[PA4-35] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

Meyhylmercury inhibits glutamine synthetase in the murine brain in vivo and in vitro

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Glutamine synthetase (GS), known as a glial-specific enzyme catalyzes the synthesis of glutamine from glutamate and ammonia and has been reported to be associated with ischemic injury and several neurological diseases. Central nervous system is a known target for methylmercury (MeHg) toxicity in mice. In this study, we investigated whether the in vitro and in vivo exposure of MeHg have adverse effects on GS. In each brain region, GS activity was measured spectrophotometrically based on the γ-glutamyl transfer reaction. In vitro exposure of MeHg (0.1 to 100 μM) produced dose-dependant decreases of GS activity in cerebellum, hippocampus and frontal cortex. 50% inhibition in the cerebellum, frontal cortex and hippocampus occurred at about 10~20 μM. MeHg inhibited GS activity in the rat brain at much lower concentrations when compared with other GS inhibitors (such as methionine sulfoximine and kainic acid). GS activity from sheep brain source was also inhibited by MeHg. In mice given MeHg intraperitoneally (2, 4, or 10 mg/kg, for 24 hr), GS activity was inhibited in mice exposed to 4 or 10 mg/kg MeHg at the hippocampus, but not the enthorhinal cortex. MeHg concentrations were determined in the frontal cortex, caudate nucleus, cerebellum and trunk blood by GC/MSD. MeHg concentrations were 1935.1 ±324.0 ng/g in the frontal cortex, 2449.5 ±503.2 ng/g in the caudate nucleus, 2226.7 ±373.5 ng/g in the cerebellum and 1669.5 ±546.2 ng/ml in the trunk blood. MeHg resulted in brain region-dependent inhibition of GS activity in vivo. Based on the results in vitro and in vivo, these data suggest that MeHg toxicity in central nerveous system be induced partly by increasing glutamate levels in the brain.

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Induction of Benchmark Dose using Subchronic Toxicity Data of Di(2-ethylhexyl) phthalate in Common Marmosets

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Di(2-ethylhexyl)phthalate is widely used in industry as plasticizers, which enhance the flexibility of polymers. The toxicological effects of DEHP in man have not been sufficiently clarified, and marked species difference with rodent study are suspected in changes such as hepatic hypertrophy, tumoral growth and proliferative changes of pancreatic acinar cells. The benchmark dose (BMD) is based on a model-derived estimate of a particular incidence level, such as 5% or 10% incidence (ED_5, ED_{10}) and comparable to the NOAEL.
Therefore, this study was conducted to induce benchmark dose from toxicological dose-response data which DEHP was administered orally to mamosets at 100, 500, 2500 mg/kg for 13 weeks. Toxicological endpoint of DEHP was selected as mean volume of peroxisomes (μm2) in male mamosets which be showed more sensitive response. For the induction of BMD, Power Mean model from Bench_C program was used for continuous response data. Estimated BMD_5 and BMD_{10} were 65.252 and 130.50mg/kg, respectively and this study identified 65.25mg/kg/day corresponding to NOAEL.

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