birth size

In utero fetal size by ultrasound between 16-35 weeks

- Weight
- Head circumference
- Femur length
- Abdominal circumference
- Biparietal diameter

Size measured at birth

- Birthweight
- Birthweight z-score
- Size-for-gestational age
 - Small-for-gestational age (SGA): < 10th percentile
 - Large-for-gestational age (LGA): > 90th percentile
- Weight-for-length measures
- Adiposity

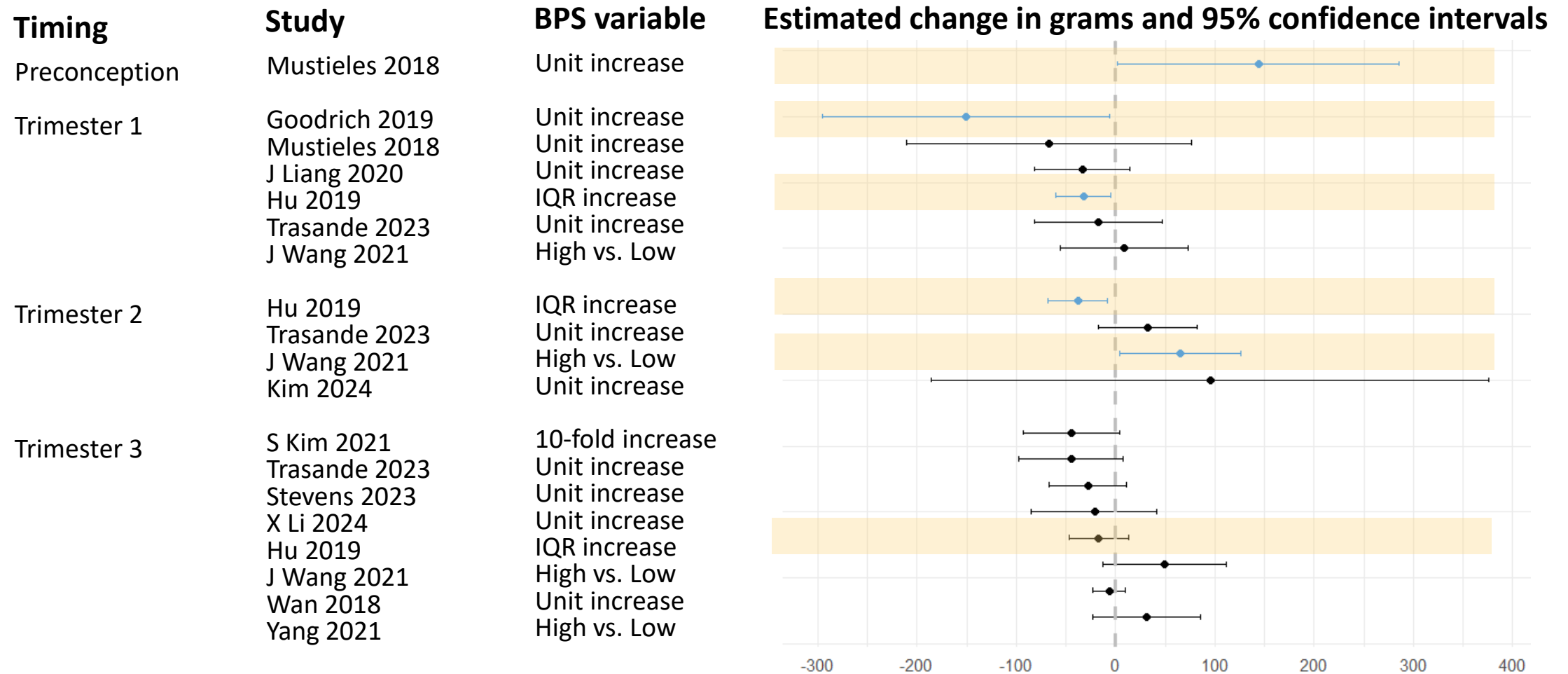


BPS and *in utero* fetal size

Outcome	Statistically Significant Associations
Weight	<i>2 of 4 studies reported significant associations:</i> • Lower in male fetuses only (<i>Ferguson 2018</i>) • Higher in full sample (<i>Sol 2021</i>)
Head circumference	<i>2 of 6 studies reported significant associations:</i> • Larger in full sample (<i>Sol 2021</i>) • Larger in female fetuses only (<i>Ferguson 2018</i>)
Femur length	<i>3 of 5 studies reported significant associations:</i> • Longer in full sample (<i>Jedynak 2022</i>) • Longer in female fetuses only (<i>Ferguson 2018</i>) • Shorter in full sample (<i>Bommarito 2024</i>)
Abdominal circumference	<i>0 of 5 studies reported significant associations</i>
Biparietal diameter	<i>0 of 3 studies reported significant associations</i>



BPS and birthweight



Developmental outcomes examined in epidemiologic studies of BPS

Birth outcomes

Infant growth

Neurodevelopment

Immune function and
related outcomes

Endocrine and
metabolic outcomes

Other outcomes

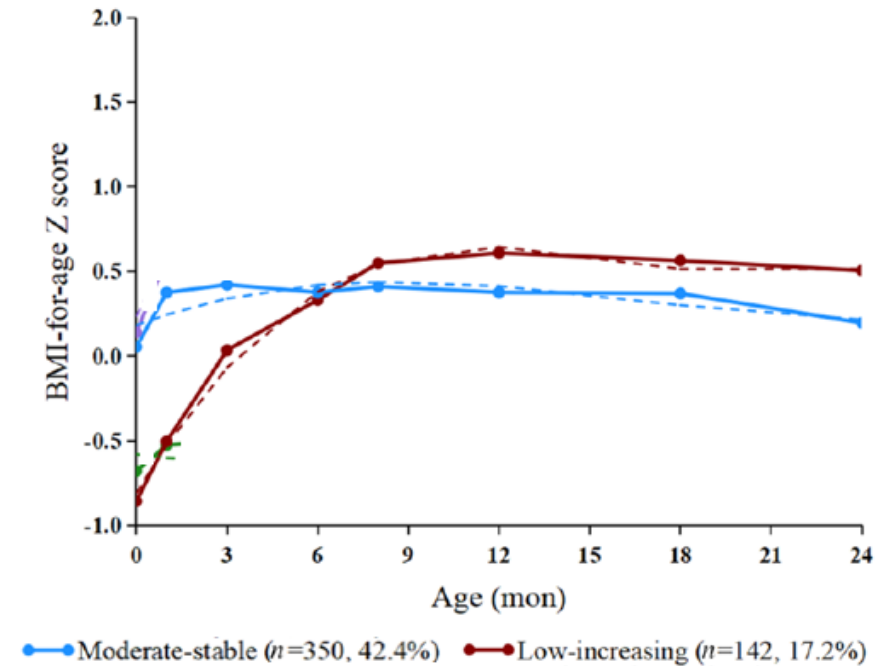


BPS and infant growth

Infant growth trajectories

2 of 5 studies reported significant associations:

- More rapid growth from birth to 6 months in females (*Y Chen 2024*)
- Higher odds of a 'low-increasing' growth trajectory vs. 'moderate-stable' trajectory from birth to 24 months (*Xiong 2023a*)



Adapted from Xiong 2023a



BPS and infant growth

Infant size after birth

5 of 7 studies reported significant associations:

- Smaller subscapular skinfold from birth to 4 years (*Blaauwendraad 2024*)
- Larger subscapular skin fold, abdominal skinfold thickness, and larger arm circumference at 6 months (*Y Chen 2024*)
- Larger BMI at 3 and 36 months (*Ouidir 2024*)
- Larger BMI at 2 years (*Lv 2024*)
- Larger fat mass percent at 3 years (*Colombini 2025*)



Developmental outcomes examined in epidemiologic studies of BPS

Birth outcomes

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metabolic outcomes

Other outcomes



Neurodevelopment outcomes

Outcome	Statistically Significant Associations
Cognitive function	<i>2 of 6 studies reported significant associations:</i> • Worse cognitive development at age 2 for those in high socioeconomic status (<i>Zhou 2025</i>) • Worse psychomotor development at age 2 (<i>Jiang 2020</i>) • Better mental development at age 2 (<i>Jiang 2020</i>)
Social-emotional development	<i>4 of 4 studies reported significant associations:</i> • Reduced eye tracking reaction time at age 2 (<i>Rolland 2025</i>) • Worse scores for internalizing behavior and emotionally reactive problems at age 26–28 months in females (<i>Geiger 2023</i>) • Worse social awareness, social cognition, and social communication at age 3 (<i>Mustieles 2023</i>) • Higher odds of emotional problems at age 4 (<i>Lei 2024</i>)



Developmental outcomes examined in epidemiologic studies of BPS

Birth outcomes

Infant growth

Neurodevelopment

Immune function and
related outcomes

Endocrine and
metabolic outcomes

Other outcomes



Immune function and related outcomes

Outcome	Statistically Significant Associations
Asthma	<i>3 of 6 studies reported significant associations:</i> ↑ at age 3 (Coiffier 2023), age 5 in males (Gaylord 2023), and age 13 in girls (Karramass et 2023) ↓ at age 13 in boys (Karramass 2023)
Lung function	<i>2 of 3 studies reported significant associations:</i> ↓ forced vital capacity and forced expiratory volume at age 13 (Karramass 2023) ↑ residual capacity and tidal volume at age 2 months (Coiffier 2023)
Wheezing	<i>1 of 3 studies reported significant associations:</i> ↓ late and persistent wheeze patterns at ages 1–11 years (Abellan 2022)
Bronchiolitis	<i>1 study reported significant associations:</i> ↑ at age 3 (Coiffier 2023)
Atopic dermatitis	<i>1 study reported significant associations:</i> ↓ at ages 5–9 in girls (Miller 2025)



Developmental outcomes examined in epidemiologic studies of BPS

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Other outcomes



Endocrine and metabolic outcomes

Outcome	Statistically Significant Associations
Thyroid stimulating hormone (TSH)	<i>2 of 3 studies reported significant associations:</i> ↓ TSH levels in newborn boys (<i>Xi 2023</i>) ↑ newborn TSH; associations consistently stronger in females (<i>Xiong 2023b</i>)
Fasting lipids, glucose, and insulin	<i>1 study reported significant associations:</i> ↓ insulin and lower glucose at ages 9–10 in boys only (<i>Sol 2020</i>) ↓ odds of high LDL at ages 9–10 in boys only (<i>Sol 2020</i>)
Follicle stimulating hormone (FSH)	<i>1 study reported significant associations:</i> ↓ FSH in newborns among normal pre-pregnancy BMI or cesarean deliveries (<i>Bigambo 2024</i>)
Urinary kisspeptin	<i>1 study reported significant associations:</i> ↑ kisspeptin levels; associations stronger at age 6 in boys (<i>Wang 2022</i>)



Developmental outcomes examined in epidemiologic studies of BPS

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Other outcomes



Other outcomes

Outcome	Statistically Significant Findings
Anogenital distance (AGD)	<i>1 study reported significant associations:</i> ↑ odds of rapid AGD growth in girls, with ↑ anus-clitoris distance and anus-fourchette distance at 48 months (<i>Chen 2025</i>)
Offspring reproductive development	<i>1 study reported significant associations:</i> • Delayed age at first menstruation at 10-13 years (<i>Blaauwendraad 2022b</i>)
Bone mineral density	<i>2 of 2 studies reported significant associations:</i> ↓ bone mineral density at age 10 (<i>van Zwol-Janssens 2020</i>) ↓ area adjusted bone mineral content at age 10 (<i>van Zwol-Janssens 2020</i>) ↓ bone mineral density at ages 3-6 in boys (<i>Liang 2023</i>)



Summary Across Evidence Streams

Developmental Toxicity of Bisphenol S



Topics discussed

- Implantation and early embryonic development
- Placental effects
- Birth/litter outcomes
- Fetal malformations and variations
- Growth effects
- Neurodevelopment
- Reproductive developmental effects
- Metabolic effects
- Immune function and related outcomes
- Circulatory system effects



Neurodevelopmental

Evidence		
Animal	Human	Mechanistic
- Δ Locomotion ↓ Cognitive function ↑ Anxiety- and depression-like behavior - Δ Social behavior	↑ Emotional problems ↑ Social behavioral problems	- Δ Neurogenesis - Δ Neurodevelopmental- and neurotransmitter-related genes

Altered (Δ), higher (↑), lower (↓).



Reproductive development

Evidence		
Animal	Human	Mechanistic
- Δ Ovarian function - Δ Pubertal onset – females - Δ Estrous cyclicity – females - Δ Reproductive function – females and males	• Delayed female pubertal onset ↑ AGD in girls	- Δ HPG axis hormone levels - Δ Endocrine-related gene and protein expression

Altered (Δ), higher (↑), lower (↓), hypothalamus-pituitary-gonad (HPG).



Metabolic Effects

Evidence		
Animal	Human	Mechanistic
↑ Adipose weight ↑ Lipid accumulation - Δ Adipocyte size	↑ Postnatal adiposity • Rapid postnatal growth	- Δ Glucose and lipid levels - Δ Fatty acid levels - Δ Hepatic and lipid metabolism markers

Altered (Δ), higher (↑), lower (↓).



Thank you!

