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Windows of sensitivity to toxic chemicals in the motor effects development☆

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Abstract

Many chemicals currently used are known to elicit nervous system effects. In addition, approximately 2000 new chemicals introduced annually have not yet undergone neurotoxicity testing. This review concentrated on motor development effects associated with exposure to environmental neurotoxicants to help identify critical windows of exposure and begin to assess data needs based on a subset of chemicals thoroughly reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR) in Toxicological Profiles and Addenda. Multiple windows of sensitivity were identified that differed based on the maturity level of the neurological system at the time of exposure, as well as dose and exposure duration. Similar but distinct windows were found for both motor activity (GD 8–17 [rats], GD 12–14 and PND 3–10 [mice]) and motor function performance (insufficient data for rats, GD 12–17 [mice]). Identifying specific windows of sensitivity in animal studies was hampered by study designs oriented towards detection of neurotoxicity that occurred at any time throughout the developmental process. In conclusion, while this investigation identified some critical exposure windows for motor development effects, it demonstrates a need for more acute duration exposure studies based on neurodevelopmental windows, particularly during the exposure periods identified in this review.

Keywords

Windows of sensitivity; Motor development; Chemical exposures; Laboratory animals

1. Introduction

Many chemicals used today are known to affect the nervous system. In addition, neurotoxicity testing is needed for approximately 2000 new chemicals manufactured each year (NTP, 2014). Developmental neurotoxicity is an important category since the developing fetus may be especially sensitive to harmful insults (Cooke, 2014; Makri et al., 2004). Developmental toxicity testing of the nervous system investigates the motor, sensory,

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and neurobehavioral development. This investigation concentrated on reports in the literature regarding effects of chemicals on motor development in mammals.

In order to understand the impact of toxic chemicals on the nervous system, one has to understand the process of nervous system development and maturation. In the human embryo, the neuroectoderm is formed from the ectoderm germ layer during the third week of gestation (Schoenwolf, 2009). This results in the formation of a strip of neuronal stem cells along the back of the embryo known as the neural plate which is the origin of the nervous system. The neural plate folds outwards to form the neural groove. Starting in the future neck region, the neural folds of this groove close to create the neural tube. The spinal cord forms from the inferior part of the neural tube. Late in the fourth week of gestation, the superior part of the neural tube starts its development into brain. During neurogenesis, individual neural cells continue to mature through the process of migration, reaching specific areas and spreading out projections to selected target sites (Bayer et al., 1993).

The timeline for *in utero* development of individual structures in humans and rodents is well understood (Daston et al., 2004; Rice and Barone, 2000) (Fig. 1). The major differences are not in the actual process of nervous system development, but in the time scale of these events. It should be noted that the process of nervous system maturation continues well beyond birth. In humans, the migration of cells continues for 7 months to two years. Myelination of some structures continues for years during childhood, and new synapses and further changes occur well into adulthood. Structural anomalies or lesions in the developing brain or changes in the neurotransmitter systems result in neurodevelopmental effects.

With the help of sonography, it is possible to visualize motoric action of fetuses. The early phases of motor development are manifested by the emergence of fetal motility in humans after about 7 weeks of pregnancy and consist of simple sideways bending of head and rump (spontaneous cyclic movements) (Lüchinger et al., 2008). At the age of 9–10 weeks, general movements develop. These movements involve the whole fetal body. Other movements *in utero* include sporadic limbs and head actions, periodic breathing, sucking, and swallowing (De Vries and Fong, 2006). Fetal movements in guinea pigs mirror those observed in human fetuses though only on a shorter time scale (Felt et al., 2012; Van Kan et al., 2009). After birth, breathing becomes continuous, but mostly general movements (i.e., non-self-directed movements) are still observed. Important changes in motor development do not emerge in infants until between two and four months post-term, when goal-directed activity of arms and legs are observed. Fig. 2 presents milestones for achievements in motor skills development during the first two years of human life (WHO, 2006). Delay in achievements of these milestones, an abnormality in muscle tone, a persistence of infantile reactions, or a diminished variation in motor behavior indicate atypical motor development in infants.

In humans, neurodevelopmental disability occurs in approximately 16–17% of live offspring, 3% of which may be directly attributed to environmental chemical exposures, while another 25% of these outcomes result from a combination of genetic susceptibility and environmental exposure (NRC, 2000). However, manifestation of neurotoxicity may occur either early or much later in life (Couse, 2008). After genetic predispositions, infectious diseases and trauma, toxic chemicals are the next major causes of these effects. Human

studies have suggested that a number of chemicals, including lead and PCBs, may be associated with atypical motor development observed in conditions such as mental retardation and cerebral palsy (Grandjean and Landrigan, 2006; Winneke, 2011). Signs that may signal early motor development problems include: regression of existing motor skills, stiffness of limbs, loose or floppy muscles, walking on toes, favoring one hand or side of the body, clumsiness, drooling and difficulty with speech and eating (www.cdc.gov/ncbddd/cp/data.html).

Large data gaps still exist with respect to motor development and establishment of windows of increased sensitivity to environmental neurotoxicants. The Environmental Protection Agency (EPA) clarified the approach to evaluating motor development in animal testing in the Guidelines for Neurotoxicity Risk Assessment (EPA, 1998). Motor activity studies were classified as those measuring "a broad class of behaviors involving coordinated participation of sensory, motor, and integrative processes … quantified as the frequency of movements over a period of time" (EPA, 1998). In contrast, motor function comprises measures of "weakness or decreased strength, tremor, incoordination, and spasms, myoclonia, or abnormal motor movements" (EPA, 1998) measured by tests of: "grip strength, swimming endurance, suspension from a hanging rod, and discriminative motor function [for strength]. Rotorod and gait assessments are used to measure coordination, while rating scales and spectral analysis techniques and be used to quantify tremor and other abnormal movements" (EPA, 1998).

The purpose of this investigation was to review available data from Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles and Addenda (http://www.atsdr.cdc.gov/toxprofiles/index.asp) related to motor development following chemical exposures and evaluate possible windows of sensitivity. In addition, an assessment of whether the design of the studies is suitable for detecting specific windows of sensitivity is intended.

2. Review of toxicological profiles

The primary literature search utilized ATSDR's Toxicological Profiles (n = 173 chemicals) and Addenda (n = 41 chemicals). The profiles and addenda were perused in search of data pertaining to motor function development in association with chemical exposure. Any profiles or addenda that documented studies with motor development endpoints in animals – including visual motor, sensorimotor, gross motor, fine motor, developmental reflexes (e.g. negative geotaxis), coordination, and locomotor activity measures – were moved into the data extraction phase (n = 32 chemicals). The following data from each study were extracted: chemical name and form; species and strain; exposure route and vehicle; exposure duration and frequency; no observed adverse effect level (NOAEL), where applicable; and lowest observed adverse effect level (LOAEL). Due to the marked differences in gestation periods between rodents, primates, and humans, our analysis of exposure durations associated with LOAEL and NOAEL values was stratified according to species. In addition, given the breadth of methods for measuring motor function documented in the literature, there was further stratification according to specific endpoint measures.

The window boundaries were ultimately based on the acute exposure studies included in the Toxicological Profiles (e.g. single-dose and short-duration studies). First, overlap of LOAEL data for each chemical was examined. During this phase of the analysis, NOAEL data were used to help validate windows and outcome data from studies with LOAEL data. If there was a study(ies) with NOAEL data that conflicted with LOAEL data from another study (same exposure duration, same dose), those exposure days were excluded from the determination of across-study and across-chemical exposure windows. Next, the window boundaries were drawn based on the widest overlap of acute exposure duration studies with LOAEL data to capture as much of the chemical-specific variability as possible. Consequently, if a study reporting LOAEL data for one chemical assessed a wider range of exposures than another study of a different chemical, the LOAEL data with the earlier exposure start date or later exposure end date were still included. The results, which include all the exposure and outcomes data from the extraction phase, are presented in Figs. 3 and 4.

2.1. Motor activity

2.1.1. Rat—Exposure and adverse effect level data were found in 27 studies assessing exposure to 19 different chemicals, providing a sufficient variety of findings from which to infer a critical window of exposure for motor activity impairment (Fig. 3). The narrowest window of exposure appears to be between gestation day (GD) 8 and 17.

While most of the studies from which LOAEL could be derived reported decreases in motor activity, cadmium (Cd) acetate, lead (Pb) acetate, methyl mercury (MeHg) (for epileptogenic activity in the rat), and endrin were associated with increased activity. The difference in the directionality of the effect does not appear to be related to dose. Not all of these studies established NOAEL or dose–response curves, which indicates a possible dose effect cannot be eliminated. Similarly, the durations of exposure do not appear to explain differences in directionality; for instance both groups of studies include short, subchronic, and chronic exposure durations.

The majority of the studies involved complete gestation or gestation plus lactation exposure durations, but it was not possible to derive a narrow gestation window based on data from two single-dose studies of cesium-137 (^{137}Cs) (Norton and Kimler, 1987, 1988), as well as three short duration studies (Desi et al., 1998; Gray et al., 1981; Nishijo et al., 2007). There was only one rat study assessing motor activity following exclusively post-natal exposure etrimethyltin hydroxide administration on post-natal day (PND) 5, precluding a rat-specific post-natal exposure window (Ruppert et al., 1983). This exposure duration overlaps with the post-natal window derived from mouse data (Fig. 4). However, this study was removed from our analysis because it involved intraperitoneal administration, which has distinctive toxicokinetics relative to oral and inhalation exposure (Klaassen and Watkins, 2010).

Chronic exposure studies not included in windows assessment appear to corroborate the window derived from the shorter duration studies, with many supporting the possibility of a post-natal exposure window (data not shown). Rodriguez et al. (Rodrıguez et al., 2002) assessed whether exposure to 2.93 mg/kg/day arsenic (As) from GD 15 through post-natal month (PNM) 4 or from PND 1 to PNM 4 affected motor activity in offspring. Data demonstrated that only the combined gestational and post-natal exposure group (males only)

but not the postnatal-only duration group exhibited aberrant, increased motor activity relative to controls. In contrast, Desi et al. (1998) observed decreased motor activity in rats exposed to 14 mg/kg/day cadmium ($CdCl_2$) from PND 1 through post-natal week (PNW) 4, thus supporting the possibility of a postnatal window of exposure. Nagymajtenyi et al. (1997) also noted reduced motor activity in male rats exposed to cadmium (7 mg/kg/day, $CdCl_2$), but they assessed continuous gestation and post-natal exposure – GD 1 to PNW 8. Similarly, Mobley et al. (1990) observed decreased motor activity in male offspring associated with continuous gestation and lactation exposure to chlorite (5.2 mg/kg/day) and chlorine dioxide (13 mg/kg/day) from GD 1 through PND 35. Further evidence supporting a post-natal exposure window comes from a manganese (Mn) exposure study demonstrating elevated motor activity in rats exposed to 22 mg/kg/day from PND 1 to PND 55 (Brenneman et al., 1998).

2.1.2. Mouse—Distinct gestation – GD 12–14 – and post-natal – PND 3–10 – windows of exposure were noted based on 19 mouse studies (6 gestational exposure, 11 post-natal exposure, 2 gestational plus post-natal exposure) documenting motor activity impairments associated with 9 chemicals (Fig. 4). However, the majority of the LOAEL data originated from investigations assessing the effects of post-natal exposure.

LOAEL from gestational exposure were found for methyl mercury (MeHg) and the flame retardant FireMaster FF-1 from three studies that only assessed female offspring. Kim et al. (2000) measured total motor activity, as well as the subcategories of central locomotion and peripheral locomotion. While the motor activity subcategory metrics appeared significant in exposed mice (increased central locomotion, reduced peripheral locomotion), total motor activity measure was comparable to control levels. Data for MeHg exposure includes both NOAEL and LOAEL data involving short-duration exposure. Interestingly, Dore et al. (2001) found no marked effect at a 6 mg/kg/day dose given on GD 7–9 but observed decreased motor activity in offspring exposed to a lower (4 mg/kg/day) dose administered on GD 12 – 14, thus demonstrating a window-specific effect. Unfortunately, the only other gestational LOAEL data also includes post-natal exposure (Tilson, 1992), which indicates the effect may, in fact, have originated from post-natal exposure. However, despite the limited number of LOAEL data, the derived gestational exposure window of mouse studies overlaps with that found in rat studies.

All but three of the post-natal exposure studies involved single or short duration exposures. In particular, the availability of NOAEL based on single-dose exposure enhanced the ability to derive this narrow window. However, the direction of effect varied. Exposures to halogenated organic compounds ammonium perfluorooctanoate, potassium perfluorooctane sulfonate, and brominated diethyl ethers 992 and 209 (BDE 992, BDE 209) (Eriksson et al., 1999, 2002; Johansson et al., 2008; Viberg et al., 2003, 2001) were associated with decreased or non-significant changes in motor activity levels, while exposure to tetrachloroethylene and DDT was associated with elevated motor activity (Eriksson et al., 1990a, 1990b; Fredriksson et al., 1993; Johansson et al., 1995, 1996). The NOAEL associated with the halogenated organic compounds derived from post-natal exposures occurring outside our derived window, with the exception of BDE 209 exposure to the highest dose (20.1 mg/kg/day versus 2.22 mg/kg/day) at PND 10 (Viberg et al., 2003, 2001).

In essence, variation in directionality of motor activity effects in mice following post-natal exposure appears chemical-specific; however, data from additional chemicals are needed to validate this hypothesis.

2.2. Motor function

2.2.1. Rat—Eighteen rat studies were found assessing motor function and exposure to 14 different chemicals during gestation and/or lactation (Fig. 3). Eight of the 18 studies (6 chemicals) specifically reported motor coordination endpoint measure data and 7 studies (6 chemicals) reported geotaxis or reflex development endpoint data. Four of the 18 gestation and/or lactation investigations of cesium and gamma radiation provided single-dose or short-duration findings. Contrary to motor activity data, with the exception of ^{137}Cs (Norton and Kimler, 1987, 1988), the directionality of the motor function effects was consistently lowered as exposures resulted in motor function deficits.

In addition, 4 motor function studies were noted assessing chronic exposure. Among the 4 chronic exposure studies reporting motor function data, one was a post-natal study [Mn chloride, ataxia (Kristensson et al., 1986)]. While this study suggests the possibility of a post-natal exposure window, no apparent additional postnatal-only exposure studies were found from which to support this finding. The remaining three studies assessed both pre- and post-natal exposure to As (Rodrıguez et al., 2002) and MeHg (Olson and Boush, 1975; Sakamoto et al., 2002). Arsenic exposure from GD 15 to PNM 4 at 2.93 mg/kg/day resulted in no observed adverse effects on motor coordination (rotarod performance), while MeHg exposure at 5 ppm from gestation to PND 55 decreased motor coordination. Similarly, exposure to 0.10 mg/kg/day MeHg hydroxide from gestation to PND 55 resulted in diminished motor function overall. Thus, these chronic Hg exposure studies are consistent with the shorter exposure study by Elsner (1991) included in Fig. 3. However, due to conflicting observations in the Norton & Kimler single-dose studies and the lack of other short-duration studies in the Toxicological Profiles, these studies were not sufficient for deriving a critical exposure window for motor function development.

2.2.2. Mouse—Twelve mouse studies were obtained of 6 chemical exposures that measured effect on motor function generally or grip strength specifically (Fig. 4). Five of these investigations evaluated two chemicals and their influence on motor coordination specifically – all of which assessed long exposure durations. Four geotaxis and reflex development studies of three chemical exposures were also noted. The window derived for mice overlaps with that of rats – GD 13–16. Two single-dose studies assessing chromium (Cr) and MeHg (Bailey et al., 2008; Inouye et al., 1985) and a short duration study of 1,1,1-trichloroethane (Jones et al., 1996) were the primary studies used to derive the exposure window. Similar to the corresponding rat studies, there was a lack of literature assessing single-dose and short-duration post-natal studies, precluding confirmation or challenging the possibility of a post-natal exposure window possible based on the longer duration studies.

With the exception of aluminum (Al) lactate, all of the LOAEL data consistently showed motor function deficits. Unlike other mouse motor function studies, those involving Al lactate assessed different measures of grip strength (Donald et al., 1989; Golub et al., 1992).

While forelimb strength was found to be decreased at all of the doses tested, hindlimb grip strength was increased in mice exposed to 155 and 250 mg/kg/day. However, a separate study by Golub et al. (1995) noted that a higher dose of 500 mg/kg/day resulted in decreased hindlimb grip strength, suggesting a dose-dependent effect for Al lactate.

Four mouse chronic exposure studies were also collected reporting motor function data associated with Al lactate (Golub et al., 2000, 1995), MeHg (Weiss et al., 2005), and toluene (Kostas and Hotchin, 1980). With the exception of the NOAEL data for Al lactate (7.5 mg/kg/day), hindlimb splay (1 ppm/day, GD1-PNM 26, (Weiss et al., 2005)), these exposures resulted in decreased grip strength (100 mg/kg/day, GD 1 – PNM 24 Al nitrate (Golub et al., 2000); 155 mg/kg/day, GD 1 – PND 170 Al lactate, (Golub et al., 1995) and motor coordination (4 mg/kg/day, GD 1 – PND 55 toluene (Kostas and Hotchin, 1980). In light of the corresponding subchronic findings, the chronic Al lactate data suggest both a dose and duration effect. For example, Golub and colleagues observed decreased hindlimb grip strength with a chronic dose of 100 or 155 mg/kg/day Al lactate, but this effect was not observed in shorter duration exposures below 500 mg/kg/day (which actually led to increased hindlimb grip strength) (Golub et al., 2000, 1995).

In summary, this evaluation confirmed that the main elements determining whether a chemical causes development of neurological motor effects are dose and timing of exposure, susceptibility of the species, and mechanism of action (MOA) of the chemical. The windows of sensitivity to environmental toxicants in the development of neurological effects are not that well defined as compared to the window for development of cleft palates. The window of sensitivity for cleft palate coincides with development of the palate itself (Buser and Pohl, 2015). In contrast, neurological effects may develop during organogenesis, proliferation and migration of nerves, differentiation and synaptogenesis, and myelination over a much broader time period. Each of these developmental processes occurs at different time stages *in utero* and even after birth. Therefore, different windows of susceptibility may be observed for different effects.

3. Select non-toxicological profile chemicals

Due to the specific scope of ATSDR's Toxicological Profiles based on Congressional mandate – substances frequently found at hazardous waste sites – other well-studied xenobiotics known to elicit developmental effects on the developing nervous system are not captured by this dataset. Thus, motor development effects associated with exposure to two well-known teratogens – ethanol and retinoic acid – are discussed below.

3.1. Ethanol

3.1.1. Motor activity—Overall, the literature on ethanol exposure and locomotor activity shows elevated activity in both animals and humans, but the human data are not specific enough to establish narrow windows of sensitivity. In a review paper, Schneider et al. (2011) concluded that studies in monkeys and rodents demonstrate that prenatal alcohol exposure adversely influenced neonatal orienting, attention and motor maturity. Similarly, a 2013 rat and mouse study assessing the effects of gestational exposure to 0.5, 1, 2 g/kg/day (ICR mice only), 4 or 6 g/kg/day (mice and Sprague–Dawley rats) ethanol from GD 6–15

observed significantly increased locomotor activity in mice offspring exposed to 6 g/kg/day and rat offspring exposed to 4 or 6 g/kg/day relative to controls (Kim et al., 2013). These behavioral observations were concomitant with decreased Methyl-CpG-binding protein 2 (MeCP2) expression (an epigenetic factor) in the prefrontal cortex and striatum, along with increased dopamine transporter and norepinephrine transporter levels in the cortex and striatum. Coles et al. (1985), assessed the effects of ethanol consumption during the entire gestation period or during the first two trimesters. The authors found that the children of mothers who consumed an average of 12 oz ethanol per week during the entire pregnancy or 14 oz per week during the first two trimesters exhibited increased motor activity.

3.1.2. Motor function—Lucas et al. (2014) recently published a meta-analysis of ten human observational studies measuring gross motor function in children (0–18 year's age) prenatally exposed to ethanol. The authors found a significantly elevated risk of deficits in balance, coordination, and ball skills (odds ratio [95% CI]: 2.9 (2.1–4.0). However, the summary effect size was calculated based on a categorical exposure measure (Yes/No fetal alcohol syndrome (FASD) diagnosis [5 studies)] or moderate/heavy/binge maternal alcohol intake [3 studies] or FASD & moderate/heavy maternal alcohol intake [3 studies]), thus precluding dose response assessment. Of the 14 studies included in the corresponding systematic review, only four of the studies reported data on specific exposure durations or time of exposure measure (Autti-Rämö and Granström, 1991; Barr et al., 1990; Coles et al., 1987; Kesmodel et al., 2013; Smith et al., 1986). However, similar to the human motor activity studies, the human data cannot identify narrow windows of sensitivity.

3.2. Retinoic acid

3.2.1. Motor activity—The neurobehavioral effects of retinoids have been studied since the 1960s, and the research was summarized in a recent review (Adams, 2010). In 1986, Nolen observed hyperactivity in Sprague Dawley rats exposed to 5 mg/kg all-trans-retinoic acid from GD 8–10 or GD 14–16 and reduced postnatal survival after exposure from GD 11–13 (Nolen, 1986). In this same study, additional rat offspring were exposed to 2, 4, or 6 mg/kg all-trans-retinoic acid from GD-14-16. Following exposure to 4 or 6 mg/kg, rats showed increased motor activity; no effects on activity were observed after exposure to 2 mg/kg, but in a separate set of tests. Similarly, Holson and colleagues also found no effects on motor activity level in Sprague–Dawley rat offspring exposed to 2.5 mg/kg all-trans-retinoic acid from GD 11–13, but this dose did reduce cerebellum weight (Holson et al., 1997). In contrast, later studies found significant deficits in ambulatory activity at this same dose and duration (Coluccia et al., 2008a), as well as with exposure from GD 8–10 (Coluccia et al., 2008b). Overall, the data suggest that the dose is the major factor in these studies to affect motor activity development.

3.2.2. Motor function—Nolen (1986) found impaired reflex development in Sprague–Dawley rats exposed to 5 mg/kg all-trans-retinoic acid from GD 8–10 or GD 14–16. Within the same study, Nolen also reported delayed negative geotaxis in offspring exposed to 4, 5, or 6 mg/kg all-trans-retinoic acid from GD 14–16. At a lower exposure of 2.5 mg/kg on GD 11–13, no effects on negative geotaxis were observed (Holson et al., 1997). On the other hand, Coluccia et al. (2008a) observed significant delays in reflex development under these

same exposure conditions. In a separate study, these authors assessed gestational exposure to 2.5 mg/kg from GD 8–10 and reported impaired motor function (Coluccia et al., 2008b). The data are not sufficient to make conclusions regarding critical windows of sensitivity for motor function effects.

4. Dose-dependency and timing for eliciting effects

Dose-dependency was demonstrated in several studies presented in Figs. 3 and 4. For example, when groups of Wistar rat pups were administered daily oral doses of 0, 1, 3, or 5 mg/kg/day MeHg on PND 1–30, typical effects including hind-limb crossing and ataxia were observed only at the highest exposure group (Sakamoto et al., 2004). Dose-dependent insufficiencies in motor coordination and learning ability were associated with histological changes indicating widespread neuronal degeneration.

The first window of sensitivity is early in the embryonic stage, when both genetic and environmental factors (multifactorial threshold) might result in neural tube defects including anencephaly, encephalocele, craniorachischisis, and spina bifida (Harris and Juriloff, 2007). In humans, neurulation starts around day 17 after fertilization and ends before day 30. In mouse, neurulation starts at GD 8.5 and completes by GD 10.5. Most of the neural tube defects, but not all such as spina bifida are incompatible with life of the offspring.

Later on during gestation, other morphologic, histopathologic, and biochemical effects may develop. Groups of guinea pigs exposed to a single dose of 11.5 mg Hg/kg as methylmercuric chloride on GD 21, 28, 35, 42 or 49 showed differences in manifestation of developmental neurotoxicity depending on the period of development when exposure occurred (Inouye and Kajiwara, 1988). Primarily developmental disturbances of the brain including smaller brains with thinner cerebral cortex, dilated lateral ventricles, reduced size of hippocampus and nucleus caudate-putamen occurred with exposures at 3, 4, or 5 weeks of pregnancy. Exposure during a later pregnancy stage (6 or 7 weeks) produced widespread focal degeneration of neurons in the neocortical region of fetal brains. A series of studies evaluated effects of chlorpyrifos (CPF) on neurotransmitter systems during development in Sprague–Dawley rats. Four developmental windows were evaluated: GD 9–12, GD 17–20, PND 1–4, and PND 11–14 (Aldridge et al., 2003). Minor effects on serotogenic system were reported following treatments during GD 9–12. Major effects were associated with treatments during GD 17–20 causing super-sensitivity to both stimulatory and inhibitory responses in signal transduction. Sensitivity declined in the late post-natal period. Chlorpyrifos exposure produced lasting up-regulation of the expression of serotonin (5-HT) synaptic protein receptors and a presynaptic transporter. It was further demonstrated that these changes were accompanied by functional changes (Aldridge et al., 2005a). Chlorpyrifos exposure on GD 17–20 and on PND 1–4 induced long-term increases in 5-HT turnover in multiple brain regions at threshold exposure levels. The changes were not correlated with the neurotransmitter content. In contrast, dopamine (DA) turnover was elevated following exposure on GD 17–20 only after doses that elicited overt toxicity. The least sensitive period for inducing changes in adenylyl cyclase signaling was GD 9–12 in another experiment in rats using the same exposure regimen (Aldridge et al., 2005b). Although the window of sensitivity was broad across developmental periods, differences

were noted in the regional locus, sex selectivity, and specific signaling protein targeted by the pesticide. In contrast, despite the use of a higher dose and the resulting increased cholinesterase inhibition, no effects on 5HT were noted after PND 11–14 exposure. Aldridge and coauthors concluded that "developmental chlorpyrifos exposure, at doses below the threshold for maternal or fetal/neonatal toxicity, and below that required for inhibition of fetal brain cholinesterase, nevertheless causes lasting disruption of 5HT synaptic activity when exposure occurs in a critical developmental window centered around the immediate perinatal period." On the other hand, an extensive review of epidemiologic studies on pesticide exposure did not find a strong correlation between adverse neurodevelopmental outcomes in infants and children and exposure (Burns et al., 2013). A thorough review of both epidemiologic and animal studies on chlorpyrifos similarly found no significant effects on motor function development in humans (Li et al., 2012).

Also in animals, there are studies that failed to show windows of sensitivity. Several studies experimented with *all-trans* retinoic acid treatments of Sprague–Dawley rats under various regiments during gestation. When female rats were treated with 2.5 mg/kg *all-trans* retinoic acid on GD 11–13, pups showed significantly delayed onset of reflexive behavior (Coluccia et al., 2008a). Representative tests of reflexive behavior included: delayed righting reflex (indicating subcortical maturation), cliff aversion (indicating integration of exteroreceptive and locomotive inputs), and pole grasping (indicating muscle strength). In addition, offspring displayed deficits in locomotor activity, motor coordination, and motor learning. The young pups showed also morphological changes in cerebellum that recovered later in life. However, some motoric effects were more pronounced with increasing age. Therefore, Coluccia et al. (2008a) concluded that not only the cerebellum was affected by the treatment, but also the cortico-cerebellar connections. The latter changes persisted. When female rats were treated on GD 8–10, similar effects were observed (Coluccia et al., 2008b). The onset of righting reflex and negative geotaxis were delayed by two days in the pups, suggesting a hindered development of vestibular reflexes and dysfunction of the cerebellum. Similar to the previous study, offspring showed deficits in locomotor activity, motor coordination, and motor learning. When the study was extended to cover the late gestation with treatments occurring on GD 14–16, the results confirmed the earlier reports (Coluccia et al., 2009). Evidence indicated that observed changes do not depend on gestational period but rather on specific tasks tested reflecting prolonged developmental period of cerebellum and its neural connections.

The difficulty encountered during interpretation of data in Figs. 3 and 4 is that most studies are designed to elicit any neurological effect in the offspring. Therefore, the exposure period is long, often encompassing gestation and postnatal periods of rodents in the experiment. Thus the information may not be helpful for extrapolating to acute human exposures in specific stages of pregnancy.

5. Interspecies differences

Experimental studies presented in this review were done in laboratory animals. To extrapolate results to be relevant to human exposures, interspecies differences must be taken into the account. There are differences among species as to the developmental stages and

timing of parturition. For example, rodents are born approximately at the time when human fetuses complete their second trimester in the uterus (Barton, 2005). Rapid brain growth appears mainly during the third trimester in humans, while in rats it appears after birth. Consequently, some effects are induced postnatally in rodents. Ototoxicity is an example of such an outcome. When Long-Evans rats were administered daily oral doses of Aroclor 1254 from GD 6 to PND 21, pups displayed low frequency hearing loss associated with a loss of outer hair cells in the Corti's organ (Crofton et al., 2000a). The authors narrowed the window of sensitivity by a cross-fostering study (Crofton et al., 2000b). The treatment regime of the dams was the same as in the previous study. However, the cross fostering resulted in 4 groups of pups: control, perinatal exposure, prenatal exposure only, and postnatal exposure only group. Aroclor 1254 caused low frequency hearing loss in pups from the perinatal and postnatal groups. Therefore, the postnatal, i.e., lactational exposure, was critical for developing the ototoxic effect. This would not apply to humans. Although the studies are not examples of motor function, they reflect maturation of the nervous system in different species.

Similar results were obtained for some other brain functions. Three groups of Wistar albino rats were treated for 10 days with oral doses of MeHg starting on PND 2, PND 15, or PND 60 (Wakabayashi et al., 1995). In newborn pups, no adverse clinical effects were observed and only minimal histological changes were noted in hippocampus and brainstem. In the PND 15 group, unsteadiness, gait disturbance, and paroxysmal convulsions were observed. Histologically, widespread neuronal degeneration encompassing cerebral neocortex, hippocampus, neostriatum, red nucleus, and other brainstem nuclei was recorded. In adults (PND 60 group), a hind-limb crossing phenomenon was found together with extensive neuronal damage in the cerebellum and spinal dorsal nerve roots. The study clearly showed developmental windows of sensitivity linked to specific effects. Wakabayashi et al. (1995) noted that the brain lesions induced postnatally in rats were similar to those observed in human fetuses poisoned by MeHg in the Minamata, Japan incident (Sakamoto et al., 2004, 1998).

An extensive review article pointed out numerous similarities and differences across species in the growth and morphological development of the brain in regards to neurogenesis, myelination, synaptogenesis, and neuronal and synaptic pruning in humans, rats, cats, dogs, monkeys, and non-human primates (Watson et al., 2006). Rats were recommended as a reliable experimental model for humans in early postnatal development. However, marked differences still exist between humans and rats in areas such as neurogenesis and myelination. At birth, humans are more advanced.

Intraspecies differences in sensitivity based on the genetic make-up of individuals also exist. For example, 88% of the litter of B10.D2 congenic strain of mice exposed to MeHg on GD 15 developed hydrocephalus (Inouye and Kajiwara, 1990). When dams of C57BL/10 (B10) or DBA/2 (D2) strain were also treated with 10 mg/kg MeHg on day 15 of pregnancy, hydrocephalus was reported in 54% and 0%, respectively.

6. Mechanism of action (MOA)

The MOA for developmental toxicants is similar to mechanisms for other toxicants. These include genetic mutations, chromosomal aberrations, diminished supplies of precursors and substrates, altered energy sources, altered osmotic balance, and enzyme inhibition. For example, retinoids are known as universal teratogens based on their ability to regulate and disrupt the *HOX* code patterns of gene expression (Carrasco and Lopez, 1994).

An early post-natal MeHg chloride exposure study by Willes et al. (1978) analyzed histological effects in four infant monkeys demonstrating both motor activity and motor function deficits following PND 1 to PND 28–29 exposure to 0.5 mg Hg/kg/day The authors noted histopathologic lesions in the cerebrum and cerebellum (minus Purkinje and granular cells in the vermis), but the peripheral nervous system remained intact. Focal cerebellar dysplasia, including the heterotopic location of Purkinje cells and granule cells, was reported in pups of rats exposed to MeHg during gestation (Sakamoto et al., 2002). In a follow-up study, the authors found that the progenitor cells labeled with retrovirus developed into astrocytes and oligodendrocytes following MeHg exposure and were accumulated abnormally in the lateral white matter of the brains of rat pups (Kakita et al., 2003). Also a deeper layer of the lateral cortex and lateral side of the striatum were affected.

7. Conclusions

Windows of sensitivity to chemical exposures during development of the neurological system were examined. A total of 136 study-relationships were found associating exposures to 32 different chemicals and neurologic effects in mammals. Several windows of sensitivity were identified that depended on the level of maturity of the neurological system at the time of exposure. Distinct windows were found for motor activity versus motor function performance. However, most laboratory studies are not designed to identify specific windows but are aimed to detect neurodevelopmental toxicity at any stage. A difference in the degree of maturity of the nervous system between humans and animals at the time of exposure needs to be taken into account. More studies assessing narrow exposure durations specific to motor development are needed to confirm our windows findings.

Abbreviations

GD	gestation day
LOAEL	lowest observed adverse effect level
NOAEL	no observed adverse effect level
PND	post-natal day
PNM	post-natal month
PNW	post-natal week

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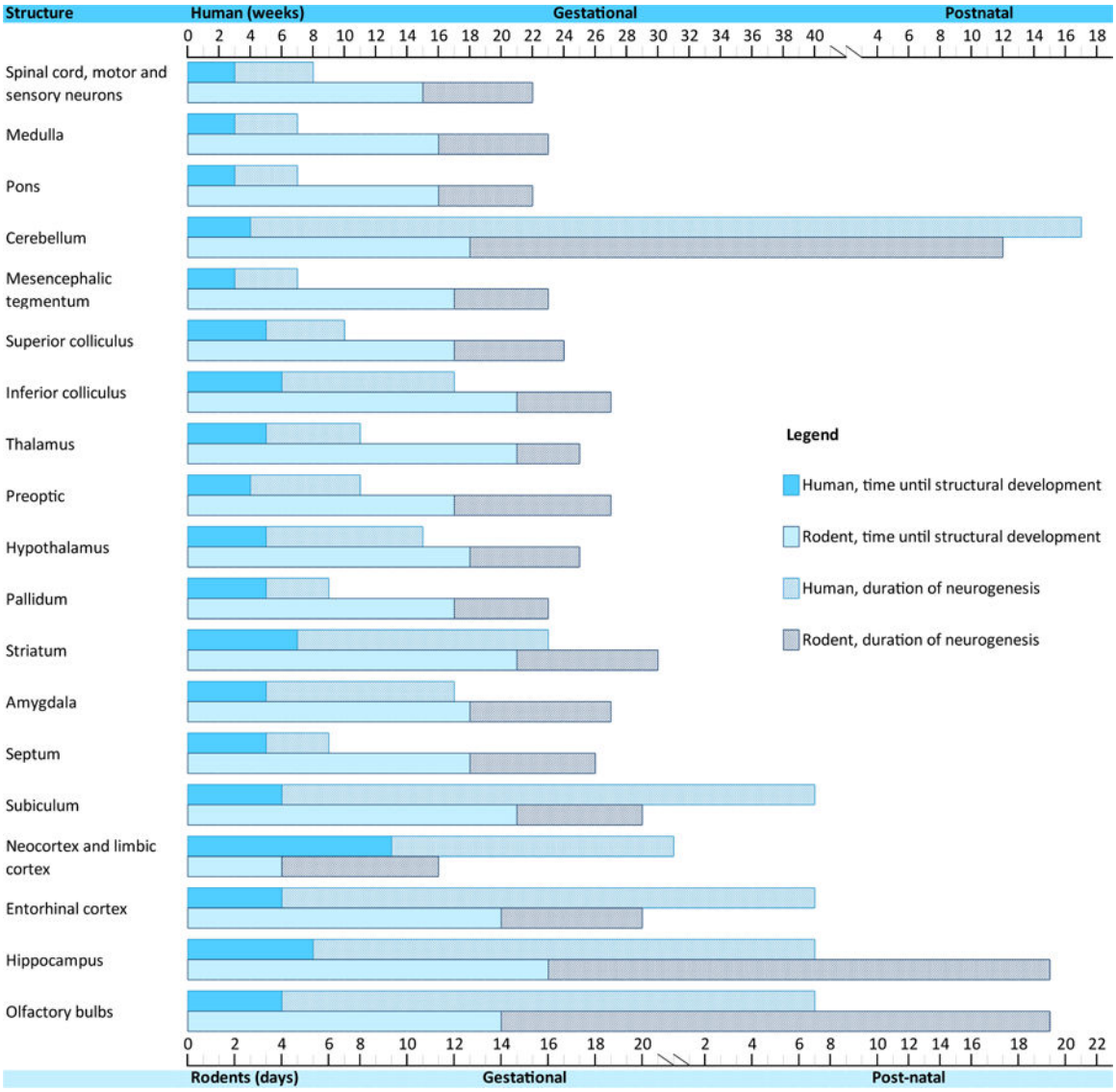


Fig. 1.

Comparison of human versus rodent timing of nervous system development. Adapted from Daston et al., 2004. Solid bars represent time until structural development, patterned bars illustrate time of origin (e.g. neurogenesis) for each nervous system structure. Human developmental windows (measured in weeks) are dark blue and rodent developmental windows (measured in days) are light blue. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

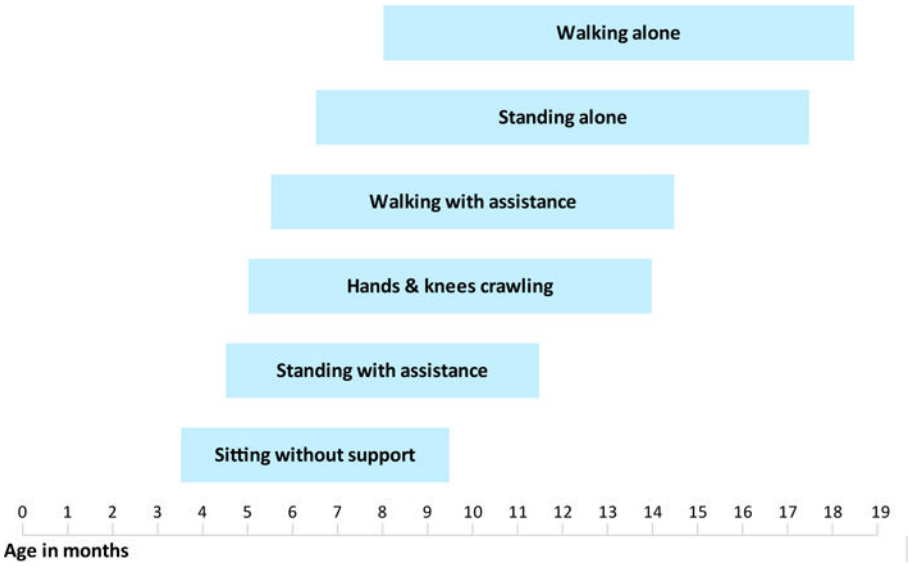
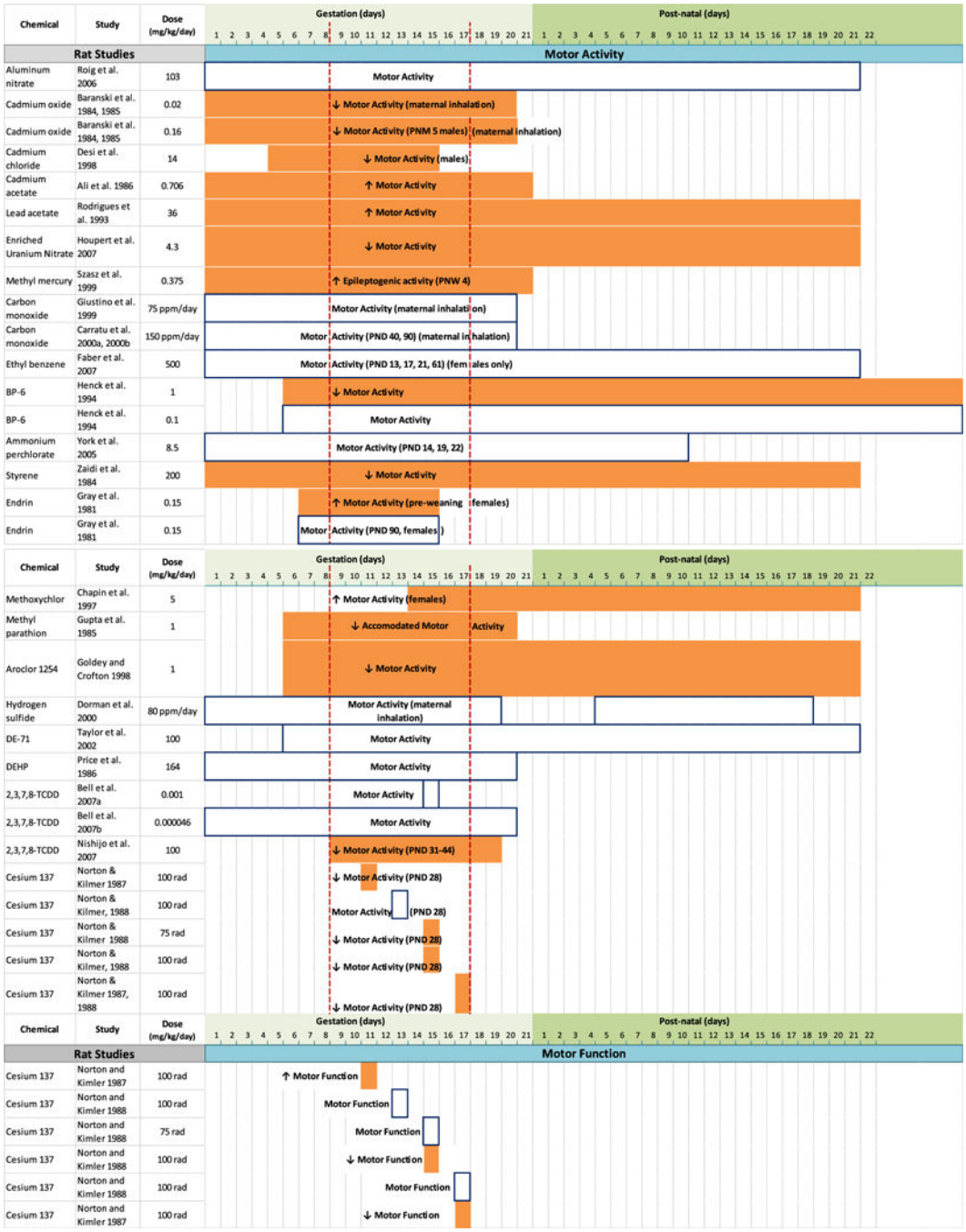


Fig. 2.
Windows of achievement for six gross motor milestones. Adapted from the World Health Organization Child Growth Standards (2006).



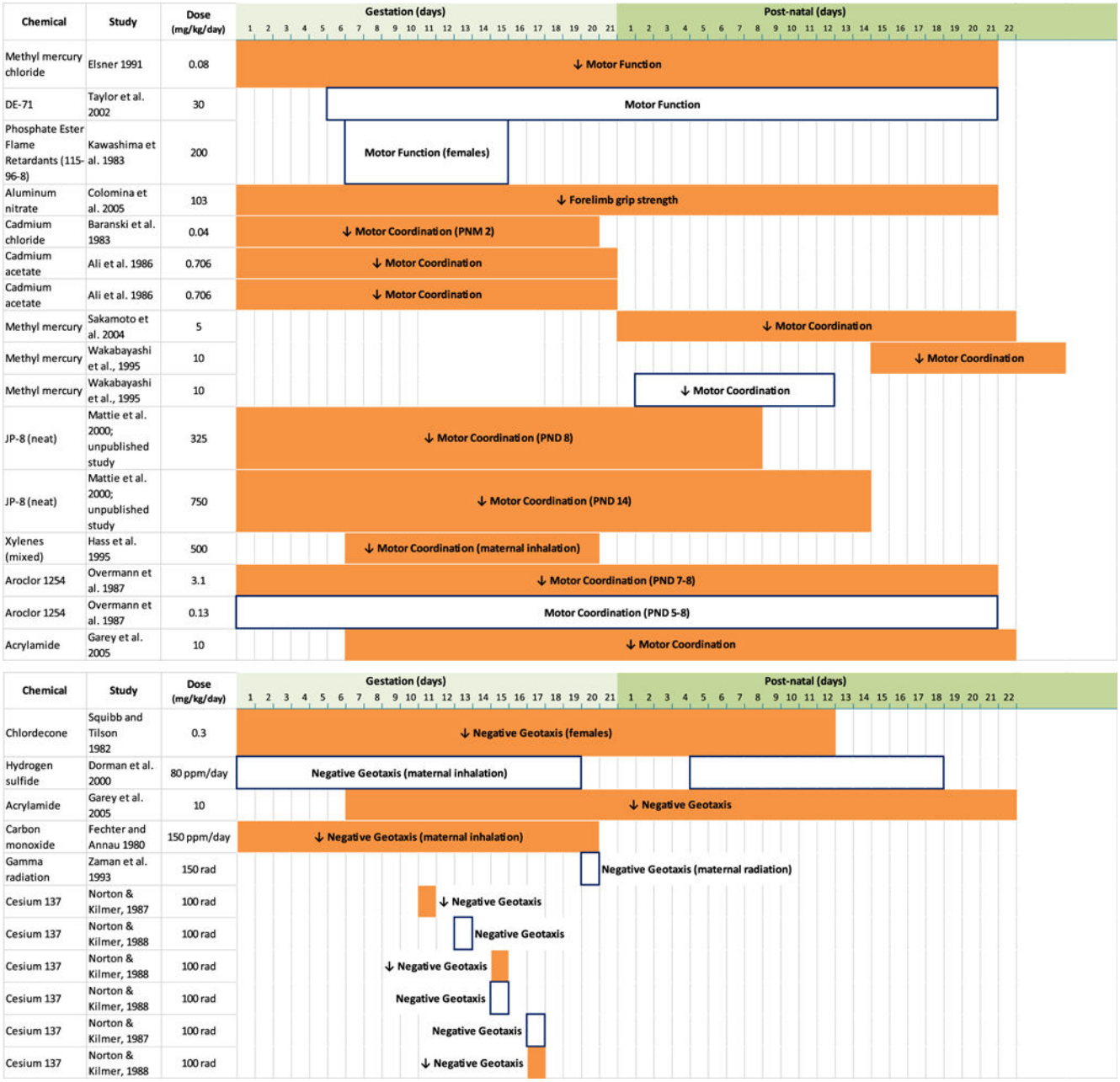
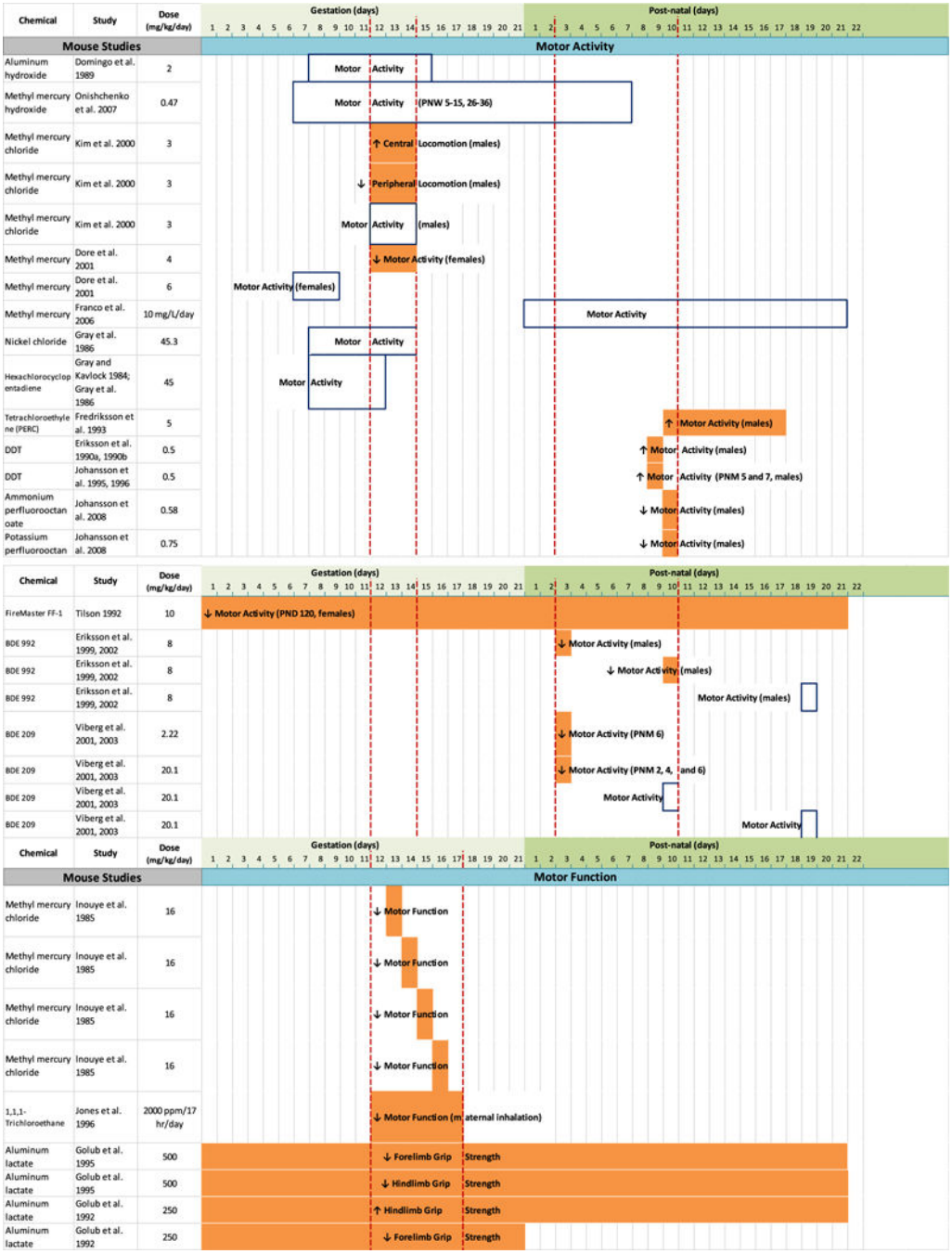


Fig. 3.

Windows of exposure in rats by motor development endpoint measure. *PND*: postnatal day; *PNW*: post-natal week; DEHP: di(2-ethylhexyl) phthalate, *DDT*: dichlorodiphenyltrichloroethane; *TCDD*: Tetrachlorodibenzo-p-dioxin; *BDE/DE*: brominated diphenyl ether mixture trade names; *JP*: jet propellant. Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant motor development effects combined with NOAEL data from short and single-dose duration studies. Time periods contained in parentheses indicate times at which endpoint measurements were taken. Open bars indicate no exposure effect; orange bars indicate significant exposure effect. (For interpretation of the references to color in this

figure caption, the reader is referred to the web version of this article.). Ali et al., 1986; Barański, 1984, 1985; Barański et al., 1983; Bell et al., 2007a, 2007b; Carratu et al., 2000a; Carratu et al., 2000b; Chapin et al., 1997; Colomina et al., 2005; Dorman et al., 2000; Faber et al., 2007; Fechter and Annau, 1980; Garey et al., 2005; Giustino et al., 1999; Goldey and Crofton, 1998; Gupta et al., 1985; Hass et al., 1995; Henck et al., 1994; Houpert et al., 2007; Kawashima et al., 1983; Manfroi et al., 2004; Mattie et al., 2000; Overmann et al., 1987; Price et al., 1986; Rodrigues et al., 1993; Roig et al., 2006; Singh, 1986; Spyker and Avery, 1977; Squibb and Tilson, 1982; Szász et al., 1999; Taylor et al., 2002; York et al., 2005; Zaidi et al., 1984; Zaman et al., 1993.



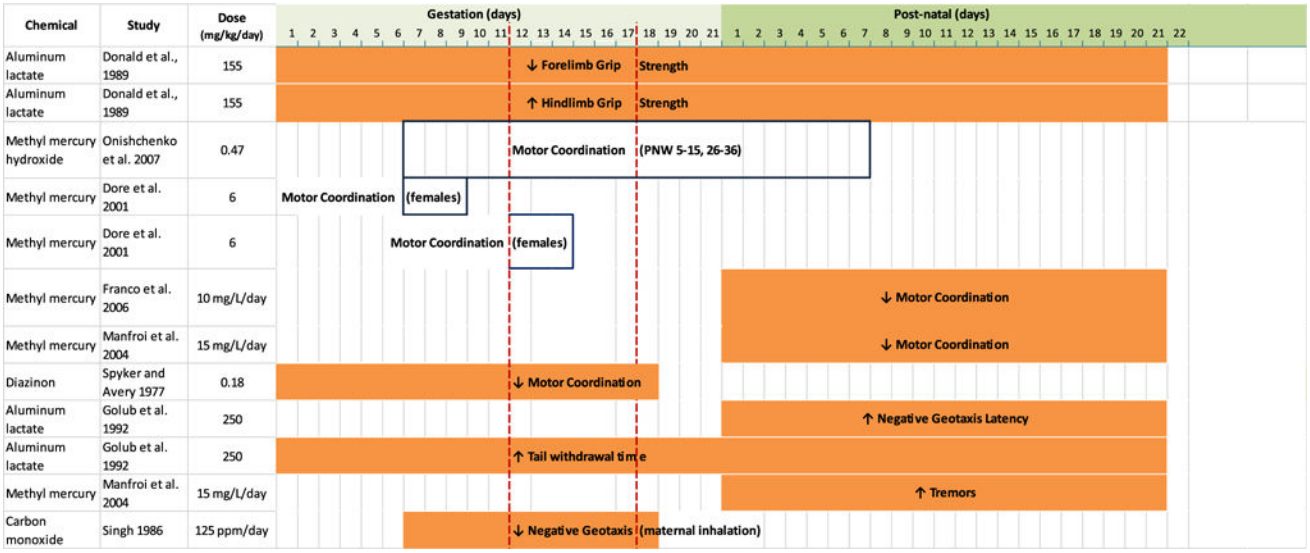


Fig. 4.

Windows of exposure in mice by motor development endpoint measure. *PND*: postnatal day; *PNW*: post-natal week; *DDT*: dichlorodiphenyltrichloroethane; *BDE/DE*: brominated diphenyl ether mixture trade names; *JP*: jet propellant. Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant motor development effects combined with NOAEL data from short and single-dose duration studies. When a study specified the type of motor function test utilized, we classified the exposure windows as pertaining to motor coordination, negative geotaxis, grip strength, or reflex NOAEL or LOAELs; if the study reported a motor function battery or did not specify a specific type motor function outcome, we gave the exposure window the broader label of motor function. Unlike motor activity, motor function studies present results pertaining to the "quality" of the movements, not the quantity. Time periods contained in parentheses indicate times at which endpoint measurements were taken. Open bars indicate no exposure effect; orange bars indicate significant exposure effect. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.). Domingo et al., 1989; Franco et al., 2006; Gray et al., 1986; Gray and Kavlock, 1984; Manfroi et al., 2004; Onishchenko et al., 2007; Singh, 1986; Spyker and Avery, 1977.