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| --- | --- | --- | --- | --- | --- |
| **Compound** | | | **AOP**  **{aopkb.oecd.org}** | | **MIE**  **{aopwiki.org}** |
| **Acetic acid** [4-Chloro-6-(2,3-xylidino)-2-pyrimidinylthio] | | | Increased (ectopic) concentration of all-trans retinoic acid (ATRA) if fetal testis leading to reduced sperm count, males.  Inhibition of fatty acid beta oxidation leading to nonalcoholic steatohepatitis (NASH)  Inhibition of RALDH2 causes reduced all-trans retinoic acid levels, leading to transposition of the great arteries.  Ionotropic gamma-aminobutyric acid receptor activation mediated neurotransmission inhibition leading to mortality.  Peroxisomal Fatty Acid Beta-Oxidation Inhibition Leading to Steatosis  Retinoic acid signalling leading to developmental toxicity  Weak acid respiratory uncoupling leading to death | | Increased (ectopic) all-trans retinoic acid concentration  Inhibition, Fatty Acid Beta Oxidation  Inhibition of ALDH1A (RALDH)  Binding at picrotoxin site, iGABAR chloride channel.  Acetylcholinesterase (AchE) Inhibition  Decreased, PPAR-alpha activation  Decreased, PPAR-beta activation  Decreased, PPAR-gamma activation  Retinaldehyde dehydrogenase inhibition  Inhibition of ALDH1A (RALDH)  Activation, AhR  Thyroperoxidase, Inhibition  Decrease, Coupling of oxidative phosphorylation |
| **Acrylamide** (prop-2-enamide) | | | **No AOP** | |  |
| **Propofol** (2,6-di(propan-2-yl)phenol) | | | **Key event**: - increase oxidation of the di-copper moiety of the hemocyanin active site.  **No AOP** | |  |
| **Caffeine** (1,3,7-trimethylpurine-2,6-dione) | | | **No AOP** | |  |
| **Chlorpyrifos** (diethoxy-sulfanylidene-(3,5,6-trichloropyridin-2-yl)oxy-lambda5-phosphane) | | | **No AOP** | |  |
| **Chlorpyrifos oxon** {diethyl (3,5,6-trichloropyridin-2-yl) phosphate} | | | Inhibition of AChE and activation of CYP2E1 leading to sensory axonal peripheral neuropathy and mortality  AOP for thyroid disorder caused by triphenyl phosphate via TRβ activation  Imbalance in redox homeostasis leading to structural damage to tissues  Organo-Phosphate Chemicals induced inhibition of AChE leading to impaired cognitive function | | Acetylcholinesterase (AchE) Inhibition  Increased, Hepatic thyroid hormone uptake/transport  Increased, Hepatic thyroid hormone uptake/transport  **NO MIE**  **NO MIE** |
| **Genistein** {5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one} | | | **Key event:-** Inhibition, 4-hydroxyphenyl-pyruvate dioxygenase (HPPD) enzyme  **No AOP** | |  |
| **Niflumic acid** {2-[3-(trifluoromethyl)anilino]pyridine-3-carboxylic acid} | | | Increased (ectopic) concentration of all-trans retinoic acid (ATRA) if fetal testis leading to reduced sperm count, males  Inhibition of fatty acid beta oxidation leading to nonalcoholic steatohepatitis (NASH)  Inhibition of RALDH2 causes reduced all-trans retinoic acid levels, leading to transposition of the great arteries  Ionotropic gamma-aminobutyric acid receptor activation mediated neurotransmission inhibition leading to mortality  Peroxisomal Fatty Acid Beta-Oxidation Inhibition Leading to Steatosis  Retinoic acid signalling leading to developmental toxicity  Weak acid respiratory uncoupling leading to death | | Increased (ectopic) all-trans retinoic acid concentration  Inhibition, Fatty Acid Beta Oxidation  Inhibition of ALDH1A (RALDH)  Activation, ionotropic GABA Receptor chloride channel  Decreased, PPAR-alpha activation  Decreased, PPAR-beta activation  Decreased, PPAR-gamma activation  Retinaldehyde dehydrogenase inhibition  Inhibition of ALDH1A (RALDH)  Activation, AhR  Decrease, Coupling of oxidative phosphorylation |
| **Pregnenolone** { 1-[(3S,8S,9S,10R,13S,14S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl]ethanone} | | | Acetylcholinesterase inhibition leading to acute mortality  Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations  Binding of electrophilic chemicals to SH(thiol)-group of proteins and /or to seleno-proteins involved in protection against oxidative stress during brain development leads to impairment of learning and memory  Binding to the picrotoxin site of ionotropic GABA receptors leading to epileptic seizures in adult brain  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development leads to neurodegeneration with impairment in learning and memory in aging  Glucocorticoid Receptor Activation Leading to Increased Disease Susceptibility  Inhibition of 17α-hydrolase/C 10,20-lyase (Cyp17A1) activity leads to birth reproductive defects (cryptorchidism) in male (mammals)  Percellome Toxicogenomics Approach for AOP Building: Case study on Pentachlorophenol  PPARalpha Agonism Leading to Decreased Viable Offspring via Decreased 11-Ketotestosterone | | Acetylcholinesterase (AchE) Inhibition  Alkylation, DNA  Binding, Thiol/seleno-proteins involved in protection against oxidative stress  Binding at picrotoxin site, iGABAR chloride channel  Binding of antagonist, NMDA receptors  Binding of antagonist, NMDA receptors  Activation, Glucocorticoid Receptor  Inhibition, Cytochrome P450 enzyme (CYP17A1) activity  **No MIE** |
| **Dexamethasone** { (8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-3-one} | | | Acetylcholinesterase inhibition leading to acute mortality  Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations  Binding of electrophilic chemicals to SH(thiol)-group of proteins and /or to seleno-proteins involved in protection against oxidative stress during brain development leads to impairment of learning and memory  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development leads to neurodegeneration with impairment in learning and memory in aging  Glucocorticoid Receptor Activation Leading to Increased Disease Susceptibility  Percellome Toxicogenomics Approach for AOP Building: Case study on Pentachlorophenol  PPARalpha Agonism Leading to Decreased Viable Offspring via Decreased 11-Ketotestosterone | | Acetylcholinesterase (AchE) Inhibition  Alkylation, DNA  Binding, Thiol/seleno-proteins involved in protection against oxidative stress  Binding of antagonist, NMDA receptors  Binding of antagonist, NMDA receptors  Activation, Glucocorticoid Receptor  Activation, PXR/SXR  Activation, PPARα |
| **4,5-Dihydro-2-mercaptoimidazole** { imidazolidine-2-thione} | | | **No AOP** | |  |
| **Diphenylamine** { N-phenylaniline} | | | **No AOP** | |  |
| **Valproic acid** { 2-propylpentanoic acid } | | | Increased (ectopic) concentration of all-trans retinoic acid (ATRA) if fetal testis leading to reduced sperm count, males  Inhibition of fatty acid beta oxidation leading to nonalcoholic steatohepatitis (NASH)  Inhibition of RALDH2 causes reduced all-trans retinoic acid levels, leading to transposition of the great arteries  Ionotropic gamma-aminobutyric acid receptor activation mediated neurotransmission inhibition leading to mortality  Peroxisomal Fatty Acid Beta-Oxidation Inhibition Leading to Steatosis  Retinoic acid signalling leading to developmental toxicity  Weak acid respiratory uncoupling leading to death | | Increased (ectopic) all-trans retinoic acid concentration  Inhibition of ALDH1A (RALDH)  Activation, ionotropic GABA Receptor chloride channel  Decreased, PPAR-alpha activation  Decreased, PPAR-beta activation  Decreased, PPAR-gamma activation  **No MIE**  **No MIE** |
| **(+/-)-Verapamil** { 2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile} | | | **No AOP** | |  |
| **Diclofenac** { 2-[2-(2,6-dichloroanilino)phenyl]acetic acid} | | | Increased (ectopic) concentration of all-trans retinoic acid (ATRA) if fetal testis leading to reduced sperm count, males  Inhibition of fatty acid beta oxidation leading to nonalcoholic steatohepatitis (NASH)  Inhibition of RALDH2 causes reduced all-trans retinoic acid levels, leading to transposition of the great arteries  Ionotropic gamma-aminobutyric acid receptor activation mediated neurotransmission inhibition leading to mortality  Peroxisomal Fatty Acid Beta-Oxidation Inhibition Leading to Steatosis  Retinoic acid signalling leading to developmental toxicity  Weak acid respiratory uncoupling leading to death | | Increased (ectopic) all-trans retinoic acid concentration  Inhibition, Fatty Acid Beta Oxidation  Inhibition of ALDH1A (RALDH)  Activation, ionotropic GABA Receptor chloride channel  Decreased, PPAR-alpha activation  Decreased, PPAR-beta activation  Decreased, PPAR-gamma activation  Retinaldehyde dehydrogenase inhibition  Inhibition of ALDH1A (RALDH)  Activation, AhR  Thyroperoxidase, Inhibition  No MIE |
| **Bisphenol A** { 4-[2-(4-hydroxyphenyl)propan-2-yl]phenol} | | | **Key Event**:- Inhibition, 4-hydroxyphenyl-pyruvate dioxygenase (HPPD) enzyme  **No AOP** | |  |
| **Clofibric acid** { 2-(4-chlorophenoxy)-2-methylpropanoic acid} | | | Increased (ectopic) concentration of all-trans retinoic acid (ATRA) if fetal testis leading to reduced sperm count, males  Inhibition of fatty acid beta oxidation leading to nonalcoholic steatohepatitis (NASH)  Inhibition of RALDH2 causes reduced all-trans retinoic acid levels, leading to transposition of the great arteries  Ionotropic gamma-aminobutyric acid receptor activation mediated neurotransmission inhibition leading to mortality  Peroxisomal Fatty Acid Beta-Oxidation Inhibition Leading to Steatosis  Retinoic acid signalling leading to developmental toxicity  Weak acid respiratory uncoupling leading to death | | Increased (ectopic) all-trans retinoic acid concentration  Inhibition, Fatty Acid Beta Oxidation  Inhibition of ALDH1A (RALDH)  Activation, ionotropic GABA Receptor chloride channel  Decreased, PPAR-alpha activation  Decreased, PPAR-beta activation  Decreased, PPAR-gamma activation  Decrease, Coupling of oxidative phosphorylation |
| **Carbendazim** { methyl N-(1H-benzimidazol-2-yl)carbamate} | | | Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development leads to neurodegeneration with impairment in learning and memory in aging | | Binding of antagonist, NMDA receptors  Binding of antagonist, NMDA receptors  Binding of antagonist, NMDA receptors  Binding of antagonist, NMDA receptors |
| **2-Butoxyethanol** { 2-butoxyethanol} | | | **No AOP** | |  |
| **Tamoxifen** { 2-[4-[(Z)-1,2-diphenylbut-1-enyl]phenoxy]-N,N-dimethylethanamine} | | | **No AOP** | |  |
| **Cyclosporin A** { (3S,6S,9S,12R,15S,18S,21S,24S,30S,33S)-30-ethyl-33-[(E,1R,2R)-1-hydroxy-2-methylhex-4-enyl]-1,4,7,10,12,15,19,25,28-nonamethyl-6,9,18,24-tetrakis(2-methylpropyl)-3,21-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecazacyclotritriacontane-2,5,8,11,14,17} | | Acetylcholinesterase inhibition leading to acute mortality  Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations  Androgen receptor antagonism leading to adverse effects in the male foetus (mammals)  Aromatase inhibition leading to reproductive dysfunction  Aryl hydrocarbon receptor activation leading to early life stage mortality, via increased COX-2  Binding of electrophilic chemicals to SH(thiol)-group of proteins and /or to seleno-proteins involved in protection against oxidative stress during brain development leads to impairment of learning and memory  Binding to the picrotoxin site of ionotropic GABA receptors leading to epileptic seizures in adult brain  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development leads to neurodegeneration with impairment in learning and memory in aging  Cyclooxygenase inhibition leading reproductive failure  Glucocorticoid Receptor Activation Leading to Increased Disease Susceptibility  Inhibition of 17α-hydrolase/C 10,20-lyase (Cyp17A1) activity leads to birth reproductive defects (cryptorchidism) in male (mammals)  Kidney toxicity induced by activation of 5HT2C  Oxidation of iron in hemoglobin leading to hematotoxicity  Percellome Toxicogenomics Approach for AOP Building: Case study on Pentachlorophenol  PPARalpha Agonism Leading to Decreased Viable Offspring via Decreased 11-Ketotestosterone  PPARα activation in utero leading to impaired fertility in males  SARS-CoV-2 spike protein binding to ACE2 receptors expressed on pericytes leads to endothelial cell dysfunction, microvascular injury and myocardial infarction. | | | Acetylcholinesterase (AchE) Inhibition  Alkylation, DNA  N/A, Androgen receptor, Antagonism  Inhibition, Aromatase  Activation, AhR  Binding, Thiol/seleno-proteins involved in protection against oxidative stress  Binding at picrotoxin site, iGABAR chloride channel  Binding of antagonist, NMDA receptors  Binding of antagonist, NMDA receptors  Inhibition, Cyclooxygenase activity  Activation, Glucocorticoid Receptor  Inhibition, Cytochrome P450 enzyme (CYP17A1) activity  Activation, 5HT2c  N/A, Parent compound is converted to the reactive metabolite and forms free radicals leading to oxidation of heme iron(II) in hemoglobin to iron(III)  Activation, PXR/SXR  Activation, PPARα  Activation, PPARα  Binding to ACE2 |
| **Tetracycline** { (4S,4aS,5aS,6S,12aR)-4-(dimethylamino)-1,6,10,11,12a-pentahydroxy-6-methyl-3,12-dioxo-4,4a,5,5a-tetrahydrotetracene-2-carboxamide} | | Binding to the picrotoxin site of ionotropic GABA receptors leading to epileptic seizures in adult brain  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development leads to neurodegeneration with impairment in learning and memory in aging  Inhibition of 17α-hydrolase/C 10,20-lyase (Cyp17A1) activity leads to birth reproductive defects (cryptorchidism) in male (mammals)  Percellome Toxicogenomics Approach for AOP Building: Case study on Pentachlorophenol  PPARalpha Agonism Leading to Decreased Viable Offspring via Decreased 11-Ketotestosterone | | | Binding at picrotoxin site, iGABAR chloride channel  Binding of antagonist, NMDA receptors  Binding of antagonist, NMDA receptors  Inhibition, Cytochrome P450 enzyme (CYP17A1) activity  Activation, PXR/SXR  Activation, PPARα |
| **2-Aminophenol** | | **No AOP** | | |  |
| **Acetaminophen** { N-(4-hydroxyphenyl)acetamide } | | Key Event:- Inhibition, 4-hydroxyphenyl-pyruvate dioxygenase (HPPD) enzyme  **No AOP** | | |  |
| **2,4,4'-Trichlorobiphenyl** { 2,4-dichloro-1-(4-chlorophenyl)benzene} | | **No AOP** | | |  |
| **Atrazine** { 6-chloro-4-N-ethyl-2-N-propan-2-yl-1,3,5-triazine-2,4-diamine} | | **No AOP** | | |  |
| **Paraquat** {1-methyl-4-(1-methylpyridin-1-ium-4-yl)pyridin-1-ium} | | Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities  Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development leads to neurodegeneration with impairment in learning and memory in aging | | | Binding of antagonist, NMDA receptors  Binding of antagonist, NMDA receptors |
| **Amiodarone** { (2-butyl-1-benzofuran-3-yl)-[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone} | | **No AOP** | | |  |
| **Kepone** { 1,2,3,4,6,7,8,9,10,10-decachloropentacyclo[5.3.0.02,6.03,9.04,8]decan-5-one} | | Binding to the picrotoxin site of ionotropic GABA receptors leading to epileptic seizures in adult brain  Inhibition of 17α-hydrolase/C 10,20-lyase (Cyp17A1) activity leads to birth reproductive defects (cryptorchidism) in male (mammals) | | | Binding at picrotoxin site, iGABAR chloride channel  Inhibition, Cytochrome P450 enzyme (CYP17A1) activity |
| **2-Ethylhexyl diphenyl phosphate** | Inhibition of AChE and activation of CYP2E1 leading to sensory axonal peripheral neuropathy and mortality  AOP for thyroid disorder caused by triphenyl phosphate via TRβ activation  Imbalance in redox homeostasis leading to structural damage to tissues  Organo-Phosphate Chemicals induced inhibition of AChE leading to impaired cognitive function | | | Acetylcholinesterase (AchE) Inhibition  Increased, Hepatic thyroid hormone uptake/transport  No MIE  No MIE | |