Endocrine disruptors also function as nervous disruptors and can be renamed endocrine and nervous disruptors (ENDs)

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**A R T I C L E   I N F O**

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**K e y w o r d s:**
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**A B S T R A C T**

Endocrine disruption (ED) and endocrine disruptors (EDs) emerged as scientific concepts in 1995, after numerous chemical pollutants were found to be responsible for reproductive dysfunction. The World Health Organization established in the United Nations Environment Programme a list of materials, plasticizers, pesticides, and various pollutants synthesized from petrochemistry that impact not only reproduction, but also hormonal functions, directly or indirectly. Cells communicate via either chemical or electrical signals transmitted within the endocrine or nervous systems. To investigate whether hormone disruptors may also interfere directly or indirectly with the development or functioning of the nervous system through either a neuroendocrine or a more general mechanism, we examined the scientific literature to ascertain the effects of EDs on the nervous system, specifically in the categories of neurotoxicity, cognition, and behaviour. To date, we demonstrated that all of the 177 EDs identified internationally by WHO are known to have an impact on the nervous system. Furthermore, the precise mechanisms underlying this neurodisruption have also been established. It was previously believed that EDs primarily function via the thyroid. However, this study presents substantial evidence that approximately 80% of EDs operate via other mechanisms. It thus outlines a novel concept: EDs are also neurodisruptors (NDs) and can be collectively termed endocrine and nervous disruptors (ENDs). Most of ENDs are derived from petroleum residues, and their various mechanisms of action are similar to those of “spam” in electronic communications technologies. Therefore, ENDs can be considered as an instance of spam in a biological context.

**1. Introduction**

Endocrine disruption (ED) or endocrine disruptors (EDs) emerged as scientific concepts in 1995 [Colborn [1]; Lindström et al. [2]; Ginsburg [3]] after numerous chemical pollutants were found to be responsible for reproductive dysfunction. This was first posited three decades prior [Carson [4]], EDs were reviewed more recently in a book [Seralini [5]], which advanced the understanding of the molecular bioaccumulation of identified xenobiotics, as well as their combined and long-term effects on the whole physiology of one or several generations. They have been identified in organisms at all levels of the ecosystem and are also ubiquitously found in the food chain.

The World Health Organization established in the United Nations Environment Programme [WHO [6]], a list of 176 compounds comprising materials, pesticides, and various pollutants (Table 1, columns 1–3) impacting not only reproduction, but also hormonal functions—directly or indirectly—primarily in mammals, including humans. This has enabled numerous countries to establish regulatory policies for the production and use of these chemicals or to manage contamination in food, air and water. Numerous political debates have been raised around regulatory thresholds, based on the effects of ENDs demonstrated on a population or a subpopulation of animals or humans, and published at epidemiological and molecular levels. The herbicide Roundup has been added as the 177th compound due to its widespread usage as a pesticide, combined with the relatively recent demonstration of its ED effects [Richard et al. [7]].

Epidemiology is not technically adapted to solve the questions on combined and long-term effects of molecules or mixtures on mammalian or human health [Mesnage et al. [8]]; this becomes further complicated when epigenetic and transgenerational impacts are studied [Skinner and Anway [9]]. For instance, pesticide accumulation is rarely measured in organs after death in order to ascertain whether they can be used as markers to correlate their levels with pathologies. Instead, the understanding of endocrine disruption may be aided by advances in the

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combined knowledge of biochemical, cellular, organic and environmental effects in experimental animal models, farm animals, wildlife observations in contaminated areas, and occupational medicine in factories producing the chemicals in question.

The endocrine system is not limited to the control of sexual reproduction and development. Endocrine disruptors may affect the thyroid as well as the glucocorticoid axis, adrenal and pancreatic systems, adipose tissue and immune or neuroendocrine targets [Laessig et al. [10]; Masuo and Ishido [11]; Weiss [12]; Leon-Olea et al. [13]]. They even possess cognitive effects [Schanz and Widholm [14]], particularly via various neuromediator interferences.

Cells communicate via either chemical or electrical signals that are transmitted within the endocrine or nervous systems. Generally, in endocrinology, hormones may have a biphasic action dependent on the receptors’ availability and concentration, resulting in time-, dose- and sex-dependent effects that vary according to the targeted tissue and the specific organism. It is thus reductionist to say, for instance, that a hormone such as estradiol “stimulates ovulation”, since it can inhibit this function when used at pharmacological doses as a pill or during embryonic or foetal life. Endocrine disruptors may thus possess the potential of exerting similar biphasic ambivalent effects.

Thus, to determine whether hormonal disruptors may also interfere directly or indirectly with neural development [Grandjean and Landrigan [15]] or functioning even in adults, either through a neuroendocrine or a more general mechanism, this study examined the scientific literature to ascertain the effects of ENDS on the nervous system—including neurotoxicity, cognition, and behaviour—of the major internationally identified (according to WHO) endocrine disruptors.

2. Materials and methods

Each compound was numbered (Nb, Table 1) out of 176 known endocrine disruptors [WHO [6]], plus Roundup. Its name was associated with the keyword “nervous” or “neurotoxicity” or “cognitive” or “behavior(u)r” on the PubMed data bank, and eventually on Google Scholar. When the references were too numerous, “or” was excluded in order to directly associate the keywords. If more than 20 references were found to be published, “review” was added to the keywords and cited. Finally, a maximum of five references were indicated, focusing on the most recent research in humans or mammals, without excluding other models. The mechanisms were documented (Table 1, column 4) as direct effects on the neurons or the nervous system, or as indirect effects, including thyroid regulation.

### Table 1

| Nb | Endocrine disruptor | Class or use | Mechanisms of nervous disruption |
|----|---------------------|--------------|---------------------------------|
| 1  | Acetochlor          | Herbicide    | Roman [28]: antithyroid agents  |
|    |                     |              | Helbing et al. [29]: thyroid hormone receptor gene expression in the brain |
|    |                     |              | Zafeiridou et al. [30]: compound action potential of the sciatic nerve |
|    |                     |              | Goldner et al. [31]: hypothyroidism |
|    |                     |              | Seok et al. [32]: central nervous system symptoms |
|    |                     |              | Lo et al. [33]: severe neurological and cardiovascular outcomes after acute poisoning |
|    |                     |              | Doicheva [34]: higher irritability, lack of coordination and orientation |
|    |                     |              | Sirohi et al. [35]: specific binding to lactoperoxidase |
|    |                     |              | Chihumuri et al. [36]: inhibit neuroprotection against amyloid peptides |
| 2  | Alachlor            | Herbicide    | Pan et al. [37]: reduction of thyroid-stimulating hormone receptors |
|    |                     |              | Roman [28]: hypothyroxinemia |
|    |                     |              | Brucker-Davis [38]: thyroid disruption in uterus or direct neurotoxicity |
|    |                     |              | Palanikumar et al. [39]: neurotoxicity by inhibition of acetylcholinesterase |
| 3  | Amitrole            | Herbicide    | Vieira et al. [40]: increase catalase activity and superoxide dismutase, glutathione reductase and peroxidase. |
| 4  | Anthracene          | PAH          | Mucio-Ramirez et al. [41]: decrease somatodendritic vasopressin release |
| 5  | Aroclor 1254        | PCB mixture  | Wei et al. [42]: oxidative stress in the brain |
|    |                     |              | Coburn et al. [43]: Inhibition of vasopressin release from magnocellular neuroendocrine cells |

(continued on next page)
| Nb | Endocrine disruptor | Class or use | Mechanisms of nervous disruption |
|----|---------------------|--------------|----------------------------------|
| 5  | BDE-209 PBDE         | PBDE         | Impacts the hypothalamo-pituitary-gonadal axis and induces fetal thyroid dysfunction. |
| 6  | BDE-47 PBDE          | PBDE         | Inhibits axonal growth via ryanojine receptor-dependent mechanisms. |
| 7  | Benzo(a)pyrene       | PAH          | Induces neurobehavioral function and monoamine, amino acid and choline neurotransmitter levels. |
| 8  | Benzo(a)anthracene   | PAH          | Increases the risk of childhood central nervous system tumors. |
| 9  | BB-153 PBB           | PBB          | Increases the risk of childhood central nervous system tumors. |
| 10 | Benzyldiene camphor  | UV filter    | Reduces expression of myelin associated genes like HMBP due to oligodendrocyte reduction. |
| 11 | Benzyl butyl phthalate | Phthalate     | Potentially neurotoxic. |
| 12 | Bisphenol A         | Plastics monomer | Induces oxidative stress in the brain. |
| 13 | Bisphenol A diglycid ether | Plastics monomer | Increases translocation of protein kinase C and decreases Ca2+ buffering in the brain. |
| 14 | Bisphenol F         | Plastics monomer | Increases the risk of childhood central nervous system tumors. |
| 15 | Bromacil            | Herbicide    | Selectively toxic to dopaminergic neurons in vivo, and this toxicity is synuclein-dependent. |
| 16 | Butylate            | Herbicide    | Activates the hypothalamo-pituitary-gonadal axis and induces fetal thyroid dysfunction. |

(continued on next page)
| Nb | Endocrine disruptor | Class or use | Mechanisms of nervous disruption |
|----|---------------------|--------------|---------------------------------|
| 23 | Butylated hydroxyanisole | Antioxidant for long preservation of food products | Miyazaki et al. [91]: quinone reductase inducer which significantly and dose dependently blocked methamphetamine-induced elevation of quinoprotein, and ameliorated methamphetamine-induced cell death. Katsuki et al. [92]: abolishes neurotoxic action of arachidonic acid. Raciti et al. [93]: affects epigenetics with negative consequences on the development of the nervous system. |
| 24 | Cadmium (Cd) | Heavy metal | Jacobo-Estrada et al. [94]: induces toxicity in fetus on the central nervous system. Zhang et al. [95]: induces autophagy in neurons promoting neurodegenerative disorders. Sanders et al. [96]: exposure may be associated with poorer cognition. Bo et al. [97]: neurotoxic on the long-term. Al-Rubai et al. [98]: reduces neuron size and cell migration at high doses. Reduction in glial fibrillary protein and tubulin III. |
| 25 | Carbamazepine | Pharmaceutical anti-epileptic | Hansen et al. [99]: induces encephalopathy with hyperammonemia, intrinsic effects on cerebral receptors. Qualtieri et al. [100]: affects tests of memory, psychomotor speed, cognitive flexibility, and attention. Lee et al. [101]: inhibits classically acetylcholinesterase in the nervous system; induces cognitive impairments by disturbed neurodevelopment. |
| 26 | Carbaryl | Insecticide | Freeborn et al. [102]: affects electroencephalogram by decreasing theta area and delta frequency, increases beta frequency. Wang et al. [103]: acetylcholinesterase is inhibited by high dose and damages the sciatic nerve. Cocco et al. [104]: chronic exposure to PCBs affects the development and function of the nervous system. |
| 27 | CB-15 | PCB | Lovato et al. [105]: a mixture of PCB can induce functional deficits and altered behavioral threat in zebrasfish. Ozcan et al. [106]: dioxin-like and non-dioxin-like PCB congeners are equally potent in causing cognitive decrements seen in children exposed prenatally to PCBs. Howard et al. [107]: binds the aryl hydrocarbon receptors with high affinity. Brucker-Davis et al. [108]: negative impact on neurocognitive development, negatively correlated on motor and expressive language in children. |
| 28 | CB-77 | Coplanar PCB | Doi et al. [109]: four-month-olds children with a low-level of prenatal exposure exhibits a preference for the upright biological motion, impairs the development functioning and brain development. |
| 29 | CB-118 | PCB | Cauli et al. [110]: impairs motor coordination at 2 months in males but not in female rats, reduces locomotor activity in females. Uwinana et al. [111]: does not appear to affect dopaminergic cells in cultures or levels of dopamine. To be further studied. Boix et al. [112]: exposition activates metabotropic glutamate receptors and that increases dopamine in females and reduces it in males. The opposite changes are observed for glutamate, in rat nucleus accumbens. |
| 30 | CB-126 | Planar PCB | Marrone et al. [113]: Ca2+ homeostasis and androgen receptor signaling pathways are primarily disrupted in cerebellum proteome, contributing toward a premature ageing and neurotoxicity. Naert et al. [114]: birds bioaccumulate in brain and the central nervous system. Enayah et al. [115]: neurotoxic, and affects dopamine turnover in vitro. |
| 31 | CB-132 | PCB | Cauli et al. [116]: many motor alterations and induces hyperactivity at adulthood in rats. Gascon et al. [117]: deleterious effects on neuropsychological development which are mainly attributable to prenatal exposure. |
| 32 | CB-138 | PCB | Morse et al. [118]: local hypothyroidism occurs in the brains of fetal and neonatal rats exposed by increase in type II thyroxine 5’-deiodinase in the brain. Boix et al. [119]: affects motor activity in rats; increased glutamate release in nucleus accumbens following activation of metabotropic glutamate receptors would be involved in reduced dopamine release. Naert et al. [114]: birds bioaccumulate in brain and the central nervous system. Kilburn [118]: it is suggested that it causes protracted neurotoxicity in patients. Kilburn and Thornton. [119]: exposure is associated with protracted impairment of neurophysiological and psychological functions. The central nervous system is the most important target. Grutsch et al. [120]: the characteristic signs of acute toxicity are hypothermia, hyperexcitability, tremors and convulsions. In human, signs of acute toxicity are tremors and convulsions. |
| 33 | CB-153 | PCB | Villanueva et al. [121]: Minor associations observed between exposure during gestation and child neurocognitive development. Balster et al. [122]: effect on operant behavior in mice. Liu et al. [123]: exposure could alter gene expression in the hypothalamic-pituitary-thyroid axis. Mårsussen et al. [124]: neurobehavioral effects, indicating adverse effects on the central nervous system: alteration of neurotransmitter functions, Ca2+: homeostasis processes, induction of protein kinase C and phospholipase A2 mobilization, and oxidative stress. Eriksson et al. [125]: significant decrease of preynaptic sodium-dependent choline uptake in mice. Burke et al. [126]: acute exposure of humans irreversibly inhibits acetylcholinesterase, and chronic exposure induces neurological deficits that range from cognitive impairments to tremors in childhood Yamada et al. [127]: inhibit neural induction via mitochondrial fusion protein mitofusin 1-mediated mitochondrial dysfunction in human stem cells. Sogor and et al. [128]: seems able to induce neurodevelopmental alterations in animals Lee et al. [129]: affects protein levels in the mice developing brain and induces persistent adult behavior and cognitive impairments; neurotoxic effects. Yeo et al. [129]: disability is improved. |
| 34 | CB-169 | Planar PCB | Baile et al. [130]: induces dyskinesia of the tongue. Sapers et al. [131]: selective serotonin reuptake inhibitor, alters spatial learning and memory, anxiety, depression in rats. |
| 35 | CB-180 | PCB | Hurley et al. [132]: induces thyroid follicular cell tumors in rodents; disrupts thyroid-pituitary homeostasis. (continued on next page) |
Table 1 (continued)

| Nb | Endocrine disruptor | Class or use | Mechanisms of nervous disruption |
|----|---------------------|--------------|----------------------------------|
| 42 | Coumaphos           | Pharmaceutical | Abdelsalam [139]: inhibition of brain of acetylcholinesterase, inhibition of brain neurotoxic esterase, plus delayed neurotoxicity. |
| 43 | Coumestrol          | Phytoestrogen  | About-Denia et al. [134]: degeneration of axons and myelin in the spinal cord. |
| 44 | D4 Cyclic siloxane  | Isoflavones   | Jantaratnotai et al. [135]: suppression of interferon regulatory factor-1 and phosphorylated STAT1 expression in lipopolysaccharide-activated microglia. |
| 45 | D5 Cyclic siloxane  | Mitotane      | Andreou et al. [136]: unusual constriction of the isolated sciatic nerve, death of nerve fibers. |
| 46 | D6 Cyclic siloxane  | Insecticide   | Fuzzard et al. [137]: due to silicone implants, myalgias, chronic fatigue, cognitive impairment. |
| 47 | Daidzein            | Insecticide   | Yu et al. [138]: perinatal exposure enhances estrogen receptor alpha expression in several brain regions such as stria terminalis, arcuate hypothalamic nucleus, and central amygdaloid nucleus. |
| 48 | Dibromochloropropane| Herbicide     | Roman GC [129]: inhibits thymoperoxidase that catalyzes iodination and thyroid hormone biosynthesis. |
| 49 | Desethylatrazine    | Metabolite    | Krieg [140]: decreases striatal dopamine levels and in synaptosomes in rat. |
| 50 | 2,4-D               | Herbicide agent orange | Yi et al. [141]: Increases various neurologic diseases; systemic atrophies affecting the nervous system, including spinal muscular atrophy, Alzheimer disease, and peripheral polyneuropathies. |
| 51 | 2,4-Dichlorophenol  | Chlorophenol  | Bortolozzi et al. [142]: changes in various neurotransmitter systems, such as serotonin (5-HT) and dopamine (DA), were proposed to mediate some of the behavioral effects in rats. |
| 52 | 3-Diltiazem         | Pharmaceutical | Evangelista de Duffard et al. [143]: increases sensitivity in dopamine D2-like brain receptor from 2, 4-dichlorophenoxyacetic acid (2,4-D)-exposed and amphetamine challenged rats. |
| 53 | 2,4-DDD (o,p"DDD)  | Insecticide and pharmaceutical mitotane | Krieg [144]: at low concentrations, it may act at acetylcholine and γ-aminobutyric acid synapses in the central nervous system to modify neurobehavioral test performance. |
| 54 | 2,4-DDT (o,p"DDD)  | Insecticide   | Stevens et al. [145]: Calcium channel blocker. |
| 55 | 4,4'-DDD (p,p"DDD) | Insecticide   | Heilmann et al. [146]: Some central nervous disorders were observed. |
| 56 | 4,4'-DDE (p,p"DDE) | Insecticide   | Lanser et al. [147]: Neuropsychologic and neurologic side effects. |
| 57 | 4,4'-DDT (p,p"DDE) | Insecticide   | Du Rostu et al. [148]: neurologic symptoms and neurotoxicity both central and peripheral. |
| 58 | D6(2-ethylhexyl) adipate | Plasticizer | Kaija et al. [149]: peripheral symptoms such as asthenia, muscle weakness, tremor, myalgia, and headache. |
| 59 | Dehydroepiandrosterone | Natural hormone | Li et al. [150]: provides robust ischemic neuroprotection but also exerts neurotoxicity when administered during ischemia and early reperfusion. |
| 60 | Dexethastone        | Synthetic steroid | Coplan et al. [151]: glucocorticoid-induced neurotoxicity. |

(continued on next page)
Table 1 (continued)

| Nb | Endocrine disruptor | Class or use | Mechanisms of nervous disruption |
|----|---------------------|--------------|----------------------------------|
| 61 | Dibutyl phthalate    | Phthalate    | Uno et al. [169]: induced degeneration and depletion of the hippocampal pyramidal and dentate granular neurons in the brains of primate fetuses. |
|    |                     |              | Wojtowicz et al. [158]: Aryl hydrocarbon receptor is involved in dibutyl phthalate induced apoptosis and neurotoxicity, while the estrogen receptors and peroxysome proliferator-activated receptor gamma signaling pathways are impaired by the phthalate. |
|    |                     |              | Farsangehfar et al. [179]: could reduce total distance movement, impair memory function an induce anxiety in mice. Significant nuclei size reduction and condensation in dentate gyrus cells. |
|    |                     |              | Yan et al. [171]: link between oxidative stress and anxiety-like behavior produced by dibutyl phthalate at high doses. |
|    |                     |              | Chantong et al. [172]: potentiation of oxidative stress and pro-inflammatory cytokine expression in microglia cells. |
|    |                     |              | Tsuji et al. [173]: Dibutyltin is neurotoxic and poly-L-lactides toxicity increases with the increase in tin concentration. |
| 62 | Dibutyltin           | Plastics stabilizer | Jenkins et al. [174]: developmental neurotoxicant; the incidence of apoptotic cell death, was increased in the neocortex and hippocampus. |
|    |                     |              | Kobayashi et al. [175]: synaptic parameters modulations; tributyltin metabolites inhibit various parameters of cholinergic activity with a potency ranking of tributyltin>- dibutyltin>- monobutyltin. |
|    |                     |              | Evangelista de Duffard et al. [146]: has effects on motor, sensory, or cognitive functions. |
| 63 | Dicofol              | Insecticide  | Lessenger et al. [176]: case report, neurological injury, cognitive and emotional difficulties persisted over an 18-month period. |
|    |                     |              | Cowie et al. [177]: disrupts proteins related to oxidative respiration and mitochondrial stress in the central nervous system. |
|    |                     |              | Schmidt et al. [178]: induced neurotoxicity by impaired mitochondrial bioenergetics and endoplasmic reticulum stress in rat dopaminergic cells. |
| 64 | Dieldrin             | Insecticide  | Babot et al. [179]: Long term exposure reduces gamma-aminobutyric acid type A and N-methyl–aspartate receptor function in primary culture of mouse cerebellar granule cells. |
|    |                     |              | Evangelista de Duffard et al [146]: motor sensory or cognitive function effects. |
| 65 | Diethylhexyl phthalate| Phthalate    | Park et al. [181]: sex-dependent effect on anxiety proneness in childhood. |
|    |                     |              | Quinnes et al. [182]: transgenerational modifications in the expression of several pituitary hormones involved in the hypothalamic-pituitary-adrenal axis and in stress hormones. |
| 66 | Mono-2-ethylhexyl phthalate| DEHP Hydrolysis product | Huang et al. [183]: prenatal exposure was associated with decreased cognitive development in the young children. |
|    |                     |              | Téllez-Rojo et al. [184]: prenatal exposure creates sex specific neurodevelopmental effects. |
|    |                     |              | Doherty et al. [185]: prenatal associations between urinary phthalates in aged mothers and brain performances in young children. |
| 67 | Mono-n-butyl phthalate| DBP Hydrolysis product | Mao et al. [186]: induce spatial cognitive deficits through altering the expression of apoptosis-related protein. |
|    |                     |              | Won et al. [187]: increased exposure exhibited supralinear associations with social, thought and attention problems in children. |
|    |                     |              | Tomihara et al. [188]: developmental deficits may stem from both in utero toxicity and aberrant maternal care. |
| 68 | Diethylstilbestrol  | Synthetic estrogen | Frye et al. [189]: effects on the aryl hydrocarbon receptor, the peroxisome proliferator-activated receptor and the retinoid X receptor, signal transduction pathways, and on calcium influx and/or neurotransmitter receptors. |
|    |                     |              | Sato et al. [190]: marked influence on synaptogenesis and neuronal vulnerability through mechanisms other than through estrogen receptors. |
| 69 | Diisononyl phthalate | Plasticizer  | Peng L [192]: oral exposure of mice induced brain damage, and oxidative stress, inflammation, and apoptosis. |
|    |                     |              | Bobeg et al. [193]: behavioral effects, spatial learning effects in perinatally exposed rats. |
| 70 | Diphenhydramine     | Antihistamine | Kim et al. [194]: Inhibitory effects on proton currents in microglial cells. |
|    |                     |              | Mansfield et al. [195]: reduced attention and increased self-reported drowsiness. |
| 71 | Dimethyl-benz(a)anthracene | PAH        | Wilken et al. [196]: caused significant decrements in vigilance and cognitive functioning. |
|    |                     |              | Vaswani et al. [197]: alterations of opioid neuropeptides such as beta endorphin, meth-enkephalin and dynorphin levels. |
|    |                     |              | Jang et al. [198]: induced acute neurotoxicity via induction of oxidative stress and pro-inflammatory responses. |
|    |                     |              | Ma et al. [199]: cause cognitive deficits and anxiety. |
| 72 | Endosulfan (alpha/beta) | Insecticide | Caudle WM [199]: can alter the normal development and potential function of neurotransmission in the frontal cortex. |
|    |                     |              | Silva et al. [200]: neurotoxicity and developmental effects in the zebrasfish. |
|    |                     |              | Silva et al. [201]: effects on brain biogenic amine levels Developmental reproductive toxicity or endocrine disruption occurs only at doses causing neurotoxicity. |
| 73 | Endrin              | Insecticide  | Bagchi et al. [202]: induced lipid peroxidation and DNA damage in brain and regional distribution of catalase activity in rat brain. |
|    |                     |              | Gray et al. [203]: alteration of central nervous system function in rats and hamsters even though endrin produces gross morphological defects only in hamsters. |
| 74 | Estradiol           | Natural hormone | Li et al. [204]: anxiety disorders, augmentation of vulnerability factors associated with anxiety disorder development; and facilitation of the maintenance of anxious symptoms post-development. |
|    |                     |              | Preciados et al. [48]: influences NRF1 regulated gene networks in the development of complex human brain diseases. |
| 75 | Estrone             | Natural hormone | Perez-Alvarez et al. [205]: neuroprotective role after ischemic injury. |
|    |                     |              | Rossetti et al. [206]: neurotoxic bind specific receptors to promote essential brain functions. |
| Nb | Endocrine disruptor | Class or use | Mechanisms of nervous disruption |
|----|---------------------|--------------|----------------------------------|
| 76 | Ethinylestradiol     | Synthetic hormone | Mahmoud et al. [207]: may influence adult hippocampal neurogenesis, with a focus on cognitive function and mood regulation. Grimm et al. [208]: may act upon neuronal bioenergetics in a delicate balance with an age-related effect that might be involved in mitochondrial dysfunction underlying neurodegenerative disorders. Porserdy et al. [209]: alteration in expression of genes involved in synaptogenesis and synaptic function. In female brains, produced significant effects on pathways connected to the circadian rhythm, cytoskeleton and motor proteins and synaptic proteins. In male brains effects on pathways related to cholesterol biosynthesis and synaptic proteins. |
| 77 | Ethylene thiourea  | Herbicide | Preciado et al. [48]: influences Nrf1 signaling pathways, and epigenomic multiple networks. Zaccarini et al. [210]: very low doses during development can affect key behavioral traits that are modulated by anxiety. Wang et al. [211]: induced abnormal innervation patterns in the anorectum of fetal rats |
| 78 | Ethylparaben         | Antifungal | Merola et al. [213]: provoked behavioral changes including trembling of head, pectoral fins and spinal cord of zebrafish. Lynch et al. [214]: displayed significant fear generalization in rats. Alward et al. [215]: this aromatase inhibitor reduced the motivation to sing as well as song acoustic stereotypy. |
| 79 | Fadrozole            | Pharmaceutical | Xing et al. [216]: dopamine neuron degeneration and aromatase activity inhibition could be respectively achieved in vivo with treatments with the product in female goldfish. Langlois et al. [217]: induced female- and male-biased sexual development on Silurana tropicalis brain mRNA levels, and reduced brain aromatase activity in frogs. |
| 80 | Fenbuconazole       | Fungicide | Hurley et al. [132]: disrupts thyroid hormone excretion. Gerald et al. [218]: affected the acquisition and, mainly, the retention of instrumental conditioning in rats. |
| 81 | Fenitrothion         | Organophosphate | Groszek et al. [219]: High concentration of the pesticides was found in adipose tissue and also in the brain. Respiratory failure was the syndrome; and inhibition of acetylcholinesterase activity persisted even for 30 days from poisoning. |
| 82 | Fenoxycarb           | Insecticide | Ram et al. [220]: Neurobehavioral changes in freshwater fish exposed to organophosphate insecticides. Lenkie et al. [221]: allatostatin may be one of the effectors in the brain by which the pesticides inhibits juvenile hormone biosynthesis in cockroach. Fertig et al. [222]: permanent sexual dysfunction and mood changes (fatigue, anxiety, depression and suicidal ideation) during treatment with this 5-alpha-reductase inhibitor. |
| 83 | Finasteride          | Pharmaceutical | Traish et al. [223]: Also non-sexual adverse effects such as diabetes, psychosis, depression, and cognitive function. Gangestad et al. [224]: sexual libido, ejaculatory disorders, disorders of the penis and testes, cognitive symptoms, and psychological symptoms. Godinho et al. [225]: toxic interactions with the central nervous system of mammals and lead to memory impairment by modulating the GABAergic system. Park et al. [181]: Progressive loss of nigrostriatal dopaminergic neurons induced by inflammatory responses to the pesticide. |
| 84 | Fipronil             | Insecticide | Magalhaes et al. [226]: acts on maternal aggressive behavior through GABA(A) receptors. Simon-Delso et al. [227]: disrupting neural transmission in the central nervous system of invertebrates, inhibits neuronal receptors. Mears et al. [228]: 4-Aminobutyric acid (GABA) and glycine are inhibitory neurotransmitters and their antagonist, fipronil, is excitatory. Golub et al. [229]: provoked greater dendritic spine synapse density in prefrontal cortex of monkeys. |
| 85 | Fluoxetine           | Pharmaceutical | Lenkie et al. [221]: allatostatin may be one of the effectors in the brain by which the pesticides inhibit juvenile hormone biosynthesis in cockroach. Fertig et al. [222]: permanent sexual dysfunction and mood changes (fatigue, anxiety, depression and suicidal ideation) during treatment with this 5-alpha-reductase inhibitor. |
| 86 | Flutamide            | Pharmaceutical | Ahmadiani et al. [233]: Anticonvulsant effects on seizures involvement of benzodiazepine receptors. GK Sidhu, et al. [234]: known to inhibit acetylcholinesterase activity, not only in insect, but in aquatic and terrestrial organisms leading to nervous abnormalities among others. Liu et al. [235]: Acute formaldehyde exposure induced early Alzheimer-like changes in mouse brain. Provoked the permeability of the blood-brain barrier, activation of astrocyte and microglia, oxidative stress and inflammation. |
| 87 | Fonofos              | Organo-phosphate | Zhang et al. [223]: Effects of neonatal treatment on hippocampal neurogenesis and synaptogenesis correlate with depression-like behaviors in preadolescent male rats. Ahmadiani et al. [233]: Anticonvulsant effects on seizures involvement of benzodiazepine receptors. |
| 88 | Formaldehyde         | Solvent | Zenderedel et al. [237]: Its neurotoxic effect depend on acetylcholinesterase activity; provoked cholinergic signal reduction in cases of cognitive dysfunction. Tulpule et al. [238]: contribute to the impaired cognitive performance and neurodegeneration in diseases. |
| 89 | Furan                | Solvent | Song et al. [239]: neurotoxic characteristics; neurological diseases. Johnston et al [240]: exhibits a peculiar mode of attack on the central nervous system |
| 90 | Galaxolide           | Synthetic musk | Ayuk-Takem et al. [241]: neurotoxicity may be associated with the inhibition of cellular; polysoprenylated methylated protein methyl esterase activity; significant risk to individuals predisposed to developing degenerative disorders. |
| 91 | Genistein            | Isoflavone | Li et al. [230]: Aromatase inhibitor reduced the motivation to sing as well as song acoustic stereotypy. |
| Nb | Endocrine disruptor               | Class or use                  | Mechanisms of nervous disruption                                                                                                                                                                                                 |
|----|----------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 92 | Hexabromocyclododecane           | Flame retardant               | Maurice et al. [248]: Short-term effects of a perinatal exposure in rats provoked impairments of early locomotor activity and sensory development. Al Mousa et al. [249]: inhibiting reticulum Ca(2+)ATPase in human neuroblastoma cells and induced cells death possibly causing neurological disorders. |
| 93 | Hexachlorobenzene                | Aromatic                     | Reed et al. [253]: exposure involved systemic impairment, as well as on nervous system. Li et al. [254]: can induce enhanced lipid peroxidation on rats, and the oxidative stress plays an important role in the mechanism of neurotoxicity. Goldy et al. [255]: behavioral teratogen, and suggests that human fetuses and sucking infants may be at risk because of the neurotoxic effects of the chemical. Nyfie et al. [256]: neural crest cell migration was inhibited by this toxicant disturbing a key neurodevelopmental process. |
| 94 | Heptachlor                       | Insecticide                  | Hong et al. [258]: induced nigral dopaminergic neuronal loss and Parkinsonism-like movement deficits in mice. Moser et al. [259]: perinatal exposure produced neurochemical and persistent neurobehavioral changes, including alterations in spatial learning and memory. Kirby et al. [260]: toxic effects of heptachlor epoxide may be responsible for loss of maximal dopamine uptake. |
| 95 | Heptachlor epoxide               | Organo-chlorine               | Yamaguchi et al. [261]: effects on calcium mediated transmitter release from brain synaptosomes of rats. Badawi et al. [262,263]: neurotoxic effects in the postnatal period of ontogeny in the rats. Murzakaev [264]: small doses affected central nervous activity. |
| 96 | Hexachlorobutadiene              | Solvent                      | Badaeva et al. [264]: small doses affected central nervous activity. Chen et al. [265]: synaptic plasticity and neuro-immune system may be two principal affected areas. Kimura et al. [266]: over-activation of aryl hydrocarbon receptor following perinatal dioxin exposure, perturbs neuronal migration and morphological development in mammalian cortex, supporting previous observations of impaired dendritic structure, cortical dysgenesis, and behavioral abnormalities. |
| 97 | Hexachlorodibenzodioxin          | Dioxin                       | Not specifically studied (see Methoxychlor). Mactutus et al. [267]: Neonatal exposure impairs early learning and retention of active avoidance in the rat. Evangelista de Duflard et al. [146]: effects on motor, sensory, or cognitive function; developmental neurotoxicant. |
| 98 | HPTE                             | Methoxychlor Metabolite      | Mactutus et al. [268]: neurotoxic profile of tremor. Mactutus et al. [269]: effect on the development of behavioral and/or neural function. Andrade et al. [270]: can induce dyshomeostasis, potentially triggering neurodegenerative disorders, such as Alzheimer’s disease and Parkinson’s disease. Championships, changes in heme synthesis have been associated with neurodegeneration. |
| 99 | Iodine (I)                       | Halogen; Essential element   | Roman [28]: Iodine deficiency as a cause of autism. Evangelista de Duflard et al. [146]: effects on motor, sensory, or cognitive function; developmental neurotoxicant. |
| 100| Kepone                           | Organo-chlorine               | Mactutus et al. [267]: Neonatal exposure impairs early learning and retention of active avoidance in the rat. Evangelista de Duflard et al. [146]: effects on motor, sensory, or cognitive function; developmental neurotoxicant. |
| 101| Lead                             | Heavy metal                  | Assi et al. [272]: wide spectrum of toxic effects, a real threat to the public health, including on the central nervous system Karri et al. [289]: lead to imbalance between the pro-oxidant elements and the antioxidants, and induced cognitive dysfunction. Cai et al. [273]: The central nervous system is particularly vulnerable. The brain accumulates metals. Aleknavic et al. [274]: induces a centrally-mediated sensitization of both autonomic and hypothalamic-pituitary-adrenal (HPA) axis. |
| 102| Levonorgestrel                    | Synthetic Estrogen           | Simone et al. [275]: in combination with ethinyl estradiol reduced brain-derived neurotrophic factor mRNA in the hippocampus resulting in a decline in learning and memory. Porcu et al. [276]: Long-term administration increased allopregnanolone levels and altered GABA(A) receptor subunit expression and anxiety-like behavior. Costa [277]: block the chloride channels of the GABA-A receptor. |
| 103| Lindane                          | Organo-chlorine              | Mariussen et al. [124]: has neurotoxic potentials after both acute and chronic exposure. Evangelista de Duflard et al. [146]: has effects on motor, sensory, or cognitive function modifying behavior. |
Table 1 (continued)

|   | Class or use | Mechanisms of nervous disruption |
|---|--------------|----------------------------------|
| 104 | Limuron | Herbicide | Lichtensteiger et al. [279]: in antiandrogenic mixtures impacted genes encoding for components of excitatory glutamatergic synapses and genes controlling migration and pathfinding of glutamatergic and GABAergic neurons, as well as genes linked with increased risk of autism spectrum disorders. Schinn et al. [280]: in mixture inhibited swimming activity of juvenile rainbow trout. Richendrfer & Creton [281]: cause abnormalities in behavior and brain size during development, zebrasfish larvae had significantly smaller forebrain and hindbrain regions. Salaam et al. [282]: affect proliferation, differentiation and viability of cultured neuropheres. Hashjin et al. [283]: induced chronic toxicity and anxiety-like behavior in the male adult zebrafish. Rastogi et al. [284]: In mixture provoked neurologic self-reported symptoms, headache, watering in eyes, and burning sensation in eye/face, cholinergic symptoms, such as insomnia, headache, muscle cramps, weakness, and anorexia, in children. High frequency of neurologic symptoms may be due to parasympathetic hyperactivity. Valvassori et al. [285]: affects the central nervous system by inhibiting acetylcholinesterase, leading to an increase of acetylcholine in the synaptic cleft, and subsequent activation of cholinergic muscarinic and nicotinic receptors, and impairs aversive-memory retention but not non-associative memory, without affecting anxiety-related behaviors. de Juode et al. [286]: poorer verbal learning outcomes in children, may affect their neurodevelopment. Brody et al. [287]: behavioral dysfunction, notably serotonin-mediated egg-laying behavior in Gaoenhabbitis elegans. Li et al. [288]: potentiation on KCNQ2 potassium channels might be the possible mechanism of this product toxicity in the nervous system. Domico et al. [289]: acute exposure to high doses produces equipotent toxic effects in both dopamine and GABA neurons. Kimura et al. [290]: nerve conduction velocities and postural sway seem to be sensitive indicators of the effects on the central and peripheral nervous system. Lucchini et al. [291]: essential metal that plays a fundamental role for brain development and functioning. Environmental exposure may lead to accumulation in the basal ganglia and development of Parkinson-like disorders. Peres et al. [292]: Various neurotransmitter systems may be impaired, especially dopaminergic, but also cholinergic and GABAergic. Talarle et al. [293]: epigenetic mechanism in product-induced neurotoxicity, development of Parkinson’s disease. Zhang et al. [294]: overexposure amplified the role of autophagy in the mechanisms of common neurodegenerative disorders. Wuuk et al. [158]: apoptotic action during early stages of neural development with crucial involvement of retinoid X receptors. Torres-Sanchez et al. [294]: prenatal exposure impaired early child neurodevelopment. Zhang et al. [153]: showed remarkable GR antagonistic properties, disruption of glucocorticoid-responsive genes. Martini et al. [295]: perinatal exposure has an organizational effect on hippocampus-dependent memory and emotional behaviors. Schuh et al. [296]: inhibited brain mitochondrial respiration and increased hydrogen peroxide production and CREB phosphorylation. De Souza et al. [297]: acute and chronic progressive neurologic injury: seizures, myoclonus, ataxia or cerebral oedema, defective neurotransmitter function and abnormal oxidative phosphorylation. Kim & Kang [289]: chronic toxic encephalopathy. Yang et al. [289]: Sub chronically and chronically, principal target PAHsite appears to be the central nervous system. Anger et al. [300]: produce slight neurotoxic effects in fumigation, reduced performance on all cognitive tests. Moshtizky et al. [301]: neural inhibition from the brain (drosophila) act before farnesoid acid, a precursor of the product. Prestwich et al. [302]: is secreted by the mandibular organs of crustaceans, role partially known. DeLeo et al. [303]: Effect on thyroid hormone action and stress in frog and mammalian culture systems. Ruszkiewicz et al. [790]: potential neurotoxicity. Bronioswka et al. [304]: affected the viability of nerve cells, most likely by enhancing the process of apoptosis. Li et al. [305]: reduction of neuronal and muscular development in zebrasfish embryos. Faas et al. [306]: effect on female sexual behavior and gene expression in sexually dimorphic brain regions after pre- and postnatal exposure in rats. Maerkel et al. [306]: Sex- and region-specific alterations of progesterone receptor mRNA levels and estrogen sensitivity in rat brain. Singh et al. [307]: induced neurotoxicity in developing neurons derived from human stem cells by activation of aryl hydrocarbon receptor. Puertas et al. [308]: showed a decrease in working memory in children. The deficit found in intellectual function during early childhood suggests that prenatal exposure may have a significant impact on school performance. Shankland [309]: enhanced the release of neurotransmitters. Direct evidence is available on cholinergic and glutaminergic junctions, but other kinds of junctions may be affected. Foran et al. [310]: Auditory hindbrain atrophy and anomalous calcium binding protein expression after neonatal exposure. Sadek et al. [311]: induced neurotoxicity by cholinergic dysfunction, Ibc1-2/Bax balance, and antioxidant enzymes gene transcripts in rats. Sasaki-Hamada et al. [312]: Changes in hippocampal synaptic functions and protein expression in obese mice. |
Table 1 (continued)

| Nb | Endocrine disruptor | Class or use | Mechanisms of nervous disruption |
|----|---------------------|--------------|----------------------------------|
| 117 | n-Butylbenzene | Chemical Synthesis Intermediate | Chalansonnent et al. [314]: a decrease in the concentrations of free malondialdehyde in brain structures was observed after acute administration of this product. Calculation of the changes in brain volumes and working memory, attention, and auditory processing, as well as increased impulsivity and anxiety. |
| 118 | Nicotine | Alkald | England et al. [315]: exposure during pregnancy and adolescence may contribute to cognitive and behavioral deficits in later life. Exposure during adolescence is associated with deficits in working memory, attention, and auditory processing, as well as increased impulsivity and anxiety. |
| 119 | Nonachlor | Organochlorine Insecticide | Perfluorodecane sulfonic acid [319]: key role in the development of hypertension-related cognitive impairment. Chlorinated Aromatic | Kim et al. [320]: key role in the development of hypertension-related cognitive impairment. |  |
| 120 | Nonylphenol | Formulant | Chen et al. [321]: long-term toxicity in the rat: effects on thyroid. Axelrad et al. [322]: effects on auditory and neurological development of rat offspring. | Bianco et al. [323]: greater accumulation in the cerebral cortex, more accumulation in the cerebellum compared to the mesencephalus and thalamus, with consequences to neural behaviour. |  |
| 121 | Norfluoxetine | Pharmaceutical | Lee et al. [324]: chronic exposure to low doses linked to the risk of developing cognitive impairment in elderly. Serafini et al. [325]: inhibited neuronal development and differentiation as indicated by the reduction of the neurotrophic factor GAP-43. | Couderc et al. [326]: perinatal exposure induced behavioral and neuro-developmental impairments. Pinna et al. [327]: selective brain steroidogenic stimulant, reduced post-traumatic stress disorder-like behavior in mice. |  |
| 122 | Octachlorodibenzo-p-dioxin | Dioxin | Tawara et al. [328]: fetal growth may be influenced by maternal total exposure to dioxins. | Ghisari et al. [329]: negative impact on fetal brain development, resulting in cognitive dysfunctions. Shikimi et al. [330]: promote Parkinjne dendritic growth during neonatal life, may be mediated by estrogen receptor in the Parkinjne cell. |  |
| 123 | Octachlorostyrene | Chlorinated Aromatic | Chu et al. [331]: 90-day toxicity in the rat: effects on thyroid. Chu et al. [332]: long-term toxicity in the rat: effects on thyroid. | Kim et al. [333]: role of background exposure in the development of dementia should be explored. Kim et al. [334]: greater cognitive decline with aging among elders with high serum concentrations of lipid metabolites in rat striatum. |  |
| 124 | Octyl-methoxycinnamate | UV filter | Russkiewicz et al. [335]: neurotoxic effect of active ingredients in sunscreen products. Axelrad et al. [336]: effects on auditory and neurological development of rat offspring. | Bianco et al. [337]: total serum thyroxine levels had an inverse association with the product. Jin et al. [338]: total serum thyroxine levels had an inverse association with the product. |  |
| 125 | Octylphenol | Formulant | Ghisari et al. [339]: negative impact on fetal brain development, resulting in cognitive dysfunctions. Shikimi et al. [340]: promote Parkinjne dendritic growth during neonatal life, may be mediated by estrogen receptor in the Parkinjne cell. | Ghisari et al. [341]: inhibitory effects on auditory and neurological development of rat offspring. Jin et al. [342]: total serum thyroxine levels had an inverse association with the product. |  |
| 126 | Oxychlorodane | Chloride | Kim et al. [343]: role of background exposure in the development of dementia should be explored. Kim et al. [344]: greater cognitive decline with aging among elders with high serum concentrations of lipid metabolites in rat striatum. | Jain [345]: increased risk for nasal carcinoma; selective brain steroidogenic stimulant, reduced post-traumatic stress disorder-like behavior in mice. |  |
| 127 | Parathion | Organophosphate Insecticide | Liu et al. [346]: effects on endocannabinoid and endocannabinoid-like lipid metabolites in rat striatum. Beard et al. [347]: positively associated with depression in male private pesticide applicators in the agricultural health study. | Liu et al. [348]: effects on endocannabinoid and endocannabinoid-like lipid metabolites in rat striatum. Beard et al. [349]: positively associated with depression in male private pesticide applicators in the agricultural health study. |  |
| 128 | Pentamethyldiethanol | Herbicide | Camplito et al. [350]: Biomarkers indicative of neurotoxicity and physiological stress in caged clams exposed to a contaminated water containing the product. Pan et al. [351]: persistent neuroinflammation, neurobehavioral and neuropathological cognitive impairment in mouse. | Camplito et al. [352]: increased effects on the central nervous system. Camplito et al. [353]: persistent neuroinflammation, neurobehavioral and neuropathological cognitive impairment in mouse. |  |
| 129 | Pentachloroethene | Chlorinated Aromatic | Hurley PM [354]: disrupted thyroid-pituitary homeostasis. Cheng et al. [355]: affected the timing and coordination of development in the central nervous system. | Hurley PM [356]: disrupted thyroid-pituitary homeostasis. Cheng et al. [357]: affected the timing and coordination of development in the central nervous system. |  |
| 130 | Pentachloronitrobenzene | Herbicide | Den Besten et al. [358]: severe effects on rats thyroid. | Den Besten et al. [359]: severe effects on rats thyroid. |  |
| 131 | Pentachlorobenzenes | Chlorinated Aromatic | Wierin et al. [360]: decreased levels of dopamine in the striatum, loss of dopaminergic neurons in the substantia nigra pars compacts and cognitive impairments. Motor coordination defects appeared at adult age after early life exposure. | Wierin et al. [361]: persistent neuroinflammation, neurobehavioral and neuropathological cognitive impairment in mouse. |  |
| 132 | Perchlorate | Oxidizer | Brent GA [362]: exposure in pregnancy impacted cognitive outcomes in children. Gilbert et al. [363]: developmental exposure altered synaptic transmission in hippocampus of the adult rat. | Brent GA [364]: exposure in pregnancy impacted cognitive outcomes in children. Gilbert et al. [365]: developmental exposure altered synaptic transmission in hippocampus of the adult rat. |  |
| 133 | Permethrin | Insecticide | Yang et al. [366]: significant effects on the central nervous system. Ren et al. [367]: Binding interactions with thyroid hormone transport proteins and potential toxicological implications. Oulhote et al. [368]: High serum concentrations at ages 5- and 7-years, but not prenatally, were associated with parent-reported behavioral problems at age 7. Ren et al. [369]: Binding interactions with thyroid hormone transport proteins and potential toxicological implications. | Yang et al. [360]: significant effects on the central nervous system. Ren et al. [361]: Binding interactions with thyroid hormone transport proteins and potential toxicological implications. Oulhote et al. [362]: High serum concentrations at ages 5- and 7-years, but not prenatally, were associated with parent-reported behavioral problems at age 7. Ren et al. [363]: Binding interactions with thyroid hormone transport proteins and potential toxicological implications. |  |
| 134 | Perfluorodecane sulfonic acid | Perfluoroalkyl substance | Perfluorooalkyl amines [364]: increased risk for nasal carcinoma; selective brain steroidogenic stimulant, reduced post-traumatic stress disorder-like behavior in mice. | Perfluorooalkyl amines [365]: increased risk for nasal carcinoma; selective brain steroidogenic stimulant, reduced post-traumatic stress disorder-like behavior in mice. |  |
| 135 | Perfluorohexane sulfonic acid | Perfluoroalkyl substance | Perfluorooalkyl amines [366]: increased risk for nasal carcinoma; selective brain steroidogenic stimulant, reduced post-traumatic stress disorder-like behavior in mice. | Perfluorooalkyl amines [367]: increased risk for nasal carcinoma; selective brain steroidogenic stimulant, reduced post-traumatic stress disorder-like behavior in mice. |  |
| 136 | Perfluorotoluic carbonic acid | Perfluoroalkyl substance | Perfluorooalkyl amines [368]: increased risk for nasal carcinoma; selective brain steroidogenic stimulant, reduced post-traumatic stress disorder-like behavior in mice. | Perfluorooalkyl amines [369]: increased risk for nasal carcinoma; selective brain steroidogenic stimulant, reduced post-traumatic stress disorder-like behavior in mice. |  |

(continued on next page)
| Nb | Endocrine disruptor | Class or use | Mechanisms of nervous disruption |
|----|---------------------|--------------|---------------------------------|
| 137 | Perfluorooctanoic acid | Perfluoroalkyl substance | Acute, embryonic exposure resulted in significant biochemical and behavioral changes in young adult zebrafish. Lien et al. [356]: prenatal exposure was found to associate with neurobehavioral symptoms related to attention deficit hyperactivity disorder among Asian seven-year-old children. Oulhote et al. [354]: sex-dimorphic associations between concentrations and strengths and difficulties. Jantzen et al. [355]: embryonic exposure resulted in significant biochemical and behavioral changes in young adult zebrafish. Oulhote et al. [354]: significant associations were found in regard to hyperactivity, peer relationship, and conduct problems, as well as internalizing and externalizing problems and autism. Ge et al. [357]: could significantly reduce the cell viability and mediate cell apoptosis in HAPI microglia cells of rat. |
| 138 | Perfluorooctane sulfonate | Perfluoroalkyl substance | Jantzen et al. [355]: embryonic exposure resulted in significant biochemical and behavioral changes in young adult zebrafish. Oulhote et al. [354]: significant associations were found in regard to hyperactivity, peer relationship, and conduct problems, as well as internalizing and externalizing problems and autism. |
| 139 | Perfluoroctanesulfon fluoride | Perfluoroalkyl substance | Starks et al. [358]: associated with better verbal learning and memory. |
| 140 | Phorate | Insecticide | Vandana et al. [359]: obvious effect on cholinesterase enzyme profile of olfactory bulb of mice after systemic administration of low doses for long terms. |
| 141 | Picrotoxin | Herbicide | Reddy et al. [360]: decreased neuronal branching and degenerating neurons, probably through a mitochondrial pathway. |
| 142 | Polyvinylchloride | Polymer; PVC | Podoli et al. [362]: acute intoxication resulted in vertigo, nausea and headache up to a narcotic effect. In patients with chronic occupational exposure, neurological disturbances included memory-motor polynuropathy, trigeminal sensory neuropathy, slight pyramidal signs and cerebellar and extrapyramidal motor disorders. Psychiatric disturbances present as neuroaesthetic or depressive syndromes. Sleep disorders and disorders of sexual functions are frequently encountered. |
| 143 | 8-Prenylnaringenin | Prenylflavonoid | Bagatin et al. [364]: panolistic effects in rats with generalized anxiety and panic disorders. Oberbauer et al. [365]: promote neuronal differentiation and neurite outgrowth and are neuroprotective. |
| 144 | Prochloraz | Fungicide | Ghisari et al. [363]: inhibitory effect on rat pituitary cell growth increasing the risk or a negative impact on fetal brain development, resulting in cognitive dysfunctions. |
| 145 | Procyomide | Fungicide | Xiang et al. [367]: potential to disrupt thyroid homeostasis, agonistic effects. |
| 146 | Prodiamine | Herbicide | Radio et al [368]: selectively increased neurite outgrowth. Gilbert et al. [369]: an impaired capacity for hippocampal neurogenesis may contribute to impairments in synaptic plasticity and cognitive deficits. |
| 147 | Propylthiouracil | Thyroid inhibitor | Kirvina et al. [366]: agonizes the aryl hydrocarbon receptor and inhibits aromatase activity. |
| 148 | Pyrene | Polycyclic Aromatic Hydrocarbon | Chen et al. [371]: behavioral impairments resulting from postnatal BaP exposure are potentially long-lasting in rats. Wormald et al. [374]: neurobehavioral deficits; gestational exposure to BaP and dioxin reduced specific indices of learning and memory, including hippocampal-based synaptic plasticity mechanisms. Takeda et al. [375]: the fetal exposure of mice to diesel exhaust affected the emotional behaviors associated with the serotonergic and dopaminergic systems in the brain. |
| 149 | Pyrimethanil | Fungicide | Hurley PM [132]: disrupt thyroid-pituitary homeostasis only. |
| 150 | Pyreproxyfen | Juvenile hormone analog | Fourrier et al. [377]: changes in social integration, acceptance by nestmates and social behaviors performance in bees. |
| 151 | Resorcinol | Disinfectant, Chemical intermediate | Motonaga et al. [370]: inhibit thyroid peroxidase to cause developmental toxicity and neurotoxicity. Roman [28]: transient maternal hypothyroxinemia resulting from dietary and/or environmental exposure to this antithyroid agent. |
| 152 | Roundup | Main herbicide worldwide | Defarge et al. [378]: its formulations decrease aromatase activity below toxic levels. Gress et al. [379]: the product altered locomotor activity in rats. Mosdeto et al. [380]: it inhibits acetylcholinesterase in fish brain. Lee et al. [381]: the product is used for trauma-focused psychotherapies. |
| 153 | Sertraline | Psychotropic | Frölich et al. [382]: selective serotonin reuptake inhibitor, which has demonstrated efficacy on neuropsychiatric behavioral symptoms in general. Liu et al. [123]: exposure could alter gene expression in the hypothalamic-pituitary-thyroid axis and thyroid hormone levels. Wyatt et al. [383]: potent peroxisome proliferators; high dose shows a depressed plasma thyroxine level, with increase in thyroid stimulating hormone. |
| 154 | Short chain chlorinated paraffins | Flame retardant; plasticizer | (continued on next page)
| Nb  | Endocrine disruptor                      | Class or use        | Mechanisms of nervous disruption                                                                                                                                                                                                 |
|-----|-----------------------------------------|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 156 | Tamoxifen                               | Pharmaceutical      | Gunderson and Daroff [384]: epilepsy and later on all effects of brain injury and post-traumatic stress disorders.                                                                                                                  |
|     |                                         |                     | St Omer et al. [385]: together with 2.4D, increased significantly the concentration of norepinephrine in whole developing brain and increased dopamine.                                                                                         |
| 157 | Tetrabromo-bisphenol A                  | Flame retardant     | Yi et al. [184]: increased the prevalence of endocrine disorders, especially in the thyroid and pituitary gland, and increased various neurologic diseases.                                                                              |
|     |                                         |                     | Denk et al. [386]: granular neurons of the olfactory bulb and dentate gyrus, vascular cells and ependymal cells throughout the brain, and peripheral sensory neurons are modified by this treatment.                                         |
|     |                                         |                     | Boele et al. [387]: Cognitive domains that rely on verbal abilities (verbal memory and fluency) seem to be at risk for deterioration after treatment.                                                                                |
|     |                                         |                     | Park et al. [388]: induced the loss of both zebrafish neurontms and hair cells in the rat cochlea in a dose-dependent manner.                                                                                                         |
|     |                                         |                     | Chen et al. [389]: induced apoptotic cell death, delayed cranial motor neuron development, inhibited primary motor neuron development and loosened muscle fiber during the early development in zebra fish.                  |
|     |                                         |                     | Jarema et al. [390]: may have developmental or pharmacological effects on the vertebrate nervous system.                                                                                                                       |
|     |                                         |                     | Wojtowicz et al. [391]: decreased the expression of PPAR-γ protein in neocortical neurons; and the mechanism of action also induced apoptotic and neurotoxic effects.                                    |
|     |                                         |                     | Holmes et al. [392]: testosterone increased the expression of COX2 and apoptosis in dopamine neurons, increased incidence of Parkinson’s disease in men compared with women.                                         |
|     |                                         |                     | Cunningham et al. [393]: reduces thyroid hormone levels by different mechanisms.                                                                                                                                               |
| 158 | Testosterone                            | Natural hormone     | Chen et al. [396]: inhibition of UDP-glucuronosyltransferases.                                                                                                                                                                 |
| 159 | Tetrachloro-dibenzo-p-dioxin            | Chlorinated dioxin  | Dos Reis-Lunardelli et al. [399]: can alter animal behavior and learning and memory in rats.                                                                                                                                 |
| 160 | Tetrachloro-dibenzo-furan               | Chlorinated dioxin  | Zamoner et al. [400]: reorganizes the cytoskeleton of glial cells through GluP phosphorylation and RhoA-dependent mechanisms.                                                                                                    |
|     |                                         |                     | Pelcova et al. [395]: neurological and neurophysiological findings in workers with chronic intoxication 50 years after exposure.                                                                                                        |
| 161 | PCB methyl sulfones                     | PCB metabolite      | Xu et al. [394]: this dioxin-like compound suppresses acetylcholinesterase activity via transcriptional downregulations in vitro.                                                                                                  |
|     |                                         |                     | Pelclova et al. [396]: PCB methyl sulfones together with 2.4D, increased significantly the concentration of norepinephrine in whole developing brain and increased dopamine.                                             |
| 162 | Tetraiodothyronine                      | Natural hormone     | X. Su et al. [401]: congeners products showed a strong inhibitory effect on the otic system development.                                                                                                                         |
| 163 | Thiazoylpyridine                        | Herbicide           | Dolfi et al. [402]: increased the prevalence of endocrine disorders, especially in the thyroid and pituitary gland, and increased various neurologic diseases.                                                                     |
| 164 | Toxaphene                               | Organo-chlorine     | Xu et al. [390]: this dioxin-like compound suppresses acetylcholinesterase activity via transcriptional downregulations in vitro.                                                                                                   |
|     |                                         |                     | Sanchez-Martín et al. [390]: aryl hydrocarbon receptor-dependent induction of apoptosis by the product in cerebellar granule cells from mouse.                                                                                 |
|     |                                         |                     | Chen et al. [396]: inhibition of UDP-glucuronosyltransferases.                                                                                                                                                                 |
| 165 | 2,4,6-Tribromophenol                    | BFR, Natural product| Kato et al. [397]: reduction of thyroid hormone levels by different mechanisms.                                                                                                                                               |
|     |                                         |                     | Chen et al. [396]: inhibition of UDP-glucuronosyltransferases.                                                                                                                                                                 |
| 166 | Trenbolone                              | Anabolic steroid    | Dong et al. [403]: differential effects on the expression of thyroid hormone system.                                                                                                                                              |
|     |                                         |                     | Quin et al. [404]: disrupted development of either the central nervous system or the hypothalamic-pituitary-gonadal axis.                                                                                                         |
|     |                                         |                     | Ishihara et al. [405]: induces oxidative neuronal injury.                                                                                                                                                                        |
|     |                                         |                     | Frye et al. [406]: effects through the aryl hydrocarbon receptor, the peroxisome proliferator-activated receptor and the retinoid X receptor, signal transduction pathways, calcium influx and/or neurotransmitter receptor. |
|     |                                         |                     | Leong et al. [407]: disrupts thyroid-pituitary homeostasis only.                                                                                                      |
|     |                                         |                     | Calcio et al. [408]: modifies chronically female amphipod Gammarus behavior.                                                                                                                                             |
|     |                                         |                     | Nishihara et al. [409]: developmental neurotoxicity and immunotoxicity in rats.                                                                                                                                              |
|     |                                         |                     | Frye et al. [408]: effects through the aryl hydrocarbon receptor, the peroxisome proliferator-activated receptor and the retinoid X receptor, signal transduction pathways, calcium influx and/or neurotransmitter receptor. |
| 167 | Tributyltin                              | Fungicide           | Kotalke [410]: neurotoxic, induces behavioral abnormalities and toxic to the developing central nervous system through AMPA receptor subunit.                                                                                |
|     |                                         |                     | Yeung [411]: neurotoxicity inducing anxiety in man.                                                                                                                                                                             |
|     |                                         |                     | Da Broi et al. [412]: produces pleasant inebriating effects with rapid dissipation, followed by central nervous system depression, coma.                                                                                          |
|     |                                         |                     | Kang et al. [413]: provokes chronic central nervous system disorders and peripheral neuropathy.                                                                                                                               |
| 168 | Trichloroethylene                       | Chlorinated solvent | Chiu WA et al. [414]: carcinogenic to humans by all routes of exposure and toxic to the central nervous system.                                                                                                                   |
|     |                                         |                     | Bale et al. [415]: interacts directly with several different classes of neuronal receptors by generally inhibiting excitatory ion channels/channels and potentiating the function of inhibitory receptors/channels.        |
| 169 | Trichlorophenol                         | Fungicide           | X. Su et al. [416]: increased the prevalence of endocrine disorders, especially in the thyroid and pituitary gland, and increased various neurologic diseases.                                                                     |
|     |                                         |                     | Dong et al. [417]: altered expression of proteins involved in nervous system development.                                                                                                                                      |
| 170 | Triclocarban                            | Antibacterial agent  | Barros et al. [418]: modified chronically female amphipod Gammarus behavior.                                                                                                                                                  |
| 171 | Triclosan                               | Antibacterial agent  | Wu et al. [419]: inhibited iodide uptake, but had differential effects on the expression of thyroid hormone synthesis-related genes and the activity of thyroid peroxidase.                                                                   |
| 172 | Triiodothyronine                        | Natural thyroid hormone | Kato et al. [410]: aryl hydrocarbon receptor-dependent induction of apoptosis by the product in cerebellar granule cells from mouse.                                                                                             |
|     |                                         |                     | Chen et al. [396]: inhibition of UDP-glucuronosyltransferases.                                                                                                                                                                 |
|     |                                         |                     | Dolfi et al. [402]: increased the prevalence of endocrine disorders, especially in the thyroid and pituitary gland, and increased various neurologic diseases.                                                                     |
|     |                                         |                     | Kato et al. [410]: aryl hydrocarbon receptor-dependent induction of apoptosis by the product in cerebellar granule cells from mouse.                                                                                             |
Each chemical compound or pollutant has been numbered (Nb) out of 177 known endocrine disruptors; its name was associated with the key word “nervous” or “neurotoxicity” or “cognitive” or “behavioral” or “immunological” or “cardiovascular” or “endocrine” or “developmental” or “behavio(u)r” or “weight” or “learning” or “memory” or “behavior” on PubMed data bank, or eventually on Google Scholar. When the number of references per compound were too numerous, “or” was excluded in order to directly associate the keywords. If more than 20 references were found to be published, “review” was added to the keywords and cited as a reference. Finally, a maximum of five references were indicated, focusing on the most recent research in humans or mammals, without excluding other models. The mechanisms of nervous disruption could be direct, on the neurons or the nervous system, or indirect, through endocrine disruption interfering with neurodevelopment or nervous system functioning, including thyroid regulation. PAH, polycyclic aromatic hydrocarbon; PCB, polychlorobiphenyl; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PFAS, perfluoroalkyl substances.

### Declaration of Competing Interest

The authors Seralini & Jungers declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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