

## Editorial:

### RECENT RESEARCH IN NEUROTOXICOLOGY

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Large projects are currently ongoing to establish in vitro systems for identification of compounds that induce neurotoxicity or developmental neurotoxicity (Hardelauf et al., 2011; Fri-mat et al., 2010). An example is the EU funded network ESNATS where human embryonic stem cells are differentiated to neuronal cells. This gives the opportunity to expose the differentiating stem cells to test chemicals during specific sensitive periods and analyze if the differentiation process is compromised. However, this is an ongoing project and it will take several years until the novel in vitro techniques can be integrated into routine toxicological testing. Current publications still include in vivo studies, for example possible neurotoxic effects of diesel exhaust in newborn mice (Tsukue et al., 2009), developmental neurotoxicity of acrylamide in rats (Takahashi et al., 2009) and oxidative stress in the cerebral cortex of rats after exposure to diphenyl ditelluride (Stangherlin et al., 2009). It remains currently difficult to predict, when it will be possible to replace conventional neurotoxicity in vivo studies by in vitro tests. The table gives an overview over recent studies in neurotoxicology or developmental neurotoxicology.

**Table 1:** Recent studies in neurotoxicology and developmental neurotoxicology

Key message	Reference
Perinatal exposure of mice to diesel exhaust increased expression levels of estrogen receptor alpha and beta, CYP1A1 and heme oxygenase-1 in the cerebrum of newborns, suggesting a possible influence of diesel exhaust inhalation on sexual differentiation.	Tsukue et al., 2009
A LC-tandem MS based technique was established that allows quantification of organophosphorothioate albumin adducts at (in vitro) concentrations as low as 1 µM parathion and chlorpyrifos. The technique offers a sensitive perspective for pesticide biomonitoring.	Noort et al., 2009
4-Pyridine aldoximine is a metabolite of the oxime acetylcholinesterase reactivator methoxime (MMB-4). 4-Pyridine aldoxime did not induce toxicity, did not alter acetylcholinesterase activity and did not modify the toxicity of sarin or cyclosarin.	Shih et al., 2009
A novel conotoxin was purified and sequenced which enhances tetrodotoxin-sensitive sodium currents in adult rat dorsal root ganglion neurons.	Wang et al., 2009
Brevetoxins are lipid soluble polyether neurotoxins linked to periodic "red tide blooms", exerting their toxicity via sodium channels. This study demonstrates that brevetoxins also induce DNA strand breaks and apoptosis.	Murrell and Gibson, 2009

**Table 1 (cont.):** Recent studies in neurotoxicology and developmental neurotoxicology

Key message	Reference
Acrylamide causes neurotoxicity by mechanisms including caspase-dependent apoptosis. This study demonstrates that acrylamide induced apoptosis in neuronal cells is associated with the decrease in intracellular GSH concentration, which can be antagonized by carboxyfullerene.	Sumizawa and Igisu, 2009
To study developmental neurotoxicity of acrylamide pregnant rats were given 25, 50 or 100 ppm in the drinking water from gestational day 6 to postnatal day 21. However, the internal concentration of acrylamide in the offspring was too low to induce neurotoxicity.	Takahashi et al., 2009
D-Serine is used as add-on therapy of treatment-refractory schizophrenia. This study presents genome wide gene expression alterations induced by D-serine in rats.	Davidson et al., 2009
This study presents the toxicokinetics of arsenic species in the brains of mice.	Juárez-Reyes et al., 2009
Occupational exposure to carbon disulfide can induce polyneuropathy in workers. This study shows that carbon disulfide leads to disruption of neurofilament homeostasis and activation of calpains in rat sciatic nerves.	Song et al., 2009
Exposure to diphenyl ditelluride via maternal milk causes oxidative stress in cerebral cortex, hippocampus and striatum of rats.	Stangherlin et al., 2009
UPD-glucuronosyltransferase enzymes can be induced in the choroid plexus of rats in vivo.	Gradinaru et al., 2009
Administration of subtoxic doses of the organophosphorus insecticide chlorpyrifos to rats causes differential expression of genes implicated in neurological functions.	Stapleton and Chan, 2009
Diazinonoxon, a metabolite of the phosphorothionate insecticide diazinon, causes neurotoxic effects on differentiating cells.	Sidiropoulou et al., 2009

## REFERENCES

- Davidson ME, Kerepesi LA, Soto A, Chan VT. D-Serine exposure resulted in gene expression changes implicated in neurodegenerative disorders and neuronal dysfunction in male Fischer 344 rats. *Arch Toxicol* 2009;83:747-62.
- Frimat JP, Sisnaiske J, Subbiah S, Menne H, Godoy P, Lampen P et al. The network formation assay: a spatially standardized neurite outgrowth analytical display for neurotoxicity screening. *Lab Chip* 2010;10:701-9.
- Gradinaru D, Minn AL, Artur Y, Minn A, Heydel JM. Drug metabolizing enzyme expression in rat choroid plexus: effects of in vivo xenobiotics treatment. *Arch Toxicol* 2009;83:581-6.
- Hardelauf H, Sisnaiske J, Taghipour-Anvari AA, Jacob P, Drabiniok E, Marggraf U et al. High fidelity neuronal networks formed by plasma masking with a bilayer membrane: analysis of neurodegenerative and neuroprotective processes. *Lab Chip* 2011; 11:2763-71.
- Juárez-Reyes A, Jiménez-Capdeville ME, Delgado JM, Ortiz-Pérez D. Time course of arsenic species in the brain and liver of mice after oral administration of arsenate. *Arch Toxicol* 2009;83:557-63.

Murrell RN, Gibson JE. Brevetoxins 2, 3, 6, and 9 show variability in potency and cause significant induction of DNA damage and apoptosis in Jurkat E6-1 cells. *Arch Toxicol* 2009;83:1009-19.

Noort D, Hulst AG, van Zuylen A, van Rijssel E, van der Schans MJ. Covalent binding of organophosphorothioates to albumin: a new perspective for OP-pesticide bio-monitoring? *Arch Toxicol* 2009;83:1031-6.

Shih TM, Skovira JW, McDonough JH. Effects of 4-pyridine aldoxime on nerve agent-inhibited acetylcholinesterase activity in guinea pigs. *Arch Toxicol* 2009;83:1083-9.

Sidiropoulou E, Sachana M, Flaskos J, Harris W, Hargreaves AJ, Woldehiwet Z. Diazinon oxon affects the differentiation of mouse N2a neuroblastoma cells. *Arch Toxicol* 2009;83:373-80.

Song F, Zhang C, Wang Q, Zeng T, Xie K. Alterations in neurofilaments content and calpains activity of sciatic nerve of carbon disulfide-treated rats. *Arch Toxicol* 2009;83:587-94.

Stangherlin EC, Ardais AP, Rocha JB, Nogueira CW. Exposure to diphenyl ditelluride, via maternal milk, causes oxidative stress in cerebral cortex, hippocampus and striatum of young rats. *Arch Toxicol* 2009;83:485-91.

Stapleton AR, Chan VT. Subtoxic chlorpyrifos treatment resulted in differential expression of genes implicated in neurological functions and development. *Arch Toxicol* 2009;83:319-33.

Sumizawa T, Igisu H. Suppression of acrylamide toxicity by carboxyfullerene in human neuroblastoma cells in vitro. *Arch Toxicol* 2009;83:817-24.

Takahashi M, Shibutani M, Nakahigashi J, Sakaguchi N, Inoue K, Morikawa T et al. Limited lactational transfer of acrylamide to rat offspring on maternal oral administration during the gestation and lactation periods. *Arch Toxicol* 2009;83:785-93.

Tsukue N, Watanabe M, Kumamoto T, Takano H, Takeda K. Perinatal exposure to diesel exhaust affects gene expression in mouse cerebrum. *Arch Toxicol* 2009;83:985-1000.

Wang L, Liu J, Pi C, Zeng X, Zhou M, Jiang X et al. Identification of a novel M-superfamily conotoxin with the ability to enhance tetrodotoxin sensitive sodium currents. *Arch Toxicol* 2009;83:925-32.