



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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ARTICLE INFO

Article history:

Received 27 January 2016

Received in revised form 19 February 2016

Accepted 25 February 2016

Available online 2 March 2016

Keywords:

Dose-response modelling

Toxicodynamics

Mercury

Neurotoxicity

Risk assessment

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.

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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; Comeau 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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