MEDICAL

Mechanisms of acrylamide induced rodent carcinogenesis 2

Acrylamide neurotoxicity: Neurological, morphological and molecular endpoints in animal models 2

Bioaccumulation and behavioural effects of depleted uranium in rats exposed to repeated inhalations 2

Developmental toxicity study with diethylene glycol dosed by gavage to CD rats and CD-1 mice 3

Host factors and genetic susceptibility: a paradigm of the conundrum of pesticide exposure and cancer associations 3

Vanadium toxicity 4

Responses to Subchronic Inhalation of Low Concentrations of Diesel Exhaust and Hardwood Smoke Measured in Rat Bronchoalveolar Lavage Fluid 4

Respiratory toxicity of multi-wall carbon nanotubes 5

Blast from the past: The Aluminum’s ghost on the Lanthanum salts 5

Efficacy and safety of hypoglycemic drugs in children with type 2 diabetes mellitus 6

Pathophysiological and clinical aspects of combat anticholinesterase poisoning 6

Cadmium and Prostate Cancer: A Critical Epidemiologic Analysis 7

Plasma aluminum: A redundant test for patients on dialysis? 7

New metabolites of di(2-ethylhexyl) phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP 7

A case of contact urticaria due to adigraf, a PVC-made material 8
Medical

Mechanisms of acrylamide induced rodent carcinogenesis
2005-11-09

Acrylamide is a monomer of polyacrylamide, used in biochemistry, in paper manufacture, in water treatment, and as a soil stabilizer. The monomer can cause several toxic effects and has the potential for human exposure either through the environment or from occupational exposure. Recently, additional concern for the potential toxicity of acrylamide in humans has arisen with the finding of acrylamide formation in some processed foods. It has been established that following chronic exposure, rats exhibited an increase in the incidence of adrenal pheochromocytomas, testicular mesotheliomas, thyroid adenomas and mammary neoplasms in F344 rats. This has raised increased concerns regarding the carcinogenic risk to humans from acrylamide exposure. Studies examining the DNA reactivity of acrylamide have been performed and have had differing results. The tissue and organ pattern of neoplastic development seen in the rat following acrylamide exposure is not consistent with that seen with other strictly DNA reactive carcinogens. Based on the pattern of neoplastic development, it appears that acrylamide is targeting endocrine sensitive tissues. In summary, acrylamide caused both an increase in DNA synthesis and DNA damage in mammalian tissues and cells suggesting that DNA reactivity and cell proliferation, in concert, may contribute to the observed acrylamide-induced carcinogenicity in the rat and has implication on the possible risk for human neoplasm development.

Authors: Klaunig, James E.; Kamendulis, Lisa M.

Full source: Advances in Experimental Medicine and Biology 2005, 561 (Chemistry and Safety of Acrylamide in Food), 49-62 (Eng)

Acrylamide neurotoxicity: Neurological, morphological and molecular endpoints in animal models
2005-11-09

Acrylamide (AA) monomer is used in numerous chemical industries and is a contaminant in potato- and grain-based foods prepared at high temperatures. Although experimental animal studies have implicated carcinogenicity and reproductive toxicity as possible consequences of exposure, neurotoxicity is the only outcome identified by epidemiological studies of occupationally exposed human populations. Neurotoxicity in both humans and laboratory animals is characterized by ataxia and distal skeletal muscle weakness. Early neuropathological studies suggested that AA neurotoxicity was mediated by distal axon degeneration. However, more recent electrophysiological and quantitative morphometric analyses have identified nerve terminals as primary sites of AA action. A resulting defect in neurotransmitter release appears to be the pathophysiological basis of the developing neurotoxicity. Corresponding mechanistic research suggests that AA impairs release by adducting cysteine residues on functionally important presynaptic proteins.

Authors: LoPachin, Richard M.

Full source: Advances in Experimental Medicine and Biology 2005, 561 (Chemistry and Safety of Acrylamide in Food), 21-37 (Eng)

Bioaccumulation and behavioural effects of depleted uranium in rats exposed to repeated inhalations
2005-11-09

Depleted uranium has numerous industrial and military uses. Contamination by inhalation of airborne compounds is probably the most important route of exposure. In humans, there are no data clearly demonstrating neurotoxicity of
Medical

uranium, yet some experimental studies suggest a link between neurological toxicity and uranium exposure. In this work, the bioaccumulation of uranium in male rats after exposure to repeated depleted uranium dioxide inhalation (30 min inhalation at 197 mg m⁻³, 4 days a week for 3 weeks) has been studied, together with the behavioral effects. The uranium concentrations in the brain 1 day after the end of the exposure period varied as follows: olfactory bulb > hippocampus > frontal cortex > cerebellum, subsequently decreasing rapidly. The spontaneous locomotion activity of exposed rats was increased 1 day post exposure and the spatial working memory was less efficient 6 days post exposure, compared with control rats. These data suggest that depleted uranium is able to enter the brain after exposure to repeated inhalation, producing behavioral changes.

Authors: Monleau, Marjorie; Bussy, Cyrill; Lestaevel, Philippe; Houpert, Pascale; Paquet, Francois; Chazel, Valerie
Full source: Neuroscience Letters 2005, 390(1), 31-36 (Eng)

Developmental toxicity study with diethylene glycol dosed by gavage to CD rats and CD-1 mice
2005-11-09
Diethylene glycol (DEG; CAS No. 111-46-6) is a widely used industrial liquid chemical with a potential for human exposure. In view of the established teratogenic effects caused by ethylene glycol in laboratory animals, the developmental toxicity of DEG was investigated in mice and rats, species known to be sensitive to the developmental toxicity of ethylene glycol. Timed-pregnant CD-1 mice and CD rats were dosed daily by gavage with undiluted DEG over gestational days (gd) 6-15. With mice there was maternal toxicity at 11,180 mg/kg/day (mortality, signs, increased water consumption) and at 2795 mg/kg/day (increased water consumption). Implantations were comparable across all groups. Fetal body weights were significantly reduced at 11,180 mg/kg/day. There were no increases in variations or malformations, either total, by category, or individually. With rats, maternal toxicity was present at 8944 mg/kg/day (mortality, signs, reduced body weight gain, reduced food consumption, increased water consumption, increased liver weight, increased kidney weight, and renal histopathology), and 4472 mg/kg/day (increased water consumption). There were no treatment-related effects on corpora lutea or implantations. Fetal body weights were reduced at 8944 mg/kg/day. There were no significant effects with respect to total or individual external or visceral variations. Individual skeletal variations were significantly increased at 8944 mg/kg/day and 4472 mg/kg/day. This pattern of delayed ossification is consistent with reduced fetal body weight. Malformations, total, by category, or individually, were similar between the control and DEG groups. Thus, under the conditions of these studies, the no-observed-effect-level (NOEL) for DEG given by gavage over gd 6-15 was 559 mg/kg/day with the mouse and 1118 mg/kg/day with the rat for maternal toxicity, and 2795 mg/kg/day with mice and 1118 mg/kg/day with rats for developmental toxicity (fetotoxicity). There were no indications of embryotoxicity or teratogenic effects at any dosage in either species.
Authors: Ballantyne, Bryan; Snellings, William M.
Full source: Food and Chemical Toxicology 2005, 43(11), 1637-1646 (Eng)

Host factors and genetic susceptibility: a paradigm of the conundrum of pesticide exposure and cancer associations
2005-11-09
Millions of people are exposed to pesticides in non-trivial ways though

Diethylene glycol (DEG; CAS No. 111-46-6) is a widely used industrial liquid chemical with a potential for human exposure.
their work, their leisure and their home environment. Women and children are understudied populations. The mode and types of pesticides to which women and children are exposed are often different from exposures experienced by men. A relatively small proportion of exposed individuals develop the uncommon cancers that have been associated with exposure to specific pesticides. Host factors, including such variables as gender, age at exposure, previous personal and family history, medical history, and genetic susceptibility have been implicated as explanations. The challenges of designing and implementing studies of pesticide exposure and cancer are examined with a special focus on the complexities of studying the environmental and occupational exposure of women to pesticides of varying toxicity using gender-appropriate methodology.

Authors: McDuffie, Helen H.
Full source: Reviews on Environmental Health 2005, 20(2), 77-101 (Eng)

Vanadium toxicity
2005-11-09
Vanadium is distributed extensively in nature. It is a trace element and is present in almost all living organisms including man. Essentiality of this element in cellular functions is yet to be established. Biological importance of vanadium was originally recognized by its ability to inhibit membrane sodium pump. Its capacity to affect the activities of various other intracellular enzyme systems and to modify physiological processes is now documented. Vanadium is used extensively in various heavy industries. The incidence of exposure to toxic levels of vanadium to industrial workers has been an increasing concern for toxicologists. Disposition of vanadium in specific tissues may be involved in the pathogenesis of certain neurological disorders and cardiovascular diseases.

Authors: Venkataraman, B. V.; Sudha, S.
Full source: Asian Journal of Experimental Sciences 2005, 19(2), 127-134 (Eng)

Responses to Subchronic Inhalation of Low Concentrations of Diesel Exhaust and Hardwood Smoke Measured in Rat Bronchoalveolar Lavage Fluid
2005-11-09
Air pollution exposure is associated with adverse health effects, but the causal components and mechanisms are unclear. Authors compared effects of daily exposure for 6 months to diesel exhaust (DE) or hardwood smoke (HWS) at 4 concentrations between 30 and 1000 µg/3 of total particulate matter, or filtered air, in male and female rats. Lactate dehydrogenase increased with exposure concentration in DE-exposed females, but in other groups, low exposure concentrations caused increases while higher concentrations had less effect. Total protein in the HWS-exposed males and females followed similar patterns. Alkaline phosphatase increased in DE-exposed females, but decreased in HWS-exposed males and females. beta-Glucuronidase decreased in HWS- and DE-exposed males, but HWS-exposed females showed decreases at low exposure concentrations and weak increases at higher exposure concentrations. Macrophage inflammatory protein-2 decreased in HWS-exposed males and females and DE-exposed females. Tumor necrosis factor-alpha levels decreased in DE-exposed females and males, but HWS-exposed males showed small increases. DE did not affect total glutathione in either gender, but HWS decreased glutathione in females, while in males, increases at low exposure concentrations but not at higher exposure levels. Thus, these two combustion emissions differentially affect
lung responses, with gender affecting response patterns. Furthermore, effects may be nonmonotonic functions of exposure levels, with maximal responses in environmentally or occupationally relevant exposure ranges.

Authors: Seagrave, JeanClare; McDonald, Jacob; Reed, Matthew; Seilkop, Steven; Mauderly, Joe
Full source: Inhalation Toxicology 2005, 17(12), 657-670 (Eng)

Respiratory toxicity of multi-wall carbon nanotubes
2005-11-09
Carbon nanotubes focus the attention of many scientists because of their huge potential of industrial applications, but there is a paucity of information on the toxicology properties of this material. The aim of this experimental study was to characterize the biological reactivity of purified multi-wall carbon nanotubes in the rat lung and in vitro. Multi-wall carbon nanotubes (CNT) or ground CNT were administered intratracheally (0.5, 2 or 5 mg) to Sprague-Dawley rats and authors estimated lung persistence, inflammation and fibrosis biochemistry and histology. CNT and ground CNT were still present in the lung after 60 days (80% and 40% of the lowest dose) and both induced inflammatory and fibrotic reactions. At 2 months, pulmonary lesions induced by CNT were characterized by the formation of collagen-rich granulomas protruding in the bronchial lumen, in association with alveolitis in the surrounding tissues. These lesions were caused by the accumulation of large CNT agglomerates in the airways. Ground CNT were better dispersed in the lung parenchyma and also induced inflammatory and fibrotic responses. Both CNT and ground CNT stimulated the production of TNF-alpha in the lung of treated animals. In vitro, ground CNT induced the overproduction of TNF-alpha by macrophages. These results suggest that carbon nanotubes are potentially toxic to humans and that strict industrial hygiene measures should to be taken to limit exposure during their manipulation.

Authors: Muller, Julie; Huaux, Francois; Moreau, Nicolas; Misson, Pierre; Heilier, Jean-Francois; Delos, Monique; Arras, Mohammed; Fonseca, Antonio; Nagy, Janos B.; Lison, Dominique
Full source: Toxicology and Applied Pharmacology 2005, 207(3), 221-231 (Eng)

Blast from the past: The Aluminum's ghost on the Lanthanum salts
2005-11-09
Hyperphosphatemia is a common serious complication of chronic renal diseases, which needs appropriate continuous treatment in order to avoid ominous side effects. Therefore, oral chelating agents able to avoid phosphate absorption by the gut are mandatory. In the past, aluminum salts, and more recently calcium and magnesium salts, and a synthetic resin polyallylamine hydrochloride have been employed, but aluminum was later abandoned, because it has been a silent killer of many uremic patients, due to subtle absorption eventually leading to toxicity on central nervous system and bone, with hallucinations, seizures, dementia, and osteomalacia, bone pain, fracturing osteodystrophy, and death. Recently, a new chelating agent able to bind dietary phosphate, namely lanthanum carbonate has been introduced, with a proven efficacy profile for short-term treatment. However, after careful examination of the very few scientific papers available to date, authors strongly advise caution before adopting, at present, lanthanum carbonate as a phosphate binder in uremic patients. In fact, notwithstanding minimized, some data are worrying: first, lanthanum ions are absorbed, though at a minimal extent, by human gut; (2) pharmacokinetic evaluations
show a greater exposure to lanthanum in uremic patients; (3) lanthanum concentration is increased tenfold in blood and fivefold in bone after short-term supplementation in uremic patients; (4) there is no proofs that lanthanum cannot cross the blood brain barrier in uremic patients; (5) lanthanum has many biological effects and is potentially highly toxic. The aluminum story should serve as cautionary tale when considering the use of new metal ions.

Authors: Canavese, Caterina; Mereu, Cristina; Nordio, Maurilio; Sabbioni, Enrico; Aime, Silvio

Full source: Current Medicinal Chemistry 2005, 12(14), 1631-1636 (Eng)

Efficacy and safety of hypoglycemic drugs in children with type 2 diabetes mellitus

2005-11-09

This study assesses the characteristics of children with type 2 diabetes mellitus and determines the efficacy and safety of drug therapies for this disease in this population. Demographic information, presenting signs and symptoms, drug history, and laboratory values were obtained in all patients. Presenting signs and symptoms were similar to those seen in adults. Patients were initially treated with metformin (14.3%), sulfonylureas (14.3%), insulin (31.0%), or combination therapy (14.3%).

Most drug regimens decreased Hb A1c (A1C) levels. Overall, patients treated with drugs had a significant decrease in A1C values, from 10.6% ± 2.7% (mean ± SD) before treatment to 8.0% ± 2.0% at 3.2-52.9 months of treatment. Adverse reactions attributed to drugs included hypoglycemia and gastrointestinal distress. Drug therapy appears to be effective in lowering A1c values in pediatric patients, although further prospective trials are necessary to determine optimal drug therapy in this population.

Authors: Benavides, Sandra; Striet, Jeffrey; Germak, John; Nahata, Milap C.

Full source: Pharmacotherapy 2005, 25(6), 803-809 (Eng)

Pathophysiological and clinical aspects of combat anticholinesterase poisoning

2005-11-09

Nerve agents are organophosphate compounds similar to those used as pesticides but with much higher toxicity. They all block the activity of the enzyme acetylcholine esterase.

Victims are intoxicated by absorption of the toxin via exposed skin or, more commonly, via inhalation of the poisonous gas. The resultant clinical picture is of hyperstimulation of both the nicotinic and muscarinic cholinergic system, which, if not promptly treated, leads to severe muscle paralysis, cardiac brady-asystole, hypersecretion from secretory glands, respiratory failure, seizures, coma and death.

If antidotal drugs are promptly administered, the clinical severity of the poisoning is attenuated or complete abortion of symptoms is obtained. The main therapeutic strategies include atropine and oximes that counteract the nerve-agent-induced muscarinic and nicotinic cholinergic symptoms, respectively. Anticonvulsants and sedatives are used to treat central nervous system acetylcholine esterase disarray.

Authors: Weinbroum, Avi A.

Full source: British Medical Bulletin 2005, 72, 119-133 (Eng)
Cadmium and Prostate Cancer: A Critical Epidemiologic Analysis
2005-11-09

Laboratory data implicate cadmium as a prostate carcinogen. However, epidemiological studies concerning the association between cadmium and prostate cancer are inconclusive. This article reviews the epidemiological literature on cadmium and prostate cancer with a special focus on highly exposed occupational cohorts. The authors searched the MEDLINE database from 1966 to 2002 for articles on cadmium and prostate cancer. In addition, the authors reviewed the experience of cohorts highly exposed to cadmium in nickel-cadmium battery plants. Of 4 descriptive studies, 3 reported a positive association between cadmium and prostate cancer. Of 10 case-control studies, 5 (50%) reported a positive association. Of 11 cohort studies, 3 (33%) found a positive association. Finally, 4 studies on cohorts exposed in occupational nickel-cadmium batteries were identified and analyzed. The summary score of the standardized mortality ratios (SMRs) was weakly but not significantly positive 1.26. In contrast to laboratory studies, epidemiological studies do not convincingly implicate cadmium as a cause of prostate cancer. Future epidemiological studies that attempt to resolve the discrepancy between laboratory and epidemiological studies of cadmium carcinogenesis may benefit from incorporating biological measures of cadmium exposure.

Authors: Sahmoun, Abe; Case, L.; Jackson, Sharon; Schwartz, Gary
Full source: Cancer Investigation 2005, 23(3), 256-263 (Eng)

Plasma aluminum: A redundant test for patients on dialysis?
2005-11-09

Aluminum toxicity as a cause of dementia, osteodystrophy and anemia in patients receiving renal dialysis was first described in the 1970s and led to the regular monitoring of aluminum in plasma and dialyzate water. However, aluminum phosphate binders have now been replaced by calcium-based binders or sevelamer and reverse osmosis (RO) water is used in the preparation of dialyzate fluid. This has reduced the exposure of dialysis patients to aluminum and it is therefore opportune to review aluminum monitoring in patients undergoing regular renal dialysis. Plasma and water aluminum results were audited over the period January 2000-January 2004, with results obtained from 9 renal dialysis units in the UK. The role of aluminum monitoring in long-term renal dialysis patients needs re-evaluation. Regular monitoring of plasma aluminum may not be required, but should be considered in any patient showing signs or symptoms of aluminum toxicity or exposed to a contaminated water supply. It is more important that RO water supplies are maintained and monitored. Environmental aluminum as a source of sample contamination should be considered and eliminated during blood collection and sample processing.

Authors: Gault, P. M.; Allen, K. R.; Newton, K. E.
Full source: Annals of Clinical Biochemistry 2005, 42(1), 51-54 (Eng)

New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP
2005-11-09

The metabolism of di(2-ethylhexyl)phthalate (DEHP) in humans was studied after three doses of 0.35 mg (4.7 mug/kg), 2.15 mg (28.7 mug/kg) and...
48.5 mg (650 μg/kg) of D4-ring-labeled DEHP were administered orally to a male volunteer. In total about 75% of the administered DEHP dose was excreted in urine after two days. Therefore, in contrast to previous studies, most of the orally administered DEHP is systemically absorbed and excreted in urine. No dose dependency in metabolism and excretion was observed. The secondary metabolites of DEHP are superior biomonitoring markers compared to any other parameters, such as MEHP in urine or blood. 5OH-MEHP and 5oxo-MEHP in urine reflect short-term and 5cx-MEHP and 2cx-MMHP long-term exposure. All secondary metabolites are unsusceptible to contamination. Furthermore, there are strong hints that the secondary oxidized DEHP metabolites—not DEHP or MEHP—are the ultimate developmental toxicants.

Authors: Koch, Holger M.; Bolt, Hermann M.; Preuss, Ralf; Angerer, Juergen

Full source: Archives of Toxicology 2005, 79(7), 367-376 (Eng)

A case of contact urticaria due to adigraf, a PVC-made material

2005-11-09

Adigraf is a plastic material applied as thin sheets that may be incised and are used, also by children, to produce artistic drawing. The principal component of adigraf is polyvinyl chloride (PVC). Di-(2-ethylhexyl) adipate is added as a plasticizer. Herein authors describe a case of a 14-year-old boy with facial angioedema and widespread urticaria, occurring 1 hour after contact with an adigraf sheet. Open patch-test with adigraf sheet showed swelling of the application site and widespread urticaria. To our knowledge, there are no similar reports of urticaria and angioedema from adigraf or similar PCV items.

Authors: Minciullo, P. L.; Patafi, M.; Ferlazzo, B.; Saija, A.; Cristani, M.; Gangemi, S.

Full source: Environmental Toxicology and Pharmacology 2005, 20(2), 381-382 (Eng)