

TEDX

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Outcome Analysis for the Low-Dose BPA Spreadsheet

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The following provides an analysis of each outcome in the Low Dose Bisphenol A Spreadsheet. The results are grouped into the following categories: Male Reproductive System Outcomes, Female Reproductive System Outcomes, Miscellaneous Outcomes, Early Offspring Outcomes, Brain/Behavior Outcomes, and Organ/System Outcomes. The total number of studies in each endpoint is reported, as well as the number of studies that demonstrated results, and the number of studies that did not. Percentages of each are also provided. The specific changes found are outlined below each of the tables. For a broader view of the data, please refer to the summary and charts.

MALE REPRODUCTIVE SYSTEM OUTCOMES																				
	testes		sperm		prostate		preputial gland		epididymis		penis		seminal vesicles		testosterone		Leydig cells		feminization	
Change	37	58%	22	65%	15	52%	1	14%	6	29%	4	44%	4	20%	6	32%	4	80%	7	70%
No change	27	42%	12	35%	14	48%	6	86%	15	71%	5	56%	16	80%	13	68%	1	20%	3	30%
Total	64		34		29		7		21		9		20		19		5		10	

Testes

- 12 weight changes (9↓, 2↑, 1 n/c)
- 3 evidence of testes/ova
- 4 germ cell changes
- 2 developmental changes
- 14 changes in mRNA expression (ER, AhR, ERβ, p450, p53, PDGFR, rm-cpy19a, ntERα, ntERβ2, N-ras, *GnRHR*, *R-ras1&2*, *GSTM*)
- 1 change in rRNA
- 3 structural damage
- 1 changes receptor action and progesterone synthesis
- 2 changes in enzyme activities
- 1 gonad resorption
- 4 hormonal/chemical changes
- 27 no changes

Sperm

- 8 ↓ in sperm count
- 4 changes in sperm production (3↓, 1↑)
- 3 ↓ in sperm efficiency
- 4 ↓ in sperm motility
- 4 damage to sperm
- 1 ↑ in DJ-1
- 1 ↓ in sperm and signs of early spawning
- 3 ↓ in sperm maturity
- 1 ↓ in fertilization & offspring quality
- 12 no changes

Prostate

- 4 ↑ weight
- 3 size changes (2↓ length, 1↑ ducts)
- 4 morphological changes
- 2 changes in AR-T877A
- 1 permanent CK10 changes in adults
- 1 ↑ in PIN lesions (100%)
- 2 ↑ in tumor growth & cancer cell proliferation
- 1 ↑ in PSA levels
- 14 no changes

Preputial Gland

- 1 ↑ weight
- 6 no changes

Epididymis

- 4 ↓ weight
- 1 deformations
- 1 increase in ERα cells
- 1 changes in metabolism
- 15 no changes

Penis

- 3 ↓ length
- 1 deformation
- 5 no changes

Seminal Vesicles

- 4 weight changes (3↓, 1↑)
- 16 no changes

Testosterone

- 3 ↓ males
- 1 ↑ in females
- 1 ↓ in steroid ratio
- 2 ↑ in serum levels
- 1 ♂ ratio of androgens to estrogens same as ♀
- 13 no changes

Leydig Cells

- 1 ↓ steroidogenic enzyme gene expression
- 1 ↓ cAMP & progesterone
- 1 ↑ in Nur77 gene expression
- 1 changes in AR regulation
- 1 no changes

Feminization

- 7 evidence of changes
- 3 no changes

FEMALE REPRODUCTIVE SYSTEM OUTCOMES														
	ovaries		vagina		uterus		breast		estrus		♀ organs		eggs/oocytes	
Change	25	81%	8	57%	23	64%	39	91%	6	55%	4	67%	21	72%
No change	6	19%	6	43%	13	36%	4	9%	5	45%	2	33%	8	28%
Total	14		36		43		11		6		29		31	

Ovaries

- 2 changes in weight (1↓, 1↑)
- 1 ↓ in growth
- 5 deformations/ morphological changes
- 2 associations with polycystic ovarian syndrome
- 1 changes in mRNA expression (↑AhR, P450c17, P450scc, StAR, ↓RAR α, p53)
- 5 ↑ in progesterone production
- 2 ↑ in testosterone synthesis
- 1 ovarian cysts
- 3 changed estradiol production (2↓, 1↑)
- 1 gonad resorption
- 1 ↑ BG-1 ovarian cancer cells
- 1 superfeminization
- 1 ↓ viable granulosa cells, ↑apoptosis
- 1 ↓ GSH and enzyme activity
- 1 ↑ lipid peroxidation
- 1 ↑ proliferation of cancer cells & ERK 1&2
- 1 ↑ MMP-9 enzyme activity
- 6 no changes

Vagina

- 2 ↓ in weight
- 4 deformations/ morphological changes
- 2 changes in vaginal opening (1↓, 1↑)
- 1 ↑ in ERα & ERβ activity
- 1 superfeminization
- 6 no changes

Uterus

- 7 changes in weight (3↓, 4↑)
- 5 deformations/ morphological changes
- 2 cornification
- 2 hyperplasia
- 2 ↑ progesterone receptor expression
- 2 changed ER expression (1↓, 1↑)
- 2 changes in gene expression/transcription
- 2 changes in HOXA expression (1↓, 1↑)
- 1 ↑ in AGF-I mRNA activity
- 1 ↑ in heat shock proteins
- 1 ↑ in AlkP in cancer cells
- 1 ↓ BPA in endometrial cancer & hyperplasia
- 1 ↓ proliferation of endometrial endothelial cells
- 1 ↑ in mitotic cells
- 1 superfeminization
- 13 no changes

Breast

- 15 changes in proliferation (1↓, 14↑)
- 2 changes in cell morphology
- 4 accelerated maturation of tissue
- 5 ↑ in TEBs, buds, & lobuloalveoli
- 2 ↓ TEBs area
- 3 ↑ in cancer, & precancerous cells
- 5 changes in ER activity
- 6 changes in gene expression/transcription
- 3 ↓ in apoptosis
- 4 ↑ hyperplastic ducts or changes in ductal tree
- 1 ↑ dehydrogenase leakage
- 1 ↑ Bloom helicase expression
- 1 cell cycle deregulation
- 1 ↓ adiponectin release
- 2 changes in adipose tissue
- 1 ↑ VEGF protein expression
- 1 protected cancer cells from cancer drugs
- 4 no changes

Estrus

- 2 ↓ in # of days between vo & estrus
- 3 increased or persistent estrus
- 1 irregular estrus
- 5 no changes

Female Organs

- 3 deformations/ morphological changes
- 1 ↑ in ERα & ERβ activity
- 2 additional female organs
- 1 superfeminization
- 2 no changes

Eggs/Oocytes

- 1 ↑ in ovulation time
- 5 egg deformations
- 2 abnormal development
- 1 ↓ vg/vn immunoreactivity
- 3 changes in maturation (2↓, 1↑)
- 1 ↑ atresia of PVG oocytes
- 9 changes in egg/germ cells/oocyte production (3↓, 6↑)
- 1 ↑ chromosomal abnormalities
- 8 no change

MISCELLANEOUS OUTCOMES																					
	body weight		genital distance		maturation		growth		mortality		LH		enzymes		proteins		DNA/ gene expression		hormones & receptor binding affinity		
Change	23	34%	5	45%	15	52%	5	50%	7	33%	1	14%	9	82%	8	89%	45	92%	19	76%	
No change	45	66%	6	55%	14	48%	5	50%	14	67%	6	86%	2	18%	1	11%	4	8%	6	24%	
Total	68		11		29		10		21		7		11		9		49		25		

Body Weight

- 22 changes (7↓, 15↑)
- 3 changes in adipocytes/ adipose tissue
- 45 no changes

Genital Distance

- 2 ↓ in distance
- 3 ↑ in distance
- 6 no changes

Maturation

- 2 ↑ in females
- 2 ↓ in males
- 7 changes both sexes (4↓, 3↑)
- 1 ↑ oocytes maturation
- 3 ↓ in T3 induced maturation
- 14 no changes

Growth

- 5 ↓ in growth
- 1 larval malformations
- 5 no changes

Mortality

- 7 increases in mortality
- 14 no changes

LH

- 1 ↓ in levels
- 6 no changes

Enzymes

- 1 ↑ in phosphotyrosine levels
- 1 ↑ in CYP content
- 1 ↑ in cAMP levels
- 1 potent antiandrogenic activity
- 4 catalase (2↓, 2↑)
- 3 glutathione s-transferase & reductase (1↓, 2↑)
- 2 changes in peroxidase (1↓, 1↑)
- 1 ↓ E2 sulfination
- 1 ↓ activity of superoxide dismutase
- 1 altered steroidogenic enzymes
- 2 no changes

Proteins

- 4 changes in heat shock proteins (1↓, 3↑)
- 1 changed regulation of protein peaks in ♀ (26↓, 13↑) in ♂ (19↓, 12↑)
- 1 irreversibly inhibited cell communication
- 1 ↑ VEGF protein expression
- 1 ↑ HSP27 protein chaperone expression
- 1 altered some globin proteins, not total content
- 1 no changes

DNA/Gene Expression

- 5 changes
- 17 upregulation of multiple genes
- 5 downregulation of genes
- 8 changes in mRNA (3↓, 5↑)
- 1 ↑ in mutations
- 1 strand breaks
- 2 ↓ in methylation
- 1 inhibits replication
- 2 ↑ in micronuclei
- 1 changes in T3 gene expression
- 3 ↑ increased gene expression
- 1 ↓ transcription levels
- 1 DNA damage in erythrocytes
- 1 expression correlated with antiestrogen ICI
- 1 expression patterns undermine apoptosis
- 1 change species specific
- 4 no changes

Hormones & Binding Affinity

- 7 binds to E α , β , γ and AR
- 3 competitively binds to hormone binding sites
- 1 interfered with estrogen signaling
- 3 stimulates ER activity or synthesis
- 2 ↑ estrogenic activity
- 1 ↑ levels of juvenile hormone
- 1 upregulates ER mRNA
- 6 no changes

EARLY OFFSPRING OUTCOMES										
	embryos		placenta		preg rate		birth rate		sex ratio	
Change	14	78%	1	100%	3	21%	5	15%	5	20%
No change	4	22%	0	0%	11	79%	29	85%	20	80%
Total	18		1		14		34		25	

Embryos

- 3 change in rate of growth (1↓, 2↑)
- 4 ↑ in embryo production
- 1 ↑ in reabsorptions
- 1 ↑ in unshelled embryos
- 2 deformations
- 1 ↓ in hatching success
- 3 changes in developmental progression (1↓, 2↑)
- 1 change in ER activation
- 1 ↓ calcein accumulation
- 1 ↑ organ development (eye)
- 4 no changes

Placenta

- 1 enzyme and gene changes in placenta
- 0 no changes

Pregnancy Rate

- 3 ↓ in pregnancy rates
- 11 no changes

Birth Rate

- 3 ↓ birth rate
- 1 ↑ in reabsorptions
- 1 ↑ in miscarriages
- 29 no changes

Sex Ratio

- 4 changes in # of males (1↓, 3↑)
- 1 ↓ # of females
- 20 no changes

BRAIN & BEHAVIOR OUTCOMES																
	brain		behavior		dendrites		hippocampus		amygdala		hypothalamus		pituitary		dopamine	
Change	35	78%	31	97%	3	100%	7	70%	1	100%	4	67%	5	45%	4	100%
No change	10	22%	1	3%	0	0%	3	30%	0	0%	2	33%	6	55%	0	0%
Total	45		32		3		10		1		6		11		4	

Brain

- 1 ↓ in dopamine neurons
- 1 ↓ weight
- 7 changes in gene expression (2↓, 5↑)
- 7 mRNA expression (↓RAR, p53, MT; ↑AhR, R-ras1&2, Vps52, LOC72325 & general)
- 7 changes in cellular activity
- 1 ↑ in ERα & ERβ expression
- 1 inhibited neuronal differentiation
- 1 no sex differences in morphology
- 4 changes in structure
- 1 ↑ pERK signaling in cerebellum
- 2 ↑ GFAP production/expression
- 2 memory impairment
- 1 ↑ in cell proliferation
- 1 changed ratio of types of neurons
- 1 changes neuronal response to testosterone
- 1 changes in methylation
- 1 changes in long term potentiation
- 10 no changes

Behavior

- 9 changes in motor activity (3↓, 6↑)
- 1 ↑ in aggression
- 7 changes in sex typed behavior
- 6 changes in anxious behavior (2↓, 4↑)
- 3 changes in maternal behavior
- 1 changes in pain response
- 3 ↑ in morphine & methamphetamine effects
- 1 ↓ in amphetamine reward in females only
- 2 changes in sexual performance
- 2 changes in social behavior
- 2 changes in play behavior
- 1 ↓ in avoidance behavior
- 1 ↓ developmental progress
- 1 no change

Dendrites

- 1 ↑ in spine density & mossy fiber growth
- 1 ↑ in astrocyte activation
- 1 ↑ in neuronal cell death
- 1 ↓ Purkinje cell dendrites
- 0 no changes

Hippocampus

- 1 ↓ in sst2 receptors
- 1 neuronal damage
- 1 ↑ intercellular Ca+
- 1 ↑ hormone conversion
- 1 ↓ CAT-IR
- 1 ↓ cholinergic fiber in CA1-3
- 1 ↑ mRNA & SRC-1 in males
- 1 interferes with synaptic response to testosterone
- 1 ↓ in astroglial spine synapses, ↑ in process density
- 3 no changes

Amygdala

- 1 ↓ in sst2 receptors
- 0 no changes

Hypothalamus

- 1 ↑ in progesterone receptors
- 1 ↑ in sst2 receptors
- 1 dose dependent changes in MAP2, synapsin I positive areas & synaptic density
- 1 ↑ in ER-labeled neurons
- 2 no changes

Pituitary

- 2 ↑ in PRL release
- 1 ↑ in PRF activity
- 1 ↑ in cell proliferation
- 1 changes in CA++
- 1 differences in species' responses
- 1 ↓ in growth hormone
- 1 ↓ in cell numbers
- 1 blocked T3 binding
- 1 ↓ prolactin production
- 1 ↑ *GnRHR* gene expression
- 6 no changes

Dopamine

- 2 ↓ in dopamine transporter
- 1 ↓ in D4 receptors
- 1 ↑ in D1 mRNA & g-protein
- 1 ↑ Ca2+ responses to dopamine
- 0 no changes

ORGAN & SYSTEM OUTCOMES

	adrenal		liver		thyroid		pancreas		kidney		spleen		bones		immune system		blood		other	
Change	1	33%	32	68%	6	60%	7	100%	5	33%	5	56%	6	75%	12	80%	19	90%	14	78%
No change	2	67%	15	32%	4	40%	0	0%	10	67%	4	44%	2	25%	3	20%	2	10%	4	22%
Total	3		47		10		7		15		9		8		15		21		18	

Adrenal

- 1 ↑ catecholamine synthesis
- 2 no changes

Liver

- 3 weight changes (2↓, 1↑)
- 3 ↑ in VTG
- 1 ↑ in [35S]GTPγS binding
- 1 histological changes
- 1 ↑ in catalase
- 1 different modes of excretion
- 1 sufficient GT activity to metabolize
- 1 antagonist activity
- 1 ↑ in MT protein
- 1 ↑ in liver damage
- 1 ↑ in esterone levels
- 7 mRNA changes (↑ER, R-ras1&2, Vtg; ↓ MT, MT-, p53, rec-cypla)
- 1 ↓ MeER1, ↑ MeER2
- 1 glucuronidated by UGT2B15
- 2 upregulation of *omChgH* and *omChgL*
- 1 ↑ GGT, alkaline phosphatase, lactate dehydrogenase
- 1 ↑ choriogenin L and H cDNA
- 1 ↓ CYP2C33-like, CYP2Y3, CYP3C1-like
- 2 ↑ *GnRHR* gene expression
- 1 ↑ lipid peroxidation
- 1 ↓ GSH, GST, GPx, GR, and CAT
- 15 no changes

Thyroid

- 1 ↓ thyroid induced metamorphosis
- 1 ↓ TRβ mRNA
- 1 ↑ Tα mRNA
- 1 ↑ hyperthyroidism followed by hypothyroidism
- 1 ↓ prolactin production
- 1 blocked T3 binding
- 1 recruits N-CoR
- 1 inhibited T3 transcription, gene expression
- 4 no changes

Pancreas

- 2 ↑ in insulin excretion
- 1 ↓ in low glucose induced Ca²⁺ oscillations
- 1 CREB activation
- 1 ↓ MeER1, ↑ MeER2
- 1 ↑ insulin content of islets
- 1 ↑ BPA, ↑ diabetes
- 0 no changes

Kidney

- 1 ↓ in weight
- 1 ↑ in reactive substances
- 1 ↑ in ERα & ERβ transcriptional activity
- 1 ↑ in lipid peroxidation, ↓ GSH activity
- 1 ↓ GST, GPx, and CAT enzymes
- 1 ↑ estrogenic activity in CV-1MCF-7 cells
- 10 no changes

Spleen

- 2 ↑ in cell proliferation
- 1 ↓ in T-cells
- 1 ↑ in CD3+, CD4+ and CD8+ cells
- 3 changes INFγ (1↓, 2↑)
- 1 ↑ TNF-α expression
- 2 ↑ IL-4 & IL-13 splenocytes
- 1 ↑ Thy1 splenocytes
- 1 ↑ IgM
- 1 ↑ IgG1 and IgG2a levels
- 1 ↓ IgGE levels
- 4 no changes

Bones

- 1 demineralization
- 1 ↓ TRAP & ALP activity
- 1 ↓ in ALF, ↑ Ca & P content
- 1 ↑ in ERα & ERβ transcriptional activity
- 1 ↑ in phagocytosis
- 1 ↓ osteoblast-like cell proliferation
- 2 no changes

Immune System

- 3 changes in IgGa activity (1↓, 2↑)
- 1 ↑ in IgG activity
- 2 changes in INFγ activity (1↓, 1↑)
- 2 ↑ in IL activity
- 1 ↓ in TNFα, NO & TNFα, iNOS mRNA
- 1 ↑ IgM, ↓ IgE
- 1 later development of proteinuria
- 1 membrane destabilization
- 1 ↓ in phosphorylation of p38 MAPK
- 1 ↓ in phagocytic activity
- 1 ↑ in Thy-1 splenocytes
- 1 ↑ transcription factor PU.1
- 1 ↑ lymphocyte & macrophage proliferation
- 1 ↑ OZ triggered superoxide production
- 1 ↑ Cd3d, cathepsin E, Ctse, Cd5 and Sod2
- 3 no changes

Blood

- 10 ↑ in plasma VTG
- 1 ↑ in plasma Zrp
- 1 ↑ Zrp in males vs females
- 1 ↑ levels of BPA in males
- 1 ↑ insulin and β-insulin levels
- 1 ↓ in serum leptin
- 1 ↑ SCE in lymphocytes
- 1 ↑ in micronuclei in erythrocytes
- 2 changes in estradiol levels (♀ 1↓, ♂ 1↑, 1↓)
- 1 ↑ estradiol/testosterone levels in both sexes
- 1 ↑ total cholesterol in ♀
- 1 ↑ trigacylglycerol, NEFA, serum glucose in ♂
- 1 changes in Ca and calcitonin levels
- 1 ↑ hemoglobin genes HbA, HbB, HbC, and downregulated HbE
- 1 altered some globin proteins
- 1 DNA damage in erythrocytes
- 2 no change

Other

- 2 ↑ *GnRHR* expression in intestines
- 1 interfered with normal development of intestines
- 2 ↑ expression of N-ras mRNA in intestines
- 1 ↓ offspring quality
- 1 immobilized invertebrates
- 1 mouthpart deformations
- 1 ↓ adiponectin release in adipocytes
- 1 association with one marker of oxidative stress
- 1 ↑ levels associated with ↑ fasting blood sugar levels.
- 1 associated with cardiovascular disease
- 1 ↓ acetylcholine esterase activity in claw muscles
- 1 suppressed MT mRNA expression in intestines
- 1 p53 mRNA in intestines
- 4 no change