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Short communication

Dose-response analysis indicating time-dependent neurotoxicity caused by organic and inorganic mercury—Implications for toxic effects in the developing brain

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ABSTRACT

A latency period preceding neurotoxicity is a common characteristic in the dose-response relationship induced by organic mercury. Latency periods have typically been observed with genotoxicants in carcinogenesis, with cancer being manifested a long time after the initiating event. These observations indicate that even a very small dose may cause extensive adverse effects later in life, so the toxicity of the genotoxic compound is dose and time-dependent. In children, methylmercury exposure during pregnancy (in utero) has been associated with delays in reaching developmental milestones (e.g., age at first walking) and decreases in intelligence, increasing in severity with increasing exposure. Ethylmercury exposure from thimerosal in some vaccines has been associated, in some studies, with autism and other neurological disorders in children. In this paper, we have examined whether dose-response data from *in vitro* and *in vivo* organic mercury toxicity studies fit the Druckrey-Küpfmüller equation $c \cdot t^n = \text{constant}$ (c = exposure concentration, t = latency period), first established for genotoxic carcinogens, and whether or not irreversible effects are enhanced by time of exposure ($n \geq 1$), or else toxic effects are dose-dependent while time has only minor influence on the adverse outcome ($n < 1$). The mode of action underlying time-dependent toxicity is irreversible binding to critical receptors causing adverse and cumulative effects. The results indicate that the Druckrey-Küpfmüller equation describes well the dose-response characteristics of organic mercury induced neurotoxic effects. This amounts to a paradigm shift in chemical risk assessment of mercurial compounds and highlights that it is vital to perform toxicity testing geared to investigate time-dependent effects.

1. Introduction

Organic mercury induced neurotoxicity has typically been observed after a preceding latency period. Even severe and fatal ethylmercury intoxications in humans featured a latency period between cessation of exposure and onset of first symptoms of 10 days to 7 weeks (Cinca et al., 1980; Magos, 2001). For methylmercury, latencies in intoxications in Iraq and Japan ranged from weeks to more than a year (Bakir et al., 1973; National Research Council, 2000; Weiss et al., 2002) and effects were proceeding even after exposure had ended 20–30 years before (Rice and Barone, 2000). When monkeys were exposed to low levels of methylmercury during their developmental phase, neurotoxicity appeared after several years (Rice, 1996). Latency periods have typically been observed with genotoxicants in carcinogenesis, with cancer being manifested a long time after the initiating event. These observations indicate that even a very small dose may cause extensive adverse effects later in life, so the toxicity of the genotoxic compound is dose and time-dependent.

Methylmercury is widely distributed throughout the environment, particularly in estuarine and marine sediments (Bryan and Langston, 1992; Compeau and Bartha, 1985; Morel et al., 1998) and accumulates in fish and birds (Greichus et al., 1973; Harris et al., 2007; Henny et al., 2005; Houserová et al., 2007; Lam et al., 2005; Polak-Juszczak, 2012; Wren, 1986). Therefore, people are likely to be continuously exposed to small amounts of methylmercury through consumption of contaminated food (Chan et al., 2010; Lin et al., 2012). Ethylmercury is used as preservative in vaccines that may be administered to pregnant women. Toxicokinetic evidence confirms that alkyl mercury compounds cross the placental barrier (Aschner and Clarkson, 1988; Bridges and Zalups, 2005; Dórea,

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2011; Dórea et al., 2013; Geier et al., 2007; Kajiwara et al., 1996; Kerper et al., 1992) and the blood-brain barrier (Apostoli et al., 2006; National Research Council, 2000).

A myriad of scientific papers have been published on the toxicology of inorganic and organic mercury compounds. However, limited data are available for quantitative analysis of time-dependent toxicity. Most animal studies did not examine effects observed at different time points over extended exposure periods. Studies of human poisoning cases widely observed a latency period but an accurate estimation of dose or concentration at the target site is difficult to obtain. Data on Iraqi poisonings presented by Bakir et al. (1973) outlined the onset of symptoms after a mean latency period in relation to mercury concentrations in the blood of intoxicated individuals. These blood samples were obtained up to 115 days after the onset of symptoms. However, animal studies demonstrate a great divergence between blood and brain concentrations after exposure has ceased, suggesting that mercury persists in the brain while clearance from the blood occurs faster (Burbacher et al., 2005; Evans et al., 1977; Magos, 2001; Vahter et al., 1995). Therefore, blood concentrations taken a long time after exposure has ceased may not be a good parameter for assessing dose- and time-dependent neurotoxicity.

2. Dose and time-dependent toxicity of alkyl mercury compounds: data analysis

Wobeser et al. (1976) published data on the relationship between methylmercury dose and the occurrence of neurotoxic clinical signs in mink. A latency period was observed in all animals exhibiting toxicity. The higher the administered dose the earlier adverse effects appeared. When examining the total dose administered to the animals in the different dose groups it becomes apparent that low doses given continuously over a long period until the occurrence of ataxia add up to a lower total dose than the total dose from higher doses over a shorter period of time (Table 1). Decreasing total doses and increasing adverse effect induction times could reflect dose and time dependencies according to the Druckrey-Küpfmüller equation (Druckrey and Küpfmüller, 1949):

$$dt^n = \text{constant} \quad (1)$$

where the exponent $n > 1$ can be regarded as an exposure-time-reinforcement factor (Tennekes and Sánchez-Bayo, 2013). A dose-time-effect analysis of the ataxia data provided by Wobeser et al. (1976) results in a value of n = 1.5 ($r^2 = 0.93$), as illustrated in Fig. 1.

Another dataset confirming that neurotoxic effects from methylmercury exposure are reinforced over time was established using data obtained by Grant (1973) in cats (Table 2). In this case, the Druckrey-Küpfmüller equation described the dose-response relationship with n = 2.9 ($r^2 = 0.71$). This high n-value may be related to the observation that cats were particularly sensitive to methylmercury exposure (Charbonneau et al., 1976). A latency period of at least 59 days was noted and clinical signs observed included ataxia and convulsions. Interestingly, when brain concentrations are correlated to the latency period in the onset of clinical signs a lower r^2 value is obtained. Mercury is known to accumulate in specific brain regions which may not have been taken into account when brain concentrations were determined.

For ethylmercury-induced effects, the Druckrey-Küpfmüller equation describes the dose-response relationship in human cortical neurotoxicity observed by Baskin et al. (2003), (Table 3) with an exposure-time-reinforcement factor of 2.81 ($r^2 = 0.8$), (Fig. 2) for concentrations ranging from 1 to 250 μM at time points between 2 and 24 h. The extremely high value of n obtained in this case indicates pronounced reinforcement of toxicity by exposure time.

Table 1
Effect of dose on onset of methylmercury-induced ataxia in mink (after data from Wobeser et al., 1976).

Dose (d) in feed (ppm)	Median time (t50) to onset of ataxia (days)	Total dose (ppm) = d·t50
1.8	69	124.2
4.8	30.5	146.4
8.3	20	166
15	17.75	266.25

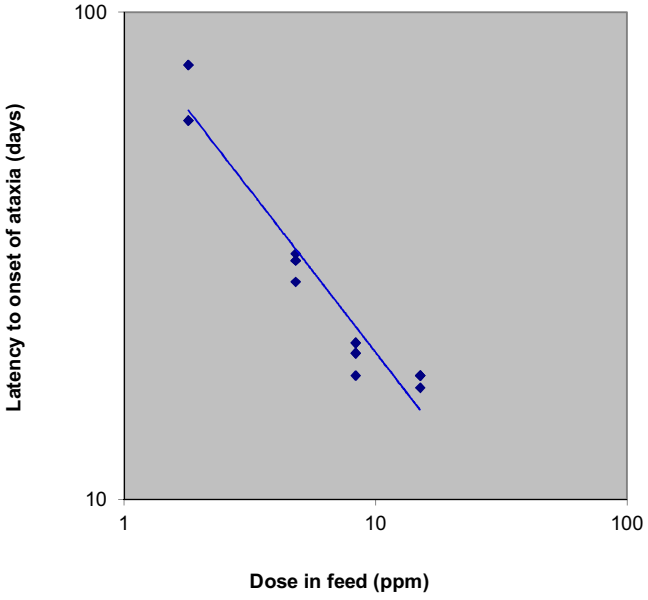

Fig. 1. Onset of ataxia in mink exposed to various doses of methylmercury in feed over time.

Table 2
Effect of methylmercury dose on the onset of neurotoxic signs in cats (after data from Grant,1973).

Daily dose (d), (mg/kg)	Latency period of clinical signs (t), (days)	Total dose (mg/kg) = d·t
0.34	71	24.14
0.44	63	27.72
0.47	68	31.96
0.55	59	32.45

Table 3
Effect of exposure concentration on latency periods of neurotoxicity in human cortical neurons exposed to ethylmercury (after data from Baskin et al., 2003).

Concentration (μM)	Time (t) to neurotoxic effect (hours)	Total dose (μM) = c·t
1	24	24
2	6	12
10	4	40
50	4	200
250	2	500

3. Pharmacokinetic and pharmacodynamic basis of mercury-induced time-reinforced neurotoxicity

Druckrey and Küpfmüller (1949) explained time-reinforced toxicity ($n > 1$) of chemicals as a result of irreversible receptor binding associated with an irreversible effect. The Druckrey-Küpfmüller theorem was recently validated for a number of genotoxic and non-genotoxic compounds, including inorganic (e.g. selenium) and organic chemicals with specific mode of action such as pesticides (Tennekes and Sánchez-Bayo, 2013).

In the case of mercury, the actual toxicant in the central nervous systems (CNS) is thought to be the divalent mercuric ion (Hg^{2+}) which is formed when organic mercury compounds such as methyl- and ethylmercury dealkylate. Once organic mercury compounds reach the brain tissue and dealkylate, Hg^{2+} gets trapped in the neurons, as it cannot permeate the blood-brain barrier. In mink and monkeys, inorganic mercury remains in the brain even months after organic mercury exposure has ended (Burbacher et al., 2005; Evans et al., 1977; Vahter et al., 1994, 1995; Wobeser et al., 1976). A recent review outlined evidence from human case studies, animal studies and modelling assessments estimating an inorganic mercury half-life in human brains of at least five to 27 years (Rooney, 2014). The "one-way" only kinetic pathway and the continuous dietary exposure lead to Hg^{2+} accumulation in the brain tissues. Neurons and glia in the cerebellum and hippocampus appear to be primary targets of this ion (Lohren et al., 2015; Pedersen et al., 1999). Hg^{2+} has electron-sharing facilities that can result in formation of covalent attachment to sulfhydryl groups of proteins, and binding of mercury species to thiol groups in amino acids, intracellular enzymes and structural proteins. For example, cysteine, glutathione and metallothionein are common targets of inorganic mercury and methylmercury (Conner and Fowler, 1993; Krupp et al., 2008). Moreover, in an interaction with cysteine, methylmercury does not only form Hg—S covalent bonds but may also bind to nitrogen and to a smaller proportion to oxygen atoms (Krupp et al., 2008). Direct binding of mercuric ion to enzymes' active sites, if the sites contain sulfhydryl groups, may lead to inactivation of the enzymes, and the interaction with thiol-containing antioxidants such as glutathione can cause increased production of reactive oxygen species that damage lipids, protein and DNA (Ercal et al., 2001). It can be envisaged that mercury neurotoxicity would result from an autocatalytic process initiated by binding of mercuric ion to sulfhydryl groups of organic macromolecules.

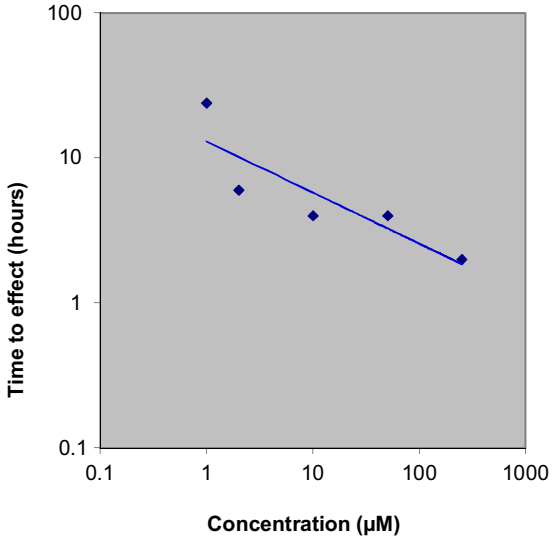

Fig. 2. Latency period of toxicity in relation to exposure concentration in ethylmercury-induced neurotoxicity in human cortical neurons in vitro.

Autocatalytic processes have been observed in the Alzheimer's- and prion-disease-associated accumulation of amyloid fibrils, which has been linked to the induction of calcium influx and reactive oxygen species (ROS) leading to neuronal degeneration and oxidative stress (Ho et al., 2001; Kupfer et al., 2009; Zetterberg and Blennow, 2013). The accumulation of cytosolic calcium has been suggested as an early and pivotal event in causing neurotoxicity as it initiates all the other neurodegenerative events including generation of ROS and apoptosis (Ekinci et al., 1999, 2000). An increased Ca^{2+} influx has also been described as fundamental to mercury toxicity. Upon binding to glutathione and metallothionein, mercury initiates alterations in membrane permeability to calcium ions leading to oxidative stress, glutathione depletion and subsequent cell death (Conner and Fowler, 1993; Klaassen, 2008; Sarafian and Verity, 1991). Ethyl-, methyl- and inorganic mercury have all been demonstrated to be cytotoxic in differentiated human and rat neuron cultures at decreasing concentrations over an increasing exposure period (Fujimura and Usuki, 2012; Lohren et al., 2015; and as discussed Baskin et al., 2003).

The effect of interest here is developmental neurotoxicity. Methylmercury exposure to the developing brain compromises neuronal proliferation, migration and as a result neuronal differentiation, synaptogenesis, tightly regulated apoptosis, and other processes vital to the formation and functioning of the nervous system (for a detailed review see Rice and Barone, 2000; Rodier, 1995). The time window which encompasses the vulnerability of the brain to disturbances of all these processes is ample. In fact, it spans from the embryonic period until well into adulthood when a recapitulation of synaptogenesis is ongoing (Rice and Barone, 2000). The structures forming at the time of exposure play a decisive role on the extent of effects that show up later in life (Rodier, 1995). Therefore, a woman who is exposed during the first trimester of pregnancy may contract deficits or defects very different from those developed by someone who is exposed during the third trimester of pregnancy. However, with an extensive window of vulnerability (with respect to time and the amount of potential insults) and regular exposure (e.g. each portion of fish consumed by pregnant women at a frequency of one or two times a week), the potential of an insult of any of the critical processes such as neurogenesis, migration, differentiation or synaptogenesis is high. One developmental perturbation can initiate a cascade or autocatalytic processes of structural or functional changes which may be manifested as developmental delays or persistent deficits (Rice and Barone, 2000). Adverse effects may also appear staggered, with initial transient deficits and reversal when compensatory capability reduces during aging. Therefore, some effects may appear late in life when plasticity is declining or neurons are gradually lost. For that reason, compensation or neuronal plasticity only covers the neurotoxic effects for a certain period of time, while due to the limited capacity of the CNS to repair damage, such effects are usually irreversible and will manifest at some point in life. Although latently proceeding tissue injuries are common phenomena of toxicant-induced etiology, CNS plasticity is an organ-specific characteristic which naturally contributes to latencies in neurodisease.

4. Conclusion

Experimental data in mammals (Tables 1 and 2) indicate that the Druckrey-Küpfmüller equation, dt^n = constant, first established for genotoxic carcinogens, also describes the dose-response characteristics of neurotoxic effects of organic mercury compounds. Exposure time reinforces the toxicant effect, since the total dose required to produce neurotoxicity decreases with increasing exposure time. Data outlined here and elsewhere (Rondeau et al., 2014; Tennekes, 2010; Tennekes and Sánchez-Bayo, 2013) demonstrate that time may reinforce toxic effects of compounds other than genotoxic carcinogens. This amounts to a paradigm shift in chemical risk assessment. The decisive elements of such dose-response relationships are irreversible receptor binding associated with an irreversible effect, and latency periods for toxicity. It is vital to perform toxicity testing geared to investigate time-dependent effects. Also, it is crucial to further explore the cascading toxic effects in the brain to provide a greater insight into the biochemical and pathological processes ongoing while no clinical signs of neurodisease have yet become apparent. The analysis outlined here indicates that there may not be a safe level of mercury exposure. We are particularly concerned about exposure during pregnancy when considering the risk of adverse neurodevelopmental effects in the unborn child. Hence, the implications of these findings are the need to limit environmental concentrations of mercury and phase out the use of ethylmercury in vaccines.

Conflict of interest

None.

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