In cerebellum, MeHg still augmented MRs in dams (87%; control Bmax: 83±17 fmol/mg prot) and pups (27%; control Bmax 119-127 fmol/mg protein) while PCB153 reduced it by ~30%. After the combined treatment, the MR changes were similar to those caused by PCB153 alone. Brain Hg levels (µg/g) were 7-9 in dams, 1.67±0.43 in males and 1.52±0.33 in females. In blood Hg values (µg/l) were 11330±2258 in dams, 1351±395 in males and 1313±397 in female pups. As observed in the brain, in the lymphocytes MeHg given alone always augmented the MR Bmax (control Bmax: 30-60 fmol/million cells). Similarly to the cerebellum, MeHg affected more markedly the adult (+139%) than the pup lymphocyte receptors (+45-85%) and PCB153 totally masked MeHg effect. MeHg enhanced cerebral and lymphocyte MRs more in dams than in pups in accordance with the higher Hg levels detected in the adult tissues. The trend of MR changes caused by MeHg and PCB153 in the lymphocytes partially mirrored that of the cerebellum (EU Grants: QLK4-CT-2001-00186; FOOD-CT-2003-506543).

1056 DEVELOPMENTAL NEUROPATHOLOGY OF METHYL MERCURY CHLORIDE.

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The susceptibility of the brain to chemicals and drugs appears to depend on its developmental stage at the time of exposure. Adverse effects on brain morphology (abnormal proliferation, differentiation and/or migration of cells) can arise, often resulting in quantitative changes, e.g. changes in neuron numbers at their final destination. Excessive neuron loss in the developing brain has negative consequences for the mental and physical abilities of the adult individual, becoming even more pronounced during senescence. However, such quantitative developmental morphological changes may go unrecognized by the morphological approach, proposed in current test guidelines for regulatory Neurotoxicity Testing, as demonstrated in the present study (American Chemistry Council, Ref.nr. 1847). A Developmental Neurotoxicity study was carried out in rats with methyl mercury chloride (MeHg) (5 dose levels). A tiered morphological approach (gross macroscopy, brain weight, slide reading, morphometry (brain layer width) was applied (EPA Guideline OPPTS 870.6300), and stereology (brain region volume, neuron number) as final step, in addition. A significant loss of cerebellar granular neurons and reduction of granular layer volume by MeHg was demonstrated using stereology. These effects, or any other effect on brain morphology, could not be depicted with previous steps in the tiered approach. The results indicate that powerful neuropathology endpoints are required to identify early effects of toxicants on developing brain morphology and suggest that stereology may provide a valuable, additional tool.

1057 PRENATAL EXPOSURE TO METHYL MERCURY OR METHYLAZOXY METHANOL: EFFECTS ON EARLY POSTNATAL MOTOR ACTIVITY.

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Developmental Neurotoxicity testing according to specific test guidelines is required for disclosure of the potential adverse effects of industrial chemicals and agricultural pesticides on the developing nervous system. Motor activity is included in these guidelines as an apical behavioural endpoint with the intent to evaluate a range of potential effects on the developing nervous system. It is known that different activity measures may be differently affected by chemicals and drugs, depending on the dose and type of agent. Also, other nervous system functions may be changed and may lead to changes in motor activity. In addition, motor activity may be indirectly affected as a result of systemic toxicity (e.g. adverse effects on body temperature or body weight). In research, supported by the American Chemistry Council (ACC Ref.nr. 1847), we studied motor activity in rats, prenatally exposed to methyl mercury chloride (MeHg) or methylazoxy methanol acetate (MAM) (5 dose levels each). MAM and MeHg were chosen as model neurotoxicants. They both affect brain morphology during development. MeHg, however, primarily causes systemic toxicity. Motor activity was tested on PN 13, 17, 21 and 60-62, as indicated in the EPA guideline OPPTS 870.6300 for Developmental Neurotoxicity testing. The results showed that prenatal exposure to MAM or MeHg affected early postnatal motor activity differently. The results will be shown and the relevance of the effects with regard to developmental neurotoxicity will be discussed in relation to the results obtained for other endpoints (maternal and developmental in-life data, and pathology).

1058 METHYLMERCURY (MEHG) ELICITS ACUTE AND LONG-TERM EFFECTS ON NEWBORN RAT HIPPOCAMPAL NEUROGENESIS THROUGH CELL CYCLE MACHINERY.

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While high MeHg exposure causes gross brain defects, effects of lower levels on development are undefined. Acute changes in early neuron production, or neurogenesis, may influence later brain formation. Previous studies indicate injected factors stimulate or inhibit proliferation by regulating cell cycle progression (Cheng, 2002;Carey, 2002). To examine acute neurotoxicant effects on DNA synthesis, we injected P7 rats with MeHg and [3H]thymidine 6h later, measuring incorporation 2h later. At 8h DNA synthesis was reduced 16% at 0.1, 50% at 3, and 80% at 30microg/g in hippocampus, indicating effects on DNA synthesis. Two weeks later, rats injected with MeHg at P7 exhibited reduced hippocampal cell number, indicated by a 17% decrease in total DNA at 3microg/g. In contrast, MeHg did not affect DNA synthesis or cell number in cerebellum though blood flow and Hg content were similar in both regions, and DNA synthesis in cultured granule precursors was inhibited 25%. To examine cell cycle mechanisms, we defined effects on E14.5 cortical precursors: At 6h DNA synthesis was reduced 49% at 3 and 98% at 10microM MeHg, with no change in cell number, suggesting a G1/S block. MeHg elicited a 75% reduction in cyclin E, the stimulatory subunit of CDK2, whose levels were unchanged. Further, MeHg did not increase either p27 or p57, CDK inhibitors commonly stimulated by endogenous anti-mitogens, such as PACAP (Carey, 2002). These studies identify the cell cycle machinery as new MeHg targets, specifically cyclin E. The decreases in DNA synthesis at 6h in hippocampus *in vivo* and cortical precursor cultures suggest MeHg inhibits neurogenesis by interfering with cell cycle progression. Furthermore, the studies indicate that MeHg rapidly and directly alters brain development through modulating regional neurogenesis. NIEHS 11256, USEPA R82939101

1059 MEHG DIFFERENTIALLY AFFECTS KINETICS OF SIPSCS OF RAT CEREBELLAR PURKINJE AND GRANULE CELLS.

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We previously showed that the GABAergic spontaneous inhibitory postsynaptic currents (sIPSCs) in Purkinje and granule cells in cerebellar slices exhibited differential sensitivity to methylmercury (MeHg). Because of the differential expression of α1 and α6 subunits of $GABA_A$ receptor in Purkinje and granule cells, and different kinetics between α1- and α6-containing $GABA_A$ receptors, we hypothesized that MeHg affects kinetics of sIPSCs in Purkinje and granule cells differently. To test this, effects of MeHg on kinetics of sIPSCs in Purkinje and granule cells in cerebellar slices were examined using whole cell recording techniques. In the control, the mean 10-90% rise time of sIPSCs in Purkinje cells was 0.84 ± 0.03 ms. For currents fitted with two exponentials, the mean fast and slow decay time constants were 9.8 ± 0.6 and 83.9 ± 46.6 ms, respectively. The fraction of the slow component to the peak current of sIPSCs in Purkinje cells was small. After MeHg exposure (10-100 µM), the mean 10-90% rise time of sIPSCs in Purkinje cells did not change significantly. Similarly, neither the mean for the fast nor the slow decay time constant was affected by MeHg. The mean fraction of the slow component to the peak current was virtually unchanged. Thus, MeHg did not appear to affect kinetics of sIPSCs in Purkinje cells. In granule cells, MeHg first transiently shortened and then prolonged the 10-90% rise time of sIPSCs. Effects of MeHg on sIPSC decay phase in granule cells were inconsistent. In most granule cells, MeHg slowed slightly sIPSC decay phase and prolonged the slow decay time constant. However in some granule cells, MeHg actually hastened the decay phase. The inconsistency in responses to MeHg may be due to different composition of $GABA_A$ receptor subunits in individual granule cells tested. In addition, the mean fraction of slow component to the peak current was decreased by MeHg. Thus, these data suggest that MeHg also differentially affects kinetics of GABAergic sIPSCs of cerebellar Purkinje and granule cells. Supported by NIH grants R01ES033299 and R01ES11662.

1060 GESTATIONAL LEAD EXPOSURE PRODUCES ROD-MEDIATED ELECTRORETINOGRAPHIC (ERG) SUPERNORMALITY AND DECREASES IN RETINAL DOPAMINE METABOLISM OF ADULT RATS.

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Children with blood lead concentrations ([BPb]) at or below 10 µg/dL have persistent impairments in retinal, auditory, cognitive and visual-motor function. Our recent study of 7-10 year old children with gestational and continuous postnatal

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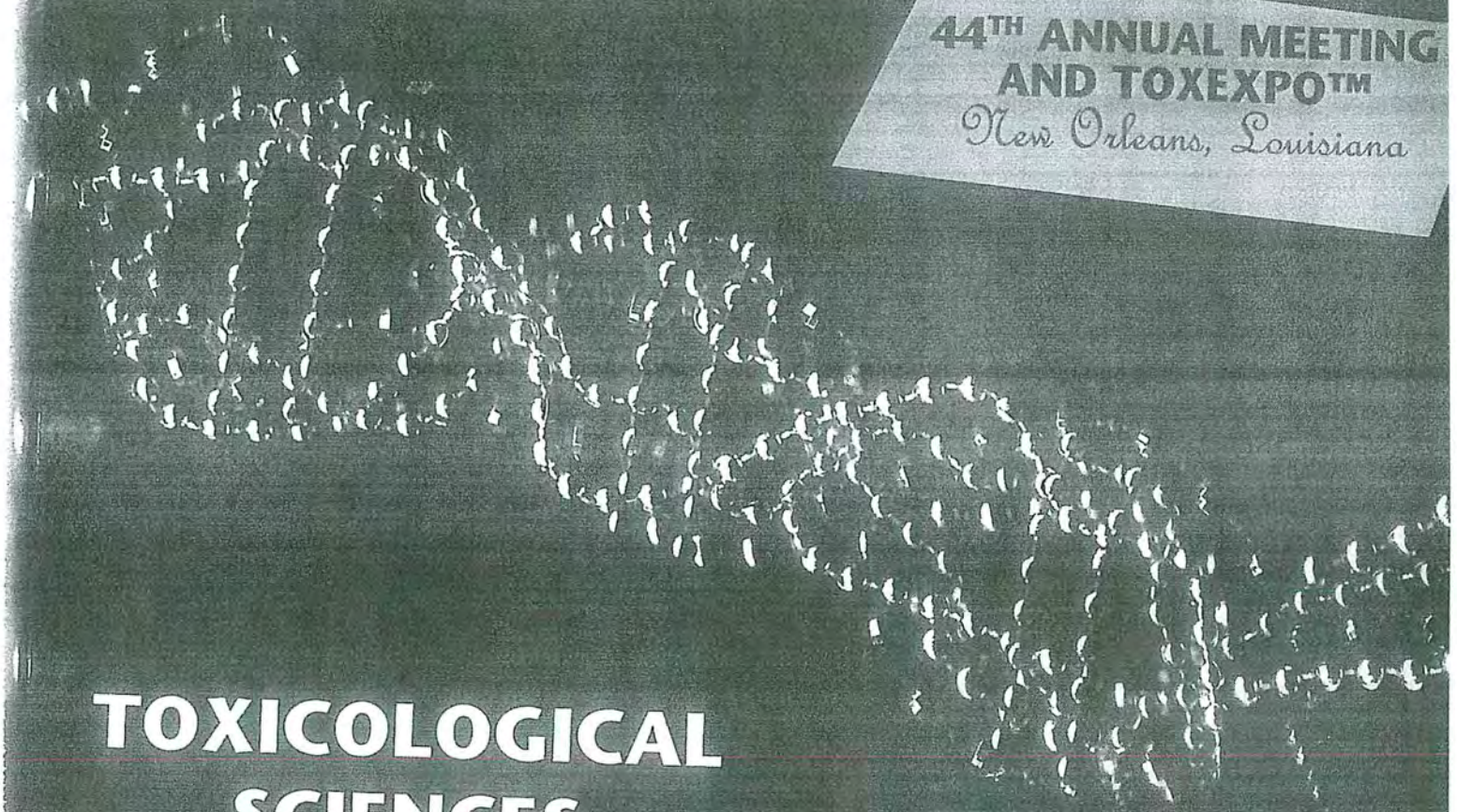

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