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Review article

Expanding the test set: Chemicals with potential to disrupt mammalian brain development

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ABSTRACT

High-throughput test methods including molecular, cellular, and alternative species-based assays that examine critical events of normal brain development are being developed for detection of developmental neurotoxicants. As new assays are developed, a "training set" of chemicals is used to evaluate the relevance of individual assays for specific endpoints. Different training sets are necessary for each assay that would comprise a developmental neurotoxicity test battery. In contrast, evaluation of the predictive ability of a comprehensive test battery requires a set of chemicals that have been shown to alter brain development after in vivo exposure ("test set"). Because only a small number of substances have been well documented to alter human neurodevelopment, we have proposed an expanded test set that includes chemicals demonstrated to adversely affect neurodevelopment in animals. To compile a list of potential developmental neurotoxicants, a literature review of compounds that have been examined for effects on the developing nervous system was conducted. The search was limited to mammalian studies published in the peer-reviewed literature and regulatory studies submitted to the U.S. EPA. The definition of developmental neurotoxicity encompassed changes in behavior, brain morphology, and neurochemistry after gestational or lactational exposure. Reports that indicated developmental neurotoxicity was observed only at doses that resulted in significant maternal toxicity or were lethal to the fetus or offspring were not considered. As a basic indication of reproducibility, we only included a chemical if data on its developmental neurotoxicity were available from more than one laboratory (defined as studies originating from laboratories with a different senior investigator). Evidence from human studies was included when available. Approximately 100 developmental neurotoxicity test set chemicals were identified, with 22% having evidence in humans.

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1. Introduction

Traditional toxicity testing requires collecting data on one chemical at a time using common laboratory species (e.g., rats, rabbits, mice). With tens of thousands of chemicals now in commerce with limited toxicology data, higher throughput methods need to be employed to enable the rapid collection of data on these chemicals (NRC, 2007). These high-throughput designs include in silico modeling, in vitro assays, and the use of small model organisms as alternative species for toxicity testing. A number of efforts, including the United States Environmental Protection Agency's (U.S. EPA) ToxCast™ program (www.epa.gov/ncct/toxcast/) and the joint U.S. EPA/NIH/FDA Tox21 initiative (ncats.nih.gov/tox21.html), are employing hundreds of high-throughput assays that investigate molecular targets and key events related to pathways that can potentially lead to adverse health effects, including reproductive and developmental toxicity (Tice et al., 2013). To date, there is limited use of high-throughput assays for endpoints relevant to developmental neurotoxicity (Bal-Price et al., 2015a).

Traditional animal testing to determine if a chemical has the potential to cause adverse effects in the developing nervous system is time and resource intensive. Studies based on U.S. EPA or the Organization for Economic Co-operation and Development (OECD) guidelines can take months to years to complete, cost hundreds of thousands of dollars, and use hundreds of laboratory animals. In light of the concern regarding the potential of environmental chemicals to contribute to neurodevelopmental disorders in children (Grandjean and Landrigan, 2006, 2014; Braun et al., 2006; Hertz-Picciotto et al., 2006; Karr, 2012), there are ongoing efforts to develop medium- and high-throughput assays to facilitate the detection of chemicals that are likely to affect brain development (Coecke et al., 2007; Bal-Price et al., 2012). The methods being developed probe multiple levels of biological organization including molecular, cellular, and alternative species (Lein et al., 2007). Due to the complexity of the events regulating brain development, along with the known and unknown modes of action of neurotoxic chemicals (Bal-Price et al., 2015b), it is unlikely that any individual assay will be sufficient to detect all chemicals with the potential to disrupt neurodevelopment. Thus, a battery of assays covering multiple molecular targets, intracellular signaling pathways, critical cellular events, and integrated neural functions is needed (Lein et al., 2007; Radio and Mundy, 2008; de Groot et al., 2013). Several references have provided general principles for developing and evaluating models and assays to screen and prioritize chemicals that affect neurodevelopment (Crofton et al., 2011, 2012; Kadereit et al., 2012). An important step in the development and evaluation of alternative methods is the use of "training set" and "test set" chemicals (as defined by consensus at the international TestSmart DNT II meeting (http://caat.jhsph.edu/programs/workshops/dnt2.html; Crofton et al., 2011). Note that this terminology should not be confused with training set data and test set data used to build and validate QSAR models. In the context of alternative methods development, the "training set" refers to chemicals that have been previously shown to reliably and consistently alter a specific endpoint that the assay is designed to assess. Typically, these are chemicals with well-documented modes of action or that have been repeatedly tested in multiple in vitro model systems. Use of these chemicals can demonstrate the relevance and performance of the assay, as well as its practical ability to test moderate numbers of chemicals in a screening mode (Judson et al., 2013). As an example, training sets for in vitro assays of the critical neurodevelopmental event of neurite outgrowth can be found in Radio et al. (2008) and Krug et al. (2013). An important consideration is that training set chemicals must be specific to the endpoint being measured, and different training sets may be necessary for each of the multiple assays that would comprise a developmental neurotoxicity test battery. A discussion of training sets for evaluation of endpoint-specific assays can be found in Crofton et al. (2011) and Kadereit et al. (2012).

In contrast to individual assay development, evaluation of the ability of a battery of in vitro assays or non-mammalian test species to predict whether chemicals are likely to affect neurodevelopment in vivo in mammals requires a different set of chemicals, described as a "test set" (Crofton et al., 2011). Test set chemicals are those that have been shown to alter brain development after in vivo exposure. Ideally, because the goal of these assays is to protect human populations, the test set should be comprised of chemicals known to produce developmental neurotoxicity in humans. However, only a small number of chemicals (e.g., methylmercury, lead, ethanol, valproic acid, PCBs, arsenic, toluene) have been well documented to alter human neurodevelopment (Giordano and Costa, 2012), and in some cases, the evidence is based on small increases in the relative risk determined in a limited set of epidemiologic studies (Grandjean and Landrigan, 2006, 2014; Kadereit et al., 2012). This small number of "known developmental neurotoxicants" is unlikely to be representative of all the potential mechanisms by which chemicals may produce developmental neurotoxicity, and thus does not comprise a sufficient test set to validate the predictive ability of a developmental neurotoxicity test battery. For example, to evaluate the predictive ability of a battery of three in vitro genotoxicity tests, Kirkland et al. (2006) tested over 700 chemicals classified as rodent carcinogens based on in vivo cancer bioassays. Similarly, a set of 60 chemicals was generated for use as a test set for evaluating alternatives to whole fish toxicity tests (Schirmer et al., 2008).

In order to develop a test set of developmental neurotoxicants, we propose that chemicals that have been demonstrated to adversely affect neurodevelopment in experimental animals should be included. This would expand the chemical space covered in the test set and presumably increase confidence in the relevance of the in vitro test battery to the in vivo outcome. It is acknowledged that animal studies must interpreted with caution when extrapolating to humans based on differences in timing of neurodevelopmental processes, size and complexity of the nervous system and pharmacokinetics between species (Rodier, 1994; Rice and Barone, 2000). Still, there is a wealth of animal data concerning developmental neurotoxicity that should be considered, and animal studies in rodents and primates are currently the basis of many regulatory decisions. The present effort was undertaken to identify chemicals with data in the peer-reviewed literature demonstrating effects on neurodevelopment in vivo. This list of chemicals provides a starting point for selecting an expanded test set that would include both potential human and animal developmental neurotoxicants.

2. Definition and criteria for developmental neurotoxicity

Neurotoxicity is defined as an adverse change in the structure or function of the central and/or peripheral nervous system following exposure to a chemical, physical, or biologic agent (US EPA, 1998). For the purposes of this review, developmental neurotoxicity was defined as a change in the structure or function of the nervous system after exposure to a substance during the period of gestation and/or lactation. For rodent species, this would include the period of the brain growth spurt (Bayer et al., 1993; Rodier, 1994). Our definition of neurotoxicity was broad by intention, in order to encompass the range of endpoints reported in the literature. Evidence of neurotoxicity from literature and other reports was classified into three categories: behavior, morphology, or neurochemistry. Behavioral endpoints included neurobehavioral impairments (e.g., motor impairments, sensory changes, learning and memory, including I.Q. in humans) as well as changes in developmental landmarks (e.g., negative geotaxis, startle response, righting response). Morphological endpoints included gross structural changes (e.g., reduced brain weight, spina bifida, and exencephaly), brain pathology and morphometry (e.g., cell death, changes in neuron or glial numbers, loss of myelin, reduced cortical thickness). Neurochemical indices included changes in neurotransmitters and/or

receptors (e.g., neurotransmitter levels, receptor number or binding affinity) and alterations in neuronal signaling (e.g. gene expression, protein phosphorylation). Neurophysiological measures (e.g., evoked potentials, EEG) were not commonly used and were included with neurochemistry. In order to rule out "pharmacologic" or acute effects of chemical exposures, changes in behavior or neurochemistry were not considered neurotoxic if they were observed only during the time immediately after chemical administration.

Since our goal is to evaluate the ability of a test battery to predict human toxicity, only mammalian (laboratory animal or human) studies published in the peer-reviewed literature and/or in existing Data Evaluation Records submitted to the U.S. EPA for registration or re-registration of chemicals were considered. Reports in which the chemical was part of a mixture, in vitro data, or reports where more than 5 g/kg of the chemical was administered (maximal dose allowed in most toxicity testing paradigms) were not included. In addition, if data were available that indicated that developmental neurotoxicity was observed only at doses that resulted in maternal death or were lethal to the fetus or offspring, the study was not considered. Although the most relevant routes of exposure for humans are oral, inhalation, or dermal, we also considered i.v., s.c., and i.p. administration since they are routinely used in animal studies.

To increase confidence in the test set, we included a very basic scientific indication of reproducibility in that we only included a chemical if data on its developmental neurotoxicity were available from more than one laboratory (defined as studies originating from laboratories with a different senior investigator). Evidence from human studies was included when available. Epidemiological studies were included when they controlled for exposure to multiple stressors (e.g., drug abuse) and contained information on the level of exposure.

3. Identification of available studies

To search for potential developmental neurotoxicants, an initial list of approximately 400 compounds was generated (Supplemental Table 1). This list was compiled based on previous reviews and publications, including Anger and Johnson (1985), Goldey et al. (1995a), Andersen et al. (2000), Spencer et al. (2000), and Grandjean and Landrigan (2006). A literature search was performed for each chemical. Our search strategy included at least the two databases: (1) PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and (2) Developmental and Reproductive Toxicology Database (DART) (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC.htm). In some cases, we also queried the International Program on Chemical Safety (IPCS) (http://www.inchem.org/). The search terms that we used were the following:

- Chemical name + developmental + neurotoxicity
- Chemical name + developmental + toxicity
- Chemical name + developmental
- Chemical name + nervous system + toxicity
- Chemical name + brain + toxicity
- Chemical name + nervous system
- Chemical name + neurotoxicity
- Chemical name + brain
- Chemical name + toxicity
- Chemical name

We found that in many cases using the "neuro" and/or the "develop" root to locate information on a neurotoxic chemical was unsuccessful and that, for many chemicals, we had to filter large numbers of publications found with the "chemical name + toxicity" search to identify relevant papers with changes in nervous system-related endpoints. Also included in the search were Data Evaluation Records for all pesticides for which there was a U.S. EPA guideline developmental neurotoxicity study. All evidence had to be publicly available in the published literature, online, or through requests under the Freedom of Information Act (http://www.epa.gov/opp00001/foia/submit.htm).

Chemicals that met the requirements for inclusion on the list of potential developmental neurotoxicants are presented in Table 1. For each chemical, two references are cited representing studies from different laboratories. In cases where there were multiple references for a chemical, those cited in the table were deemed representative. For chemicals with supporting human data, one additional reference is cited. Also, due to the physiological relationship of primates and modern humans, data from primate studies are cited in Table 1. Additional information and references on the potential developmental neurotoxicity of each chemical has been summarized and is included in Supplemental Document 1. The summarized information is not necessarily comprehensive but provides a basis for further examination of the putative neurodevelopmental effects of the chemical. Chemicals with developmental neurotoxicity data limited to one laboratory are listed in Supplemental Table 2.

4. Selection of developmental neurotoxicants for a test set

The list of chemicals in Table 1 represents a starting point for the compilation of a test set for assessing alternative methods for developmental neurotoxicity based on documented effects on the developing nervous system in vivo. Generation of a test set for use in the laboratory, however, will have to be based on a careful consideration of both the general principles of developmental neurotoxicity and chemical-specific characteristics. Consideration of dose is one example. For less studied chemicals, there is often sparse or no data on expected exposures in humans, much less information on dose to the target organ (fetal or neonatal brain) in either humans or experimental animals. Without this information the relevance of animal data, as well as the choice of in vitro concentrations, may be difficult to ascertain. Outlined below are some of the basic issues that should be considered when identifying test set chemicals for use in evaluating the ability of an assay or battery of assays to detect potential developmental neurotoxicants.

1. *Human* versus *animal data*. Although Table 1 contains many more chemicals with animal data only, chemicals with human data represent the "gold standard" since they provide evidence of neurodevelopmental effects in the species of interest. In some cases, especially with pharmaceuticals, there is corresponding information on chemical exposure and chemical concentration in the mother's blood, umbilical cord blood, or urine. There may also be information regarding chemical concentrations in neonatal blood or urine samples. Knowledge of exposure levels and concentrations associated with adverse effects on neurodevelopment can provide insight into the selection and relevance of concentrations to be used in the test system being evaluated. Chemicals with a history of human data tend to be well studied in animals and other experimental systems in order to understand the mode or mechanism of action. This can inform the evaluation of whether the test system has the appropriate targets or biological pathways involved in the expression of developmental neurotoxicity. Thus, chemicals with both human and animal data should be considered as top candidates for inclusion in a test set.
2. *Direct* versus *indirect actions on CNS development*. A number of the chemicals identified as developmental neurotoxicants in vivo act indirectly to impact neurodevelopment via alteration of non-neural systems. For example, methimazole is well documented to induce developmental neurotoxicity by decreasing circulating thyroid hormone through the inhibition of thyroperoxidase in the thyroid gland (Darbra et al., 2003). Another example is carbon monoxide, which results in developmental neurotoxicity after binding to hemoglobin and causing hypoxia (Mactutus and Fechter, 1984). Thus, chemicals with a known mode of action that involves dysregulation

Table 1
Chemicals with data demonstrating effects on neurodevelopment.

Chemical	Species	Exposure	Dose/Route	Endpoint	Reference
Acrylamide	Rodent		20 mg/kg, oral	Neurochemistry	Agrawal and Squibb (1981)
	Rodent	Pre-/postnatal	0.5–10 mg/kg, oral	Behavior	Garey et al. (2005)
Allethrin	Rodent	Postnatal	0.2–42 mg/kg, oral	Behavior, neurochemistry	Ahlbom et al. (1994)
	Rodent	Postnatal	0.7 mg/kg, oral	Neurochemistry	Pauluhn and Schmuck (2003)
Aluminum*	Rodent	Pre-/postnatal	400 mg/kg, oral	Behavior	Muller et al. (1990)
	Rodent	Pre-/postnatal	60–125 mg/kg, oral	Behavior	Golub et al. (1995)
	Human	Postnatal	45 μg/kg, i.v.	Behavior	Bishop et al. (1997)
6-aminonicotinamide	Rodent	Prenatal	8 mg/kg, i.p.	Morphology	Chamberlain (1970)
	Rodent	Prenatal	8 mg/kg, i.p.	Morphology	Yamada et al. (1991)
Amphetamine	Rodent	Prenatal	0.5 mg/kg, s.c.	Behavior	Nasello and Ramirez (1978)
	Rodent	Prenatal	0.5–2 mg/kg, s.c.	Behavior	Vorhees (1985)
Arsenic*	Rodent	Pre-/postnatal	37 mg/L, water	Behavior	Rodriguez et al. (2002)
	Rodent	Pre-/postnatal	10–100 mg/L, water	Behavior	Xi et al. (2009)
	Human	Pre-/postnatal	Drinking water	Behavior	Hamadani et al. (2011)
Aspartame	Rodent	Pre-/postnatal	1500–5000 mg/kg, oral	Behavior	Brunner et al. (1979)
	Rodent	Prenatal	500 mg/kg, oral	Behavior	Dow-Edwards et al. (1989)
Azacytidine	Rodent	Prenatal	4 mg/kg, i.p.	Morphology	Rodier and Reynolds (1977)
	Rodent	Prenatal	10 mg/kg, i.p.	Morphology	Ueno et al. (2002)
Benomyl	Rodent	Prenatal	62 mg/kg, oral	Morphology	Ellis et al. (1988)
	Rodent	Prenatal	15-1000 mg/kg, oral	Morphology	Vergieva (1998)
Benzene	Rodent	Postnatal	550 mg/kg, oral	Behavior	Tilson et al. (1980)
	Rodent	Prenatal	0.1 mg/kg, s.c.	Behavior	Lo Pumo et al. (2006)
Bisphenol A	Rodent	Prenatal	20 μg/kg, s.c.	Morphology	Nakamura et al. (2006)
	Rodent	Pre-/postnatal	50–500 μg/kg, oral	Behavior	Kuwahara et al. (2013)
	Primate	Prenatal	400 μg/kg, oral	Morphology	Elsworth et al. (2013)
Bis(tri-n-butyltin)oxide	Rodent	Prenatal	2.5–10 mg/kg, oral	Behavior	Crofton et al. (1989)
	Rodent	Postnatal	2–4 mg/kg, i.p.	Morphology, neurochemistry	O'Callaghan and Miller (1988a)
Bromodeoxyuridine	Rodent	Prenatal	300–500 mg/kg, i.p.	Morphology	Skalko et al. (1971)
	Rodent	Prenatal	50 mg/kg, i.p.	Behavior, neurochemistry	Kuwagata et al. (2004)
Butylated hydroxyanisole	Rodent	Pre-/postnatal	500 mg/kg, oral	Behavior	Stokes and Scudder (1974)
	Rodent	Pre-/postnatal	100–600 mg/kg, oral	Behavior	Vorhees et al. (1981)
Cadmium*	Rodent	Prenatal	4 mg/kg, i.p.	Morphology	Webster and Messerle (1980)
	Rodent	Pre-/postnatal	3–14 mg/kg, oral	Behavior	Desi et al. (1998)
	Human	Prenatal	oral	Behavior	Kippler et al. (2012)
Caffeine	Rodent	Prenatal	4.5 mg/kg, oral	Behavior	Groisser et al. (1982)
	Rodent	Prenatal	70 mg/kg, oral	Morphology	Tanaka et al. (1983)
Carbamazepine*	Rodent	Postnatal	100 mg/kg, i.p.	Morphology	Kim et al. (2007)
	Human	Prenatal	Oral	Behavior	Poblano et al. (2002)
	Human	Prenatal	Oral	Behavior	Meador et al. (2011)
Carbon monoxide	Rodent	Prenatal	150 ppm, inhal.	Behavior	Mactutus and Fechter (1984)
	Rodent	Prenatal	150 ppm, inhal.	Neurochemistry	Mereu et al. (2000)
Chlordecone	Rodent	Postnatal	1 mg/kg, s.c.	Behavior	Tilson et al. (1982)
	Rodent	Pre-/postnatal	10 mg/kg, i.p.	Behavior	Cooper et al. (1985)
Chlordiazepoxide*	Rodent	Pre-/postnatal	1 mg/kg, i.p.	Behavior	Adams (1982)
	Rodent	Prenatal	10–20 mg/kg, s.c.	Behavior	Kurishingal et al. (1992)
	Human	Prenatal	Oral	Behavior, morphology	Milkovich and van den Berg (1974)
Chlorine dioxide	Rodent	Postnatal	14 mg/kg, oral	Behavior	Orme et al. (1985)
	Rodent	Postnatal	14 mg/kg, oral	Morphology	Toth et al. (1990)
Chlorpromazine	Rodent	Prenatal	3 mg/kg, s.c.	Behavior	Clark et al. (1970)
	Rodent	Pre-/postnatal	15 mg/kg, i.m.	Morphology	Hannah et al. (1982)
Chlorpyrifos*	Rodent	Postnatal	1–5 mg/kg, s.c.	Neurochemistry, behavior	Dam et al. (2000)
	Rodent	Pre-/postnatal	3–6 mg/kg, oral	Behavior	Ricceri et al. (2006)
	Human	Prenatal	oral, inhal.	Behavior	Rauh et al. (2006)
Cocaine	Rodent	Prenatal	40 mg/kg, s.c.	Behavior	Goodwin et al. (1992)
	Rodent	Prenatal	20 mg/kg, s.c.	Morphology	Lu et al. (2012)
Colcemid	Rodent	Prenatal	1 mg/kg, i.p.	Morphology	Webster et al. (1973)
	Rodent	Prenatal	0.7 mg/kg, i.p.	Morphoolgy	Petit and Isaacson (1977)
Colchicine	Rodent	Prenatal	0.4 mg/kg, s.c.	Morphology, behavior	Petit and Isaacson (1976)
	Rodent	Prenatal	1 mg/kg, i.p.	Morphology	Herken (1985)
Cyclophosphamide	Rodent	Postnatal	20–45 mg/kg, s.c.	Behavior	Preache and Gibson (1976)
	Rodent	Prenatal	7.5–15 mg/kg, i.p.	Morphology	Xiao et al. (2007)
Cypermethrin	Rodent	Postnatal	1.49 mg/kg, oral	Behavior, neurochemistry	Nasuti et al. (2007)
	Rodent	Prenatal	1.25–5 mg/kg, oral	Neurochemistry	Singh et al. (2015)
Cytosine arabinoside	Rodent	Prenatal	50 mg/kg, s.c.	Morphology, behavior	Adlard et al. (1975)
	Rodent	Postnatal	30 mg/kg, s.c.	Morphology	Yamano et al. (1983)
Deltamethrin	Rodent	Postnatal	0.7 mg/kg, oral	Behavior, neurochemistry	Eriksson and Fredriksson (1991)
	Rodent	Prenatal	0.75 mg/kg, i.p.	Morphology	Kumar et al. (2013)
Dexamethasone*	Rodent	Prenatal	0.2–0.8 mg/kg, s.c.	Morphology	Carlos et al. (1992)
	Rodent	Postnatal	1.5 mg/kg, s.c.	Morphology, behavior	Ferguson et al. (2001)
	Human	Postnatal	0.25 mg/kg/d, i.v.	Morphology	Murphy et al. (2001)
Diazepam	Rodent	Prenatal	2.5 mg/kg, s.c.	Behavior	Nicosia et al. (2003)
	Rodent	Pre-/postnatal	10 mg/kg, s.c.	Behavior	Frieder et al. (1984)
Diazinon	Rodent	Prenatal	0.2–9 mg/kg, s.c.	Behavior	Spyker and Avery (1977)
	Rodent	Postnatal	0.5–2 mg/kg, s.c.	Behavior	Timofeeva et al. (2008)
Dieldrin	Rodent	Pre-/postnatal	0.35 μg/kg, oral	Behavior	Olson et al. (1980)

Table 1 (*continued*)

Chemical	Species	Exposure	Dose/Route	Endpoint	Reference
	Rodent	Prenatal	10 mg/kg, i.p.	Neurochemistry	Brannen et al. (1998)
Di-(2-ethylhexyl) phthalate	Rodent	Prenatal	75–225 mg/kg, oral	Morphology	Tyl et al. (1988)
	Rodent	Pre-/postnatal	15–135 mg/kg, oral	Behavior	Tanaka (2002)
Diethylstilbestrol	Rodent	Postnatal	0.1 μg, s.c.	Behavior	Mihalick (2003)
	Rodent	Prenatal	0.1 μg/kg, oral	Behavior, neurochemistry	Kaitsuka et al. (2007)
Dioxin	Rodent	Prenatal	.025–1.0 μg/kg, oral	Behavior	Schantz et al. (1996)
	Rodent	Prenatal	.020–1.8 μg/kg, oral	Behavior	Hojo et al. (2002)
	Primate	Prenatal	5–25 ppt, diet	Behavior	Schantz and Bowman (1989)
Diphenylhydantoin*	Rodent	Prenatal	100 mg/kg, oral	Behavior	Vorhees et al. (1995)
	Rodent	Postnatal	10–35 mg/kg, oral	Morphology, behavior	Hatta et al. (1999)
	Human	Prenatal	6–450 mg, oral	Behavior	Scolnik et al. (1994)
Domoic acid	Rodent	Prenatal	0.6 mg/kg, i.v.	Neurochemistry, morphology	Dakshinamurti et al. (1993)
	Rodent	Prenatal	1 mg/kg, i.p.	Behavior	Tanemura et al. (2009)
Epidermal Growth Factor	Rodent	Postnatal	3.5 mg/kg, s.c.	Behavior	Calamandrei and Alleva (1989)
	Rodent	Postnatal	1.75 mg/kg, s.c.	Behavior	Futamura et al. (2003)
Ethanol*	Rodent	Prenatal	2.9 g/kg, i.p.	Morphology	Sulik et al. (1984)
	Rodent	Prenatal	4 g/kg, oral	Behavior	Vorhees and Fernandez (1986)
	Human	Prenatal	Oral	Morphology, behavior	Jones et al. (1973)
Ethylenethiourea	Rodent	Prenatal	15–45 mg/kg, oral	Morphology	Khera and Tryphonas (1985)
	Rodent	Prenatal	12–45 mg/kg, oral	Morphology	Saillenfait et al. (1991)
Fluoride*	Rodent	Prenatal	0.13 mg/kg, s.c.	Behavior	Mullenix et al. (1995)
	Rodent	Pre-/postnatal	25–100 mg/l, water	Behavior, neurochemistry	Jiang et al. (2014)
	Human	Pre-/postnatal	Drinking water	Behavior	Choi et al. (2012)
5-Fluorouracil	Rodent	Prenatal	10–30 mg/kg, i.p.	Morphology	Kuwagata et al. (1998)
	Rodent	Prenatal	30 mg/kg, i.p.	Morphology	Kumar et al. (2006)
Fluoxetine	Rodent	Postnatal	10 mg/kg, i.p.	Behavior	Ansorge et al. (2008)
	Rodent	Prenatal	12 mg/kg, oral	Behavior	Olivier et al. (2011)
Haloperidol	Rodent	Prenatal	80–245 mg/kg, i.p.	Morphology	Gill et al. (1982)
	Rodent	Prenatal	2.5–5 mg/kg, s.c.	Neurochemistry	Scalzo et al. (1989)
Halothane	Rodent	Pre-/postnatal	25–100 ppm, inhal.	Neurochemistry, behavior	Uemura et al. (1985)
	Rodent	Prenatal	50,000 ppm, inhal.	Behavior	Koëter and Rodier (1986)
Heptachlor	Rodent	Pre-/postnatal	0.03–3 mg/kg, oral	Neurochemistry, behavior	Moser et al. (2001a)
	Rodent	Pre-/postnatal	3 mg/kg, oral	Neurochemistry	Caudle et al. (2005)
Heroin	Rodent	Pre-/postnatal	5 mg/kg, i.p.	Behavior	Lasky et al. (1977)
	Rodent	Prenatal	10 mg/kg, i.p.	Neurochemistry, behavior	Yanai et al. (1992)
Hexachlorobenzene	Rodent	Prenatal	10–100 mg/kg, oral	Behavior	Goldey and Taylor (1992)
	Rodent	Pre-/postnatal	4–16 mg/kg, oral	Behavior	Lilienthal et al. (1996)
Hexachlorophene*	Rodent	Postnatal	10 mg/kg, oral	Morphology	Ulsamer et al. (1975)
	Rodent	Postnatal	3%, dermal	Behavior, morphology	Shuman et al. (1975)
	Human	Postnatal	3%, dermal	Morphology	Anderson et al. (1981)
Hydroxyurea	Rodent	Prenatal	375–500 mg/kg, i.p.	Behavior	Butcher et al. (1973)
	Rodent	Prenatal	400–800 mg/kg, i.p.	Morphology	Woo et al. (2004)
3,3′-iminodipropanenitrile	Rodent	Postnatal	75–300 mg/kg, i.p.	Behavior	Crofton et al. (1993)
	Rodent	Postnatal	100 mg/kg, s.c.	Behavior, neurochemistry	Dawson et al. (1998)
Ketamine	Rodent	Postnatal	20 mg/kg, s.c.	Morphology	Ikonomidou et al. (1999)
	Rodent	Postnatal	50 mg/kg, s.c.	Morphology, behavior	Fredriksson et al. (2004)
	Primate	Behavior	20 mg/kg, i.v.	Behavior	Paule et al. (2011)
Lead*	Rodent	Postnatal	20–300 ppm, water	Behavior	Stangle et al. (2007)
	Primate	Postnatal	50–100 μg/kg, oral	Behavior	Rice and Karpinski (1988)
	Human	Pre-/postnatal	Oral	Behavior	Canfield et al. (2003)
Lidocaine	Rodent	Prenatal	6 mg/kg, i.m.	Behavior	Smith et al. (1986)
	Rodent	Prenatal	6 mg/kg, i.m.	Behavior	Teiling et al. (1987)
Lysergic acid diethylamide	Rodent	Prenatal	0.1–1 μg, i.p.	Morphology	Auerbach and Rugowski (1967)
	Rodent	Prenatal	5 μg/kg, i.p.	Morphology, neurochemistry	Hoff (1976)
Maneb	Rodent	Prenatal	120–480 mg/kg, oral	Morphology	Chernoff et al. (1979)
	Rodent	Postnatal	0.5–10 ppm, diet	Behavior	Sobotka et al. (1972)
Manganese*	Rodent	Pre-/postnatal	2 mg/kg, oral	Behavior	Betharia and Maher (2012)
	Rodent	Postnatal	25–50 mg/kg, oral	Behavior	Beaudin et al. (2013)
	Human	Pre-/postnatal	Drinking water	Behavior	Bouchard et al., 2011
Methanol	Rodent	Prenatal	2%, water	Behavior	Infurna and Weiss (1986)
	Rodent	Pre-/postnatal	4500 ppm, inhal.	Behavior	Stern et al. (1997)
	Primate	Prenatal	200–1800 ppm, inhal.	Behavior	Burbacher et al. (1999)
Methimazole	Rodent	Pre-/postnatal	02.mg/ml, water	Behavior	Darbra et al. (2003)
	Rodent	Prenatal	0.02%, water	Morphology	Auso et al. (2004)
Methotrexate	rodent	Postnatal	0.05 mg/kg, i.p.	Morphology	Igarashi et al. (1989)
	Rodent	Prenatal	5 mg/kg, i.p.	Behavior	Kabova et al. (2000)
Methylazoxymethanol	Rodent	Prenatal	1–25 mg/kg, i.p.	Morphology, neurochemistry	Tamaru et al. (1988)
	Rodent	Prenatal	22 mg/kg, i.p.	Behavior	Featherstone et al. (2007)
Methylmercury*	Rodent	Pre-/postnatal	0.5–6.4 ppm, water	Behavior	Newland and Rasmussen (2000)
	Rodent	Pre-/postnatal	4 ppm, water	Morphology	Markowski et al. (1998)
	Human	Prenatal	Diet	Behavior	Grandjean et al. (1997)
Methyl parathion	Rodent	Prenatal	1–1.5 mg/kg, oral	Behavior, neurochemistry	Gupta et al. (1985)
	Rodent	Postnatal	0.2–0.9 mg/kg, oral	Behavior	Johnson et al. (2009)
Monosodium glutamate	Rodent	Prenatal	5 mg/kg, s.c.	morphology	Murakami and Inouye (1971)
	Rodent	Postnatal	1–2 mg/kg, s.c.	Morphology, behavior	Kubo et al. (1993)

(*continued on next page*)

Table 1 (*continued*)

Chemical	Species	Exposure	Dose/Route	Endpoint	Reference
	Primate	Postnatal	1–4 g/kg, oral, s.c.	Morphology	Olney et al. (1972)
MPTP	Rodent	Prenatal	2.8 mg/kg, s.c.	Neurochemistry	Furune et al. (1989)
	Rodent	Prenatal	5 mg/kg, s.c.	Neurochemistry	Ochi et al. (1991)
Naloxone	Rodent	Prenatal	40 mg/kg, i.p.	Behavior	Vorhees (1981)
	Rodent	Prenatal	5 mg/kg, s.c.	Morphology, behavior	Shepanek et al. (1989)
Naltrexone	Rodent	Postnatal	1–50 mg/kg, s.c.	Morphology	Zagon and McLaughlin (1986)
	Rodent	Postnatal	1 mg/kg, s.c.	Behavior	de Cabo de la Vega et al. (1995)
Nicotine	Rodent	Prenatal	2 mg/kg, s.c.	Behavior	Levin et al. (1996)
	Rodent	Postnatal	66 μg/kg, s.c.	Behavior	Eriksson et al. (2000)
	Primate	Prenatal	0.7 mg/kg, s.c.	Neurochemistry, morphology	Slotkin et al. (2005)
Ozone	Rodent	Prenatal	1 ppm, inhal.	Morphology	Rivas-Manzano and Paz (1999)
	Rodent	Pre-/postnatal	0.6 ppm, inhal.	Behavior	Dell'Omo et al. (1995)
Paraquat	Rodent	Postnatal	0.07–0.36 mg/kg, oral	Behavior	Fredriksson et al. (1993b)
	Rodent	Prenatal	10 mg/kg, i.p.	Behavior, Neurochemistry	Miranda-Contreras et al. (2005)
Parathion	Rodent	Postnatal	1.3–1.9 mg/kg, s.c.	Behavior, neurochemistry	Stamper et al. (1987)
	Rodent	Postnatal	0.9 mg/kg, s.c.	Morphology, neurochemistry	Veronesi and Pope (1990)
Penicillamine	Rodent	Prenatal	3200–4800 mg/kg, oral	Morphology	Wiley and Joneja (1978)
	Rodent	Prenatal	0.17–1.66%, diet	Morphology	Keen et al. (1983)
Perchlorate	Rodent	Pre-/postnatal	0.1–10 mg/kg, water	Morphology	York et al. (2004)
	Rodent	Pre-/postnatal	30–1000 ppm, water	Neurochemistry	Gilbert and Sui (2008)
Permethrin	Rodent	Postnatal	34 mg/kg, oral	Behavior, neurochemistry	Nasuti et al. (2007)
	Rodent	Prenatal	2–75 mg/kg, oral	Morphology, behavior	Imanishi et al. (2013)
Phenobarbital*	Rodent	Prenatal	0.3%, diet	Behavior	Yanai et al. (1989)
	Rodent	Postnatal	75 mg/kg, i.p.	Behavior	Forcelli et al. (2012)
	Human	Prenatal	Oral	Behavior	Motamedi and Meador (2006)
Phenylacetate	Rodent	Prenatal	500 mg/kg, s.c.	Morphology	Lacey (1986)
	Rodent	Postnatal	200–500 mg/kg, s.c.	Morphology	Loo et al. (1978)
Polybrominated diphenyls*	Rodent	Postnatal	21 μmol/kg, oral	Behavior	Viberg et al. (2006)
	Rodent	Pre-/postnatal	0.03–1 mg/kg, oral	Behavior	Koenig et al. (2012)
	Human	Pre-/postnatal	Oral	Behavior	Eskenazi et al. (2013)
Polychlorinated biphenyls*	Rodent	Postnatal	0.18–5.1 mg/kg, oral	Behavior	Eriksson and Fredriksson (1996)
	Rodent	Pre-/postnatal	1–6 mg/kg, oral	Behavior, morphology	Yang et al. (2009)
	Human	Prenatal	Oral	Behavior	El Majidi et al. (2013)
Propranolol	Rodent	Prenatal	10–20 mg/kg, water	Behavior	Speiser et al. (1983)
	Rodent	Postnatal	5 mg/kg, i.p.	Behavior	Hilakivi et al. (1988)
Propylthiouracil	Rodent	Pre-/postnatal	1–25 ppm, water	Behavior	Goldey et al. (1995b)
	Rodent	Pre-/postnatal	1–10 ppm, water	Morphology	Gilbert et al. (2014)
Retinoic acid*	Rodent	Prenatal	2–6 mg/kg, oral	Behavior	Nolen (1986)
	Rodent	Prenatal	50–100 mg/kg, oral	Behavior	Jensh et al. (1990)
	Human	Prenatal	1–2 mg/kg, oral	Behavior	Adams and Lammer (1991)
Tebuconazole	Rodent	Pre-/postnatal	100–1000 ppm, diet	Behavior, morphology	US EPA (2000)
	Rodent	Pre-/postnatal	6–60 mg/kg, oral	Behavior	Moser et al. (2001b)
Tellurium	Rodent	Prenatal	500–3000 ppm, diet	Morphology	Duckett (1972)
	Rodent	Postnatal	1.0%, diet	Morphology	Morell et al. (1994)
Terbutaline*	Rodent	Postnatal	10 mg/kg, s.c.	Morphology	Rhodes et al. (2004)
	Human	Prenatal	Oral, s.c.	Behavior	Connors et al. (2005)
Tetrahydrocannabinol*	Rodent	Pre-/postnatal	5 mg/kg, oral	Behavior, Neurochemistry	Campolongo et al. (2007)
	Rodent	Prenatal	0.15 mg/kg, i.v.	Behavior	Silva et al. (2012)
	Human	Prenatal	Inhal.	Behavior	Goldschmidt et al. (2012)
Thalidomide	Rodent	Prenatal	100 mg/kg, oral	Behavior	Vorhees et al. (2001)
	Rodent	Prenatal	500 mg/kg, oral	Morphology	Miyazaki et al. (2005)
Toluene	Rodent	Pre-/postnatal	1200 ppm, inhal.	Behavior	Hass et al. (1999)
	Rodent	Pre-/postnatal	8000–12,000 ppm, inhal.	Behavior	Bowen et al. (2005)
Triamcinolone	Primate	prenatal	10 mg/kg, i.m.	Morphology	Michejda and Hodgen (1985)
	Primate	Prenatal	10 mg/kg, i.m.	Morphology	Tarara et al. (1989)
Tri-*n*-butyltin	Rodent	Prenatal	1–5 mg/kg, oral	Behavior	Gardlund et al. (1991)
	Rodent	Pre-/postnatal	1–100 μg/kg, oral	Behavior	Si et al. (2012)
Trichlorfon	Rodent	Pre-/postnatal	150–1750 ppm, diet	Behavior, Morphology	US EPA (2003)
	guinea pig	Prenatal	125 mg/kg, s.c.	Morphology	Mehl et al. (1994)
Trichloroethylene	Rodent	Pre-/postnatal	312–1250 ppm, water	Behavior	Tayor et al. (1985)
	Rodent	Postnatal	50–290 mg/kg, oral	Behavior	Fredriksson et al. (1993a)
Triethyl lead	Rodent	Postnatal	4 mg/kg, i.p.	Morphology	Konat and Clausen (1974)
	Rodent	Postnatal	4.5–9 mg/kg, s.c.	Behavior, morphology	Booze and Mactutus (1990)
Triethyltin	Rodent	Postnatal	3–6 mg/kg, i.p.	Neurochemistry	O'Callaghan and Miller, (1988b)
	Rodent	Postnatal	3–5 mg/kg, i.p.	Behavior, Morphology	Freeman et al. (1994)
Trimethyltin	Rodent	Postnatal	1 mg/kg, oral	Behavior	Miller et al. (1982)
	Rodent	Postnatal	6 mg/kg, i.p.	Morphology	Chang (1984)
Valproic acid*	Rodent	Prenatal	200 mg/kg, oral	Behavior	Vorhees (1987)
	Rodent	Postnatal	150 mg/kg, i.p.	Behavior	Chomiak et al. (2010)
	Human	Prenatal	750 mg, oral	Behavior	Christensen et al. (2013)

* Human data available.

of non-neural systems such as hemodynamics or circulating hormone levels would be unlikely to be detected using in vitro assays that are based solely on neural tissues. In light of this, chemicals known to act directly on the developing nervous system would be the most appropriate for inclusion in a test set. However, acknowledgement of the role of indirect actions of chemicals leading to impaired neurodevelopment will likely contribute to the development and use of alternative models (e.g., hormone disruption in zebrafish)

and specific assays based on documented adverse outcome pathways (e.g., inhibition of thyroperoxidase; Paul et al., 2014) that can be incorporated into a test battery for predicting developmental neurotoxicity.

3. *Parent compound* versus *metabolite*. A well-known drawback to most in vitro test systems is the lack of metabolic capabilities. Xenobiotic metabolism may also exist to a different degree in small alternative species. Xenobiotic metabolism is generally considered to detoxify parent compounds, but in some cases, it can generate toxic metabolites. The lack of xenobiotic biotransformation using in vitro models produces two potential errors. First, the inability to detoxify parent toxicants overestimates the risk posed by that compound in vivo. Second, the lack of bioactivation (generation of toxic metabolites) leads to the misclassification of chemicals known to be active in vivo as inactive in vitro. For the test set, the active metabolite should be used. Even better is the inclusion of the parent/metabolite pair, which would provide some indication of the metabolic capabilities of the assays in the test battery.
4. *Chemical properties*. At a practical level, test set compounds must be amenable to dissolution into an aqueous assay media or buffer system. In most in vitro systems and alternative species models, compounds are dissolved in aqueous solutions or in an organic solvent (DMSO, ethanol) that is miscible with water. Thus, preliminary studies may be needed to confirm that a test set chemical can be prepared in the vehicle at the appropriate stock concentration and remains in solution at the final dilution in the test system. Compounds with high volatility can also cause problems in aqueous media, and special exposure conditions (e.g. a closed environmental chamber) may be required to assure that they remain at the desired concentration. In order to examine the applicability of the test battery to a large chemical space, test set chemicals exhibiting a wide diversity of chemical properties (e.g. logP, molecular weight) and chemical classes (e.g. metals, organo metals, pesticides, pharmaceuticals) should be considered.
5. *Extrapolation of exposure and dose*. While the route of exposure and dose levels are clearly spelled out in most animal studies, in many cases, the target organ concentration in the fetal or neonatal brain is not known. Test set chemicals where some measure of internal dose to the mother, fetus, or offspring is available are desirable in order to ground the concentration ranges used in a test battery. In addition, the doses used in animal studies can be much higher than the exposure estimated or measured in humans. Information on human exposure to a test set chemical, if available, can be used to judge the relevance of the dose levels used in experimental animal studies. In the absence of this type of information, in vitro and alternative species assays should test chemicals over a wide range of concentrations.
6. *Mode of action/Adverse outcome pathway*. Knowledge of the mode of action and adverse outcome pathways can inform the evaluation of whether the test battery has assays expressing the appropriate targets or biological pathways thought to be key events leading to developmental neurotoxicity. There are a number of pathways that are known to be important in neurodevelopment, and pathway-specific chemicals have been proposed that are especially useful as part of a "training set" for assay development (Kadereit et al., 2012). However, a primary issue in generating test sets to evaluate alternative test methods is the lack of basic knowledge on the mode of action for environmental chemicals known to produce developmental neurotoxicity. This has led to the suggestion that multiple assays should be used in a test battery which includes a comprehensive complement of molecular targets, intracellular signaling pathways and critical cellular events thought to be involved in normal brain development. There are a number of known developmentally neurotoxic chemicals with well-established relationships between exposure and neurological disorders in humans for which a definitive mode of action has not been established (e.g., lead, methyl mercury, and ethanol). Even with thousands of published papers on these three human developmental neurotoxicants, no definitive mode of action or adverse outcome pathway have been constructed. Recently, however, several molecular initiating events and cellular responses have been postulated for neurotoxic and developmental neurotoxic outcomes (Bal-Price et al., 2015b), providing a basis for test set chemical selection.

5. Conclusion

There has been a rise in the number of infants and children identified with some form of neurodevelopmental abnormality. While the etiology of neurodevelopmental disorders can, in some cases, be attributed to genetic factors, in many cases, the cause is unknown. Because some environmental chemicals have been clearly shown to result in damage to the developing brain in both humans and animals, routine testing of all chemicals with potential for human exposure is warranted. In response to the limitations imposed by the use of animal-based testing, there has been a surge in the development of alternative assays based on in vitro and small non-mammalian test systems that are more efficient in terms of throughput and cost. As developmental neurotoxicologists began to explore alternative assays, it was recognized that methods were needed to assess their performance, including their predictive ability. The most straightforward way to do this is to demonstrate concordance between in vivo developmental neurotoxicity test results and results from testing the same chemicals in the alternative assays. The ideal case would select chemicals known to induce developmental neurotoxicity in humans, the so called "gold standards." In the absence of a significant number of known human developmental neurotoxicants, we have provided a list of chemicals with demonstrated effects in animals based on peer-reviewed literature and U.S. EPA developmental neurotoxicity guideline studies. This list provides a greater number of chemicals from which to select a test set of chemicals for evaluation of the predictive ability of alternative methods and assays. It is not meant to be a prescriptive list, but rather to provide a starting point. The actual chemicals selected for a test set will depend upon the specific conditions of the assay and the intended purpose of the results (e.g. prioritization or hazard decisions).

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Transparency document

The Transparency document associated with this article can be found, in online version.

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