**Supplementary Figure 1. Geometric mean (95% confidence intervals, Cis) of whole blood lead (Pb) concentrations in children aged 1-2 years stratified by sex, NHANES 2015-2016 (N=361).** Symbols represent unadjusted geometric mean blood Pb and bars represent 95% CIs in males (n = 189) and females (n = 172) aged 1-2 years. Data originated from a single primary sampling unit (PSU). We conservatively centered at the sample grand mean rather than the stratum mean using the “lonely.psu” option in the ‘survey’ R package. Because PSUs are usually single counties, these results may not be fully representative of this segment of the U.S. population (1-2 year olds).

![Chart, box and whisker chart

Description automatically generated]()

**Supplementary Table 1. Percentiles and geometric means (95% confidence intervals, CIs) for whole blood metal concentrations in NHANES 2015-2016 (N = 4,987).** Blood metals were measured in all participants 1-11 years old (N= 1,813) and in a one-half random subsample of participants 12 years and older (N=3,174).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Metal** | **N** | **10th** | **90th** | **Median (25th, 75th)** | **Geometric mean (95% CI)** | **LOD** | **N (%) < LOD** |
| Pb (µg/dL) | 4987 | 0.35 | 2.14 | 0.78 (0.5, 1.32) | 0.82 (0.78, 0.87) | 0.07 | 5 (0.1%) |
| Cd (µg/L) | 4987 | 0.07 | 0.81 | 0.22 (0.13, 0.4) | 0.24 (0.23, 0.25) | 0.10 | 1277 (25.6%) |
| Mn (µg/L) | 4987 | 6.36 | 14.82 | 9.52 (7.7, 11.95) | 9.59 (9.38, 9.80) | 0.99 | 0 (0%) |
| Hg (µg/L) |  |  |  |  |  |  |  |
| *Total* | 4987 | 0.20 | 2.54 | 0.60 (0.33, 1.26) | 0.68 (0.62, 0.74) | 0.28 | 1270 (25.5%) |
| *Methyl* | 4937 | 0.08 | 2.30 | 0.38 (0.14, 1.03) | 0.41 (0.37, 0.47) | 0.12 | 1343 (27.2%) |
| *Inorganic* † | 4937 | - | - | - | - | 0.27 | 4201 (85.1%) |
| *Ethyl* † | 4937 | - | - | - | - | 0.16 | 4882 (98.9%) |

Abbreviations: Pb, lead; Cd, cadmium; Mn, manganese; Hg, mercury; LOD, limit of detection.  
The LOD values are all in µg/L, with the exception of Pb which is in µg/dL.  
†Not evaluated in this analysis due to the high % of values < LOD.  
Analyses were conducted in R using the ‘survey’ package to account for NHANES complex sampling design and weights.

**Supplementary Table 2. Number and percentage of samples below the LOD for a given metal, sex, and age group.** Values for the LOD are shown in Supplementary Table 1.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **N (%) < LOD** | | | | |
| **Sex** | **Life Stage** | **Pb** | **Cd** | **Mn** | **Total Hg** | **MeHg** |
| Male | Child | 1 (0.11%) | 515 (55.6%) | 0 (0%) | 415 (44.8%) | 410 (44.3%) |
| Female | Child | 0 (0%) | 486 (54.8%) | 0 (0%) | 370 (41.7%) | 378 (44.6%) |
| Male | Adolescent | 0 (0%) | 83 (26.9%) | 0 (0%) | 106 (34.3%) | 99 (32.0%) |
| Female | Adolescent | 2 (0.65%) | 66 (21.5%) | 0 (0%) | 96 (31.3%) | 112 (36.5%) |
| Male | Adult | 1 (0.10%) | 77 (8.0%) | 0 (0%) | 106(11.0%) | 125 (12.9%) |
| Female | Adult | 1 (0.10%) | 42 (4.1%) | 0 (0%) | 101 (10.0%) | 139 (13.7%) |
| Male | Elderly | 0 (0%) | 5 (1.7%) | 0 (0%) | 38 (13.2%) | 41 (14.3%) |
| Female | Elderly | 0 (0%) | 3 (1.0%) | 0 (0%) | 38 (13.1%) | 39 (13.4%) |

Abbreviations: Pb, lead; Cd, cadmium; Mn, manganese; Hg, mercury; MeHg, methyl mercury; LOD, limit of detection. The LOD values are all in µg/L, with the exception of Pb which is in µg/dL.  
The life stages are defined as follows: child, age < 12 years; adolescent, age 12-21 years; adult, age 22-65 years; elderly, age > 65 years.

**Supplementary Table 3. Geometric means (95% confidence intervals, CIs) of whole blood metal concentrations stratified by sex, NHANES 2015-2016.** Blood metals were measured in all participants 1-11 years old (N= 1,813) and in a one-half random subsample of participants 12 years and older (N=3,174).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Males** | | **Females** | |  |
| **Metal** | **N (%)** | **Geometric mean (95% CI)** | **N (%)** | **Geometric mean (95% CI)** | **p-value‡** |
| Pb (µg/dL) | 2488 (48.80%) | 0.92 (0.87, 0.98) | 2499 (51.20%) | 0.74 (0.68, 0.79) | 2.58E-05 |
| Cd (µg/L) | 2488 (48.80%) | 0.22 (0.20, 0.23) | 2499 (51.20%) | 0.26 (0.25, 0.28) | 1.77E-05 |
| Mn (µg/L) | 2488 (48.80%) | 8.99 (8.76, 9.23) | 2499 (51.20%) | 10.20 (9.97, 10.43) | 1.40E-08 |
| Hg, total (µg/L) | 2488 (48.80%) | 0.68 (0.63, 0.74) | 2499 (51.20%) | 0.68 (0.61, 0.75) | 0.95 |
| Hg, methyl (µg/L) | 2460 (48.76%) | 0.43 (0.38, 0.48) | 2477 (51.24%) | 0.40 (0.34, 0.46) | 0.22 |

Abbreviations: Pb, lead; Cd, cadmium; Mn, manganese; Hg, mercury.  
‡p-value determined using design-based t-test comparing blood metal levels of males and females.  
All percentages are weighted to account for NHANES complex sampling design and survey weights.

**Supplementary Table 4. Geometric means (95% confidence intervals, CIs) of whole blood metal concentrations stratified by sex and age group, NHANES 2015-2016.** Blood metals were measured in all participants 1-11 years old (N= 1,813) and in a one-half random subsample of participants 12 years and older (N=3,174).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Geometric Mean (95% CI)** | | | | | | |
| **Sex** | **Life Stage** | **Pb** | **Cd** | **Mn** | **Total Hg** | **N** | **MeHg** | **N** |
| Male | Child | 0.67 (0.60, 0.74) | 0.092 (0.088, 0.096) | 10.22 (9.86, 10.58) | 0.33 (0.31, 0.36) | 926 | 0.16 (0.15, 0.18) | 902 |
| Female | Child | 0.62 (0.57, 0.67) | 0.094 (0.09, 0.10) | 10.94 (10.57, 11.32) | 0.33 (0.30, 0.36) | 887 | 0.16 (0.14, 0.18) | 869 |
| Male | Adolescent | 0.55 (0.52, 0.58) | 0.13 (0.12, 0.15) | 9.73 (9.44, 10.02) | 0.42 (0.37, 0.48) | 309 | 0.23 (0.19, 0.27) | 309 |
| Female | Adolescent | 0.40 (0.37, 0.43) | 0.15 (0.13, 0.16) | 11.09 (10.41, 11.80) | 0.38 (0.34, 0.42) | 307 | 0.20 (0.17, 0.23) | 307 |
| Male | Adult | 0.98 (0.92, 1.05) | 0.25 (0.23, 0.28) | 8.74 (8.44, 9.05) | 0.82 (0.76, 0.89) | 966 | 0.55 (0.49, 0.61) | 962 |
| Female | Adult | 0.74 (0.68, 0.80) | 0.32 (0.30, 0.34) | 10.27 (10.06, 10.48) | 0.83 (0.75, 0.91) | 1014 | 0.50 (0.43, 0.58) | 1012 |
| Male | Elderly | 1.60 (1.46, 1.74) | 0.34 (0.30, 0.39) | 8.46 (7.97, 8.98) | 0.85 (0.72, 1.01) | 287 | 0.60 (0.48, 0.74) | 287 |
| Female | Elderly | 1.29 (1.20, 1.39) | 0.37 (0.35, 0.41) | 8.93 (8.45, 9.43) | 0.80 (0.68, 0.94) | 291 | 0.52 (0.42, 0.65) | 289 |
|  |  |  |  |  |  | 4987 |  | 4937 |

Abbreviations: Pb, lead; Cd, cadmium; Mn, manganese; Hg, mercury; MeHg, methyl mercury.  
Geometric means are all in µg/L, except for Pb which is in µg/dL.  
The life stages are defined as follows: child, age < 12 years; adolescent, age 12-21 years; adult, age 22-65 years; elderly, age > 65 years.

**Supplementary Table 5. Summary of experimental evidence of sex-specific neurological outcomes for lead (Pb).** Table summarizes behavioral/emotional, cognitive, epigenetic, and other effects reported to exhibit sex differences following Pb exposure in experimental studies.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sex-specific Neurological Outcomes: Experimental Evidence** | | | | | | | | |
| ***Developmental (prenatal and early postnatal)*** | | | | | | | | |
| Behavioral/emotional effects | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Kasten-Jolly et al., 2012 | BALB/ cAnNTac mice | Developmental period; 21 days | 0, 20 ppm, oral, drinking water | Aggressiveness | Intruder assay | Aggressive behavior towards cage mates | - | M > F |
| Exploratory behavior | Exploratory behavior test | - | Reduced spatial memory and exploratory activity | M < F |
| de Souza Lisboa et al., 2005 | Wistar rats | Pregnancy and Lactation | 10 mg, oral, daily gavage | Anxiety | Open field test | Higher | High | M > F |
| Depression | Forced swim test | High | Higher | M < F |
| Sobolwski et al., 2020 | C57BL/6 mice | 2 months prior to mating up to 3 generations; 8 weeks | 100 ppm, oral, drinking water | Behavioral | Schedule-controlled behavior | Lower | Higher | M < F |
| Locomotor activity | Lower | Higher | M < F |
| Elevated plus maze | Lower | Higher | M < F |
| Biochemical | Serum corticosterone | Lower | Higher | M < F |
| ***Developmental (weaning-adult exposure)*** | | | | | | | | |
| Behavioral/emotional effects | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Soeiro et al., 2007 | Swiss mice | PND 21, subchronic (70 day exposure; 30 day reversal) | 0, 50, 100 or 500 ppm, oral, drinking water | Antidepressant effect | Forced swim test | 50 ppm | 500 ppm | M > F |
|  |  |  |  | Antidepressant effect | Tail suspension test | 50 ppm | 50 ppm | M = F |
|  |  |  |  | Anxiety | Elevated plus maze | 500 ppm | - | M > F |
| Mansouri et al., 2012 | Wistar rats | One month; Young adult | 0, 50 ppm, oral, drinking water | Blood Pb levels | - | Higher | - | M > F |
| Plasma Pb levels | - | Higher | - |
| Brain Pb levels | - | Higher | - |
| Myoinositol levels | - | Higher in hippocampus | - |
| Spatial memory | Spatial memory test | Reduced performance at blood Pb levels below 10 µg/dL |  |
| Object recognition | Object recognition memory test | - |  |
| Motor coordination | Rotarod | - |  |
| Hyperactivity | Open field test | Reduced performance at blood Pb levels below 10 µg/dL | - |
| Cognitive alterations | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Anderson et al., 2016 | Long Evans rats | 10 days before GD 10-PND 21; PND 1-21; PND 21-55 | 150 ppm, 375 ppm and 750 ppm, oral | Associative memory | Trace fear conditioning | 150 and 750 ppm (perinatal exposure at day 2) | 150 ppm (early exposure at day 2 and 10); 150 ppm postnatal exposure at day 10) | M = F (affected differentially) |
| Jett et al., 1997 | Long Evans rats | 10 days prior to breeding to PND 21 | 0, 250 ppm | Spatial learning | Morris water maze test | Longer escape tendency on day 4 and 8 | More pronounced effect at PND 21 | M < F |
| Epigenetic alterations | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Schneider et al., 2013 | Long Evans rats | Early perinatal (day 21), PND 0-21, and PND 0-55 | 0, 150, 375 and 750 ppm, oral, chow diet | DNMT1 in hippocampus | - | Decrease (perinatal) | Decrease (early postnatal) | M = F (affected differentially) |
| DNMT3A | - | Altered (perinatal) | Altered (early postnatal) |
| MeCP2 expression | - | - | Reduced (perinatal) |
| G. Singh et al., 2018 | Long Evans rats | Early perinatal (day 21), PND 0-21, and PND 0-55 | 0, 150, 375 and 750 ppm, oral, chow diet | Methylation pattern | Hypermethylation | Brain physiology | NA | M = F (affected differentially) |
| Hypomethylation | Learning/memory suppressor gene | Innate immunity & signal transduction |
| Other effects | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Flores-Montoya et al., 2015 | C57BL/6 mice | PND 0-28 | 0, 30, or 330 ppm orally via dam's milk | Olfactory memory | Novel odor recognition test | Linear decrease with increasing blood Pb | Decrease only at 30 ppm | M = F (affected differentially) |
| Blood Pb levels | - | Higher | - | M > F |
| Leasure et al., 2008 | C57BL/6 mice | 14 days before mating to PND 10 | 27, 55, and 109 ppm, oral | Obesity | - | Late onset | - | M > F |
| Spontaneous Motor Ability | - | Decrease | - |  |
| Amphetamine Induced Motor Activity | - | Increase | - |  |
| Motor coordination | Rotarod test | Decrease | - |  |
| Neurotransmitter levels | - | Altered dopamine; Increased forebrain utilization at 27 ppm | - |  |

M: Males; F: Females; PND: Postnatal day; GD: Gestational day; ppm: parts per million; DNMT1: DNA methyltransferase 1; DNMT3A: DNA methyltransferase 3 alpha; MeCP2: Methyl-CpG binding protein 2; NA: Not available.   
\*not significant

**Supplementary Table 6. Summary of experimental evidence of sex-specific neurological outcomes for mercury (Hg).**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sex-specific Neurological Outcomes: Experimental Evidence** | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Thomas et al., 1982 | Long Evans rats | 7, 15, 20, 24, or 56 days | 1 mol radioactive 203MeHg/kg, subcutaneous, single dose | Hg whole body retention | - | Increased retention in rats dosed at PND 56 only | - | M > F |
| Rossi et al., 1997 | Sprague Dawley rats | Prenatal (GD 7-PND 7); 6 months | 0.5 mg/kg MeHg per day, oral | Locomotor activity and spatial learning ability | Motion detection and swim maze | Decrease, reversed by administering a low dose of d-amphetamine (0.5 mg/kg) | - | M > F |
| Tyrosine hydroxylase expression | Immunohistochemistry | - | - | - |
| Giménez-Llort et al., 2001 | C57BL/6 mice | Early gestational-PND 21; 12 weeks | 0.5 mg/kg MeHg per day, oral, drinking water | TrxR1 activity | - | Decrease | Slight increase\* | M > F |
| Glutathione peroxidase activity | - | Decrease | Slight increase\* | M > F |
| TrxR1, GPx1 expression in cerebrum and cerebellum | qRT-PCR | Decrease | Increase | M > F |
| Malagutti et al., 2009 | Swiss albino mice | 2 weeks; 2 months | 40 mg/L, oral, drinking water | Locomotor activity | Open field test | Decrease (-52%), prevented by administration of ﻿17-estradiol | Decrease (-30%) | M > F |
| Motor function | Rotarod test | Impaired (53% decrease in falling latency), administration of ﻿17-estradiol | - | M > F |
| Cerebellar lipid peroxidation | - | Increase (+60%) | - | M > F |
| Cerebral glutathione reductase activity | - | Increase (+25%) | - | M > F |
| Cerebellar glutathione peroxidase activity | - | Decrease (-43%) | - | M > F |
| Curtis et al., 2010 | Prairie voles | 10 weeks; ≥ 59 day-old | 60 ppm (mg/L) HgCl2, oral, drinking water | Social interaction | Isolation vs. contact with an unfamiliar same-sex conspecific | Less contact with stranger | - | M > F |
| Dopamine-mediated behavior | Locomotor activity in response to amphetamine (0.5 mg/kg) | Blunted response | - | M > F |
| Curtis et al., 2011 | Prairie voles | 10 weeks; ≥ 59 day-old | 60 ppm (mg/L) HgCl2, oral, drinking water | TNFα protein expression in the cerebellum and hippocampus | qRT-PCR | Increase | - | M > F |
| Chemokines (CCL2 and CXCL10) | qRT-PCR | - | - | - |
| Soto et al., 2019 | Prairie voles | 10 weeks; 169 days | 60 ppm (mg/L) HgCl2, oral, drinking water | HPA activity | Plasma corticosterone levels after interaction with an unfamiliar same-sex conspecific | Lower | - | M > F |

M: Males; F: Females; MeHg: Methyl mercury; HgCl2: Mercuric chloride; GD: Gestational day; PND: Postnatal day; TrxR1: Thioredoxin; GPx1: Glutathione peroxidase 1; TNFα: Tumor necrosis factor alpha; HPA: Hypothalamic-pituitary-adrenal; qRT-PCR: Real-time quantitative reverse transcription PCR.  
\*not significant

**Supplementary Table 7. Summary of experimental evidence of sex-specific neurological outcomes for manganese (Mn).**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sex-specific Neurological Outcomes: Experimental Evidence** | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Zheng et al., 2000 | Sprague Dawley rats | Single dose; 2 months | 6.0 mg Mn/kg MnCl2, IV/oral or 20 mg MMT/kg, oral | Toxicokinetic profile | - | Greater elimination constant | Greater AUC and longer half-life | M = F (affected differentially) |
| Zhang et al., 2003 | Sprague Dawley rats | 6 weeks; - | 7.5, 15.0, and 30.0 mg/kg body weight, IP | Activity of respiratory chain complexes I–IV | - | Decrease in body weight in 15.0 and 30.0 mg/kg group; Decreased MAO in 7.5 mg/kg group | Decreased MAO in 7.5 and 30 mg/kg groups | M = F (affected differentially) |
| Dorman et al., 2004 | Sprague Dawley rats | 6 weeks and 16 months; 90 days, 5 days/week | 0.01, 0.1, and 0.5 mg/m3 MnSO4, 0.1 mg/m3 Mn phosphate, inhalation | Mn levels in brain, lung, and blood | - | Highest increases in olfactory bulb and lungs in young males | Slight increase | M > F |
| Erikson et al., 2004 | Sprague Dawley rats | 6 weeks and 16 months; 90 days, 5 days/week | 0.01, 0.1, and 0.5 mg/m3 MnSO4, 0.1 mg/m3 Mn phosphate, inhalation | Oxidative stress in the brain | - | Decreased GS in hypothalamus, increased GS levels in the hippocampus, depleted glutathione in olfactory bulb in young and aged males | Increased GS in olfactory bulb, reduced glutathione levels in the striatum | M = F (affected differentially) |
| Madison et al., 2011 | FVB mice | Single dose on day 0, 3, and 6; 12 weeks | MnCl2–4H2O (50 mg/kg), SC | Medium spiny neuron morphology | - | Longer total dendritic length and higher dendritic branching | Higher total spine density | M > F |
| Yamagata et al., 2017 | Wistar rats | 30 days; - | 1 or 5 mg/kg Mn, IP | Depressive behavior | Forced swim test | Higher increase in immobility time at 1 mg/kg but not at 5 mg/kg | Increase in immobility time | M > F |
| Open field test | Greater decrease in crossings between quarters and fewer rearings at 5 mg/kg | Decrease | M > F |
| Chi et al., 2017 | C57BL/6 mice | 13 weeks; 8 weeks | 100 ppm MnCl2, oral, drinking water  (~20 mg/kg body weight/day) | Gut bacterial compositions | 16S RNA sequencing | Increase in abundance of Firmicutes and Bacteroidetes | Decrease in *Firmicutes* population | M = F (affected differentially) |
| Gene expression | Metagenomics sequencing | Increased expression of tryptophan synthase and reduced expression of glutamate carboxylase | Reduced expression of tryptophan synthase | M = F (affected differentially) |
| Freeman et al., 2020 | C57BL/6 mice | 6 weeks; 8–10 weeks | 0.5 g/L MnCl2 or1,000 mg MnCl2/kg dry sediment, oral, drinking water | Motor coordination | Rotarod test | Higher | High | M > F |
| Balance and exploratory rearing behavior | Cylinder test | Higher | High | M > F |
| Balance and motor coordination | Beam traversal test | Higher | High | M > F |

M: Males; F: Females; MnCl2: Manganese chloride; MnSO4: Manganese sulfate; MMT: methylcyclopentadienyl manganese tricarbonyl; AUC: area under the plasma concentration-time curve; IV: Intravenous; IP: Intraperitoneal; SC: Subcutaneous; MAO: monoamine oxidase; GS: Glutamine synthetase.

\* not significant

**Supplementary Table 8. Summary of experimental evidence of sex-specific neurological outcomes for cadmium (Cd).**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sex-specific Neurological Outcomes: Experimental Evidence** | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Ishitobi et al., 2007 | C57BL/6 mice | GD 1-PND 12; - | 10 ppm Cd, oral, drinking water | Thyroid hormone and sex hormone related gene expression | - | Reduced expression of estrogen receptor beta | Lower expression of progesterone receptor, estrogen receptor alpha, and neurogranin | M = F (differentially affected) |
| Castillo et al., 2012 | Wistar rats | Prenatal (whole pregnancy period) | 50 ppm CdCl2, oral, drinking water | DNA methylation of fetal hepatic GR promoter | - | Lower expression of DNMT1a, CpG sites in the liver GR promoter region were significantly more hypermethylated | Lower methylation in the liver GR promoter region | M = F (differentially affected) |
| Birth weight and size | - | Low birth weight | Lower birth weight | M < F\* |
| Zhang et al., 2019 | ApoE3-KI [knock-in] & ApoE4-KI mouse model | 14 weeks; 8 weeks | 0.6 mg/L CdCl2, oral, drinking water | Hippocampus-dependent memory | Novel object location test | Early manifestation of spatial working memory deficits | Spatial working memory deficits occur relatively late compared to males | M > F |
| T-maze test | Significant decrease in spontaneous alternation | Significant decreases in spontaneous alternation | M = F |

M: Males; F: Females; GD: Gestational day; PND: Postnatal day; CdCl2: Cadmium chloride; ppm: Parts per million; GR: glucocorticoid receptor; DNMT1a: DNA methyltransferase 1 alpha.

\*not significant

**Supplementary Table 9. Summary of experimental evidence of sex-specific outcomes for arsenic (As).**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sex-specific Outcomes: Experimental Evidence** | | | | | | | | |
| **Reference** | **Species** | **Exposure; Age** | **Dose (external)** | **Domain** | **Assessment** | **Effect on Males** | **Effect on Females** | **Vulnerable sex** |
| Bardullas et al., 2009 | C57BL/6 mice | 4 months; 3 months | 0.05, 0.5, 5.0, and 50 mg/L, oral, drinking water | Locomotor activity | Spontaneous locomotor activity test | Hyperactivity seen only after 4 months at 0.5 and 5.0 mg/L | Early onset of increase in horizontal activity and stereotypy counts at 0.5 and 5.0 mg/L | M < F |
| Expression of tyrosine hydroxylase and antioxidant genes | - | Striatum showed a significant decrease of Trx-1 mRNA levels at all doses | Significant decrease in Trx-1 mRNA levels at all doses was observed only in the nucleus accumbens | M < F |
| As in brain | - | Higher | Relatively lower | M > F\* |
| Masuda et al., 2018 | Crj:CD (Sprague Dawley) rats | 28 days, 6 weeks | 0.3, 1.2, and 5.0 mg/kg/day of DPAA(V), oral, drinking water | DPAA(V) in CNS tissues | - | Higher in temporal-occipital lobe, brainstem, spinal cord, liver, kidneys, and lungs at 0.3 mg/kg; higher in frontal-parietal lobe and cerebellum at 1.2 mg/kg | Higher in kidneys at 1.2 mg/kg | M > F |
| Allan et al., 2015 | C57BL/6 mice | 10 days prior to mating-gestation; 55 days | 50 ppb, oral, drinking water | Expression of GR and 11β- Hsd isozymes | - | - | Resistant to As-induced changes in GR, 11β-Hsd-1 and 11β-Hsd-2 protein levels, higher levels of GSH/GSSH | M > F |

M: Males; F: Females; ppb: Parts per billion; DPAA(V): Arsenic diphenylarsinic acid; GR: Glucocorticoid receptor; Hsd: Hydroxysteroid dehydrogenase; Trx-1: Thioredoxin; GSH: Glutathione; GSSH: Glutathione disfulfide (reduced form of glutathione).

\*not significant