Single and 28-day repeated dose toxicity studies of botulinum toxin type A(BTA) were carried out in ICR mice and SD rats, respectively. In the single dose toxicity study, BTA was injected intraperitoneally to male and female mice at a single dose of 40, 59, 89, 133 and 200 ng/kg. All animals died from 59 ng/kg. Some clinical signs were observed in most of both sexes from 59 ng/kg, but no signs were seen in all animals at 40 ng/kg. The results showed that the $LD_{50}$ of BTA might be in the range of 40-59 ng/kg in both sexes. In the repeated dose toxicity study, the test material was administered intradermally for 28 days at doses of 0(control), 1.25, 2.5, 5.0 and 10.0 ng/head/50 $\mu\ell$ saline in male and female rats. BTA treatment significantly decreased the body weight gain rate in male of 5.0 ng/head and over and in female of 10.0 ng/head compared to control. One or more relative organ weights were increased significantly from 5.0 ng/head compared to control in both sexes. Serum biochemistry revealed increases in AST, ALT, CPK, total protein and albumin in male, and increases in AST and ALT and decreases in $K^+$ and $Cl^-$ in female without dose-dependent manners. In the histopathological study, BTA treatment induced atrophy of skeletal muscle in both sexes from 2.5 ng/head. When the antibodies to toxin were determined in all animals, a significant increase in serum antibodies was observed from 5.0 ng/head. The results showed that the NOAEL of BTA might be 1.25 ng/head for 28-day repeated dose toxicity in rats. (Supported by a sub-grant from Ministry of Commerce, Industry and Energy for Medy-Tox Inc.).

**[PA4-30]** [ 04/17/2003 (Thr) 14:00 - 17:00 / Hall P ]

## Cadmium induces neurotoxicity via activation of JNK and c-JUN in human neuroblastoma cell

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Occupational exposure to cadmium (Cd) can result in brain disorders and olfactory dysfunction is the most well-known symptom. Recently Cd has been shown to induce apoptosis by activating MAPKs in various cell types. However, intracellular signaling pathways of Cd-induced cytotoxicity in neuronal cells is not known well. Thus, in the present study, we studied role of JNK and its well-known downstream transcription factor, c-JUN, in Cd-induced neuronal cell death. Treatment of SH-SY5Y cell, a human neuroblastoma cell line, with Cd caused cytotoxicity in a concentration- and time-dependent manner as measured by the MTT assay; LD50 was approximately 25 uM after 24h incubation with Cd. Cd-induced cytotoxicity involved apoptosis as determined by TUNEL staining. Western blot analysis showed that JNK was phosphorylated by Cd (1- 250 uM); its activation was seen as early as 1h after Cd exposure and thereafter sustained until 12h. In contrast, p38 was phosphorylated only at the high dose (100 uM) of Cd while Erk was not activated at all. In addition, c-JUN was also phosphorylated by Cd. Stable expression of dominant negative mutant construct of MKK4 reduced the Cd-induced cytotoxicity as well as c-JUN phosphorylation, suggesting that phosphorylation of JNK/c-JUN is responsible for cytotoxic effects mediated by Cd. Moreover, treatment of cells with N-acetyl-L-cysteine (1 mM), a free radical scavenger, increased cell viability significantly. Taken together, oxidative stress induced in cells by Cd may cause cytotoxicity, and phosphorylation of JNK and c-JUN is involved in cadmium-induced cytotoxicity in neuronal cells.
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**[PA4-31]** [ 04/17/2003 (Thr) 14:00 - 17:00 / Hall P ]

## PAH regualtion of CYP1 gene in MCF-7 & ZR-75-1 human breast cancer cells

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