

厚生労働行政推進調査事業費補助金（化学物質リスク研究事業）
OECDプロジェクトでの成果物を厚生労働行政に反映させるための研究

令和5年度分担研究報告書

行動解析を中心とした発達神経毒性評価に関する情報収集

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研究要旨

本研究は、化学物質やその混合物の安全性を評価するための国際的な合意を推進する経済協力開発機構（OECD: Organisation for Economic Co-operation and Development）の試験法ガイドライン（TG: Test Guideline）プログラム各国調整官作業グループ（WNT: Working Group of National Co-ordinators of the TGs programme）において、日本で開発された種々のTGやガイダンス文書（GD: Guidance Document）、毒性発現経路（AOP: Adverse Outcome Pathway）などの世界各国が必要とする成果物を公定化させるとともに、他国が提案するOECD大型プロジェクトに関与し、その成果物に日本の主張を反映させ、その成果を化学物質の審査及び製造等の規制に関する法律（化審法）や毒物及び劇物取締法（毒劇法）などの我が国の厚生行政に反映させることを目的とする。

今年度の分担研究として、昨年度に引き続き、実験動物（げっ歯類）を対象とした発達神経毒性評価の現状や被験物質の種類、用いられる行動解析およびガイドラインとの関連について調査を行った。現在までの文献調査により得られた、行動試験を用いた発達神経毒性に関連する学術論文の内容について、追加で文献を収集するとともに、被験物質の種類や評価内容、毒性試験ガイドラインへの準拠等を整理し、リスト化を行った。

A. 研究目的

本分担研究では、昨年度に引き続き、これまでの国内外における発達神経毒性評価の現状、特に行動解析および関連するガイドラインについて情報収集を行うとともに課題を抽出する。加えて、OECDで検討されている発達神経毒性のGDの開発に寄与することを目的とする。

B. 研究方法

発達神経毒性評価のための行動解析に関する情報収集：

昨年度に引き続き、これまでの国内外における発達神経毒性評価の現状について情報収集を行った。発達神経毒性評価の現状についての文献調査には、医学・生物学分野の学術文献検索データベースであるPubMedおよびMEDLINEを用いた。また、収集した文献については、記載されている情報の整理を行った。

<文献検索に用いたキーワード>

mice, rats, rodents, neurodevelopmental, developmental, neurotoxicity, test guideline

検索後、タイトル、雑誌情報、アブスト

ラクトを確認し、下記(1)～(3)の内容を含む文献を選択した。

- (1) げっ歯類(マウス、ラット)を用いた実験報告
- (2) 化学物質曝露による影響評価
- (3) 曝露時期、投与期間、用量等の実験条件や、解析に用いた行動試験の具体的な記載

(倫理面への配慮)

本研究は、動物を用いない調査研究である。

C. 研究結果

情報収集：

発達神経毒性評価に係る毒性情報として、昨年度までに収集した文献および新たに追加した文献について、被験物質の種類や行動解析の項目ごとに論文の整理を行った。最終的に、本分担研究に適切な文献内容を精査し、115報をリスト化した(表1)。その結果、被験物質については、農薬(26報)、医薬品(24報)、産業化学物質(65報)、その他(9報)であった。行動解析の項目については、認知機能(受動回避試験、モリス水迷路等)を用いた文献が最も多く、次いで運動および感覚機能(オープンフィールド試験、ロータロッド試験等)を用いたものが多かった。また、ガイドライン上要求されないが、社会性(超音波発声、ホームケージ、3チャンバーテスト等)の行動解析を取り入れている文献も存在し、これらの文献は主に農薬の曝露影響を評価したものであった。

ガイドラインに準拠(または参照)している文献は21報と、調査文献の約2割が該当した。一方で、その内容としては、投与時期、あるいは解析項目など、限定

的な引用が多くを占め、学術文献の動向調査として本研究で抽出したものについては、完全に準拠して行われている文献はほとんど存在しなかった。

D. 考察

これまでに調査したガイドラインにおける行動解析の検出方法を見ると、化学物質が及ぼし得る脳高次機能に対する試験の必要性は認識されているが、未だ不十分な部分があると考えられた。この点、発達神経毒性に関する解析として、OECDガイドラインにも記載されている従来の運動機能や認知機能(特に学習・記憶)に加え、社会性(超音波発声、ホームケージ、3チャンバーテスト等)の評価を行っている文献については、影響の検出にも成功しており、現行のガイドラインを補強する評価手法として、その重要性を示唆するものであると考えられた。また、ガイドラインを参考とする文献が少ないことについては、現行ガイドラインに準拠した発達神経毒性試験の実施に当たり、試験項目の多さや複雑さ、加えて試験実施のためのコストが課題になることを反映していると考えられた。

今回得られた情報のみならず、発達神経毒性に関する文献は年々増加傾向にあり、曝露時期の情報、被験物質、解析に用いる行動試験、ガイドラインへの準拠等、文献情報の整理により、引き続き情報収集を行うことが重要となる。

E. 健康危険情報

特になし

F. 結論

本研究で得られた発達神経毒性の文献

情報や、関連する OECD からの提案資料に対するコメント募集への参画による、国際貢献を通して得られた情報は、今後も、OECD プロジェクトに日本の意見や結果を反映させるために重要であり、引き続き厚生労働行政に活用できるよう調査を進めていく必要があると考えられる。

G. 研究発表

G-1. 論文発表

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G-2 学会発表

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2. 齊藤洋克. ネオニコチノイド系農薬ばく露による雄マウスの情動認知行動解析, 第 50 回日本毒性学会学術年

会 (2023.6.21, 横浜)

3. 齊藤洋克. 農薬等の化学物質ばく露によって生じる情動認知行動毒性, 第 45 回日本中毒学会総会・学術集会 (2023.7.15, さいたま)

H. 知的財産権の出願・登録状況
(予定を含む。)

H-1. 特許取得

なし

H-2. 実用新案登録

なし

H-3. その他

なし

表 1. 発達神経毒性に関する文献情報および解析に用いられた行動試験リスト

Author	Animal	Chemical	Dose/Route	Exposure	Behavioral test of offspring	Reference to U.S. Environmental Protection Agency (EPA) guidelines (OPPTS 870.6300) or OECD guidelines (TG 426)
Yang et al., 2021	Mouse(ICR)	Folic acid (FA)	drinking water	3.75 mg/L Pre-/postnatal	Open field / Three-chamber social approach and social novelty / Elevated plus-maze / Rotarod / Morris water maze	×
Zhang et al.,2021	Rat(Sprague-Dawley)	Sodium fluoride (NaF)	drinking water	25, 50, 100 mg/L Pre-/postnatal	Morris water maze	×
Li et al., 2021	Mouse(Kunming)	Simazine	p.o.	50, 200 μ g/kg Pre-/postnatal	Open field / Grip strength / Swimming	×
Biney et al., 2021	Mouse(ICR)	Monosodium glutamate (MSG)	p.o.	2, 4 g/kg Prenatal	Elevated plus-maze / Open field / Forced swim / Tail suspension / Y-maze / Morris water maze	×
Yang et al., 2021	Rat(Sprague-Dawley)	Decabromodiphenyl ether (PBDE-209)	p.o.	300 mg/ kg Prenatal	Morris water maze	×
Gilbert et al., 2021	Rat(Long-Evans)	PFHxS (Perfluoroalkyl substance perfluorohexane sulfonate) Triclosan	p.o.	50 mg/kg (PFHxS) 300 mg/kg (triclosan) Pre-/postnatal	Trace fear conditioning / Acoustic startle and prepulse inhibition	×
Su et al., 2021	Mouse(C57BL/6J)	Titanium dioxide nanoparticles (TiO ₂ -NPs)	p.o.	150 mg/kg Prenatal	Neonatal sensory and motor development / Open field / Elevated plus-maze / Y-maze	×
Zhou et al., 2021	Mouse(C57BL/6)	Nicotine	drinking water	200 μ g/ml Pre-/postnatal	Neonatal sensory and motor development / Open field	×
Roberts et al., 2021	Rat(Sprague-Dawley)	Calcium cyclamate Propylthiouracil(PTU)	drinking water(calcium cyclamate) i.p.(PTU)	250, 500, 1,000 mg/kg(Calcium cyclamate) 0.5 mg/kg(PTU)/positive control Pre-/postnatal	Functional observational battery / Locomotor activity / Auditory startle pre-pulse inhibition / Morris water maze	○
Rigobello et al., 2021	Rat(Wistar)	Paracetamol (PAR)	p.o.	35, 350 mg/kg Pre-/postnatal	Nest-seeking / Behavioural stereotypy / Three-chamber sociability / Open field / Three chamber sociability	○
Xin et al., 2021	Mouse(ICR)	NaF	drinking water	100 ppm Postnatal	Novel object recognition / T-maze	×
Kaikai et al., 2021	Mouse(Swiss)	Metam sodium (MS)	p.o.	50, 100, 150 mg/kg Pre-/postnatal	Neonatal sensory and motor development / Rotarod / Elevated plus-maze / Light-dark box transition / Splash / Tail suspension / Novel object recognition / Step-through passive avoidance	×
Htway et al., 2021	Mouse(C3H)	Sodium arsenite	drinking water	85 ppm (85 mg/L) Pre-/postnatal	Three-chamber social behavior	×
Liu et al., 2021	Rat(Sprague-Dawley)	Paraquat (PQ) Maneb (MB)	p.o.	5, 10 mg/kg (PQ) 20, 35 mg/kg (MB) Postnatal	Eight-arm radial maze / Shuttle box / Step down	×
Zhong et al., 2021	Mouse(C57BL/6)	Triphenyl Phosphate (TPHP)	p.o.	0.5, 5, 50 mg/kg Postnatal	Y-maze / Novel object recognition	○
Coullery et al., 2020	Rat(Wistar)	Glyphosate (Nphosphonomethyl-glycine)	i.p.	24, 35 mg/kg Postnatal	Neonatal sensory and motor development / Locomotor activity / Morris water maze / Contextual fear conditioning	×
Yang et al., 2020	Mouse(ICR)	Fenvalerate	p.o.	0.2, 1.0, 5.0 mg/kg Postnatal	Open field / Elevated plus-maze / Morris water maze	×
Komada et al., 2020	Mouse(ICR)	Di-2-ethylhexyl phthalate (DEHP)	p.o.	30, 100 mg/kg Postnatal	Step-through passive avoidance	×
Kimura et al., 2020	Mouse(C57BL/6J)	2,3,7,8- TeBDF 2,3,8- TrBDF 2,3,7,8- TeCDD	p.o.	9, 45 μ g/kg (2,3,7,8- TeBDF) 75.6, 378 μ g/kg (2,3,8- TrBDF) 0.6, 3.0 μ g/kg (2,3,7,8- TeCDD) Prenatal	IntelliCage / USV recording	×
Dong et al., 2020	Rat(Sprague-Dawley)	2, 2', 4, 4'-tetrabromodiphenyl ether (PBDE-47)	p.o.	0.1, 1.0, 10 mg/kg Pre-/postnatal	Open field	×

表 1. (続き)

Author	Animal	Chemical	Dose/Route	Exposure	Behavioral test of offspring	Reference to U.S. Environmental Protection Agency (EPA) guidelines (OPPTS 870.6300) or OECD guidelines (TG 426)
Carr et al., 2020	Rat(Sprague-Dawley)	Chlorpyrifos (CPF)	exposed orally	0.5, 0.75, 1.0 mg/kg Postnatal	Open field / Elevated plus-maze / Social interactions	×
Kaikai et al., 2020	Mouse(Swiss)	Metam sodium	p.o.	50, 100, 150 mg/kg Prenatal	Neonatal sensory and motor development / Open field / Tail suspension / Splash / Y-maze / Step-through passive avoidance	×
Klein et al., 2020	Rat(Wistar)	Paracetamol (PAR)	p.o.	350 mg/kg Prenatal	Nest seeking / Behavioral stereotypy / Three-chamber sociability / Open field / Elevated plus-maze / Hot plate	×
Li et al., 2019	Rat(Sprague-Dawley)	Sevoflurane	inhalation	3% (with 60% oxygen and 40% nitrogen) Postnatal	Morris water maze	×
Morris-Schaffer et al., 2019	Mouse(C57BL/6)	Diesel exhaust particles (NIST SRM 1650b)	inhalation	13 $\mu\text{g}/\text{m}^3$ Postnatal	Locomotor assay / Operant behavior apparatus and fixed interval schedule (temporal learning)	×
Zhang et al., 2018	Mouse(ICR)	PM2.5	intratracheal instillation	3.75, 7.5, 15 mg/kg Pre-/postnatal	Open field / Morris water maze / Shuttle-box	×
Chandravanshi et al., 2019	Rat	Sodium arsenite	p.o.	2, 4 mg/kg Pre-/postnatal	Neonatal sensory and motor development / Y-maze / Passive avoidance	×
Morris-Schaffer et al., 2018	Mouse(C57BL/6J)	Concentrated ambient ultrafine particles (CAPS, <100nm in aerodynamic diameter) 60% oxygen	inhalation	Postnatal	Locomotor assay / Operant behavior apparatus and fixed interval schedule (temporal learning)	×
Kimura and Tohyama, 2018	Mouse(C57BL/6J)	2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)	p.o.	0.6, 3.0 $\mu\text{g}/\text{kg}$ Prenatal	USV recording / Motor activity	×
Laugeray et al., 2017	Mouse(CBA/J)	Cypermethrin (CYP)	Intranasal	5, 20 mg/kg Pre-/postnatal	Neonatal sensory and motor development / Ultrasound vocalization / Open field / Elevated plus-maze / Three-chambered sociability / Novel cage with no sawdust / Forced swimming / Tail suspension	○
Malloul et al., 2017	Mouse(Swiss)	Paint thinner	Inhalation	300, 600 ppm	Neonatal sensory and motor development / Rotarod / Open field / Elevated plus-maze / Tail suspension / Splash / Step-through inhibitory avoidance / Puzzle box	○
Laugeray et al., 2018	Mouse(ICR)	β -N-methylamino-L-alanine (BMAA)	intranasally	50 mg/kg Pre-/postnatal	Neonatal sensory and motor development / Horizontal bars / Parallel bars / Open field / Forced swimming / Habituation/dishabituation olfactory / Social partition	○
Harry et al., 2014	Rat(Sprague-Dawley)	3,3',4,4'-tetrachloroazobenzene (TCAB)	p.o.	0.1, 1.0, 10 mg/kg Pre-/postnatal	Functional observational battery (FOB) / Locomotor activity / Startle response and pre-pulse startle inhibition (PPI) / Forelimb and hindlimb grip strength / Conditioned avoidance / Morris water maze / Delayed non-matched to position	×
Sano et al., 2016	Mouse(C57BL/6J)	Acetamiprid (ACE)	p.o.	1.0, 10.0 mg/kg Pre-/postnatal	Light-dark transition / Male sexual behavior / Male aggressive behavior / Female sexual behavior / IntelliCage (Behavioral flexibility)	×
Aung et al., 2016	Mouse(C3H)	NaAsO ₂	Drinking water	85 ppm (85 mg/L) Prenatal	IntelliCage (behavioral flexibility)	×
Kumar et al., 2016	Rat(Sprague-Dawley)	Methyl methimazole(positive control) Monocrotophos Lead acetate	drinking water p.o.	0.02% (Methyl methimazole) 0.3 mg/kg (Monocrotophos) 0.2% (Lead acetate) Pre-/postnatal	Photoactometry (motor activity) / Morris water maze / Elevated plus-maze	×
Maurice et al., 2015	Rat(Wistar)	Hexabromocyclododecane (α -HBCDD)	p.o.	22, 66 ng/kg Pre-/postnatal	Neonatal sensory and motor development / Ultrasonic vocalizations / Open field / Elevated-plus maze	○
Moser et al., 2015	Rat(Long-Evans)	Tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) Tris(2-chloro-2-ethyl)phosphate (TCEP)	p.o.	TDCIPP (15, 50, 150 mg/kg) TCEP (12, 40, 90 mg/kg) Pre-/postnatal	Neonatal sensory and motor development / Functional observational battery / Elevated zero-maze / Morris water maze	×
Laugeray et al., 2014	Mouse(C57BL/6)	Glufosinate ammonium (GLA)	Intranasal	0.2, 1 mg/kg Pre-/postnatal	Ultrasonic vocalization / Neonatal sensory and motor development / Three-chambered sociability / Social interaction / Habituation/dishabituation olfactory / Elevated plus-maze	×
Singh et al., 2015	Rat(Charles-Foster)	Venlafaxine (VEN)	p.o.	25, 40, 50 mg/kg Prenatal	Open field	×

表 1. (続き)

Author	Animal	Chemical	Dose/Route	Exposure	Behavioral test of offspring	Reference to U.S. Environmental Protection Agency (EPA) guidelines (OPPTS 870.6300) or OECD guidelines (TG 426)
Liu et al., 2014	Mouse(BALB/c)	Sodium fluoride(NaF)	drinking water	2, 5, 10 mg/L Postnatal	Locomotor activity / Novel object recognition / Morris water maze / Elevated-plus maze / Tail suspension / Forced swimming	×
Marty et al., 2013	Rat(Sprague-Dawley)	2,4-Dichlorophenoxyacetic acid (2,4-D)	feeding	100, 300, 600, 800 ppm Pre-/postnatal	Functional observational battery (FOB)	×
Zhang et al., 2013	Rat(Sprague-Dawley)	2,2',4,4',5,5'-hexa-brominated diphenyl ether (BDE-153)	i.p.	1, 5, 10 mg/kg Postnatal	Step-down passive avoidance / Step-through passive avoidance / Morris water maze / Open field	×
Cordova et al., 2012	Rat(Wistar)	Manganese chloride (MnCl ₂)	i.p.	5, 10, 20 mg/kg Postnatal	Rotarod / Open field	×
Cole et al., 2012	Mouse(PON1 knockout)	Chlorpyrifos-oxon	s.c.	0.15, 0.18, 0.25 mg/kg Postnatal	Neonatal sensory and motor development / Rotarod / Startle/pre-pulse inhibition / Open field / Countertextual and cued fear conditioning / Water radial-arm maze / Morris water maze	×
Ta et al., 2011	Mouse(C57BL/6J)	2,2',4,4'- tetrabromodiphenyl ether (BDE-47)	feeding	0.03, 0.1, 1 mg/kg Pre-/postnatal	Neonatal sensory and motor development / Ultrasonic vocalization / Social dyadic interaction / Elevated plus-maze / Rotarod / Acoustic startle and pre-pulse inhibition / Locomotor activity / Fear conditioning / Morris water maze	×
Axelstad et al., 2011	Rat(Wistar)	Mancozeb	gavage	50, 100, 150 mg/kg Pre-/postnatal	Motor activity / Radial arm maze / Startle/pre-pulse inhibition	×
Bieseimer et al., 2011	Rat(Sprague-Dawley)	Decabromodiphenyl ether (DecaBDE)	p.o.	1, 10, 100, 1,000 mg/kg Pre-/postnatal	Neonatal sensory and motor development / Motor activity / Auditory startle response / Biel water maze	○
Stump et al., 2010	Rat(Sprague-Dawley)	BPA (4,4'-isopropylidene-2-diphenol)	feeding	0.15, 1.5, 75, 750, 2250 ppm Pre-/postnatal	Neonatal sensory and motor development / Motor activity / Auditory startle response / Biel water maze	○
Karlsson et al., 2009	Rat(Wistar)	β-N-methylamino-L-alanine (BMAA)	s.c.	200, 600 mg/kg Postnatal	Multivariate concentric square field / Elevated plus-maze / Open field / Radial arm maze	×
Xi et al., 2009	Rat(Wistar)	Sodium arsenite (NaAsO ₂)	drinking water	10, 50, 100 mg/L Pre-/postnatal	Neonatal sensory and motor development / Rotarod / Step-down avoidance / Square water maze	×
Butenhoff et al., 2009	Rat(Sprague-Dawley)	Potassium perfluorooctanesulfonate (K ⁺ PFOS)	p.o.	0.1, 0.3, 1.0 mg/kg Pre-/postnatal	Functional observation battery / Acoustic startle response / Locomotor activity / Biel maze swimming	○
Berman et al., 2008	Mouse(SJL/J)	Thimerosal (sodium ethylmercury thiosalicylate)	i.m.	39.8 μg/kg (total) Postnatal	Neonatal sensory and motor development / Open field / Rotarod / Pre-pulse inhibition / Elevated plus-maze / Social preference/novelty	×
Ehman et al., 2007	Rat(Sprague-Dawley)	Dimethyl tin dichloride (DMT)	drinking water	3, 15, 74 ppm Pre-/postnatal	Runway learning / Motor activity (figure-eight chambers) / T-maze / Morris water maze	×
Faber et al., 2007	Rat(Sprague-Dawley)	Ethylbenzene	Inhalation	25, 100, 500 ppm Pre-/postnatal	Functional observational battery / Motor activity sessions / Acoustic startle / Biel water maze	○
Zhang et al., 2021	Mouse(ICR)	Bisphenol A (BPAF)	p.o.	0.34, 3.4, 34 mg/kg Pre-/postnatal	Morris water maze	×
Mshaty et al., 2020	Mouse(C57BL/6J)	PFOS	p.o.	0.1, 0.25, 1 mg/kg Postnatal	Object location / Object recognition / Visual discrimination	×
Zhang et al., 2019	Rat(Sprague-Dawley)	Bisphenol A (BPA)	i.p.	0.5, 50, 5000 μg/kg Postnatal	Y-maze	×
Alipour et al., 2019	Rat(Wistar)	Chlorpyrifos (CPF)	s.c.	1 mg/mL Postnatal	Drug challenges in radial arm maze / Sweet taste preference / Forced swim	×
Moore et al., 2019	Rat(Sprague-Dawley)	Sodium arsenate dibasic heptahydrate (AsV)	drinking water(pregnant rats) p.o.(offsprings)	2.33, 4.67, 7.00 mg/kg Pre-/postnatal	Neonatal sensory and motor development	×

表 1. (続き)

Author	Animal	Chemical	Dose/Route	Exposure	Behavioral test of offspring	Reference to U.S. Environmental Protection Agency (EPA) guidelines (OPPTS 870.6300) or OECD guidelines (TG 426)
Philippot et al., 2019	Mouse(C57BL/6)	Paraquat dichloride hydrate (1,1'-dimethyl-4,4'-bipyridinium dichloride hydrate)	p.o. (Paraquat)	0.02, 0.2 mg/kg (Paraquat)	Spontaneous behaviour in a novel home environment / Radial arm maze	×
Laporte et al., 2018	Rat(Wistar)	Gamma radiation(¹³⁷ Cs)	body irradiate (gamma radiation)	100, 300 mGy (Gamma radiation)	Neonatal reflex / Open field / Fear conditioning / Prepulse inhibition of the acoustic startle	○
Heimfarth et al., 2018	Rat(Wistar)	Chlorpyrifos (CPF)	p.o.	1.0, 2.0 mg/kg	Open field / Object recognition	×
Syed et al., 2016	Rat(Wistar)	Methylmercury (MeHg)	p.o.	Postnatal	Neonatal sensory and motor development / Open field / Rotarod	×
Slotkin et al., 2015	Rat(Sprague-Dawley)	Bifenthrin (BIF) β-cyfluthrin (CYF)	p.o.	54 mg/kg (BIF) 651 mg/kg (CYF)	Novel object recognition	×
Felice et al., 2014	Rat(Sprague-Dawley)	Nicotine Chlorpyrifos	s.c.	3 mg/kg (Nicotine) Prenatal 1 mg/kg (Chlorpyrifos) Postnatal	Social discrimination paradigm / Olfactory habituation/dishabituation	×
Jiang et al., 2014	Mouse(ICR)	Chlorpyrifos (CPF)	p.o.	6 mg/kg Prenatal	Morris water maze	×
Francis-Oliveira et al., 2013	Rat(Wistar)	NaF	drinking water	25, 50, 100 mg/L Pre-/postnatal	Sucrose preference / Novelty-suppressed feeding	○
Ferguson et al., 2012	Rat(Sprague-Dawley)	Fluoxetine (FLX)	gavage	5 mg/kg Pre-/postnatal	Novelty preference / Open field activity / Motor coordination / Barnes maze / Acoustic startle / Water maze performance	×
Curran et al., 2012	Rat(Sprague-Dawley)	Bisphenol A (BPA; 2,2-Bis(4-hydroxyphenyl)propane) EE2 (17α ethinyl estradiol)	p.o.	2.5, 25.0 μg/kg (BPA) 5.0, 10.0 μg/kg(EE2) Prenatal	Open field / Acoustic startle with pre-pulse inhibition (PPI) / Novel object recognition / Morris water maze	×
Poirier et al., 2011	Mouse(C57BL/6J)	PCB mixture (10 mg/kg each of non-coplanar PCB 105, 118, 138, 153 and 180 and a ratio of coplanar PCB 77 (5 mg/kg), 126 (25 μg/kg) and 169 (250 μg/kg))	p.o.	15 ml/kg Pre-/postnatal	Functional observational battery (FOB) / T-maze / Morris water maze / Motor activity	○
Billauer-Haimovitch et al., 2009	Rat(Sprague-Dawley)	Aluminum citrate	drinking water	30, 100, 300 mg/kg Pre-/postnatal	Morris water maze	×
Montgomery et al., 2008	Mouse(heterogeneous stock (HS/lbg))	Chlorpyrifos (CPF)	s.c.	1, 3, 5, 10, 20 mg/kg Prenatal	Footprint assessment / Rotarod / Open field / Morris water maze	×
Timofeeva et al., 2008	Mouse(C57BL/6)	Methylmercury (MeHg)	feeding	0.11mg/kg(total) Prenatal	T-maze spontaneous alteration / Figure-8 locomotor activity / Prepulse inhibition / Radial-arm maze	×
Ema et al., 2008	Rat(Sprague-Dawley)	Diazinon (DZN)	s.c.	0.5, 2 mg/kg Postnatal	Neonatal sensory and motor development / Locomotor activity / Conditioned avoidance response	○
Roegge et al., 2008	Rat(Sprague-Dawley)	Polysorbate 80 (PS80)	drinking water	0.035, 0.245, 1.864, 16.783 ml/kg Pre-/postnatal	Elevated plus-maze / Novelty-suppressed feeding / Chocolate milk anhedonia / Porsolt forced swim	×
Wu et al., 2016	Rat(Sprague-Dawley)	Diazinon (DZN)	s.c.	0.5, 2 mg/kg Prenatal	Open field / Tail suspension	×
Haijima et al., 2017	Mouse(C57BL/6J)	Hydroquinone Isotretinoin Tacrolimus	s.c.	0.01g cream/20g (hydroquinone) 0.25g gel/20g (isotretinoin) 0.01g ointment/20g postnatal	Home cage / Open field / Rotarod	×
Diana et al., 2020	Rat(Sprague-Dawley)	4-hydroxy-2',3,3',4',5'-pentachlorobiphenyl (OH-PCB 106)	p.o.	0.05, 0.5 mg/kg Pre-/postnatal	Open field / Elevated plus-maze / Social novelty	×
Xu et al., 2009	Rat(Sprague-Dawley)	Midazolam N ₂ O Isoflurane (Iso)	i.p.(midazolam) inhalation(N ₂ O, isoflurane)	9 mg/kg (midazolam) 70% nitrous oxide (N ₂ O) 0.75% isoflurane (Iso) Postnatal	Morris water maze	×
		Lead acetate	drinking water	0.2%, water Pre-/postnatal		×

表 1. (続き)

Author	Animal	Chemical	Dose/Route	Exposure	Behavioral test of offspring	Reference to U.S. Environmental Protection Agency (EPA) guidelines (OPPTS 870.6300) or OECD guidelines (TG 426)
Buratovic et al., 2018	Mouse(NMRI)	Gamma radiation (¹³⁷ Cs) Ketamine	external whole body (gamma radiation) s.c. (ketamine)	50, 100, 200 mGy (gamma radiation) 7.5 mg/kg (ketamine) Postnatal	Spontaneous behaviour / Morris water maze	×
Yoshida et al., 2008	Mouse(C57BL/6J)	Methylmercury (MeHg)	feeding	5 μg/g diet Pre-/postnatal	Open field / Passive avoidance / Morris water maze	×
Jiang et al., 2021	Mouse(C57BL/6)	Sevoflurane	inhalation	3% with 40% O ₂ Postnatal	Morris water maze	×
Lin et al., 2014	Mouse(C57BL/6)	Atrazine (ATR)	drinking water	0.03, 3, 30 mg/L Pre-/postnatal	Open field / Pole / Grip strength / Marble burying / Novel object recognition / Forced swim	×
Molina et al., 2011	Rat(Sprague-Dawley)	Manganese (II) chloride tetrahydrate, lead (II) acetate trihydrate	drinking water	4.79 mg/ml (Mn) 2.84 mg/ml (Pb) Pre-/postnatal	Elevated plus-maze	×
Fan et al., 2020	Rat(Sprague-Dawley)	Isoflurane (ISO) Streptozotocin (STZ)	inhalation (ISO) i.p. (STZ)	2% (ISO) 65 mg/kg (STZ)	Morris water maze	×
Cordova et al., 2013	Rat(Wistar)	Manganese chloride (MnCl ₂)	i.p.	5, 10, 20 mg/kg Postnatal	Rotarod / Open field	×
Umezawa et al., 2018	Mouse(NMRI)	Carbon black Printex 90 nanoparticles	inhalation	4.6, 37 mg/m ³ Prenatal	Open field	×
Xi et al., 2015	Rat(Sprague-Dawley)	Yttrium nitrate	p.o.	5, 15, 45 mg/kg Pre-/postnatal	Neonatal sensory and motor development / Locomotor activity / Morris water maze / Rotarod / Hot plate	○
Atluri et al., 2018	Rat(Sprague-Dawley)	(3β,5β,17β)-3-hydroxyandrostane-17-carbonitrile (3β-OH), ketamine (KET)	i.p.	5, 10mg/kg(3β-OH) 20, 40mg/kg(ketamine) Postnatal	Eight-arm radial arm maze	×
Ujházy et al., 2011	Rat(Wistar)	Synthetic pyridoindole derivative SMe1EC2 (2-ethoxycarbonyl-8-methoxy-2,3,4,4a,5,9b-hexahydro-1H-pyrido-[4,3b] indolinium chloride)	p.o.	5, 50, 250 mg/kg Pre-/postnatal	Neonatal sensory and motor development / Open field	○
Yahalom et al., 2011	Rat(Sprague-Dawley)	Bupivacaine	Intrathecal Injections	3.75, 7.5 mg/kg Postnatal	Hot plate / Rotarod	×
Sahoo et al., 2010	Rat(Wistar)	Mirtazapine	p.o.	3.6, 7.2 mg/kg Prenatal	Neonatal sensory and motor development / Rotarod / Open field / Elevated plus-maze / Modified water maze	×
Win-Shwe et al., 2015	Mouse(BALB/c)	Diesel exhaust (DE) DE-origin secondary organic aerosol (DE-SOA)	Whole-body exposure	Pre-/postnatal	Olfactory-based spatial learning / Odor discrimination and motor function	×
Zhao et al., 2014	Rat(Sprague-Dawley)	Methylmercury (MeHg), 2,20,4,40,5-pentabromodiphenyl ether(BDE-99)	drinking water(MeHg) p.o.(BDE-99)	2.0 μg/mL (2.0 ppm)(MeHg) 0.2 mg/kg(BDE-99) Pre-/postnatal	Neonatal sensory and motor development / Rotorod / Morris water maze	×
Peres et al., 2015	Rat(Wistar)	Manganese chloride (MnCl ₂)	i.p.	5, 10, 20 mg/kg Postnatal	Olfactory discrimination / Open field / Object recognition / Social recognition / Rotarod	×
Axelstad et al., 2008	Rat(Wistar)	6-propyl-2-thiouracil (PTU)	p.o.	0.8, 1.6 or 2.4 mg/kg Pre-/postnatal	Motor activity and habituation capability / Morris water maze / Radial arm maze	○
Shen et al., 2013	Rat(Sprague-Dawley)	Sevoflurane	inhalation	1, 2, 3, 4% Postnatal	Morris water maze	×
Xiao et al., 2020	Rat(Sprague-Dawley)	Lanthanum nitrate	p.o.	2, 20, 60 mg/kg Prenatal	Morris water maze / Hindlimb strength / Hot plate / Grip strength	○
Singh et al., 2016	Rat(Wistar)	Risperidone (RIS)	p.o.	0.8, 1.0, 2.0 mg/kg Prenatal	Open field / Elevated plus-maze	×

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Author	Animal	Chemical	Dose/Route	Exposure	Behavioral test of offspring	Reference to U.S. Environmental Protection Agency (EPA) guidelines (OPPTS 870.6300) or OECD guidelines (TG 426)
Eriksson et al., 2010	Mouse(NMRI)	Methyl mercury (MeHg) ⁶⁰ Co gamma-radiation	p.o. (MeHg) body irradiate (⁶⁰ Co gamma-radiation)	0.40, 4.0 mg/kg (MeHg) 0.2, 0.5 Gy (⁶⁰ Co gamma- radiation)	Spontaneous behaviour / Morris water maze	×
Betharia et al., 2012	Rat(Sprague-Dawley)	Lead (II) acetate trihydrate (Pb) Manganese (II) chloride tetrahydrate (Mn)	drinking water	10 µg/mL (Pb) 2 mg/mL (Mn) Pre-/postnatal	Morris water maze / Open field	×
Singh and Tripathi, 2015	Rat(Wistar)	Quetiapine	p.o.	55, 80, 100 mg/kg Pre-/postnatal	Morris water maze / Passive avoidance	×
Yu et al., 2013	Rat(Sprague-Dawley)	Propofol	i.p.	75 mg/kg Postnatal	Morris water maze	×
Oshiro et al., 2014	Rat(Long-Evans)	Ethyl alcohol	inhalation	5000, 10,000, 21,000 ppm Prenatal	Fear conditioning / Morris water maze / Delayed spatial alternation and delayed matching-to-position / Choice reaction time	×
Bushnell et al., 2015	Rat(Long-Evans)	Gasoline Gasoline-ethanol blends	inhalation	3000, 6000, 9000 ppm Prenatal	Functional observational battery (FOB) / Motor activity	×
Ait-Bail et al., 2016	Mouse(Swiss)	Paraquat	p.o.	10, 20 mg/kg Prenatal	Neonatal sensory and motor development / Rotarod / Open field / Elevated plus-maze / Novel object recognition	×
Cauli et al., 2013	Rat(Wistar)	PCB 153 (2,2',4,4',5,5'-hexachlorobiphenyl) PCB 126 (3,3',4,4',5-pentachlorobiphenyl) Methylmercury (MeHg)	oral	1 mg/kg (PCB153) 100 ng/kg (PCB126) 0.5 mg/kg (MeHg) Pre-/postnatal	Rotarod / Spontaneous locomotor and vertical motor activity	×
Elnar et al., 2012	Mouse(Swiss)	Non-dioxin-like-polychlorinated biphenyls	p.o.	1, 10, 100 ng/kg Pre-/postnatal	Neonatal sensory and motor development / Open field / Water escape pole climbing / Elevated plus-maze / Light-dark box / Morris water maze / Tail suspension	○
Hoshi and Ohtsuka, 2009	Rat(Sprague-Dawley)	Di-n-butyl phthalate (DBP)	feeding	10 µg/kg, 1.0 mg/kg Prenatal	Stereotyped behaviors	×
Johansson et al., 2008	Mouse(NMRI)	Perfluorooctane sulfonate (PFOS) Perfluorooctanoic acid (PFOA) Perfluorodecanoic acid (PFDA)	p.o.	0.75, 11.3 mg/kg (PFOS) 0.58, 8.70 mg/kg (PFOA) 0.72, 10.8 mg/kg (PFDA) Postnatal	Spontaneous behaviour / Nicotine-induced behaviour / Elevated plus-maze	×
Komada et al., 2014	Mouse(ICR)	Bisphenol A (BPA)	p.o.	20, 200 µg/kg Prenatal	Newborn activity	×
Miller-Rhodes et al., 2014	Rat(Long-Evans)	Hexabromocyclododecane (HBCD)	p.o.	3, 10, 30 mg/kg Prenatal	Functional observation battery (FOB) / Forelimb grip / Locomotor activity / Lever press training and random-ratio schedule / Go/No Go operant	×
Philippot et al., 2016	Mouse(NMRI)	Dronabinol Ibuprofen	s.c.	2, 10, 50 mg/kg (Dronabinol) 6, 30, 150 mg/kg (total)(Ibuprofen) Postnatal	Spontaneous behavior	×
Rice et al., 2007	Mouse(C57BL/6J)	Decabrominated diphenyl ether (decaBDE)	p.o.	6, 20 mg/kg Postnatal	Functional observation battery (FOB)	○