

TEDX

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**Mammalian Outcome Analyses
for the Low Dose Bisphenol A Spreadsheet
June 2009**

The following analyses examine the data in the Low Dose Bisphenol A Spreadsheet. They are meant to compliment and more specifically enumerate the results of the data compilation included in the summary and charts. The studies are grouped by timing of exposure and the results are listed below. For a broader view of the data, please refer to the summary and charts.

Gestational (n= 109)

MALE REPRODUCTIVE SYSTEM OUTCOMES										
	testes	sperm	prostate	preputial gland	epididymis	penis	seminal vesicles	testosterone	Leydig cells	feminization
Change	11	5	8	1	4	1	2	2	2	0
No change	14	8	9	5	11	3	11	8	0	1
Total	25	13	17	6	15	4	13	10	2	1
% Change	44%	38%	47%	17%	27%	25%	15%	20%	100%	0%

Testes:

- changes in weight (increase and decrease)
- decreased RAR alpha mRNA in testes
- increased AhR mRNA expression, PDGFR α and β mRNAs
- strong trend for increasing Sertoli cell numbers per unit volume and per testes
- descent delayed
- increase in Sertoli cells by weight and per volume unit
- increase thiobarbituric acid reactive substances
- significant decreases in p23 mRNA/18s rRNA at 1mg/kg

Sperm:

- decrease in percentage of moving sperm
- deformed nucleus in some spermatids (25%)
- deformed heads in some spermatazoa
- ectoplasmic specialization completely absent
- decreased sperm & spermatid number and daily sperm production in adulthood
- reduced sperm efficiency
- increase in sperm production

Prostate:

- changes in weight (3 increases, 1 no change)
- increase in the number and size of dorsolateral prostate ducts and an overall increase in prostate duct volume
- induced prostate growth and branching in the presence and absence of testosterone
- altered the differentiation pattern of periductal stromal cells in ventral prostate
- periductal stroma larger layer of fibroblasts at day 30
- decreased expression of androgen receptor
- increased stromal cellular proliferation
- induced (100%) mostly high grade PIN lesions following adult exposure to estradiol + testosterone
- severe atypia with nuclear elongation and irregular size, cellular piling and adenoma formation
- increased cell proliferation in high-grade PIN regions
- low basal rates of apoptosis except for areas of PIN
- induced permanent CK10 expression in basal cells of the adult prostate

Preputial gland:

- increased weight

Epididymis:

- reduced weight
- increased percentage of Er alpha+ cells

Penis:

- urethra was malformed in the colliculus region and significantly constricted where it enters the bladder

Seminal vesicles:

- decrease in weights

Testosterone:

- transient increase in plasma levels
- increase in total serum levels

Leydig:

- decreased steroidogenic enzyme gene expression
- induces Nur77 gene expression in a dose dependent manner and stimulates progesterone synthesis

Feminization:

- no changes

FEMALE REPRODUCTIVE SYSTEM OUTCOMES							
	ovaries	vagina	uterus	breast	estrus	♀ organs	eggs/ oocytes
Change	6	5	11	10	6	0	1
No change	2	3	7	1	3	2	1
Total	8	8	18	11	9	2	2
% Change	75%	63%	61%	91%	67%	0%	50%

Ovaries:

- increase in weight
- corpora lutea absent at PND 28
- decreased RAR alpha mRNA in ovaries
- increased AhR mRNA expression
- increase in blood-filled ovarian bursae
- increase in percentage of ovarian tissue occupied by antral follicles
- decrease in percentage of corpora lutea
- ovarian cysts at 100 µg/kg

Vagina:

- decreased weight
- reduced thickness of epithelium, no keratinization, full length Erα variant at 64 kDa not expressed
- changes in vaginal opening (1 delay, 1 accelerated)
- epithelium thinner
- lack of corpora lutea and cornification

Uterus:

- changes in weight (increase and decrease)
- significantly decreased Erβ expression
- cystic endometrial hyperplasia at 100 µg/kg
- 5 & 7-fold increase in HOXA10 expression at .5 & 1 mg/kg post administration. 5 & 9-fold increase at 2 weeks.
- decreased volume of the endometrial lamina propria, increased incorporation of bromodeoxyuridine into the DNA of endometrial gland epithelial cells, and increased expression of estrogen receptor-alpha (ER alpha) and progesterone receptor in the luminal epithelium of the endometrium and subepithelial stroma
- 4 fold increase in weight in dams
- cornified vaginal smears
- increase in blotted uterine weight in one experiment at 200mg
- stimulated ER-a and ER-b mediated transcription in COS-7 and endometrial cancer cells
- significantly increased TRAP220
- decreased levels of mRNAs encoding for Hoxa 10 and Hoxa 11 in neonatal & adult rats
- incorporation of BrdU decreased
- failed to upregulate Erα in response to estradiol and progesterone
- increased SMRT expression
- downregulated Hoxa 10 and Hoxa 11 mRNA in adult rats

Breast:

- increase in # TEBS, total area of TEBS, TEBS/area and TEB area/ductal area in E2 (0.5) challenged CD-1 mice.
- lower TEB area/area measured in E2 (1.0) challenged CD-1 mice.
- increase in ductal length in E2 (1.0) challenged CD-1 mice.
- fewer TEBS, lower TEBS/area and TEBS area/area in E2 (1.0) challenged C57B16 mice.
- increase in TEBS, and alveolar buds, and lobuloalveoli
- significant increase in all ductal and alveolar structures at 6 months
- 60% increase in percentage of alveoli that contained secretory product
- increase in number of TEBS, and total area occupied by TEBS
- slowed down ductal invasion of the stroma and shortened length of ductal tree
- decline in number of apoptotic cells
- increased expression of Wnt4
- increased number of lateral branches
- 3-4 fold increases in the incidence of hyperplastic ducts
- cribriform-like structures in 250 & 1000 groups. Structures characterized as carcinoma in situ
- increase in Ki67-positive epithelial cells and a higher percentage of Erα-positive cells
- increase in the percentage of hyperplastic ducts
- increase in both stromal nuclear density and number of mast cells
- fibroblastic stroma replaced normal adipose tissue
- increased numbers of NMU induced hyperplastic lesions
- 13.3% developed malignancies in low NMU group - 70% cancer incidence in high NMU group

- increased ductal area and extension
- obliterated interuterine position effects
- changes shape and size of epithelial cells and increases number
- delayed lumen formation
- decreased density of fat pad and localization of cells
- may be altering the development of adipocytes
- accelerated mammary gland differentiation
- increase in number of terminal ducts at PND 21 and 100
- increase in type 1 lobules at PND 35
- decrease in volume fraction of ducts and increase in alveolar buds for 0.25 µg/kg group at 3 & 9 months
- at 9 months, increased volume fraction of alveolar buds in 2.5 µg/kg group
- interductal hyperplasias in all BPA treated adults
- cell proliferation increased 5x in beaded ducts and 8x higher in neighboring alveolar buds

Estrus:

- decreased the number of days between vaginal opening & estrus
- cycle length elongated, percentage of time in diestrus phase longer
- increased percentage of mice in persistent state of estrus and/or metestrus
- increased estrus phase
- irregular estrus cycles

♀ organs:

- no changes

Eggs:

- increase in synaptic abnormalities including incomplete synapses, and cells with end-to-end association between nonhomologous SCs
- aberration in number and distribution of MLH1 foci along the SCs both in fetal ovaries and 4wk old female ovaries
- increased # of hyperploid eggs and in 2 cell embryos of 4-5 wk old females
- exposure mimics the effects of ERβ loss-of -function mutation implying BPA acts as an estrogen antagonist, not a mimic in this system

MISCELLANEOUS OUTCOMES								
	body weight	genital distance	maturation	growth	mortality	LH	DNA/ gene expression	hormones & receptor binding affinity
Change	16	4	5	1	2	1	7	4
No change	29	5	8	1	4	3	3	1
Total	45	9	13	2	6	4	10	5
% Change	36%	44%	38%	50%	33%	25%	70%	80%

Body weight:

- changes in weight (increase and decrease) in both dams and pups
- reduction in dam weight gain during pregnancy
- increase in dam weight during lactation

Genital distance:

- reduced AGD in male 250 µg/kg group
- decreased on PND 15 & 21
- increased in males but not females
- increased

Maturation:

- vaginal opening earlier, and earlier age at first estrus
- later testes descent
- early puberty
- accelerated puberty

Growth:

- suppressed juvenile growth

Mortality:

- reduced pup survival
- increased number of live pups at weaning

LH:

- decreased serum levels

DNA/gene expression:

- expression of Math3, Ngn2, Hes1, LICAM, and THRalpha was significantly upregulated at E14.5
- reduced DNA methylation at CpGs 49-56
- PDE4D4 message areas markedly higher
- variation in gene expression
- slightly increased midbrain gene expression of Drd4, Avpr2, Npy, Tac2, Fgf10 & Nppc
- at PND 21, 31 genes upregulated and 2 genes downregulated in 25 µg group

- at PND 21, 65 genes upregulated in 250 µg group
- at PND 35, 2 genes upregulated in 25 µg group
- at PND 35, 29 genes upregulated and 19 downregulated in 250 µg group
- at PND 50, 189 genes upregulated in 25 µg group, 3 downregulated
- at PND 50, 88 genes upregulated, and 5 down regulated in 250 µg group
- at PND 100, 5 genes upregulated and 6 downregulated in 25 µg group
- at PND 100, 330 genes upregulated and 91 down regulated in 250 µg group
- decreased levels of mRNAs encoding for Hoxa 10 and Hoxa 11 in neonatal & adult rats
- increased SMRT expression
- partial methylation or demethylation at multiple loci
- Vps52 mRNA and LOC72325 mRNA expression was up-regulated

Hormones & Binding affinity:

- induced prostate AR binding
- in adult human male serum, BPA shows greater estrogenic activity than either octylphenol or nonylphenol
- BPA over 500x more estrogenic than octylphenol in mouse fetuses
- increased binding affinity

EARLY OFFSPRING OUTCOMES					
	embryos	placenta	preg rate	birth rate	sex ratio
Change	4	1	1	1	1
No change	1	0	8	20	16
Total	5	1	9	21	17
% Change	80%	100%	11%	5%	6%

Embryos:

- faster growth from 2 into 8 cell embryos
- rates of development to the blastocyst stages increased
- frequency of developing to the blastocyst stage decreased
- faster growth at 8 cell and blastocyte stages
- higher doses decrease #of blastocytes and increase in trophoblast areas
- stimulated blastocyst formation at concentrations of 1 & 3 nM
- activated ERs at 1ppm

Placenta:

- females: increased NOR-1 mRNA, COUP-TF alpha, GCNF, SF-1 and PNR, decreased RORy mRNA, PRmRNA
- males: increased ER beta and LXR alpha receptors and PR mRNA, decreased COUP-TF alpha, GCNF, SF-1 and PNR

Pregnancy rate:

- fewer implantation sites in combined BPA groups

Birth rate:

- decreased at 200 µk/kg

Sex ratio:

- increased number of males

BRAIN & BEHAVIOR OUTCOMES								
	brain	behavior	dendrites	hippocamp	amygdala	hypoth	pituitary	dopamine
Change	16	27	1	4	1	1	0	4
No change	3	0	0	0	0	1	1	0
Total	19	27	1	4	1	2	1	4
% Change	84%	100%	100%	100%	100%	50%	0%	100%

Brain:

- slightly increased midbrain gene expression of Drd4, Avpr2, Npy, Tac2, Fgf10 & Nppc
- significantly decreased the levels of gene expression of dopamine transporter at 8 weeks more than 0.5-fold.
- deficit in dopamine neurons
- increased AhR mRNA expression
- decreased RAR alpha mRNA in cerebra and cerebella
- increased T4 expression and RC3/Neurogranin expression in dentate gyrus
- increased expression of ERs alpha and beta at 5 and 13 weeks in dorsal raphe nucleus
- BrdU-labeled cells were decreased in the ventricular zone of BPA-treated mice at E14.5 and E16.5, whereas they were increased in the cortical plate at E14.5
- abnormal thalamocortical & corticothalamic projections and disordered arrangement of neurons in layers V & VI
- eliminated sex differences in tissue section #
- decreased # of Th neurons in females with most difference in the medial part of the AVPV

- no sex differences in mid AVPV
- memory impairment
- increase thiobarbituric acid reactive substances
- delayed spatial learning/memory in males
- reduced weight
- stimulates pERK1 and pERK2 signaling in the cerebellar granule cells
- partial methylation or demethylation at multiple loci
- Vps52 mRNA and LOC72325 mRNA expression was up-regulated
- interfered with long term potentiation (LTP) in DL-striatum at PND 12-32 & produced long term potentiation instead of long term depression (LTD) at PND 28
- potentiation of basal synaptic efficacy in PD28 rats induced due to the increase in presynaptic glutamate release
- D1R antagonist inhibited increase of presynaptic release in PD28 BPA-rats

Behavior:

- increased aggression at 8 weeks, but diminished by week 12
- conditioned response to the rewarding property of amphetamines completely dampened in females only
- dams in oil/BPA groups nursed less, spent more time nest building, more time grooming, more time out of the nest, and resting out of the nest.
- oil/BPA and BPA/BPA groups spent more time resting alone.
- F1 dams fed BPA during pregnancy spent more time being active
- pups of BPA/Oil dams took longer to complete the righting reflex
- impaired sexual differentiation in rearing and struggling behavior
- facilitated depression-like behavior
- increased hyperactivity
- increased anxiety
- no change in aggression
- dose dependant increase in spontaneous motor activity
- significant hyperactivity at 4-5 weeks of age
- increased spontaneous motor activity in both dark and light phases
- no sex differences in behavior
- impaired sexual differentiation in rearing and struggling behavior and facilitated depression-like behavior
- changes in gender dependent behavior acquisition
- reduced specific components of maternal behavior, both active and passive
- increased ano-genital licking to males than to females
- eliminated sex typed behaviors
- place preference for morphine related experiences in 3 µg/kg prenatally exposed group
- increased morphine induced activity
- increased place preference for morphine
- males - reduced anxiety
- females - reduced motor activity
- both - reduced exploration behavior
- increase in defensive behavior in males
- impaired sex performance in males
- increase in sexual motivation and receptive behavior in females
- enhanced reward and motor effects of morphine
- increase in pain responses in first 30 min, then decrease in pain responses
- increased time in light
- increased neophobia in females
- reduced impulsive behavior in all
- feminized behavior in males
- reduced response to AMPH in males
- decreased playful interactions, defeminized some aspects of female behavior
- increase in anxious behavior in 200 µg/kg group
- inverted sex differences in open field behavior
- inverted sex differences lc volume
- increased motor activity in males
- delayed entry into dark compartment in passive avoidance test
- showed significantly fewer avoidance responses and failure to avoid electrical unconditioned stimuli
- failed to show an increase in locomotion in a monoamine-disruption test
- low dose increased female play directed at females
- all doses decreased sociosexual exploration in males
- all doses increased sociosexual exploration in females
- high dose decreased social interest in both genders
- low dose increased social interest at vaginal opening in both genders

- all doses decreased female crawl under behavior

Dendrites

- caused robust activation of midbrain astrocytes
- caused biphasic response in neurone/glia cocultures with activation at 100 fM, 1pM, 10pM, 100nM or 1µM and no activation at 10FM, 100pM, 1nM or 10nM.
- effects were not reversed by tamoxifen or androgens.
- highest concentrations induced neuronal cell death

Hippocampus

- mg/L most facilitated the synthesis of "androstenedione to testosterone" and on the conversion of "testosterone to estrodial"
- diminished levels of the low-affinity sst2 receptors in gyrus dentate, stratum radiatum lacunosum CA1 layer
- decreased levels of CAT-IR in widespread regions
- decreased cholinergic fiber in CA1, CA2 and CA3
- up-regulated expression levels of mRNA and protein of SRC-1 in males

Amygdala

- diminished levels of low-affinity sst2 receptors, particularly in the cortico-medial nucleus

Hypothalamus:

- enhanced levels of high-affinity sst2 receptors, particularly in the periventricular nucleus

Pituitary

- no changes

Dopamine:

- significantly decreased the levels of gene expression of dopamine transporter at 8 weeks more than 0.5-fold.
- reduction of D4 receptor and transporter
- increased Ca2+ responses to dopamine at the lowest doses
- G-protein activation
- up-regulation of expression of D1 receptor mRNAs

ORGAN & SYSTEM OUTCOMES							
	adrenal	liver	thyroid	kidney	spleen	immune system	blood
Change	0	4	1	1	2	2	1
No change	1	5	1	4	1	0	0
Total	1	9	2	5	3	2	1
% Change	0%	44%	50%	20%	67%	100%	100%

Adrenal:

- no changes

Liver:

- one reduced weight, one no change in weight
- increase catalase
- stimulated [35S]GTPγS binding induced by dopamine
- sufficient GT activity to efficiently metabolize BPA to its nonestrogenic metabolite at low doses

Thyroid

- dams showed transient hyperthyroidism
- males exhibited a transient hyperthyroidism followed by hypothyroidism

Kidney:

- increased glutathione peroxidase, thiobarbituric acid reactive substances
- one reduced weight, one no change in weight

Spleen:

- increased numbers of CD3+, CD4+ and CD8+ cells
- increased secretion of IFN-g and IL4s
- decreased expression KJI-26+T cells
- increased IL-4 & IL-13 splenocytes
- decreased INFg
- decreased accumulation of CD4+CD25+Foxp3+ T cells
- increased levels of serum OVA-specific IgG1 and IgG2a levels

Immune system:

- increased anti-HEL IgG
- increased anti-HEL IgG2a
- at PND 50, Cd3d, cathepsin E, Ctse, Cd5 and Sod2 upregulated in 25 µg group

Blood:

- females - increased total cholesterol
- males - increased triacylglycerol, NEFA, and serum glucose

Immature (n=4)

MALE REPRODUCTIVE SYSTEM OUTCOMES					FEMALE REPRODUCTIVE SYSTEM OUTCOMES
	sperm	prostate	epididymis	testosterone	breast
Change	0	0	0	1	0
No change	1	1	1	1	1
Total	1	1	1	2	1
% Change	0%	0%	0%	50%	0%

Testes, Sperm, Prostate, Epididymis, Penis:

- no change

Testosterone:

- lower levels of serum testosterone

Breast:

- no changes

MISCELLANEOUS OUTCOMES				EARLY OFFSPRING OUTCOMES	BRAIN & BEHAVIOR OUTCOMES		ORGAN & SYSTEM OUTCOMES
	body weight	maturation	mortality	birth rate	behavior	hypoth	blood
Change	0	0	0	0	1	1	1
No change	2	1	1	1	0	0	0
Total	2	1	1	1	1	1	1
% Change	0%	0%	0%	0%	100%	100%	100%

Body weight, Maturation, Mortality, Birth rate:

- no changes

Behavior:

- change in immature play behavior
- change in latency to intromission in adults
- smaller proportion of males reached ejaculation within 30 minutes

Hypothalamus:

- increased ER-labeled neurons in the ARC and MPA on PND 37
- increased ER-labeled neurons in the MPA in females on PND 90

Blood:

- at PND 90 increased estradiol levels in males and estradiol/testosterone ratio in both sexes

Multi-generational Exposure (n=4)

MALE REPRODUCTIVE SYSTEM OUTCOMES							FEMALE REPRODUCTIVE SYSTEM OUTCOMES				
	testes	sperm	prostate	epididymis	penis	seminal vesicles	ovaries	vagina	uterus	breast	estrus
Change	2	1	0	0	0	1	1	0	1	0	0
No change	2	2	3	3	1	2	2	2	2	1	2
Total	4	3	3	3	1	3	3	2	3	1	2
% Change	50%	33%	0%	0%	0%	33%	33%	0%	33%	0%	0%

Testes:

- reduced paired testes weight
- damage to seminiferous tubule

Sperm:

- decreased spermatogenesis
- damage to acrosome state

Prostate, Epididymis, Penis:

- no changes

Seminal vesicles:

- increased weight at 0.018 ppm of F1 generation males

Ovaries:

- reduced paired ovary weights

Uterus:

- reduced uterine weight in F0

Vagina, Breast, Estrus:

- no changes

MISCELLANEOUS OUTCOMES						EARLY OFFSPRING OUTCOMES			
	body weight	genital distance	maturation	growth	mortality	embryos	preg rate	birth rate	sex ratio
Change	0	1	1	0	0	0	0	1	0
No change	4	1	1	1	3	1	3	3	2
Total	4	2	2	1	3	1	3	4	2
% Change	0%	50%	50%	0%	0%	0%	0%	25%	0%

Body weight, Growth, Mortality:

- no changes

Genital distance:

- decreases in urogenital distance in all F2 females

Maturation:

- PPS delayed in F2 males.

Embryos, Pregnancy rate, Sex ratio:

- no changes

Birth rate:

- decline in birth rate in first and second generation

BRAIN & BEHAVIOR OUTCOMES				ORGAN & SYSTEM OUTCOMES			
	brain	behavior	pituitary	liver	kidney	spleen	immune system
Change	0	0	0	1	0	0	0
No change	1	1	1	1	2	2	1
Total	1	1	1	2	2	2	1
% Change	0%	0%	0%	50%	0%	0%	0%

Brain, Behavior, Pituitary:

- no changes

Liver:

- reduced liver weight in males, increased in females

Kidney, Spleen, Immune system:

- no changes

Adult (n=50)

MALE REPRODUCTIVE SYSTEM OUTCOMES								
	testes	sperm	prostate	preputial gland	epididymis	penis	seminal vesicles	testosterone
Change	6	7	2	0	2	0	1	1
No change	4	2	3	1	2	1	3	2
Total	10	9	5	1	4	1	4	3
% Change	60%	78%	40%	0%	50%	0%	25%	33%

Testes:

- decreased absolute weight, increased relative weight
- decreased weight
- suppressed the increase in germ cell per Sertoli cell, and decrease in testicular weight
- decreased amounts of cortactin
- deficient ectoplasmic specialization
- decreased ER beta, increased ER alpha
- decreased ER beta mRNA expression
- decrease in GSH activity in male rats
- decrease in antioxidant enzyme CAT in anemic males

Sperm:

- total and relative sperm counts reduced
- daily sperm production decreased
- reduction in sperm efficiency
- reductions dose dependent
- epididymal sperm counts reduced
- decrease in sperm motility & count
- decrease in daily sperm production
- decrease in sperm counts in 0.002 mg/kg group

- deformation of spermatids' nuclei and acrosomes
- increased expression of DJ1
- sperm deformation and ectoplasmic specialization between the Sertoli cell and spermatids were also affected

Prostate:

- increase in prostate weight
- increased tumor growth, tumor cell proliferation
- increased PSA at all stages

Preputial gland:

- no changes

Epididymis:

- decreased epididymal weight
- complete degeneration of the caput corpus and cauda epididymidis
- decrease in superoxide dismutase, glutathione peroxidase in the cauda epididymidis, and an increase in lipid peroxidation in the epididymis

Penis:

- no changes

Seminal vesicles:

- decrease in weight

Testosterone:

- increase in females

FEMALE REPRODUCTIVE SYSTEM OUTCOMES						MISCELLANEOUS OUTCOMES					
	ovaries	vagina	uterus	breast	eggs/ oocytes	body weight	mortality	LH	enzymes	proteins	DNA/ gene expression
Change	4	1	7	1	3	1	0	0	1	1	1
No change	0	1	3	1	0	9	1	2	1	0	0
Total	4	2	10	2	3	10	1	2	2	1	1
% Change	100%	50%	70%	50%	100%	10%	0%	0%	50%	100%	100%

Ovaries:

- increased ovarian weight
- high levels of serum BPA in women with polycystic ovary syndrome
- BPA higher in women with polycystic ovarian syndrome
- increase in lipid peroxidation in anemic rats
- decrease in GSH activity in female rats
- decrease in antioxidant enzymes GST, GPx, GR and CAT in anemic females

Vagina:

- continuous release dose ~ 0.3mg/kg resulted in hypertrophy, hyperplasia and mucus secretion in F344 rats only - no effects in SD rats

Uterus:

- increased weight in uterus
- stroma and miometrium increase in thickness at 2mg
- continuous release dose ~ 0.3mg/kg resulted in hypertrophy, hyperplasia and mucus secretion in F344 rats only - no effects in SD rats
- increased heat shock proteins
- increase AGF-1 mRNA
- induced proliferation of uterine luminal epithelium cells
- increase in mitotic cells
- increased in ER transcription
- decreased endometrial and myometrial thickness
- decreased expression of C3 gene
- significantly lower levels of BPA in cases of endometrial hyperplasia complex and endometrial cancer

Breast:

- significantly increased conversion of immature structures to mature (lobular maturation)
- increased epithelial cell proliferation by 143%

Eggs/oocytes:

- meiotic aneuploidy of oocytes
- decrease in mean number of zygotes harvested
- increase of metaphase II oocytes showing premature centromere separation in more than 2 dyads
- increased spindle/chromosome alignment abnormalities at 200 µg/kg BPA and casein diet and at 200 & 500 µg/kg BPA with soy diet

Body weight:

- higher BPA levels in obese women

Mortality, LH:

- no change

Enzymes:

- decreased activity of superoxide dismutase, catalase, glutathione reductase & glutathione peroxidase

- dose dependent increase in hydrogen peroxide generation and lipid peroxidation

Proteins:

- increased heat shock proteins

DNA/gene expression:

- dose response in F344, no response in SD

EARLY OFFSPRING OUTCOMES				BRAIN & BEHAVIOR OUTCOMES				
	embryos	preg rate	birth rate	brain	behavior	hippocamp	hypoth	pituitary
Change	1	2	2	4	1	1	1	1
No change	1	0	1	0	0	0	0	1
Total	2	2	3	4	1	1	1	2
% Change	50%	100%	67%	100%	100%	100%	100%	50%

Embryos:

- # of reabsorptions of fetuses from BPA treated males higher

Pregnancy rate:

- decreased pregnancy rate
- number of females impregnated by BPA treated males significantly reduced

Birth rate:

- increased rate of reabsorptions
- mothers with serum BPA of 5.23 ng/ml had a significantly higher rate of miscarriage

Brain:

- increased expression of DJ1
- increased progesterone receptor cells in preoptic area
- inhibited the CA1 PSSD response to estradiol
- interferes with the synaptogenic response to testosterone in the mPFC and hippocampus
- decrease in astroglial spine synapses, compensatory increase in astroglial process density

Behavior:

- increased social investigation and reduced several exploratory behaviors during pair formation

Hippocampus:

- interferes with the synaptogenic response to testosterone in the mPFC and hippocampus
- decrease in astroglial spine synapses, compensatory increase in astroglial process density

Hypothalamus:

- increased progesterone receptor cells in the VMH

Pituitary

- increases PRL release from anterior pituitary
- increases PRL release and cell proliferation in GH3 cells
- increased PRF activity
- significant differences in responses between SD and F344 rats

ORGAN & SYSTEM OUTCOMES										
	adrenal	liver	thyroid	pancreas	kidney	spleen	bones	immune system	blood	other
Change	0	5	0	3	1	0	1	3	4	2
No change	1	2	1	0	2	1	1	0	1	0
Total	1	7	1	3	3	1	2	3	5	2
% Change	0%	71%	0%	100%	33%	0%	50%	100%	80%	100%

Adrenal:

- no changes

Liver:

- reduced Cd induced MT-1 mRNA and MT protein and increased liver damage
- sufficient GT activity to efficiently metabolize BPA to its nonestrogenic metabolite at low doses
- total amount of BPA glucuronidated lower in nonpregnant vs pregnant rats
- decrease in biliary excretion in pregnant rat
- venous excretion - fetus exposed more
- reduced Cd induced MT-1 mRNA and MT protein and increased liver damage
- sex differences as well
- above normal concentrations of GGT, alkaline phosphatase, lactate dehydrogenase
- increase in lipid peroxidation & decrease in antioxidant enzymes GST, GPx, GR and CAT in female anemic rats only
- decrease in GSH activity & antioxidant enzyme CAT in anemic male rats only

Thyroid:

- no changes

Pancreas:

- rapid increase in plasma insulin levels
- longer exposure increases beta-insulin content in pancreas
- 1-SD change in BPA concentration associated with diabetes
- insulin content increased at 100 µg/kg
- ERα involved in insulin increases

Kidney:

- increase in lipid peroxidation in both male and female anemic rats & decrease in GSH activity
- no change in antioxidant enzymes in males
- decrease in antioxidant enzymes GST, GPx, and CAT in anemic females

Spleen:

- no changes

Bones:

- demineralization of bones

Immune system:

- interleukin (IL)-4 increased
- decreased INFγ, IgG2a
- later development of proteinuria
- production of IL-4 and IL-10, but not that of IL-13
- markedly increased in Ts-infected mice inoculated orally
- anti-HEL Ig2a production and INF-g significantly enhanced
- IL-4 secretion augmented

Blood:

- rapid increase in plasma insulin levels
- longer exposure increases beta-insulin content
- serum leptin decreased
- no change in triglycerides
- no change in serum iron levels
- showed significant association with the SCEs measured in treated and untreated lymphocytes
- higher BPA levels in males

Other:

- 1-SD change in BPA concentration associated with cardiovascular disease
- association with one marker of oxidative stress
- high BPA levels were associated with increased fasting blood sugar levels.