Environ Health Perspect

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Supplemental Material

Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis

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Figure S1: Meta-analysis sensitivity analysis to effects from replacing Chen et al. (2014) estimate with Zhang et al. (2016) estimate evaluating same cohort of children at later time point (7 years instead of 5 years)

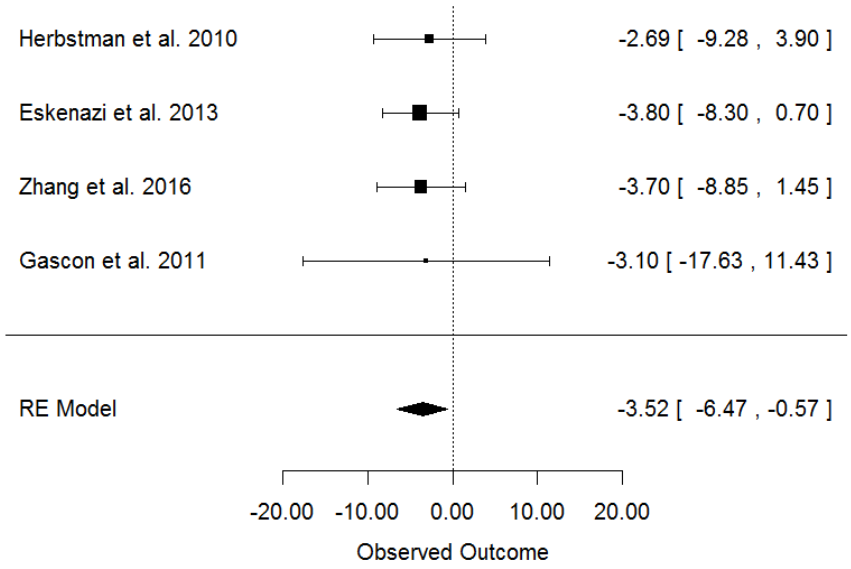
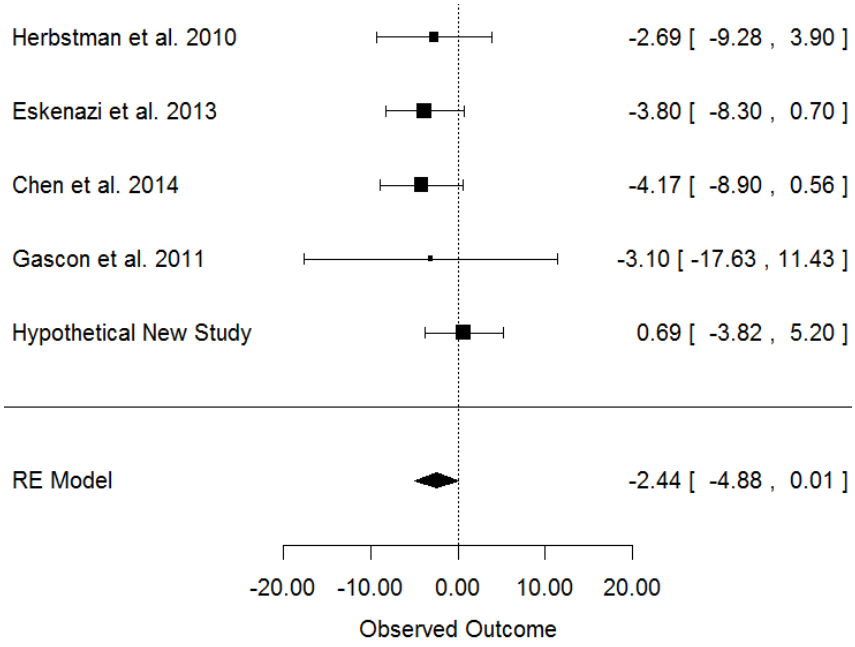


Figure S2: Meta-analysis sensitivity analysis to effects from an additional new study

(A) Association estimate from a hypothetical new study to change the meta-analysis association to non-significant (95% confidence interval overlapping zero)



(B) Association estimate from a hypothetical new study to change the meta-analysis association estimate > 0 (opposite direction)

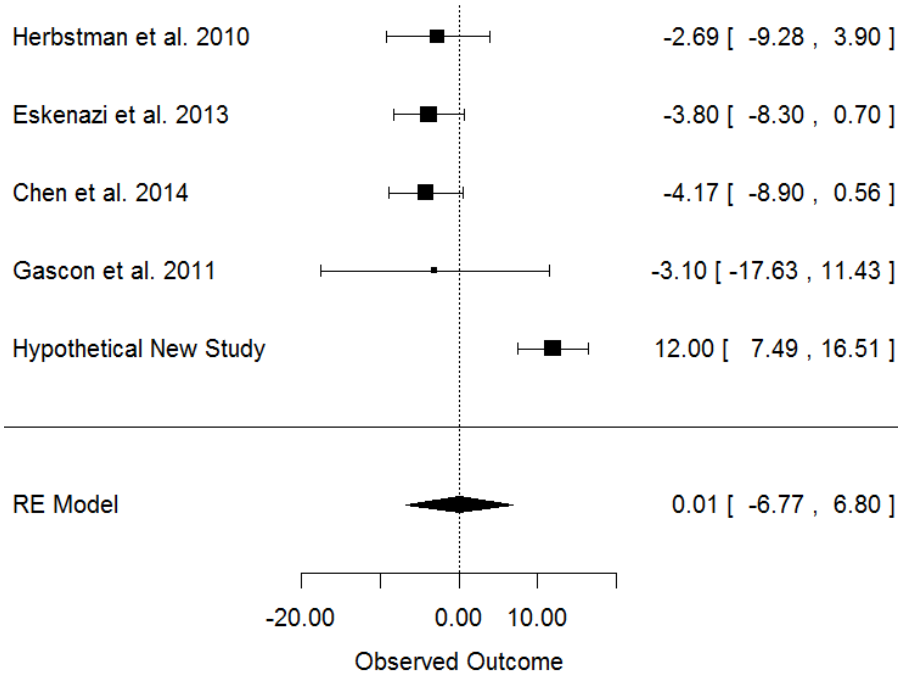


Table S1: Database-specific search terms

PubMed search strategy:

Search	**PubMed**
#1 Substance terms: Controlled vocabulary	"Flame Retardants"[Mesh] OR "Flame Retardants" [Pharmacological Action] OR "Halogenated Diphenyl Ethers"[Mesh] OR ("Phenyl Ethers"[Mesh:NoExp] AND ("1974/01/01"[PDAT] : "2008/12/31"[PDAT])) OR "pentabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,3',4,4',6,6'-octabromodiphenyl ether" [Supplementary Concept] OR "decabromobiphenyl ether" [Supplementary Concept] OR "tribromodiphenyl ether 28"[Supplementary Concept] OR "2,2',4,4'-tetrabromodiphenyl ether" [Supplementary Concept] OR "2,2',4,5'-tetrabromodiphenyl ether" [Supplementary Concept] OR "hexabromodiphenyl ether 154" [Supplementary Concept] OR "2,2',4,4',5,6'-hexabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,4,4',5',6-heptabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,3',4,5,5',6,6'-nonabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,3',4,4',5,6,6'-nonabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,3',4,4',5,5',6-nonabromodiphenyl ether" [Supplementary Concept] OR "2,2',4,4',5,5'-hexabrominated diphenyl ether" [Supplementary Concept] OR "hexabrominated diphenyl ether 153" [Supplementary Concept] OR "pentabrominated diphenyl ether 100" [Supplementary Concept] OR "5-OH-BDE-47" [Supplementary Concept] OR "6-OH-BDE-47" [Supplementary Concept]
#2 Substance terms: text word	flame retard*[tw] OR fire retard*[tw] OR fireproofing agent*[tw] OR "FireMaster"[tw] OR "Bromkal"[tw] OR diphenyl ether deriv*[tw] OR halogenated diphenyl*[tw] OR brominated diphenyl*[tw] OR PBDE*[tw] OR polybrominated diphenyl*[tw] OR polybromodiphenyl*[tw] OR PBDP*[tw] OR BDE*[tw] OR pentabromodiphenyl*[tw] OR c-pentaBDE*[tw] OR PentaBDE*[tw] OR "PeBDE"[tw] OR "DE 71"[tw] OR "DE71"[tw] OR "pentabrominated diphenyl"[tw] OR "pentabrominated diphenyls"[tw] OR "PBDPO"[tw] OR "Planelon PB 501"[tw] OR pentabromo deriv*[tw] OR pentabromophenyl*[tw] OR octabromodiphenyl*[tw] OR c-octaBDE*[tw] OR OctaBDE*[tw] OR "OcBDE"[tw] OR "Octabrom"[tw] OR octabromo deriv*[tw] OR "OBDE"[tw] OR "OBDPO"[tw] OR "octabrominated diphenyl"[tw] OR "octabrominated diphenyls"[tw] OR decabromodiphenyl*[tw] OR c-decaBDE*[tw] OR DecaBDE*[tw] OR "DeBDE"[tw] OR "DBDPO"[tw] OR "decabrominated diphenyl"[tw] OR

	"decabrominated diphenyls"[tw] OR decabromo deriv*[tw] OR "Decabrom"[tw] OR "Berkflam B 10E"[tw] OR "FR 300BA"[tw] OR "FR 300 BA"[tw] OR tribromodiphenyl*[tw] OR "tribrominated diphenyl"[tw] OR "tribrominated diphenyls"[tw] OR "TrBDE"[tw] OR tribromo deriv*[tw] OR tetrabromodiphenyl*[tw] OR TetraBDE*[tw] OR "TeBDE"[tw] OR "TBDE"[tw] OR "BPDE"[tw] OR tetrabromo deriv*[tw] OR "TBDP"[tw] OR "tetrabrominated diphenyl"[tw] OR "tetrabrominated diphenyls"[tw] OR hexabromodiphenyl*[tw] OR HexaBDE*[tw] OR "HxBDE"[tw] OR "hexabrominated diphenyl"[tw] OR "hexabrominated diphenyls"[tw] OR hexabromo deriv*[tw] OR heptabromodiphenyl*[tw] OR HeptaBDE*[tw] OR "HeBDE"[tw] OR "heptabrominated diphenyl"[tw] OR "heptabrominated diphenyls"[tw] OR heptabromo deriv*[tw] OR nonabromodiphenyl*[tw] OR NonaBDE*[tw] OR "NoBDE"[tw] OR "nonabrominated diphenyl"[tw] OR "nonabrominated diphenyls"[tw] OR nonabromo deriv*[tw]
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	"Spatial Behavior"[Mesh] OR "Hyperkinesis"[Mesh] OR "Brain/drug effects"[Mesh]
#7 Outcome terms: Text word	neurodevelopment*[tw] OR neurotoxic*[tw] OR neurobehav*[tw] OR neuropsychologic*[tw] OR neurocogniti*[tw] OR psychologic*[tw] OR aptitude*[tw] OR mental*[tw] OR intelligence*[tw] OR "IQ"[tw] OR intellectual*[tw] OR language*[tw] OR comprehension*[tw] OR impulsiv*[tw] OR "ADHD"[tw] OR "ADDH"[tw] OR "ADHS"[tw] OR "AD/HD"[tw] OR "hkd"[tw] OR hyperactiv*[tw] OR hyper activ*[tw] OR hyperkin*[tw] OR hyper kin*[tw] OR attention defic*[tw] OR attention related*[tw] OR inattention*[tw] OR inattentiv*[tw] OR "sustained attention"[tw] OR "attention span"[tw] OR attention dysfunc*[tw] OR attention disorder*[tw] OR "distractibility"[tw] OR Behavioral*[tw] OR behavioural*[tw] OR behavior defic*[tw] OR behaviour defic*[tw] OR behavior dysfunc*[tw] OR behavior disorder*[tw] OR behaviour disorder*[tw] OR behavior effect*[tw] OR behaviour effect*[tw] OR behavior checklist*[tw] OR behaviour checklist*[tw] OR disruptive behav*[tw] OR disruption behav*[tw] OR disruptive disorder*[tw] OR disruption disorder*[tw] OR defiance behav*[tw] OR defiant behav*[tw] OR defiance disorder*[tw] OR defiant disorder*[tw] OR spontaneous behav*[tw] OR externalizing behav*[tw] OR "cognitive"[tw] OR "cognition"[tw] OR "psychomotor"[tw] OR "learning"[tw] OR "memory"[tw] OR executive function*[tw] OR executive control*[tw] OR executive dysfunction*[tw] OR executive impairment*[tw] OR motor abilit*[tw] OR motor activit* [tw] OR "motor performance"[tw] OR motor function*[tw] OR motor skill*[tw] OR "fine motor"[tw] OR "vigilance"[tw] OR "reaction time"[tw] OR "processing speed"[tw] OR "response inhibition"[tw] OR "Stanford Binet"[tw] OR Binet Test*[tw] OR "Bender Gestalt Test" OR Aphasia Test*[tw] OR Bayley*[tw] OR "Wechsler"[tw] OR "WISC"[tw] OR McCarthy Scale*[tw] OR "Continuous Performance Test"[tw] OR "Continuous Performance Tests"[tw] OR "Continuous Performance Task"[tw] OR "Continuous Performance Tasks"[tw] OR Conners*[tw] OR "CRS-T"[tw] OR "CRS-P"[tw] OR "academic achievement"[tw] OR "scholastic achievement"[tw] OR brain disorder*[tw] OR brain damage*[tw] OR brain dysfunct*[tw]
#8	#6 OR #7
#9	#5 AND #8

Web of Science and Biosis Previews:

Search	**Web of Science & Biosis Previews**
#1 Substance terms: topic search	TS=("flame retard*" OR "fire retard*" OR "fireproofing agent*" OR "FireMaster" OR "Bromkal" OR "diphenyl ether deriv*" OR "Halogenated Diphenyl*" OR "Brominated Diphenyl*" OR PBDE* OR "Polybrominated Diphenyl*" OR polybromodiphenyl* OR PBDP* OR BDE* OR pentabromodiphenyl* OR "c-pentaBDE*" OR PentaBDE* OR "PeBDE" OR "DE 71" OR "DE71" OR "pentabrominated diphenyl*" OR "PBDPO" OR "Planelon PB 501" OR "pentabromo deriv*" OR Pentabromophenyl* OR octabromodiphenyl* OR "c-octaBDE*" OR OctaBDE* OR "OcBDE" OR "Octabrom" OR "octabromo deriv*" OR "OBDE" OR "OBDPO" OR "octabrominated diphenyl*" OR decabromodiphenyl* OR "c-decaBDE*" OR DecaBDE* OR "DeBDE" OR "DBDPO" OR "decabrominated diphenyl*" OR "decabromo deriv*" OR "Decabrom" OR "Berkflam B 10E" OR "FR 300BA" OR "FR 300 BA" OR tribromodiphenyl* OR "tribrominated diphenyl*" OR "TrBDE" OR "tribromo deriv*" OR tetrabromodiphenyl* OR TetraBDE* OR "TeBDE" OR "TBDE" OR "BPDE" OR "tetrabromo deriv*" OR "TBDP" OR "tetrabrominated diphenyl*" OR hexabromodiphenyl* OR HexaBDE* OR "HxBDE" OR "hexabrominated diphenyl*" OR "hexabromo deriv*" OR heptabromodiphenyl* OR HeptaBDE* OR "HeBDE" OR "heptabrominated diphenyl*" OR "heptabromo deriv*" OR nonabromodiphenyl* OR NonaBDE* OR "NoBDE" OR "nonabrominated diphenyl*" OR "nonabromo deriv*")
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#3	#1 OR #2
#4 Outcome terms: topic search	TS=(neurodevelopment* OR neurotoxic* OR neurobehav* OR neuropsychologic* OR neurocogniti* OR psychologic* OR aptitude* OR mental* OR intelligence* OR "IQ" OR intellectual* OR Language* OR comprehension* OR impulsiv* OR "ADHD" OR "ADDH" OR "ADHS" OR "AD/HD" OR "hkd" OR hyperactiv* OR (hyper NEAR/1 active*) OR hyperkin* OR (hyper NEAR/1 kin*) OR "inattention" OR inattentiv* OR "distractibility" OR behavioral* OR behavioural* OR "sustained attention" OR "attention span" OR "attention related" OR (attention* NEAR/3 defic*) OR (attention* NEAR/3 dysfunc*) OR (attention* NEAR/3 disorder*) OR (behav* NEAR/3 defic*) OR (behav* NEAR/3 dysfunc*) OR (behav* NEAR/3 disorder*) OR (disrupt* NEAR/3 disorder*) OR (disrupt* NEAR/3 behav*) OR (defian* NEAR/3 disorder*) OR (defian* NEAR/3 behav*) OR (behav* NEAR/1 effect*) OR (behav* NEAR/1 checklist*) OR (spontaneous NEAR/1 behav*) OR (externalizing NEAR/1 behav*) OR "cognitive"

	OR "cognition" OR "psychomotor" OR "learning" OR "memory" OR (executive NEAR/1 function*) OR "executive control" OR "executive dysfunction" OR "executive impairment" OR (motor NEAR/1 abiliti*) OR "motor performance" OR (motor NEAR/1 function*) OR (motor NEAR/1 skill*) OR (motor NEAR/1 activit*) OR "fine motor" OR "vigilance" OR "reaction time" OR "processing speed" OR "response inhibition" OR "Stanford Binet" OR "Binet Test" OR "Binet tests" OR "Bender Gestalt Test" OR "Aphasia Test" OR "Aphasia Tests" OR Bayley* OR "Wechsler" OR "WISC" OR "McCarthy Scale" OR "McCarthy Scales" OR "Continuous Performance Test" OR "Continuous Performance Tests" OR "Continuous Performance Task" OR "Continuous Performance Tasks" OR Conners* OR "CRS-T" OR "CRS-P" OR "academic achievement" OR "scholastic achievement" OR (brain NEAR/3 disorder*) OR (brain NEAR/3 damage*) OR (brain NEAR/3 dysfunct*))
#5	#3 AND #4

Embase:

Search	**Embase**
#1 Substance terms: controlled vocabulary	'flame retardant'/de OR '2,2`,4,4`,5,5` hexabromodiphenyl ether'/exp OR 'polybrominated diphenyl ether'/exp OR 'diphenyl ether derivative'/exp
#2 Substance terms: title, abstract, trade name, registry number	((flame NEXT/1 retard*) OR (fire NEXT/1 retard*) OR (fireproofing NEXT/1 agent*) OR "FireMaster" OR "Bromkal" OR ('diphenyl ether' NEXT/1 deriv*) OR (Halogenated NEXT/1 Diphenyl*) OR (Brominated NEXT/1 Diphenyl*) OR PBDE* OR (Polybrominated NEXT/1 Diphenyl*) OR polybromodiphenyl* OR PBDP* OR BDE* OR pentabromodiphenyl* OR PentaBDE* OR "PeBDE" OR "DE 71" OR "DE71" OR "pentabrominated diphenyl" OR "pentabrominated diphenyls" OR "PBDPO" OR "Planelon PB 501" OR (pentabromo NEXT/1 deriv*) OR Pentabromophenyl* OR octabromodiphenyl* OR OctaBDE* OR "OcBDE" OR "Octabrom" OR "OBDE" OR "OBDPO" OR (octabromo NEXT/1 deriv*) OR "octabrominated diphenyl" OR "octabrominated diphenyls" OR decabromodiphenyl* OR DecaBDE* OR "DeBDE" OR "DBDPO" OR "decabrominated diphenyl" OR "decabrominated diphenyls" OR (decabromo NEXT/1 deriv*) OR "Decabrom" OR "Berkflam B 10E" OR "FR 300BA" OR "FR 300 BA" OR tribromodiphenyl* OR "tribrominated diphenyl" OR "tribrominated diphenyls" OR "TrBDE" OR (tribromo NEXT/1 deriv*) OR tetrabromodiphenyl* OR TetraBDE* OR "TeBDE" OR "TBDE" OR "BPDE" OR (tetrabromo NEXT/1 deriv*) OR "TBDP" OR "tetrabrominated diphenyl" OR "tetrabrominated diphenyls" OR hexabromodiphenyl* OR HexaBDE* OR "HxBDE" OR "hexabrominated diphenyl" OR "hexabrominated diphenyls" OR

	(hexabromo NEXT/1 deriv*) OR heptabromodiphenyl* OR HeptaBDE* OR "HeBDE" OR "heptabrominated diphenyl" OR "heptabrominated diphenyls" OR (heptabromo NEXT/1 deriv*) OR nonabromodiphenyl* OR NonaBDE* OR "NoBDE" OR "nonabrominated diphenyl" OR "nonabrominated diphenyls" OR (nonabromo NEXT/1 deriv*)):ti,ab,tn,rn
#3 Substance CAS number: title, abstract, registry number	("7025-06-1" OR "6876-00-2" OR "101-55-3" OR "51452-87-0" OR "446254-14-4" OR "147217-72-9" OR "171977-44-9" OR "147217-71-8" OR "33513-66-3" OR "51930-04-2" OR "6903-63-5" OR "189084-59-1" OR "83694-71-7" OR "46438-88-4" OR "2050-47-7" OR "147217-74-1" OR "147217-75-2" OR "407606-55-7" OR "147217-73-0" OR "147217-76-3" OR "337513-67-4" OR "446254-15-5" OR "446254-16-6" OR "147217-77-4" OR "337513-75-4" OR "337513-53-8" OR "41318-75-6" OR "337513-56-1" OR "155999-95-4" OR "65075-08-3" OR "189084-60-4" OR "147217-78-5" OR "446254-17-7" OR "147217-80-9" OR "147217-79-6" OR "147217-81-0" OR "337513-54-9" OR "337513-68-5" OR "446254-18-8" OR "446254-19-9" OR "446254-20-2" OR "446254-22-4" OR "5436-43-1" OR "337513-55-0" OR "243982-82-3" OR "446254-23-5" OR "189084-57-9" OR "446254-24-6" OR "446254-25-7" OR "446254-31-5" OR "446254-32-6" OR "446254-33-7" OR "446254-34-8" OR "189084-61-5" OR "446254-37-1" OR "446254-38-2" OR "327185-09-1" OR "446254-39-3" OR "189084-62-6" OR "446254-40-6" OR "446254-41-7" OR "446254-42-8" OR "189084-63-7" OR "446254-43-9" OR "93703-48-1" OR "446254-45-1" OR "446254-48-4" OR "103173-66-6" OR "446254-50-8" OR "446254-51-9" OR "182346-21-0" OR "446254-53-1" OR "446254-54-2" OR "446254-55-3" OR "446254-55-3" OR "446254-57-5" OR "446254-59-7" OR "446254-61-1" OR "446254-64-4" OR "38463-82-0" OR "60348-60-9" OR "189084-64-8" OR "446254-65-5" OR "446254-66-6" OR "446254-67-7" OR "446254-68-8" OR "373594-78-6" OR "446254-69-9" OR "446254-71-3" OR "446254-72-4" OR "446254-74-6" OR "446254-77-9" OR "446254-78-0" OR "189084-65-9" OR "446254-80-4" OR "189084-66-0" OR "182677-30-1" OR "243982-83-4" OR "68631-49-2" OR "207122-15-4" OR "35854-94-5" OR "189084-58-0" OR "189084-67-1" OR "207122-16-5" OR "189084-68-2" OR "1163-19-5" OR "109945-70-2" OR "113152-37-7" OR "113172-79-5" OR "139598-16-6" OR "139749-52-3" OR "145538-74-5" OR "32534-81-9" OR "32536-52-0" OR "40088-47-9" OR "446254-27-9" OR "446255-20-5" OR "446255-22-7" OR "49690-94-0" OR "63936-56-1" OR "64589-00-0" OR "68928-80-3" OR "85446-17-9" OR "36483-60-0" OR "437701-79-6" OR "446255-26-1" OR "117948-63-7" OR "446255-30-7" OR "61262-53-1" OR "405237-85-6" OR "39275-89-3" OR "13654-09-6" OR "61288-13-9" OR "446255-39-6" OR "337513-72-1" OR "366791-32-4" OR "2050-47-7"):ti,ab,rn
#4	#1 OR #2 OR #3

#5 Outcome terms: controlled vocabulary	'psychologic test'/de OR 'aptitude test'/exp OR 'Child Behavior Checklist'/exp OR 'intelligence test'/exp OR 'language test'/exp OR 'learning test'/exp OR 'mental test'/exp OR 'neuropsychological test'/exp OR 'psychologic assessment'/exp OR 'Wechsler Memory Scale'/exp OR 'mental disease'/de OR 'behavior disorder'/exp OR 'learning disorder'/exp OR 'memory disorder'/exp OR 'mental deficiency'/exp OR 'mental function'/de OR 'cognition'/exp OR 'sensorimotor function'/exp OR 'behavior'/de OR 'adolescent behavior'/de OR 'aggression'/exp OR 'behavior change'/exp OR 'behavior control'/exp OR 'child behavior'/exp OR 'motor activity'/exp OR 'hyperkinesia'/exp OR 'verbal behavior'/exp OR 'behavior assessment'/de OR 'individual behavior assessment'/exp OR 'mental disease assessment'/de OR 'behavior disorder assessment'/de OR 'mental function assessment'/de OR 'cognition assessment'/exp OR 'psychophysiologic assessment'/exp OR 'human development'/exp OR 'neurotoxicity'/exp OR 'developmental disorder'/exp OR 'disorders of higher cerebral function'/exp OR 'motor performance'/exp OR 'nervous system development'/de OR 'brain development'/exp
#6 Outcome terms: title, abstract	(neurodevelopment* OR neurotoxic* OR neurobehav* OR neuropsychologic* OR neurocogniti* OR psychologic* OR aptitude* OR mental* OR intelligence* OR "IQ" OR intellectual* OR language* OR comprehension* OR impulsiv* OR "ADHD" OR "ADDH" OR "ADHS" OR "AD/HD" OR "hkd" OR hyperactiv* OR (hyper NEXT/1 active*) OR hyperkin* OR (hyper NEXT/1 kin*) OR "inattention" OR inattentiv* OR "distractibility" OR Behavioral* OR behavioural* OR "sustained attention" OR "attention span" OR "attention related" OR (attention* NEAR/3 defic*) OR (attention* NEAR/3 dysfunc*) OR (attention* NEAR/3 disorder*) OR (behav* NEAR/3 defic*) OR (behav* NEAR/3 dysfunc*) OR (behav* NEAR/3 disorder*) OR (disrupt* NEAR/3 disorder*) OR (disrupt* NEAR/3 behav*) OR (defian* NEAR/3 disorder*) OR (defian* NEAR/3 behav*) OR (behav* NEXT/1 effect*) OR (behav* NEXT/1 checklist*) OR (spontaneous NEXT/1 behav*) OR (externalizing NEXT/1 behav*) OR "cognitive" OR "cognition" OR "psychomotor" OR "learning" OR "memory" OR (executive NEXT/1 function*) OR "executive control" OR "executive dysfunction" OR "executive impairment" OR (motor NEXT/1 abiliti*) OR "motor performance" OR (motor NEXT/1 function*) OR (motor NEXT/1 skill*) OR (motor NEXT/1 activit*) OR "fine motor" OR "vigilance" OR "reaction time" OR "processing speed" OR "response inhibition" OR "Stanford Binet" OR "Binet Test" OR "Binet tests" OR "Bender Gestalt Test" OR "Aphasia Test" OR "Aphasia Tests" OR Bayley* OR "Wechsler" OR "WISC" OR "McCarthy Scale" OR "McCarthy Scales" OR "Continuous Performance Test" OR "Continuous Performance Tests" OR "Continuous Performance Task" OR "Continuous Performance Tasks" OR Conners* OR "CRS-T" OR "CRS-P" OR "academic achievement" OR "scholastic achievement" OR (brain NEAR/3 disorder*) OR (brain NEAR/3 damage*) OR (brain NEAR/3 dysfunct*)):ti,ab
#7	#5 OR #6
#8	#4 AND #7

Toxline and DART:

Search	**Toxline**
#1 Substance terms: all fields	"flame retard*" OR "fire retard*" OR "fireproofing agent*" OR "FireMaster" OR "Bromkal" OR "diphenal ether derivative" OR "Halogenated Diphenyl" OR "Brominated Diphenyl" OR PBDE* OR "Polybrominated Diphenyl" OR polybromodiphenyl* OR PBDP* OR BDE* OR pentabromodiphenyl* OR "c-pentaBDE*" OR PentaBDE* OR "PeBDE" OR "DE 71" OR "DE71" OR "pentabrominated diphenyl" OR "PBDPO" OR "Planelon PB 501" OR "pentabromo deriv*" OR Pentabromophenyl*
#2 Substance terms: all fields	octabromodiphenyl* OR "c-octaBDE*" OR OctaBDE* OR OcBDE OR Octabrom OR "octabromo deriv*" OR OBDE OR OBDPO OR "octabrominated diphenyl" OR decabromodiphenyl* OR "c-decaBDE*" OR DecaBDE* OR DeBDE OR DBDPO OR "decabrominated diphenyl" OR "decabromo deriv*" OR Decabrom OR "Berkflam B 10E" OR "FR 300BA" OR "FR 300 BA" OR tribromodiphenyl* OR "tribrominated diphenyl" OR TrBDE OR "tribromo deriv*" OR tetrabromodiphenyl* OR TetraBDE* OR TeBDE OR TBDE OR BPDE OR "tetrabromo deriv*" OR TBDP OR "tetrabrominated diphenyl" OR hexabromodiphenyl* OR HexaBDE* OR HxBDE OR "hexabrominated diphenyl" OR "hexabromo deriv*" OR heptabromodiphenyl* OR HeptaBDE* OR HeBDE OR "heptabrominated diphenyl" OR "heptabromo deriv*" OR nonabromodiphenyl* OR NonaBDE* OR NoBDE OR "nonabrominated diphenyl" OR "nonabromo deriv*"
#3 Substance terms: all fields	"7025-06-1" OR "6876-00-2" OR "101-55-3" OR "51452-87-0" OR "446254-14-4" OR "147217-72-9" OR "171977-44-9" OR "147217-71-8" OR "33513-66-3" OR "51930-04-2" OR "6903-63-5" OR "189084-59-1" OR "83694-71-7" OR "46438-88-4" OR "2050-47-7" OR "147217-74-1" OR "147217-75-2" OR "407606-55-7" OR "147217-73-0" OR "147217-76-3" OR "337513-67-4" OR "446254-15-5" OR "446254-16-6" OR "147217-77-4" OR "337513-75-4" OR "337513-53-8" OR "41318-75-6" OR "337513-56-1" OR "155999-95-4" OR "65075-08-3" OR "189084-60-4" OR "147217-78-5" OR "446254-17-7" OR "147217-80-9" OR "147217-79-6" OR "147217-81-0" OR "337513-54-9" OR "337513-68-5" OR "446254-18-8" OR "446254-19-9" OR "446254-20-2" OR "446254-22-4" OR "5436-43-1" OR "337513-55-0" OR "243982-82-3" OR "446254-23-5" OR "189084-57-9" OR "446254-24-6" OR"446254-25-7" OR "446254-31-5" OR "446254-32-6" OR "446254-33-7" OR "446254-34-8" OR "189084-61-5"
#4 Substance terms: all fields	"446254-37-1" OR "446254-38-2" OR "327185-09-1" OR "446254-39-3" OR "189084-62-6" OR "446254-40-6" OR "446254-41-7" OR "446254-42-8" OR "189084-63-7" OR "446254-43-9" OR "93703-48-1" OR "446254-45-1" OR "446254-48-4" OR "103173-66-6" OR "446254-50-8" OR "446254-51-9" OR "182346-21-0" OR "446254-53-1" OR "446254-54-2" OR "446254-55-3" OR "446254-55-3" OR "446254-57-5" OR "446254-59-7" OR "446254-61-1" OR "446254-64-4" OR "38463-82-0" OR "60348-60-9" OR "189084-64-8" OR "446254-65-5" OR "446254-66-6" OR "446254-67-7" OR "446254-68-8" OR "373594-78-6" OR "446254-69-9" OR "446254-71-3"OR "446254-72-4" OR "446254-74-6" OR "446254-77-9" OR "446254-78-0" OR "189084-65-9" OR "446254-80-4" OR "189084-66-0" OR "182677-30-1" OR "243982-83-4"
#5 Substance terms: all	"68631-49-2" OR "207122-15-4" OR "35854-94-5" OR "189084-58-0" OR "189084-67-1" OR "207122-16-5" OR "189084-68-2" OR "1163-19-5" OR

fields	"109945-70-2" OR "113152-37-7" OR "113172-79-5" OR "139598-16-6" OR "139749-52-3" OR "145538-74-5" OR "32534-81-9" OR "32536-52-0" OR "40088-47-9" OR "446254-27-9" OR "446255-20-5" OR "446255-22-7" OR "49690-94-0" OR "63936-56-1" OR "64589-00-0" OR "68928-80-3" OR "85446-17-9" OR "36483-60-0" OR "437701-79-6" OR "446255-26-1" OR "117948-63-7" OR "446255-30-7" OR "61262-53-1" OR "405237-85-6" OR "39275-89-3" OR "13654-09-6" OR "61288-13-9" OR "446255-39-6" OR "337513-72-1" OR "366791-32-4" OR "2050-47-7"
#6	#1 OR #2 OR #3 OR #4 OR #5
#7 Outcome terms: all fields	Neurodevelopment* OR Neurotoxic* OR Neurobehav* OR Neuropsychologic* OR neurocogniti* OR Psychologic* OR Aptitude* OR mental* OR intelligence* OR "IQ" OR Intellectual* OR Language* OR Comprehension*
#8 Outcome terms: all fields	Impulsiv* OR "ADHD" OR "ADDH" OR "ADHS" OR "AD/HD" OR "hkd" OR hyperactiv* OR "hyper activ*" OR hyperkin* OR "hyper kin*"
#9 Outcome terms: all fields	"attention defic*" OR "attention related*" OR inattention* OR inattentiv* OR "sustained attention" OR "attention span" OR "attention dysfunc*" OR "attention disorder*" OR "distractibility"
#10 Outcome terms: all fields	Behavioral* OR behavioural* OR "behavior defic*" OR "behaviour defic*" OR "behavior dysfunc*" OR "behaviour dysfunc*" OR "behavior disorder*" OR "behaviour disorder*"
#11 Outcome terms: all fields	"behavior effect*" OR "behaviour effect*" OR "behavior checklist*" OR "behaviour checklist*" OR "disruptive behav*" OR "disruption behav*" OR "disruptive disorder*" OR "disruption disorder*" OR "defiance behav*" OR "defiant behav*" OR "defiance disorder*" OR "defiant disorder*"
#12 Outcome terms: all fields	"spontaneous behav*" OR "externalizing behav*" OR "cognitive" OR "cognition" OR "Psychomotor" OR "learning" OR "memory" OR "vigilance" OR "reaction time" OR "processing speed" OR "response inhibition"
#13 Outcome terms: all fields	"executive function*" OR "executive control*" OR "executive dysfunction*" OR "executive impairment*" OR "motor abilit*" OR "motor activit*" OR "motor function*" OR "motor skill*" OR "fine motor" OR "motor performance"
#14 Outcome terms: all fields	"Binet" OR "Bender Gestalt Test" OR "Aphasia Test*" OR Bayley* OR "Wechsler" OR "WISC" OR "McCarthy Scale*" OR "Continuous Performance Test*" OR "Continuous Performance Task*" OR Conners* OR "CRS-T" OR "CRS-P"
#15 Outcome terms: all fields	"academic achievement" OR "scholastic achievement" OR "brain disorder*" OR "brain damage*" OR "brain dysfunct*"
#16 Outcome terms: all fields	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17 Outcome terms: all fields	#6 AND #16

Table S2: Toxicological websites and grey literature databases searched

Toxicological websites	*Grey literature databases*
• ATSDR Interaction Profiles http://www.atsdr.cdc.gov/interactionprofiles/index.asp • ATSDR Toxicological Profiles http://www.atsdr.cdc.gov/toxprofiles/index.asp • CalEPA Office of Environmental Health Hazard Assessment http://www.oehha.ca.gov/risk.html, http://oehha.ca.gov/air.html • Chem ID http://chem.sis.nlm.nih.gov/chemidplus/ • DART http://toxnet.nlm.nih.gov/newtoxnet/dart.htm • EPA Acute Exposure Guideline Levels http://www.epa.gov/oppt/aegl/chemlist.htm • EPA IRIS internet www.epa.gov/iris • EPA NEPIS and NSCEP http://www.epa.gov/nscep/ • EPA Science Inventory http://cfpub.epa.gov/si/ • EPA Substance Registry System http://ofmpub.epa.gov/sor_internet/registry/substreg/searchandretrieve/substancesearch/search.do • Health Canada First Priority List Assessments http://www.hcsc.gc.ca/hecs sesc/exsd/psl1.htm • Health Canada Second Priority List Assessments http://www.hcsc.gc.ca/hecs sesc/exsd/psl2.htm • Hazardous Substances Data Bank http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB • IPCS INCHEM http://www.inchem.org/ • NIOSHTIC 2 http://www2.cdc.gov/nioshtic 2/Nioshtic2.htm • Toxicology Data Network http://toxnet.nlm.nih.gov/ • RTECS Toxcenter http://www.cdc.gov/niosh/rtecs/default.html • WHO assessments – CICADS, EHC http://www.who.int/ipcs/assessment/en/ • USEPA Health and Environmental Studies Online http://hero.epa.gov/ • FIFRA docket: http://www.regulations.gov	• Google: http://www.google.com • Google Scholar: http://scholar.google.com/ • Database of federally-funded scientific research: Science.gov • ScienceResearch.com (Science federated search engine by Deep Web Technologies): http://scienceresearch.com/ • Oaister database (an open-source repository of difficult-to-access, academically-oriented digital resources): http://www.oclc.org/oaister • Open Grey: http://www.opengrey.eu/

Table S3: Data Extraction Fields and Description

Field	Tab	Field Type	Instructions
Study Design*	Gen. Study Info.	Combo Box	Study Design: Choose the study design type from the dropdown list.
Chemical	Gen. Study Info.	Combo Box	Choose the chemical evaluated in the study. If the chemical does not exist in the drop down list, it needs to be associated with the assessment in the "Assessment Management Tools" of the main form.
Source of Funding	Gen. Study Info.	Text Box	Study funding source details: Indicate the source of funding for this study. This text may appear in appendix tables so be as concise as possible by using acronyms for common funding sources (US EPA, NSF, NIH/NIEHS) and NOT including grant numbers. Examples: US EPA, NIH/NIEHS, NIH/NIDDK. More specific information on funding, e.g.., grant number, can be added as a field note (if desired)
Does the author report a COI or financial disclosure?	Gen. Study Info.	Combo Box	Authors' declared conflicts of interest: Indicate whether the authors report a conflict of interest (COI) or financial disclosure.
COI details	Gen. Study Info.	Text Box	Conflict of Interest Details: Enter details about the COI if reported by the authors. This will not happen often.
Source of Funding Type	Gen. Study Info.	Combo Box	Study funding source: Select the source of funding type.
General Study Objectives	Gen. Study Info.	Text Box	What are the study objectives?: Enter a brief description of the study objectives.
Description of Population	Study Population	Text Box	Cohort: Enter the official name of the cohort or another brief description of the population studied (e.g., distinguishing feature, job occupation, type of clinical population, or work site). Only capitalize proper nouns; separate phrases with semicolons; no ending punctuation. Examples: "HEALS" "Northwestern Taiwan residents" "NHANES" "glass industry workers employed for more than 10 yrs." "Yucheng residents over age 60 exposed to contaminated rice oil and similar unexposed subjects"
Lifestage	Study Population	Combo Box	Select a descriptor for the population that comprises the cohort.
Country(ies)	Study Population	Text Box	Sites of Data Collection, Country: Select the country where the study population was observed. If multiple countries were studied, use the "add multi" button to select more than one. To save time looking through the list, you can begin typing the country name and DRAGON will provide auto-fill options.
Region	Study Population	Text Box	Sites of Data Collection, Region: Enter the region(s) where the study population is observed; use the most specific region information available and separate multiple entries with a semicolon (;). List US locations as: City, ST (two letter state abbreviation). If just an area, write: northwest (direction with lower case).
State(s)	Study Population	Combo Box	Sites of Data Collection, State: Choose the state if in United States.

Field	Tab	Field Type	Instructions
Demographic Data Type	Study Population	Text Box	Age and Co-morbidities, variable: Enter the name of the demographic variable, such as "age" or "education status". Enter for age for all experimental groups where data are available and also for any other comorbidities listed in the study.
Population/Sub-group	Study Population	Text Box	Age and Co-morbidities, population: Enter the population or subgroup you want to enter data for. This might be "total population", "exposed", "unexposed", "cases", etc.
Demographic Description	Study Population	Text Box	Age and Co-morbidities, description: Enter a description of the demographic being entered. For example, if you chose a demographic variable that is categorical, you enter each of the categories in different rows. An example might be the demographic variable "Smoking status" where the demographic descriptions would be "Currently smoked", "Stopped Smoking within last 5 years", "Never smoked", etc.
Format	Study Population	Combo Box	Age and Co-morbidities, format: Select the format of the data. This will indicate whether the data presented in the paper are means, means with standard deviations, ranges, etc.
Centrality	Study Population	Text Box	Autopopulates based on the demographic data format.
Centrality Value	Study Population	Text Box	Enter the demographic value.
Variance	Study Population	Text Box	Autopopulates based on the demographic data format.
Variance Value	Study Population	Text Box	Enter the demographic value.
Lower Limit	Study Population	Text Box	Autopopulates based on the demographic data format.
Upper Limit Value	Study Population	Text Box	Enter the demographic value.
Evaluation of Population	Study Population	Text Box	Enter any additional population information from related studies that supplements the information from this main study.
Description of Reference Pop	Study Population	Text Box	Description of reference group: Provide information on how the reference population was selected or recruited. For case-control study (one with exposed and unexposed individuals), how were controls or unexposed groups selected? "controls randomly selected to frequency match the cases by age and sex." If lowest exposure group selected as the reference group, describe and note any possible issues. Example, no issues: "all subjects recruited in same manner and group with water concentrations lower than 10 ppb used as reference group." Example, potential issues: "all subjects recruited in same manner; reference group consisted of subjects exposed to<10 ppb, however, group significantly younger than other exposure groups and age not adjusted for"
Exclusion Criteria	Study Population	Text Box	Inclusion/exclusion criteria/recruitment strategy: Describe the criteria used to exclude subjects in the study population. Complete sentences are not necessary. List separate elements with a semicolon in between; capitalize the very first letter; do not use a period at the end. If not specified in the paper, type "Not specified". Examples: "No glucose data available"
Number Eligible to Participate (N) - Cases or Exposed	Study Population	Text Box	Sample size of cohort, eligible, exposed: Enter the size of the exposed population or number of cases eligible to participate in the study, if provided. For example, a cohort study might have a total population of 10,000 members although only a subset of the population was invited to participate in the specific study.

Field	Tab	Field Type	Instructions
Number Eligible to Participate (N) - Controls or Reference	Study Population	Text Box	Sample size of cohort, eligible, reference: Enter the size of the reference or control population eligible to participate in the study, if provided.
Number Eligible to Participate (N) - Total Population	Study Population	Text Box	Sample size of cohort, eligible, total: Enter the size of the population eligible to participate in the study, if provided. For example, a cohort study might have a total population of 10,000 members although only a subset of the population was invited to participate in the specific study.
Number Invited to Participate (N) - Cases or Exposed	Study Population	Text Box	Sample size of cohort, invited, exposed:Enter the size of the exposed population before any were eliminated, missing, or lost. For case-control, enter number of cases.
Number Invited to Participate (N) - Controls or Reference	Study Population	Text Box	Sample size of cohort, invited, reference:Enter the size of the reference or control population before any were eliminated, missing, or lost, if provided.
Number Invited to Participate (N) - Total Population	Study Population	Text Box	Sample size of cohort, invited, total:Primarily relevant to cohort and cross-sectional studies: Enter the size of the population invited to participate in the study, if provided. This will be compared to the study population size in order to determine the participation rates. For example, this population may include the entire region or occupational population prior to any applied inclusion and exclusion criteria. For case-control studies, SKIP and enter target population below in Exposed Population Metrics and Reference Population Metrics.
Number Who Participated (N) - Cases or Exposed	Study Population	Text Box	Sample size of cohort, included, exposed:Enter the total number of subjects in the exposed group, minus any exposed subjects that were identified as a "reference" group. The sum of the exposed population size and the control population size should equal the study size.
Number Who Participated (N) - Controls or Reference	Study Population	Text Box	Sample size of cohort, included, reference: Enter the total number of subjects in the control or "reference" group. The sum of the exposed population size and the control/reference population size should equal the study size.
Number Who Participated (N) - Total Population	Study Population	Text Box	Sample size of cohort, included, total:Enter the size of the population that was eventually evaluated for exposure and health outcomes. This number should be less than or equal to the "target population" and represents the number of subjects in the study after the inclusion and exclusion criteria were applied to the target population. For example, this population may include the occupational population minus any prior smokers. Or, it may include all inhabitants of a region minus those that did not answer the door on the day of interview. May not be available for all studies or could be the sum of study populations for exposed and reference below.
Description of Losses in Selection and Recruitment Process	Study Population	Memo	Participation/follow-up rates: If there was a follow-up period where the health status of subjects was followed but subjects were lost from the study, explain how this loss to follow-up was addressed in the statistical analysis. Use short phrases separated by semicolon (;). End with period (.). Example: "29 subjects lost to follow-up because they moved out of the region; excluded from statistical tests since health outcome could not be determined."
(none)	Study Population	Combo Box	Select a qualifier if the follow-up length was equal to, less, than, or greater than a specific duration.

Field	Tab	Field Type	Instructions
Length of Follow-up	Study Population	Text Box	Study duration: Length of the follow-up period when subjects were followed and assessed for health outcome. Enter a single number or a range as a appropriate and add units (years, months, days); only enter for cohort (prospective or retrospective) studies or nested case-control studies. Examples: "5-17 years", "2 months"
Enrollment/recruitment Years	Study Population	Text Box	Study dates: Enter the year or range of years when participants were followed.
Evaluation of Selection/recruitment Process	Study Population	Text Box	Study design details and other relevant details: enter any additional details related to study design or to the population selection as a whole.
Exposure Surrogate	Exposure Measurement	Combo Box	Source of exposure data: specify whether the data are from biomonitoring-blood, biomonitoring-urine, environmental monitoring (include matrix in details), emissions-based models (include specific model in details), questionnaire (include specific determinant of exposure in details), or other (specify in details).
Exposure Surrogate Units	Exposure Measurement	Text Box	Select the units for the exposure surrogate. If the correct units are not here, enter them as a new entry. Do not convert the units; enter them exactly as they appear in the study.
Exposure Measurement Level	Exposure Measurement	Combo Box	Indicate whether exposure was measured at the group or individual level in the study. Blood, serum, plasma, urine, and hair measurements are often individual, while drinking water and diet measurements are often at the group level. Exceptions do occur.
Format	Exposure Measurement	Combo Box	Exposure values for study group: Select the format of the data. This will indicate whether the data presented in the paper are means, means with standard deviations, ranges, etc.
Centrality	Exposure Measurement	Text Box	Autopopulates based on the exposure format.
Centrality Value	Exposure Measurement	Text Box	Enter the exposure value.
Variance	Exposure Measurement	Text Box	Autopopulates based on the exposure format.
Variance Value	Exposure Measurement	Text Box	Enter the exposure value.
Lower Limit	Exposure Measurement	Text Box	Autopopulates based on the exposure format.
Lower Limit Value	Exposure Measurement	Text Box	Enter the exposure value.
Upper Limit	Exposure Measurement	Text Box	Autopopulates based on the exposure format.
Upper Limit Value	Exposure Measurement	Text Box	Enter the exposure value.

Field	Tab	Field Type	Instructions
Exposure Category Definition	Exposure Measurement	Text Box	Enter a text descriptor that differentiates the current exposure category definition from others in the paper or others entered in DRAGON. Click the + to expand and see the exposure levels for a category. Should correspond to exposure surrogate units (i.e., they could be added to the end of this to make a phrase). This may include multiple descriptors in order to fully distinguish the entry. Usually, similar exposure metrics that were assessed separately for men and women should be entered as two separate exposure categories. Example: "Mean blood lead concentration, men". Example: "Mean drinking water concentration, women, no kidney disease".
Lifestage at exposure	Exposure Measurement	Combo Box	Exposure measurement timing: Select the life stage at which exposure occurred, if specified. Use "multiple" if exposure occurred over lifetime or if population ages vary. If not specified and you cannot extrapolate, choose "cannot be determined."
Source	Exposure Measurement	Text Box	Source of Information: Enter the table or figure (or text) from which the exposure category and level data was extracted. Example: "Table 6, upper portion". Example: "Text, page 667, second paragraph"
Sex	Exposure Measurement	Combo Box	Sex: Enter the sex of subjects in each exposure category.
Description of Exposure	Exposure Measurement	Text Box	Exposure source details, range of concentrations, chemicals, and frequency: Enter details about the source of exposure data, list the range of concentrations of air polluation measured (list any specific components of air pollution) with units, and indicate the frequency of exposure measurements (if taken more than once) and the number of replicate measurements taken. Also, list any other chemical information here related to the air pollutants measured. Use complete sentences.
Exposure Sampling Year Range	Exposure Measurement	Text Box	Exposure measurement timing details: enter information about when exposure was measured, especially relative to when the outcomes were assessed.
Group	Exposure Measurement	Text Box	Enter the population or subgroup you want to enter data for. This might be "total population", "exposed", "unexposed", "cases", etc.
Evaluation of Exposure	Exposure Measurement	Text Box	Enter any additional exposure information from related studies that supplements the information from this main study.
Search:	Outcome Measurement	Text Box	Type a search term and select the filter button to limit the endpoint list.
Outcome	Outcome Measurement	Text Box	Outcomes measured, controlled vocabulary: The health outcome name is from a controlled vocabulary list. Double click from the list above to add the outcome to the list. You can also use the search bar to help find a particular word in the outcomes list. The study may call the health outcome something slightly different. Please contact a manager if you are unsure what health outcome to select. Also find the checkboxes at the end of the row. Check the first if the health outcomes have no statistical results reported in the paper. In the second, check if the statistical results are not being entered in epiDRAGON at this time.

Field	Tab	Field Type	Instructions
Outcome Name In Study	Outcome Measurement	Text Box	Outcomes measured, exactly as in study: Enter the exact wording of the health outcome used in the study. The outcome name as entered will appear in the output tables, so some longer names may be truncated by the data extractor if appropriate.
Diagnostic Method	Outcome Measurement	Combo Box	Method of autism assessment, general: Select the method of diagnosis determination. You may only enter one. If multiple diagnostic types were used, include that information in the diagnostic description field.
Diagnostic Description	Outcome Measurement	Text Box	Method of autism assessment, detailed: Use short phrases, all lower case, separated by semicolons. This may include more detail about the method used and conclusions about how reliable the method of diagnosis was compared with other available methods. Also, if ICD codes were used to as part of the outcome assessment, indicate the codes here. Example: "cancers determined through annual health exams, home visit interviews, household registration data checks, cancer registry, and death certification" "identified by review of death certificates with ICD 9 code 188"
Outcome Sampling Years	Outcome Measurement	Text Box	Enter range of years when outcomes were assessed. Example: "1990-1991" "1976"
ICD used	Outcome Measurement	Combo Box	Enter which version of the ICD codes was used. If the author originally used an older ICD list (e.g., ICD7) and converted to a newer list (e.g., ICD9), then enter the codes from the original list and note the conversion in the Diagnostic Description field. If ICD code not mentioned, choose not reported.
Evaluation of Outcome Measure	Outcome Measurement	Text Box	Number of subjects analyzed and number of missing participants: Include information about how many subjects were analyzed for each outcome and how many were missing. Also, enter any outcome information from related studies that may supplement the information from this main study.
Statistical Finding Selections	Confounding and Analysis	Combo Box	Choose an existing statistical finding from the drop down or click Add New to begin a new Statistical Finding.

Field	Tab	Field Type	Instructions
Description of Population Matching	Confounding and Analysis	Text Box	This field should contain only information from the study, not an evaluation of matching. For most relevant study types, a control (or reference) population must be determined. This control population should have similar demographics to the exposed population. Describe how the control population and reference population demographic statistics were assessed to ensure the reference population demographics matched the exposed population demographics. Often the relevant demographics include sex, age, and ethnicity/race. For occupational studies, the occupation of the reference group is also important. For certain chemicals or for certain health outcomes, other demographics may be important, such as education status, smoking status, or others. Example: "A population consisting of a similar ethnic and age demographics in a neighboring region in China was selected for the control population. The paper provides information showing that age and sex were both similar in the two populations, although smoking status was not evaluated." Example: "The study made no mention of how matching was assessed, and no demographic information is provided separately by exposure group." Example: "The study made no mention of how matching was assessed, although the reference population was selected from amongst other United States steel-mill workers who likely had the same age profile as the exposed population."
Confounding Considered in Study Design	Confounding and Analysis	Text Box	Were known confounders accounted for by study design?: List all confounders that were included in the study design. This is different than the confounders that were eventually included in the statistical analysis. These confounders are ones considered when choosing either the target population (the whole population considered for the study) or the study population (those that eventually participated in the study). Use short complete sentences. Example: "Smoking status was ascertained by survey and all smokers or those living in homes with smokers were excluded from the study population." This information may overlap somewhat with the exclusion criteria.
Adjustment factors considered in the analysis	Confounding and Analysis	Memo	Were known confounders accounted for by the analysis, considered: Click the "Add Factors" link to enter confounders that were considered as part of the statistical analysis. This list might not include all the ones that were eventually included in the statistical model if some were found to have no effect on the results
Adjustment factors included in the analysis	Confounding and Analysis	Memo	Were known confounders accounted for by the analysis, included: Click the "Add Factors" link to enter confounders that were included in the statistical analysis. This list should only include those that were actually included in the ultimate statistical model. If a confounder is not on the list, type it in to add it.
Reason for Excluding Adjustment Factors in Final Model	Confounding and Analysis	Text Box	If some of the confounders in the "considered" list did not make it into the final "included" list, enter a description of why they were excluded. Example: "Education status was considered as a potential confounder but did not significantly affect the model."

Field	Tab	Field Type	Instructions
Source in Study	Confounding and Analysis	Text Box	Enter the location in the study where the statistical conclusion information can be found; Table X, Page Y in the study reference or section in text (section number/title, page number)
Confounder	Confounding and Analysis	Text Box	Indicate which confounder was considered. Enter a new row for each confounder.
Dichotomous/Continuous	Confounding and Analysis	Combo Box	Indicate whether the confounder is dichotomous (categorical) or continuous.
Included in Final Analysis	Confounding and Analysis	Check Box	Indicate whether the current confounder was included in the analysis.
Description	Confounding and Analysis	Text Box	Enter any additional information regarding this confounder. For example, if the confounder is dichotomous how many levels are considered. If the confounder is continuous, indicate the evaluated range.
Other Comments on Confounding	Confounding and Analysis	Text Box	Enter any additional comments on confounding (e.g., if the study is evaluating an occupational exposure, indicate any co-exposures that may have occurred.)
Evaluation of Confounding	Confounding and Analysis	Text Box	Enter any additional confounding information from related studies that supplements the information from this main study.
Description of Statistical Analysis	Confounding and Analysis	Text Box	Enter information about the statistical method, including the type of regression or analysis (by name) that was used and any other information that might be pertinent to assessing the reliability of the statistical method.
Other Method Notes	Confounding and Analysis	Text Box	Enter any other information from the study (other than confounders, matching, outcome/exposure timing, missing data, coexposures, exposure assessment, and outcome assessment) that may introduce bias into the study and how the bias was accounted for.
Evaluation of Statistical and Analytical Approaches	Confounding and Analysis	Text Box	Enter any additional statistical analysis and results information from related studies that supplements the information from this main study.
Level	Results	Text Box	
Stat. Est.	Results	Text Box	Enter the numerical value for the statistical metric for the particular exposure level/group. For the reference group, the value will be either 1 or 0.
Lower CI	Results	Text Box	Enter the lower end of the confidence interval.
Upper CI	Results	Text Box	Enter the upper end of the confidence interval.
CI Units	Results	Combo Box	Enter whether the confidence interval is the 95%, 90%, etc. Leave blank for reference group. Enter "NA" if not applicable.
# w/ Outcome	Results	Text Box	Number of people in exposure group with outcome; leave blank if not available. If the value is calculated or inferred from the study, put the value in square brackets.
# w/o Outcome	Results	Text Box	Number of people in exposure group without outcome; leave blank if not available. If the value is calculated or inferred from the study, put the value in square brackets.
Total in Group	Results	Text Box	Enter total number of people in exposure group; leave blank if not available. If the value is calculated or inferred from the study, put the value in square brackets.

Field	Tab	Field Type	Instructions
Prevalence/Incidence	Results	Text Box	Enter the prevalence or incidence as a percentage; leave blank if not available. If the value is calculated or inferred from the study, put the value in square brackets. After the value, enter (P) if the value is a prevalence and (I) if the value is an incidence.
Variance	Results	Text Box	Enter the standard error or standard deviation for the statistical metric value, if given.
Variance Type	Results	Combo Box	Choose standard deviation or standard error to correspond to value entered in variance column.
P Value Qualifier	Results	Text Box	Select the appropriate qualifier that describes the p-value in the next field ("<", ">", etc.)
P value	Results	Text Box	If a test was done to determine whether the exposure group is statistically different from the control group (as opposed to an overall trend test across all groups), enter the p-value from the analysis here.
Notes	Results	Memo	Miscellaneous comments by reviewer regarding data analysis: Use phrases separated by semicolons (;) to make note of any observations pertaining to a single exposure group.
Results	Did author test for trend?	Did author test for trend?	Indicate whether a test for trend was performed by the study authors.
Results	Trend Description	Trend Description	Select whether the authors found a positive, negative, null, or unknown trend. A trend is positive if the statistical test indicates that exposure led to an increase in risk of a health outcome.
Results	Test Value Type	Test Value Type	Select the type of metric provided for the trend test. If the selection is not on the list, add it.
Results	Test Value Modifier	Test Value Modifier	Select the inequality symbol associated with the test value.
Results	Test Value	Test Value	Enter a p-value (or other statistic, if reported) for the author's trend test.
Results	Is trend monotonic?	Is trend monotonic?	Select if the trend is monotonic (consistently increasing or consistently decreasing) or non-monotonic (e.g., goes up with increasing exposure for low exposures and goes down with increasing exposure for high exposures).
Results	Author Conclusion on Trend		Enter a supporting description in the text box describing the authors' main conclusions about the health outcome for that exposure group. Use one or a few complete sentences. Example: "The authors conclude there is no evidence of a statistical relationshi
Results	Data Extractor Observations on Trend		If the authors did not perform a trend test or provide conclusions on the trend, select the option that best describes the statistical results.
Results	Data Extractors Comments on Trend		Note any of your own conclusions that are not necessarily reported by the author.

Table S4: Characteristics and risk of bias ratings of Adgent et al. (2014)

Study Element	Description
Design	Prospective birth cohort
Participants	184 mother-child pairs for intelligence outcomes and 192 mother-child pairs for ADHD and attention-related behavior outcomes from the Pregnancy, Infection, and Nutrition Babies Study in Central North Carolina between 2004-2006
Exposure	BDEs 28, 47, 99, 100, and 153 measured in breast milk three months postpartum
Comparator	Children with lower levels of breast milk PBDE measurements (first quartile concentrations as referent)
Outcomes	Mullen Scales of Early Learning (MSEL) composite score and Behavior Assessment System for Children (BASC)-2 (attention and hyperactivity subscales) assessed at 36 months

Bias domain	Authors' judgment	Support for judgment
Source population representation	Probably low	No evidence for selection bias. Authors found no difference in exposure between those who did or did not complete full outcome assessment. The internal validity of this study is valid, since study authors were make conclusions for breastfeeding mothers and not the generalized population.
Blinding	Low	Outcome assessors not aware of exposure levels.
Exposure assessment	Low	No concern about differential exposure assessment; thorough QA/QC reported in cited reference.
Outcome assessment	Low	No concern about differential outcome assessment or reliability.
Confounding	Probably high	Analyses accounted for 5 of 10 Tier I important confounders: did not include marital status, maternal use of alcohol during pregnancy, maternal depression, gestational exposure to ETS, exposure to other neurotoxic agents. However, they did include breastfeeding duration, fatty acids in breastmilk, and maternal stress.
Incomplete outcome data	Probably low	Proportion of missing outcomes not different by exposure.
Selective outcome reporting	Low	All pre-specified outcomes reported.
Conflict of interest	Low	Authors from universities, NIEHS or CDC and declared no COI; support from NIEHS, USEPA and CDC.
Other sources of bias	Low	No other potential sources of bias identified.

Table S5: Characteristics and risk of bias ratings of Chao et al. (2011)

Study Element	Description
Design	"Post hoc analysis of previous studies"—cohort study where data was re-analyzed subsequent to collection from a prospective birth cohort
Participants	Mother-infant pairs recruited from 4 hospitals in Southern Taiwan, analyses based on 70 (exclusive or partial breast-feeding for first 6 months) between 2007-2010. Ding-Yan et al. 2010 (Chao et al. appears to be a later analysis including Ding-Yan cohort but with more recruitment)
Exposure	BDEs 28, 47, 99, 100, 153, 154, 183, 196, 197, 203, 206, 207, 208, 209, and sum of all 14 measured in breast milk at birth
Comparator	Children with lower levels of breast milk PBDE measurements (2-fold increase

	comparison)
Outcomes	Bayley Scales of Infant and Toddler Development (BSID)-III cognitive and language subscales assessed at 8-12 months

Bias domain	Authors' judgment	Support for judgment
Source population representation	Probably high	Exclusions of high number of participants and no analysis to show this selection bias did not impact the results.
Blinding	Probably high	There is insufficient information about blinding to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not adequately blinded, as described by the criteria for a judgment of high risk of bias.
Exposure assessment	Probably low	Non-standard method that doesn't appear validated in other studies--has been revised from a standard method.
Outcome assessment	Probably low	No QA/QC described; No sensitivity analyses were conducted to suggest the influence of outcome misclassification would be minimal; there is no discussion as to whether the Bayley scale was culturally biased for this population.
Confounding	Probably high	The study controlled only for maternal age, pre-pregnancy BMI, sex, gestational age and age for testing Bayley scores.
Incomplete outcome data	Low	The study does not directly address number of children who had both exposure and outcome data; while exposure is clearly documented for all 70 children included there is no corresponding descriptive presentation of the outcome data for all 70 children--presumably all 70 children included had outcome data.
Selective outcome reporting	Low	The study outcome was Bayley scores and it was reported.
Conflict of interest	Low	Supported by a grant (NSC96-2628-E-020-001-MY3) from the National Science Council, Taiwan. The authors report no conflicts of interest.
Other sources of bias	Low	No other potential sources of bias identified.

Table S6: Characteristics and risk of bias ratings of Chen et al. (2014)

Study Element	Description
Design	Prospective birth cohort
Participants	179-285 mother-child pairs depending on age of assessment for intelligence outcomes and 165-240 mother-child pairs depending on age of assessment for ADHD and attention-related outcomes from Cincinnati Ohio enrolled between 2003-2006
Exposure	BDE 47 and sum of BDEs 47, 99, 100, 153 measured in maternal serum during week 16 of gestation
Comparator	Children with lower levels of maternal serum PBDE measurements (10-fold increase comparison)
Outcomes	Bayley Scales of Infant and Toddler Development (BSID)-II Mental Development Index (MDI) and Psychomotor Development Index (PDI) assessed at 12, 24, 36 months; Wechsler Preschool and Primary Scale of Intelligence (WPPSI)-III Full Scale Intelligence Quotient (FSIQ) assessed at 60 months. Behavior Assessment System for Children (BASC)-2 attention and hyperactivity subscales assessed at 2, 3, 4, 5 years

Bias domain	Authors' judgment	Support for judgment
Source population representation	Low	No evidence for selection bias. Authors found no difference in exposure between those who did or did not complete full outcome assessment.
Blinding	Low	"…assessors conducted the neurobehavioral assessments without knowledge of maternal PBDE levels."
Exposure assessment	Low	No concern about differential exposure assessment. CDC is "gold standard" method; LOD reported in cited reference; QA/QC blanks reported, although not quantified in this paper.
Outcome assessment	Low	No concern about differential outcome assessment or reliability.
Confounding	Probably low	Analyses accounted for all Tier I important confounders except maternal use of alcohol during pregnancy.
Incomplete outcome data	Low	Demographic profile of participants tested at age 5 years is very similar to enrolled cohort, and were also similar in terms of PBDEs and Bayley scores at ages 1-3 years.
Selective outcome reporting	Low	Although there was one outcome (binary PDI<85) without results reported, there were many outcomes in this study and other measures of PDI (linear mixed model results) were included.
Conflict of interest	Low	Authors from universities, hospitals or CDC and declared no COI; support from NIEHS and Passport Foundation.
Other sources of bias	Low	No other potential sources of bias identified.

Table S7: Characteristics and risk of bias ratings of Cowell et al. (2015)

Study Element	Description
Design	Prospective birth cohort
Participants	329 pregnant women who delivered singleton babies at 1 of 3 downtown New York hospitals in close proximity to the World Trade Center site between 2001-2002; 109 mother-child pairs evaluated for attention-related behavioral problems at age 4 and 107 mother-child pairs evaluated at age 6
Exposure	BDE 47, 85, 99, 100, 153, 154, 183 measured in cord blood at birth
Comparator	Children with lower levels of cord blood PBDE measurements (3-fold increase comparison; also compared lowest 80% exposure category to highest 20%)
Outcomes	Child Behavior Checklist (CBCL) administered beginning at age 3 years annually through age 7 years

Bias domain	Authors' judgment	Support for judgment
Source population representation	Probably low	Authors compare the subset of 210 participants with cord blood plasma PBDE measurements and the subsets of those with PBDE measurements and CBCL attention problem scores at age 4 (n=109) and 6 years (n=107). Authors reported two significant differences in the age of mothers and missing TONI-2 intelligence test scores.
Blinding	Low	Authors confirmed that all study investigators were blinded.
Exposure assessment	Probably low	Absence of quantitative information about standards recovery and repeatability, but information present on QA/QC.
Outcome assessment	Probably low	Valid tests - no QA QC reported.
Confounding	Probably low	Did not control for: home inventory, maternal use of alcohol during pregnancy, or maternal depression.
Incomplete outcome data	Probably high	Concerns regarding missing outcome data at each follow-up time on almost half the cohort of 210 with cord blood PBDE measurements; no argument is presented that would invalidate the possibility of a selection bias (i.e., likelihood that outcome data is missing is related both to outcome status and exposure).
Selective outcome reporting	Low	All of the study's pre-specified outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review were reported in the pre-specified way.
Conflict of interest	Low	This research was supported by the September 11th Fund of the New York Community Trust and United Way of New York City; the New York Times 9/11 Neediest Fund; the National Philanthropic Trust; National Institute of Environmental Health Sciences, and U.S. Environmental Protection Agency. The authors declare they have no actual or potential competing financial interests.
Other sources of bias	Low	No other potential sources of bias identified.

Table S8: Characteristics and risk of bias ratings of Gascon et al. (2011)

Study Element	Description
Design	Prospective birth cohort
Participants	Cord blood: 88 mother-child pairs for intelligence outcomes and 77 mother-child pairs for ADHD and attention-related behavioral outcomes, serum: 244 mother-child pairs for intelligence outcomes and 220 mother-child pairs for ADHD and attention-related behavioral outcomes from Menorca, Spain enrolled between 1997-1998
Exposure	BDE-47 measured in cord blood and in child serum at 4 years of age
Comparator	Children with lower levels of cord blood or maternal serum PBDE measurements (below the LOQ as referent)
Outcomes	McCarthy Scales of Children's Abilities (MSCA) total cognitive function score and Attention Deficit Hyperactivity Disorder (ADHD)- Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV for attention deficit and hyperactivity assessed at 4 years

Bias domain	Authors' judgment	Support for judgment
Source population representation	Probably low	Details on inclusion/exclusion criteria for this study were lacking.
Blinding	Low	Exposure was quantified by a biological measure; ADHD was assessed by the teacher so it unlikely that the teacher had knowledge of exposure.
Exposure assessment	Low	The exposures were assessed using validated methods and at the same time for all participants; either from cord blood or serum levels at age 4.
Outcome assessment	Low	Teacher reports valid teachers are recognized as being excellent observers of children's neurodevelopment QA QC presented/discussed.
Confounding	Low	Study controlled for all important confounders listed in protocol.
Incomplete outcome data	Low	Missing values were statistically imputed for a small proportion of samples (0.4%-5.2%).
Selective outcome reporting	Low	ADHD results were pre-specified and reported as described in the methodology.
Conflict of interest	Low	This study was supported by Instituto de Salud Carlos III, Red de Grupos INMA and partially supported by the Fundació La Caixa, the Instituto de Salud Carlos III, Red de Centros RCESP. The Guxens study (REF ID 3054) which describes the cohort also specifically states "Conflict of interest: None declared."
Other sources of bias	Low	No other potential sources of bias identified.

Table S9: Characteristics and risk of bias ratings of Gascon et al. (2012)

Study Element	Description
Design	Prospective birth cohort
Participants	290 mother-child pairs from Gipuzkoa, Basque Country and Sabadell Catalonia Spain between 2004-2008
Exposure	BDEs 47, 99, 100, 153, 154, 183, 209, and sum of all seven measured in breastmilk
Comparator	Children born to women with lower levels of PBDE measurements in colostrum (10-fold increase comparison)
Outcomes	Bayley Scales of Infant and Toddler Development (BSID) mental and psychomotor score assessed at 12-18 months

Bias domain	Authors' judgment	Support for judgment
Source population representation	Low	The descriptions and/or data document potential for selection effects, however, adequate support was given indicating that potential selection effects were not differential across both exposure and outcome. There were significant differences between included/ excluded children related to outcome - there were no differences related to exposure.
Blinding	Low	It is not expected that the persons performing the laboratory analysis of the PBDEs would have knowledge of the neurological testing results. The paper states specifically that "Psychologists were not aware of any exposure information."
Exposure assessment	Low	Standard validated methods with QA/QC.
Outcome assessment	Low	Children's cognitive and psychomotor development was assessed using the Bayley Scales of Infant Development (BSID). All testing was done in the health care center by one of the four specially trained psychologists in the presence of the mother. Psychologists were not aware of any exposure information. To limit interobserver variability, they applied a strict protocol, including training sessions where interobserver differences were quantified. Three sets of interobserver-reliability tests were conducted for each rater during fieldwork, and resulting intraclass correlations were 0.90 for the BSID mental scale. Cronbach's alpha coefficient, a measure of internal consistency, was 0.78 for the mental scale. Scores were standardized for child's age in days at test administration using a parametric method to estimate age-specific reference intervals.
Confounding	Probably low	The study appropriately accounted for most but not all of the important confounders (Tier I), AND this is not expected to introduce substantial bias.
Incomplete outcome data	Low	Participants were followed long enough to obtain outcome measurements and missing data were imputed using appropriate methods.
Selective outcome reporting	Low	The study's pre-specified outcome (neurodevelopment) outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review have been reported in the pre-specified way (BSID scores).
Conflict of interest	Low	This study was funded by grants from Instituto de Salud Carlos, Spanish Ministry of Health, Generalitat de Catalunya-CIRIT, Department of Health of the Basque Government, the Provincial Government of Gipuzkoa, and Fundación Roger Torné. The authors declare they have no actual or potential competing interests.
Other sources of bias	Low	No other potential sources of bias identified.

Table S10: Characteristics and risk of bias ratings of Gump et al. (2014)

Study Element	Description
Design	Cross sectional epidemiology study
Participants	43 children from Oswego County New York ages 9-11 years at time of study

Exposure	BDEs 28, 47, 99, 100 measured in child whole blood approximately 1 week before testing (~ 10 years old)
Comparator	Children with lower levels of blood PBDE measurements (across 1-unit increases)
Outcomes	Parental Strengths and Difficulties Questionnaire (SDQ) hyperactivity-inattention subscale assessed between 9-11 years

Bias domain	**Authors' judgment**	**Support for judgment**
Source population representation	Low	No data to support the assumption that the study sample did not differ, by exposure, from those not tested.
Blinding	Low	Authors confirmed that all study investigators were blinded.
Exposure assessment	Probably low	There were some low standards recovery affecting confidence in methods, but this is not expected to impact study sample differentially.
Outcome assessment	Low	Based on expert input from day-long meeting re the assessment instruments (performance tasks and parent questionnaire).
Confounding	High	Only 3 of the important confounders accounted for.
Incomplete outcome data	Low	No or only 1 missing data.
Selective outcome reporting	Low	All pre-specified outcomes reported.
Conflict of interest	Low	No COI statement, but all authors and funding from academia.
Other sources of bias	High	PBDE exposure was measured the week prior to assessing ADHD outcomes, raising concerns regarding whether the exposure truly preceded the outcome.

Table S11: Characteristics and risk of bias ratings of Eskenazi et al. (2013)

Study Element	**Description**
Design	Prospective birth cohort
Participants	231 to 256 (depending on intelligence outcome assessed) and 285-323 (depending on ADHD and attention-related behavioral outcomes assessed) mother-child pairs from Salinas Valley California enrolled in the CHAMACOS Study between 1999-2000
Exposure	BDEs 17, 28, 47, 66, 85, 99, 100, 153, 154, 183, SUM of 47, 99, 100, 153, and sum of all ten measured in maternal prenatal (at pregnancy or during delivery) and child serum samples (at 7-year visit)
Comparator	Children with lower levels of maternal prenatal or child PBDE measurements (10-fold increase comparison)
Outcomes	Wechsler Preschool and Primary Scale of Intelligence (WPPSI)-III performance Intelligence Quotient (IQ) at 60 months, Wechsler Intelligence Scale for Children (WISC)-IV full scale IQ (FSIQ) at 72 months; Child Behavior Checklist (CBCL) attention problems, CBCL Attention Deficit Hyperactivity Disorder (ADHD), Kiddie Continuous Performance Test (K-CPT) errors of commission, K-CPT errors of omission, K-CPT ADHD Confidence Index assessed at 5 years; Conners' ADHD/DSM-IV Scales (CADS) maternal report ADHD index, Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV total scale with inattentive and hyperactivity/impulsivity subscales, Behavior Assessment System for Children (BASC)-2 maternal report hyperactivity scale and attention problems scale, CADS teacher report ADHD index and DSM-IV total scale with inattentive and hyperactivity/impulsivity subscales, BASC-2 teacher report hyperactivity scale and attention problems scale assessed at 7 years

Bias domain	Authors' judgment	Support for judgment
Source population representation	Low	Despite cohort attrition they analyzed the data and show there are not important differences (i.e., parental PBDE levels, between source population and study population).
Blinding	Low	Authors confirmed that all study investigators were blinded.
Exposure assessment	Low	Samples were analyzed at CDC using validated methods. Quality control samples (blanks and spikes) were included in each run.
Outcome assessment	Low	Valid tests used and teacher report considered reliable - bilingual psychometrician did testing, and children were assessed in their dominant language. However, there is no discussion of QA/QC between psychometricians.
Confounding	Low	Analyses accounted for all Tier I important confounders.
Incomplete outcome data	Low	There is no discussion of missing outcome data; there is some but not a lot of missing data.
Selective outcome reporting	Low	All pre-specified outcomes reported.
Conflict of interest	Low	The authors declare they have no actual or potential competing financial interests.
Other sources of bias	Low	No other potential sources of bias identified.

Table S12: Characteristics and risk of bias ratings of Herbstman et al. (2010)

Study Element	Description
Design	Prospective birth cohort
Participants	152 mother-child pairs who delivered babies at 1 of 3 downtown New York hospitals in close proximity to the World Trade Center after September 11, 2001
Exposure	BDE 47, 99, 100, 153 measured in cord blood at birth
Comparator	Children with lower levels of cord blood PBDE measurements (3-fold increase comparison; also first quartile concentrations as referent)
Outcomes	Bayley Scales of Infant and Toddler Development (BSID)-II Mental Development Index (MDI), BSID-II Psychomotor Development Index (PDI), and Wechsler Preschool and Primary Scale of Intelligence, Revised Edition (WPPSI-R) full scale intelligence quotient (FSIQ). BSID measured at 12, 24, and 36 months, WPPSI-R measured at 48, 72 months

Bias domain	Authors' judgment	Support for judgment
Source population representation	Probably low	Although they compared the characteristics of the group of 152 for whom both cord blood measurements and "a neurodevelopmental test" were available, the numbers on which analyses at the different follow-up ages were conducted were less than 152 (118, 117, 114, 104, and 96 at 12, 24, 36, 48, and 72 months). No comparisons are presented of the characteristics of these subsamples compared to the full cohort of 329, the subset of 210 with cord blood measurements, of the subsample of 152.
Blinding	Low	Authors confirmed that all study investigators were blinded.
Exposure assessment	Probably low	Absence of quantitative information about standards recovery and repeatability, but information present on QA/QC.
Outcome assessment	Probably low	Valid tests - no QA QC reported.
Confounding	Probably low	Did not control for: home inventory, maternal use of alcohol during pregnancy, or maternal depression.
Incomplete outcome data	Probably high	Concerns regarding missing outcome data at each follow-up time on almost half the cohort of 210 with cord blood PBDE measurements; no argument is presented that would invalidate the possibility of a selection bias (i.e., likelihood that outcome data is missing is related both to outcome status and exposure).
Selective outcome reporting	Low	All of the study's pre-specified outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review were reported in the pre-specified way.
Conflict of interest	Low	This research was supported by the September 11th Fund of the New York Community Trust and United Way of New York City; the New York Times 9/11 Neediest Fund; the National Philanthropic Trust; National Institute of Environmental Health Sciences, and U.S. Environmental Protection Agency. The authors declare they have no actual or potential competing financial interests.
Other sources of bias	Low	No other potential sources of bias identified.

Table S13: Characteristics and risk of bias ratings of Hoffman et al. (2012)

Study Element	Description
Design	Prospective birth cohort
Participants	222 mother-child pairs in North Carolina in the Pregnancy, Infection, and Nutrition Babies Study enrolled between 2001-2005
Exposure	BDEs 28, 47, 99, 100, 153, and sum of five measured in breastmilk three months postpartum
Comparator	Children with lower levels of breast milk PBDE measurements (below the median concentrations as referent)
Outcomes	Infant-Toddler Social and Emotional Assessment (ITSEA)-activity/impulsivity and attention regulation subscales measured at 24-36 months

Bias domain	Authors' judgment	Support for judgment
Source population representation	Low	The descriptions and/or data as indicated the potential for selection effects and there was no support indicating that potential selection effects were not differential across both exposure and outcome, however, selection factors appeared to be well-understood, were measured in the data set, and appropriate adjustment post hoc techniques were used to control for selection bias.
Blinding	Low	The authors report that mothers were not aware of the levels of PBDEs in their breast milk at the time the ITSEA was completed. They also report that study staff was not aware of a child's ITSEA scores or PBDE exposures through breast milk at the time the HOME was administered. It is assumed that the lab did not have access to the neurological testing results.
Exposure assessment	Low	Breast milk samples were obtained and analyzed for PBDEs using validated methods with QA/QC.
Outcome assessment	Probably low	Mothers completed the Infant–Toddler Social and Emotional Assessment (ITSEA), of their child between 24 and 36 months of age.
Confounding	Probably low	With the exception of "exposure to other neurotoxic agents," the study accounted for all of the Tier 1 confounders or reported why a Tier 1 confounder was evaluated but omitted (i.e., HOME Inventory). It seems like a significant shortcoming that measurement of lead was not conducted.
Incomplete outcome data	Low	The following missing data were reported: missing tobacco use during pregnancy n = 2; missing breast-feeding duration n = 4; missing social-emotional competency n = 1.
Selective outcome reporting	Low	All of the study's pre-specified outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review were reported in the pre-specified way.
Conflict of interest	Low	This research was supported by grants from the U.S. Environmental Protection Agency and the National Institute of Environmental Health Sciences. The work of K.H. was supported by the NIEHS Environmental Biostatistics Training Program. The work of M.A. on this project was supported [in part] by the Intramural Research Program of the National Institutes of Health, NIEHS. The authors declare they have no actual or potential competing financial interests.
Other sources of bias	Low	No other potential sources of bias identified

Table S14: Characteristics and risk of bias ratings of Lin et al. (2010)

Study Element	Description
Design	Prospective birth cohort
Participants	Mother-infant pairs (n=35) recruited from 4 hospitals in Southern Taiwan, analyses based on 35 (exclusive or partial breast-feeding for first 6 months) enrolled between 2007-2008. Related to Chao et al. 2011 (Ding-Yan appears to be an early subset of Chao et al, presented for a conference)
Exposure	BDEs 47, 99, 100, 153, 154, 196, 197, 206, 207, 208, 209, and sum of all eleven,

	measured in breast milk
Comparator	Children with lower levels of breast milk PBDE measurements (across 1-unit increases)
Outcomes	Bayley Scales of Infant and Toddler Development (BSID)-III with cognitive and language subscales assessed at 8-13 months

Bias domain	**Authors' judgment**	**Support for judgment**
Source population representation	Probably high	As previously noted there is no evidence presented in paper as to whether there was/was not selection bias from the source population.
Blinding	Probably high	There is insufficient information about blinding to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not adequately blinded, as described by the criteria for a judgment of high risk of bias.
Exposure assessment	Low	The paper references Koh et al 2010 - the method cited was a revision of a standard method with much detail provided. QA/QC addressed.
Outcome assessment	Probably high	Outcomes were assessed and defined consistently across all study participants, using a valid and reliable measures - the Bayley Scales of Infant and Toddler Development, Third Edition but there was no QA/QC described; No sensitivity analyses were conducted to suggest the influence of outcome misclassification would be minimal; there is no discussion as to whether the Bayley scale was culturally biased for this population.
Confounding	Probably high	The study controlled only for maternal age, pre-pregnancy BMI, sex, gestational age and age for testing Bayley scores.
Incomplete outcome data	Probably low	No report of missing data; study reports total number of children with outcome/exposure measurements but no mention of any attrition over the course of study.
Selective outcome reporting	High	Missing results reported in the study; not all of the adjusted ORs are reported for the primary outcome.
Conflict of interest	Low	Funding for study came from Taiwan National Science Foundation, although authors have no declaration of whether they have other conflicts of interest.
Other sources of bias	Low	No other potential sources of bias identified.

Table S15: Characteristics and risk of bias ratings of Roze et al. (2009)

Study Element	**Description**
Design	Prospective birth cohort
Participants	62 mother-child pairs from northern providences of Netherlands enrolled between 2001-2002
Exposure	BDEs 47, 99, 100, 153, 154 measured in maternal blood during 35th week of pregnancy
Comparator	Children with lower levels of maternal blood PBDE measurements (across 1-unit increases)
Outcomes	Child Behavior Checklist (CBCL) internalizing and externalizing problems subscale and parental Attention Deficit Hyperactivity Disorder (ADHD) questionnaire with items on sustained attention and selective attention assessed at 5-6 years

Bias domain	Authors' judgment	Support for judgment
Source population representation	Low	There were 90 women in the cohort - do not know how many women were asked to participate and how many refused; of the 90 women, they were able to analyze 69 samples (due to cost limitations) and they chose the 69 randomly but did not state the method of randomization.
Blinding	Probably high	No discussion in paper to indicate that the outcome assessment was made by a study investigator that was blinded to the exposure assessment.
Exposure assessment	Low	The exposures were assessed at the same time in pregnancy for all participants using validated methods; blank samples to correct for background exposures; LOD were reported; internal and external standards were used; recovery rates were reported; QC was reported with inter-laboratory QC done by 3 labs using pooled blood sample.
Outcome assessment	Probably low	Valid test, no QA QC reported.
Confounding	Probably high	Did not account for most of the Tier 1 confounders.
Incomplete outcome data	High	Only reporting on statistically significant findings.
Selective outcome reporting	Low	All of the study's pre-specified (primary and secondary) outcomes – i.e., Motor, cognitive and behavioral, outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review have been reported in the pre-specified way.
Conflict of interest	Low	Financial support was given to the project "COMPARE" by the European commission RD. The 2008 Meijer paper with the exposure data were also funded by the EU Commission R&D - The authors declare they have no competing financial interests.
Other sources of bias	Low	No other potential sources of bias identified.

Table S16: Characteristics and risk of bias ratings of Sagiv et al. (2015)

Study Element	Description
Design	Prospective birth cohort
Participants	622 mother-child pairs from Salinas Valley California in the CHAMACOS Study of children born between 2000-2002, recruited in two waves (when mother was pregnant during 1999-2000 or during expansion efforts in 2009-2011
Exposure	BDEs 17, 28, 47, 66, 85, 99, 100, 153, 154, 183, SUM of 47, 99, 100, 153, and sum of all ten measured in maternal prenatal (at pregnancy or during delivery) and child serum samples (at 9-year visit)
Comparator	Children with lower levels of maternal prenatal or child PBDE measurements (10-fold increase comparison)
Outcomes	Neurobehavioral assessments (Conners' Continuous Performance Test (CPT)-II, Wechsler Intelligence for Children Fourth Edition (WISC-IV), Conners' Attention Deficit Hyperactivity Disorder (ADHD)/ Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Scales, Parent Versions (CADS-P), and Behavioral Assessment System for Children, 2nd Edition Parent Report (BASC-2) completed at ages 9, 10.5, and 12 years

Bias domain	Authors' judgment	Support for judgment
Source population representation	Low	Despite cohort attrition they analyzed the data and show there are not important differences(i.e., parental PBDE levels, between source population and study population).
Blinding	Low	Authors confirmed that all study investigators were blinded.
Exposure assessment	Low	Samples were analyzed at CDC using validated methods. Quality control samples (blanks and spikes) were included in each run.
Outcome assessment	Low	Valid tests used and teacher report considered reliable - bilingual psychometrician did testing, and children were assessed in their dominant language. However, there is no discussion of QA/QC between psychometricians.
Confounding	Low	Analyses accounted for all Tier I important confounders.
Incomplete outcome data	Low	There is no discussion of missing outcome data; there is some but not a lot of missing data.
Selective outcome reporting	Low	All pre-specified outcomes reported.
Conflict of interest	Low	The authors declare they have no actual or potential competing financial interests.
Other sources of bias	Low	No other potential sources of bias identified.

Table S17: Characteristics and risk of bias ratings of Shy et al. (2011)

Study Element	Description
Design	Prospective birth cohort
Participants	Randomly recruited from 4 hospitals in southern Taiwan, 36 infants included in analyses between 2007-2008. Possibly same cohort as Chao et al. or at the very least similar recruitment processes.
Exposure	BDEs 15, 28, 47, 49, 99, 100, 153, 154, 183, 196, 197, and sum of eleven measured in cord blood at birth
Comparator	Children with lower levels of cord blood PBDE measurements (below the median concentrations as referent)
Outcomes	Bayley Scales of Infant and Toddler Development (BSID)-III cognitive and language subscales assessed at 8-12 months

Bias domain	Authors' judgment	Support for judgment
Source population representation	Probably high	Progressive reduction in the numbers at each stage (160 to 95 to 80 to 54 to 36)-- the 36 on which analyses are based are not very representative of the 160 invited to participate.
Blinding	Probably high	There is insufficient information about blinding to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not adequately blinded, as described by the criteria for a judgment of high risk of bias.
Exposure assessment	Low	The exposures were assessed at the same time (at birth) all participants using validated methods; The methods are referenced in Lin et all 2011 which describe a validated method and QA/QC.
Outcome assessment	Probably high	No information presented about the training of the individuals who administered the Bayley Scales. No discussion regarding training or ongoing QA/QC (e.g., inter-examiner reliability; intra-examiner reliability over time, etc.).
Confounding	Probably high Low	The study controlled only for maternal age, pre-pregnancy BMI, and parity.
Incomplete outcome data	Low	Outcome reporting was complete for all 36 samples.
Selective outcome reporting	Low	Bayley Scales of Infant and Toddler Development results were pre-specified and reported as described in the methodology.
Conflict of interest	Low	This work was supported by grants from the National Science Council and the National Health Research Institutes in Taiwan. The authors declare that there are no conflicts of interest.
Other sources of bias	Low	No other potential sources of bias identified.

Table S18: Characteristics and risk of bias ratings of Zhang et al. (2016)

Study Element	Description
Design	Prospective birth cohort
Participants	231 mother-child pairs from Cincinnati Ohio enrolled between 2003-2006
Exposure	Ten PBDE congeners (BDE-17, -28, -47, -66, -85, -99, -100, -153, -154, -183) measured in maternal serum during week 16 of gestation
Comparator	Children with lower levels of maternal serum PBDE measurements (10-fold increase comparison)
Outcomes	Wechsler Intelligence Scale for Children-IV (WISC-IV) full scale intelligence quotient (FSIQ); Behavioral Assessment System for Children (BASC)-2 Externalizing Problems score assessed at age 8 years

Bias domain	Authors' judgment	Support for judgment
Source population representation	Low	No evidence for selection bias. Authors found no difference in exposure between those who did or did not complete full outcome assessment.
Blinding	Low	"The assessors conducted the neurobehavioral assessments without knowledge of maternal serum PBDE and PCB concentrations."
Exposure assessment	Low	No concern about differential exposure assessment. CDC is "gold standard" method; LOD reported in cited reference; QA/QC blanks reported, although not quantified in this paper.
Outcome assessment	Low	No concern about differential outcome assessment or reliability.
Confounding	Probably low	Analyses accounted for all Tier I important confounders except maternal use of alcohol during pregnancy.
Incomplete outcome data	Low	Authors state that there was no significant difference in PBDE concentrations measured during pregnancy or demographic characteristics between the subjects included in their analysis and those not included (data not shown).
Selective outcome reporting	Low	Reading skills, IQ, and externalizing problem results were pre-specified and reported as described in the methodology.
Conflict of interest	Low	Authors from universities, hospitals or CDC and declared no COI; support from NIEHS US EPA. Competing financial interest declaration revealed no activities directly related to present study.
Other sources of bias	Low	No other potential sources of bias identified.

List of excluded studies (n=1788)

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Instructions for making risk of bias determinations

Human Studies
Please answer LOW RISK, PROBABLY LOW RISK, PROBABLY HIGH RISK, HIGH RISK or NOT APPLICABLE and provide details/justification.
Note: These criteria for judging risk of bias are for human studies only since we are not evaluating animal studies in this case study. These questions have also been modified from previous applications of the Navigation Guide, with edits intended so that answering "Yes" to each question aligns with a rating of "High risk of bias", "Probably Yes" → "Probably high risk of bias", "Probably No" → "Probably low risk of bias" and "No" → "Low risk of bias."

1. Are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

EITHER:

a) The descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates were sufficiently detailed, and adequate data were supplied on the distribution of relevant study sample and population characteristics to support the assertion that risk of selection effects was minimal.

OR

b) Although the descriptions and/or data as indicated in "a" above suggested the potential for selection effects, adequate support was given indicating that potential selection effects were *not* differential across both exposure and outcome.

OR

c) Although the descriptions and/or data as indicated in "a" above suggested the potential for selection effects and there was no support indicating that potential selection effects were *not* differential across both exposure and outcome, selection factors appeared to be well-understood, were measured in the data set, and appropriate adjustment post hoc techniques were used to control for selection bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information about participant selection to permit a judgment of low risk of bias, but there is indirect evidence which suggests that

inclusion/exclusion criteria, recruitment and enrollment procedures, and participation and follow-up rates were consistent across groups as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about participant selection to permit a judgment of high risk of bias, but there is indirect evidence which suggests that inclusion/exclusion criteria, recruitment and enrollment procedures, and participation and follow-up rates were inconsistent across groups, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

a) There were indications from descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates, or data on the distribution of relevant study sample and population characteristics that risk of selection effects were substantial; and
b) There was no support to indicate that potential selection effects were *not* differential across both exposure and outcome; and
c) Adjustment post hoc techniques were not used to control for selection bias.

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that participant selection is not an element of study design capable of introducing risk of bias in the study.

2. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

Any of the following:

- No blinding, but the review authors judge that the outcome measures as well as the exposure measures are not likely to be influenced by lack of blinding (such as differential outcome assessment where the outcome is assessed using different measurement or estimation metrics across exposure groups, or differential exposure assessment where exposure is

assessed using different measurement or estimation metrics across diagnostic or outcome groups); or
- Blinding of key study personnel was ensured, and it is unlikely that the blinding could have been broken; or
- Some key study personnel were not blinded, but exposure and outcome assessment was blinded and the non-blinding of others is unlikely to introduce bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information about blinding to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was adequately blinded, as described by the criteria for a judgment of low risk of bias. For example, investigators were effectively blinded to the exposure and/or outcome groups if the exposure was measured by a separate entity and the outcome was obtained from a hospital record.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about blinding to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not adequately blinded, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

Any of the following:
- No blinding or incomplete blinding, and the outcome measures or exposure measures is likely to be influenced by lack of blinding (i.e., differential outcome or exposure assessment); or
- Blinding of key study personnel attempted, but likely that the blinding could have been broken so as to introduce bias; or
- Some key study personnel were not blinded, and the non-blinding of others was likely to introduce bias.

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that blinding is not an element of study design capable of introducing risk of bias in the study.

3. Were exposure assessment methods lacking accuracy?
Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

The reviewers judge that there is low risk of exposure misclassification, i.e.,:

- There is high confidence in the accuracy of the exposure assessment methods, such as methods that have been tested for validity and reliability in measuring the targeted exposure; or
- Less-established or less direct exposure measurements are validated against well-established or direct methods

AND if applicable, appropriate QA/QC for methods are described and are satisfactory, with at least three of the following items reported, or at least two of the following items reported plus evidence of satisfactory performance in a high quality inter-laboratory comparison:

- Limit of detection or quantification;
- standards recovery;
- measure of repeatability;
- investigation and prevention of blanks contamination.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

There is insufficient information about the exposure assessment methods to permit a judgment of low risk of bias, but there is indirect evidence which suggests that methods were robust, as described by the criteria for a judgment of low risk of bias. Studies only reporting that the QA/QC items above, if relevant, were satisfactory but not reporting all of the actual numbers may receive a judgment of “probably low risk of bias.”

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

There is insufficient information about the exposure assessment methods to permit a judgment of high risk of bias, but there is indirect evidence which suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

The reviewers judge that there is high risk of exposure misclassification and any one of the following:

- There is low confidence in the accuracy of the exposure assessment methods; or
- Less-established or less direct exposure measurements were not validated and are suspected to introduce bias that impacts the outcome assessment (example: participants are asked to report exposure status retrospectively, subject to recall bias)
- Uncertain how exposure information was obtained

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

> There is evidence that exposure assessment methods are not capable of introducing risk of bias in the study.

4. Were outcome assessment methods lacking accuracy?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

> The reviewers judge that there is low risk of outcome misclassification, i.e.:
>
> - Outcomes were assessed and defined consistently across all study participants, using valid and reliable measures; or
> - Less-established or less direct outcome measurements are validated against well-established or direct methods; or
> - Appropriate sensitivity analyses were conducted that suggest the influence of outcome misclassification would be minimal
> - AND, if applicable, appropriate QA/QC for methods is described and is satisfactory.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

> There is insufficient information about the outcome assessment methods to permit a judgment of low risk of bias, but there is indirect evidence which suggests that methods were robust, as described by the criteria for a judgment of low risk of bias. Appropriate QA/QC for methods are not described but the review authors judge that the outcome and the outcome assessment are objective and uniform across study groups.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

> There is insufficient information about the outcome assessment methods to permit a judgment of high risk of bias, but there is indirect evidence which suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

> The reviewers judge that there is high risk of outcome misclassification and any one of the following:
>
> - There is low confidence in the accuracy of the outcome assessment methods; or

- Less-established or less direct outcome measurements are not validated and are suspected to introduce bias that impacts the outcome assessment
- Uncertain how outcome information was obtained

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

> There is evidence that outcome assessment methods are not capable of introducing risk of bias in the study.

5. Was potential confounding inadequately incorporated?

List of important potential confounders, collectively generated by review authors (DA, BPL, JM) prior to the initiation of screening for studies based on expert opinion and knowledge gathered from the literature (Eskenazi et al. 2013; Watkins et al. 2013):

Tier I: Important confounders

- Home Inventory
- Maternal age
- Maternal education
- Marital status
- Maternal use of alcohol during pregnancy
- Maternal depression
- Household income/poverty (measure of socioeconomic status (SES))
- Gestational exposure to environmental tobacco smoke (active)
- Child sex
- Exposure to other neurotoxic agents (i.e., lead)

Tire II: Other potentially important confounders:

- Birth weight or gestational age
- Number of children in the home
- Father's presence in the home
- Preschool and out-of-home child care attendance
- Psychometrician, location and language of assessment

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

> The study appropriately assessed and accounted for (i.e., matched, stratified, or statistically controlled for) all important confounders (Tier I), or reported that important confounders were evaluated and omitted because inclusion did not

substantially affect the results. The determination of specific confounders may also be informed by, but not limited to, the studies included in the overall review,

AND the study appropriately assessed and accounted for (i.e., matched, stratified, or statistically controlled for) other potentially important confounders relevant (Tier II), or reported that these confounders were evaluated and omitted because inclusion did not substantially affect the results,

AND the important potential confounders were measured consistently across study groups using valid and reliable methods, or the influence of covariate measurement error was determined, through sensitivity analysis, to be minimal.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

The study appropriately accounted for most but not all of the important confounders (Tier I),

AND this is not expected to introduce substantial bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

The study evaluated some but not all of the important confounders (Tier I),

AND some but not all of the other potentially important confounders relevant (Tier II),

AND this is expected to introduce substantial bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

The study did not account for or evaluate multiple important confounders (Tier I),

AND did not account for or evaluate multiple other potentially important confounders relevant (Tier II),

OR the important potential confounders were inappropriately measured and/or inappropriately analyzed across study groups.

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that outcome assessment methods are not capable of introducing risk of bias in the study.

6. Were incomplete outcome data inadequately addressed?

Criteria for a judgment of LOW risk of bias (i.e., answer: “No”):

> Participants were followed long enough to obtain outcome measurements OR any one of the following:
>
> - No missing outcome data; or
> - Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); or
> - Attrition or missing outcome data balanced in numbers across exposure groups, with similar reasons for missing data across groups; or
> - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a relevant impact on the exposure effect estimate; or
> - For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a relevant impact on the observed effect size; or
> - Missing data have been imputed using appropriate methods

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

> There is insufficient information about incomplete outcome data to permit a judgment of low risk of bias, but there is indirect evidence which suggests incomplete outcome data was adequately addressed, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

> There is insufficient information about incomplete outcome data to permit a judgment of high risk of bias, but there is indirect evidence which suggests incomplete outcome data was not adequately addressed, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

> Participants were not followed long enough to obtain outcome measurements OR any one of the following:
>
> - Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across exposure groups; or
> - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce biologically relevant bias in intervention effect estimate; or

- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce biologically relevant bias in observed effect size; or
- Potentially inappropriate application of imputation.

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that incomplete outcome data is not capable of introducing risk of bias in the study.

7. Does the study report appear to have selective outcome reporting?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

All of the study's pre-specified (primary and secondary) outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review have been reported in the pre-specified way.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information about selective outcome reporting to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of selective reporting, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about selective outcome reporting to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of selective reporting, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

Any one of the following:

- Not all of the study's pre-specified primary outcomes (as outlined in the protocol, methods, abstract, and/or introduction) have been reported; or
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; or

- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect); or
- One or more outcomes of interest are reported incompletely

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that selective outcome reporting is not capable of introducing risk of bias in the study.

8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

The study did not receive support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples include the following:

- Funding source is limited to government, non-profit organizations, or academic grants funded by government, foundations and/or non-profit organizations;
- Chemicals or other treatment used in study were purchased from a supplier;
- Company affiliated staff are not mentioned in the acknowledgements section;
- Authors were not employees of a company with a financial interest in the outcome of the study;
- Company with a financial interest in the outcome of the study was not involved in the design, conduct, analysis, or reporting of the study and authors had complete access to the data;
- Study authors make a claim denying conflicts of interest;
- Study authors are unaffiliated with companies with financial interest, and there is no reason to believe a conflict of interest exists;
- All study authors are affiliated with a government agency (are prohibited from involvement in projects for which there is a conflict of interest or an appearance of conflict of interest).

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

> There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

> The study received support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples of support include:
>
> - Research funds;
> - Chemicals, equipment or testing provided at no cost;
> - Writing services;
> - Author/staff from study was employee or otherwise affiliated with company with financial interest;
> - Company limited author access to the data;
> - Company was involved in the design, conduct, analysis, or reporting of the study;
> - Study authors claim a conflict of interest

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

> There is evidence that conflicts of interest are not capable of introducing risk of bias in the study.

9. Did the study appear to have other problems that could put it at a risk of bias?

Criteria for a judgment of LOW risk of bias (i.e., answer: “No”):

> The study appears to be free of other sources of bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: “Probably No”):

> There is insufficient information to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of other threats to validity.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: “Probably Yes”):

There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of other threats to validity, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

There is at least one important risk of bias. For example, the study:

- Had a potential source of bias related to the specific study design used; or
- Stopped early due to some data-dependent process (including a formal-stopping rule); or
- The conduct of the study is affected by interim results (e.g. recruiting additional participants from a subgroup showing greater or lesser effect); or
- Has been claimed to have been fraudulent; or
- Had some other problem

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