RELEVANT RESEARCH SECTION

submitted by DENISE NICHOLS

Here is a list of studies information submitted by Denise Nichols:

1) Azithromycin in Chronic Fatigue Syndrome (CFS), an analysis of clinical data.

2) The evolution of depleted uranium as an environmental risk factor: lessons from other metals.

3) CFS

4) Anthrax Vaccine Information

5) ALS - Amyotrophic lateral sclerosis

6) Diethyl-m-toluamide (DEET)

7) Parkinson's Disease - Epidemological Study20. Battle Lines Form Up Gulf War Veterans Demand The Truth (August 31, 2009)

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1. CFS - Azithromycin in Chronic Fatigue Syndrome (CFS), an analysis of clinical data

Vermeulen RC,

Scholte HR.

CFS and Pain Research Center Amsterdam, Waalstraat 25-31, 1078 BR Amsterdam, The Netherlands. rv@cvscentrum.nl. **ABSTRACT: BACKGROUND: CFS is a clinical state with defined symptoms, but undefined cause. The patients may show a chronic state of immune activation and treatment with an antibiotic in this subgroup has been suggested. METHODS: In a retrospective study, the response of CFS patients to azithromycin, an antibiotic and immunomodulating drug, has been scored from the patients records and compared with clinical and laboratory data. Azithromycin was not the first choice therapy, but offered when the effect of counseling and L-carnitine was considered insufficient by the patient and the clinician. RESULTS: Of the 99 patients investigated, 58 reported a decrease in the symptoms by the use of azithromycin. These responding patients had lower levels of plasma acetylcarnitine. CONCLUSION: The efficacy of azithromycin in the responsive patients could be explained by the modulating effect on a chronic primed state of the immune cells of the brain, or the activated peripheral immune system. Their lower acetylcarnitine levels may reflect a decreased antioxidant defense and/or an increased consumption of acetylcarnitine caused by oxidative stress.**

PMID: 16911783 [PubMed - in process]

1: J Autoimmun. 2006 Oct 27; [Epub ahead of print] Links

Fibromyalgia, infection and vaccination: Two more parts in the etiological puzzle.

Ablin JN,

Shoenfeld Y,

Buskila D.

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As the pathogenesis of fibromyalgia continues to raise debate, multiple putative triggers have been implicated. The current review summarizes the available data linking fibromyalgia to either infection or vaccination. Multiple infectious agents have been associated with the development of either full-blown fibromyalgia (e.g. hepatits C), or with symptom complexes extensively overlapping with that syndrome (e.g. chronic Lyme disease). The cases of Lyme disease, mycoplasma, hepatits C and HIV are detailed. Despite the described associations, no evidence is available demonstrating the utility of antibiotic or anti-viral treatment in the management of fibromyalgia. Possible mechanistic links between fibromyalgia and HIV are reviewed. Associations have been described between various vaccinations and symptom complexes including fibromyalgia and chronic fatigue syndrome. The case of Gulf War syndrome, a functional multisystem entity sharing many clinical characteristics with fibromyalgia is discussed, with emphasis on the possibility of association with administration of multiple vaccinations during deployment in the Persian Gulf and the interaction with stress and trauma. Based on this example a model is proposed, wherein vaccinations function as co-triggers for the development of functional disorders including fibromyalgia, in conjunction with additional contributing factors.

PMID: 17071055 [PubMed - as supplied by publisher]

1: J Affect Disord. 2006 Sep 26; [Epub ahead of print] Links

Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): Indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut-intestinal permeability.

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Mihaylova I,

Leunis JC.

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There is now evidence that chronic fatigue syndrome (CFS) is accompanied by immune disorders and by increased oxidative stress. The present study has been designed in order to examine the serum concentrations of IgA and IgM to LPS of gram-negative enterobacteria, i.e. Hafnia alvei; Pseudomonas aeruginosa, Morganella morganii, Proteus mirabilis, Pseudomonas putida, Citrobacter koseri, and Klebsiella pneumoniae in CFS patients, patients with partial CFS and normal controls. We found that the prevalences and median values for serum IgA against the LPS of enterobacteria are significantly greater in patients with CFS than in normal volunteers and patients with partial CFS. Serum IgA levels were significantly correlated to the severity of illness, as measured by the FibroFatigue scale and to symptoms, such as irritable bowel, muscular tension, fatigue, concentration difficulties, and failing memory. The results show that enterobacteria are involved in the etiology of CFS and that an increased gut-intestinal permeability has caused an immune response to the LPS of gram-negative enterobacteria. It is suggested that all patients with CFS should be checked by means of the IgA panel used in the present study and accordingly should be treated for increased gut permeability.

PMID: 17007934 [PubMed - as supplied by publisher]

1: J Clin Virol. 2006 Nov;37(3):139-50. Epub 2006 Sep 15. Links

Chronic fatigue syndrome.

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Kerr JR.

Chronic Fatigue Syndrome (CFS) Group, Department of Cellular & Molecular Medicine, St. George's University of London, Cranmer Terrace, London SW17 0RE, United Kingdom.

Chronic fatigue syndrome (CFS) is thought to have a worldwide prevalence of 0.4-1% with approximately 240,000 patients in the UK. Diagnosis is based on clinical criteria and critically depends on exclusion of other physical and psychiatric diseases. Studies of pathogenesis have revealed immune system abnormalities and chronic immune activation, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, brain abnormalities, evidence of emotional stress (comprising host aspects) and evidence of exogenous insults, for example, various microbial infections (Epstein-Barr virus, enteroviruses, parvovirus B19, Coxiella burnetii and Chlamydia pneumoniae), vaccinations and exposure to organophosphate chemicals and other toxins (comprising environmental aspects). Emotional stress appears to be very important as it reduces the ability of the immune system to clear infections, it's presence has been shown to determine whether or not an individual develops symptoms upon virus infection, and it leads to activation of the HPA axis. But, emotional stress is distinct from depression, the presence of which precludes a diagnosis of CFS. There is no specific treatment for CFS other than the much underutilised approach of specific treatment of virus infections. Current priorities are to understand the molecular pathogenesis of disease in terms of human and virus gene expression, to develop a diagnostic test based on protein biomarkers, and to develop specific curative treatments.

PMID: 16978917 [PubMed - in process]

1: Soc Work Health Care. 2006;43(4):85-98. Links

Iraqi Gulf War Veteran Refugees in the U.S.:PTSD and Physical Symptoms.

Jamil H,

Nassar-McMillan SC,

Salman WA,

Tahar M,

Jamil LH.

, 15400 W McNichols, 2nd Floor, Detroit, MI, hjamil@med.wayne.edu.

Veterans of the Gulf War present various symptoms and maladies. Reports by governmental and private entities have yielded mixed results and have been fraught with criticisms of biased research design. The vast majority of these studies have focused on U.S. veterans, with a much smaller number focusing upon British veterans. Very few have examined Iraqi Gulf War veterans. Our study involves administering a health issues questionnaire to a sample of Iraqi Gulf War veteran refugees in the U.S. Results indicate relationships between Post-Traumatic Stress Disorder (PTSD) scores and health outcome measures of chronic fatigue, fibromyalgia, functional status, quality of life, and health care utilization in terms of frequency and level of intensity. Implications for further inquiry are presented.

PMID: 16966311 [PubMed - in process]

Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study.

Hickie I,

Davenport T,

Wakefield D,

Vollmer-Conna U,

Cameron B,

Vernon SD,

Reeves WC,

Lloyd A;

Dubbo Infection Outcomes Study Group.

Brain and Mind Research Institute, Sydney University, Sydney, NSW 2050, Australia.

OBJECTIVE: To delineate the risk factors, symptom patterns, and longitudinal course of prolonged illnesses after a variety of acute infections. DESIGN: Prospective cohort study following patients from the time of acute infection with Epstein-Barr virus (glandular fever), Coxiella burnetii (Q fever), or Ross River virus (epidemic polyarthritis). SETTING: The region surrounding the township of Dubbo in rural Australia, encompassing a 200 km geographical radius and 104,400 residents. PARTICIPANTS: 253 patients enrolled and followed at regular intervals over 12 months by self report, structured interview, and clinical assessment. OUTCOME MEASURES: Detailed medical, psychiatric, and laboratory evaluations at six months to apply diagnostic criteria for chronic fatigue syndrome. Premorbid and intercurrent illness characteristics recorded to define risk factors for chronic fatigue syndrome. Self reported illness phenotypes compared between infective groups. RESULTS: Prolonged illness characterised by disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance was evident in 29 (12%) of 253 participants at

six months, of whom 28 (11%) met the diagnostic criteria for chronic fatigue syndrome. This post-infective fatigue syndrome phenotype was stereotyped and occurred at a similar incidence after each infection. The syndrome was predicted largely by the severity of the acute illness rather than by demographic, psychological, or microbiological factors. CONCLUSIONS: A relatively uniform post-infective fatigue syndrome persists in a significant minority of patients for six months or more after clinical infection with several different viral and non-viral micro-organisms. Post-infective fatigue syndrome is a valid illness model for investigating one pathophysiological pathway to chronic fatigue syndrome.

PMID: 16950834 [PubMed - indexed for MEDLINE]

1: J Clin Pathol. 2006 Aug 25; [Epub ahead of print] Links

Long-chain polyunsaturated fatty acids and the pathophysiology of myalgic encephalomyelitis (chronic fatigue syndrome).

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Evidence is put forward to suggest that myalgic encephalomyelitis, also known as chronic fatigue syndrome, may be associated with persistent viral infection. In turn, such infections are likely to impair the ability of the body to biosynthesize n-3 and n-6 long-chain polyunsaturated fatty acids by inhibiting the delta-6 desaturation of the precursor essential fatty acids alpha-linolenic acid and linoleic acid. In turn, this would impair the proper functioning of cell membranes, including cell signalling, and have an adverse effect of the biosynthesis of eicosanoids from the long-chain polyunsaturated fatty acids

dihomo-a-linolenic acid, arachidonic acid and eicosapentaenoic acid. These actions might offer an explanation for some of the symptoms and signs of myalgic encephalomyelitis. A potential therapeutic avenue may be offered by bypassing the inhibition of the enzyme delta-6-desaturase by administering both virgin cold-pressed non-raffinated evening primrose oil and eicosapentaenoic acid. The former would supply gamma-linolenic acid and lipophilic pentacyclic triterpenes. The gamma-linolenic acid can readily be converted into dihomo-a-linolenic acid and thence arachidonic acid, while triterpenes have important free radical scavenging, cyclooxygenase and neutrophil elastase inhibitory activities. Furthermore, both arachidonic acid and eicosapentaenoic acid are, at relatively low concentrations, directly virucidal.

PMID: 16935966 [PubMed - as supplied by publisher]

1: Clin Chim Acta. 2006 Jul 14; [Epub ahead of print] Links

beta-Alanine and gamma-aminobutyric acid in chronic fatigue syndrome.

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Theodorsson E,

Evengard B.

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BACKGROUND: Due to the occurrence of sleep disturbances and fatigue in chronic fatigue syndrome (CFS), an investigation was performed to examine if there is an abnormal excretion of gamma-aminobutyric acid (GABA) and/or its structural analogue beta-alanine in the urine from CFS patients. Both GABA and beta-alanine are inhibitory neurotransmitters in the mammalian central

nervous system. METHODS: The 24 h urine excretion of GABA and beta-alanine was determined by isotope dilution gas chromatography mass spectrometry in 33 CFS patients and 43 healthy controls. The degree of symptoms in both patients and controls was measured by grading of three typical CFS symptoms using a Visual Analogue Scale. RESULTS: Men had a significantly higher excretion of both beta-alanine and GABA than women. Comparing CFS patients with healthy controls showed no significant difference in excretion of neither beta-alanine nor GABA. No correlation was found between the excretion of beta-alanine or GABA and any of the three characteristic CFS symptoms measured. However, two female and two male CFS patients excreted considerably higher amounts of beta-alanine in their 24 h urine samples than control subjects. CONCLUSIONS: Increased excretion of beta-alanine was found in a subgroup of CFS patients, indicating that there may be a link between CFS and beta-alanine in some CFS patients.

PMID: 16934791 [PubMed - as supplied by publisher]

1: Environ Health Perspect. 2006 Oct;114(10):1553-7. Links

Persistence of symptoms in veterans of the First Gulf War: 5-year follow-up.

Ozakinci G,

Hallman WK,

Kipen HM.

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BACKGROUND: During the 1990-1991 Gulf War, approximately 700,000 U.S. troops were deployed to the Persian Gulf theater of operations. Of that number, approximately 100,000 have presented medical complaints through various registry and examination programs. OBJECTIVES: Widespread symptomatic illness without defining physical features has been reported among veterans of the 1991 Gulf War. We ascertained changes in symptom status between an initial 1995 symptom evaluation and a follow-up in 2000. METHODS: We assessed mailed symptom survey questionnaires for 390 previously surveyed members of the U.S. Department of Veterans Affairs Gulf War Registry for changes over the 5-year interval in terms of number and severity of symptoms. RESULTS: For the cohort as a whole, we found no significant changes in symptom number or severity. Those initially more symptomatic in 1995 showed some improvement over time, but remained much more highly symptomatic than those who had lesser initial symptomatology. CONCLUSIONS: The symptom outbreak following the 1991 Gulf War has not abated over time in registry veterans, suggesting substantial need for better understanding and care for these veterans.

PMID: 17035142 [PubMed - in process]

1: Psychoneuroendocrinology. 2006 Oct 14; [Epub ahead of print] Links

Enhanced cortisol suppression to dexamethasone associated with Gulf War deployment.

Golier JA,

Schmeidler J,

Legge J,

Yehuda R.

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OBJECTIVE: To examine whether PTSD or post-deployment health symptoms in veterans of the first Gulf War (Operation Desert Shield/Storm) are associated with enhanced suppression of the pituitary-adrenal axis to low-dose dexamethasone (DEX). METHOD: Plasma cortisol and lymphocyte glucocorticoid receptor (GR) number were measured at 08:00h on two consecutive days, before and after administration of 0.5mg of DEX at 23:00h in 42 male Gulf War veterans (14 without psychiatric illness, 16 with PTSD only, and 12 with both PTSD and MDD) and 12 healthy male veterans not deployed to the Gulf War or another war zone. RESULTS: In the absence of group differences in basal cortisol levels or GR number, Gulf War veterans without psychiatric illness and Gulf War veterans with PTSD only had significantly greater cortisol suppression to DEX than non-deployed veterans and Gulf War veterans with both PTSD and MDD. Gulf War deployment was associated with significantly greater cortisol suppression to DEX controlling for weight, smoking status, PTSD, and MDD; PTSD was not associated with response to DEX. Among Gulf War veterans musculoskeletal symptoms were significantly associated with cortisol suppression and those who reported taking anti-nerve gas pills (i.e., pyridostigmine bromide) during the war had significantly greater DEX-induced cortisol suppression than those who did not. CONCLUSIONS: The data demonstrate that alterations in neuroendocrine function are associated with deployment to the Gulf War and post-deployment musculoskeletal symptoms, but not PTSD. Additional studies are needed to examine the relationship of enhanced glucocorticoid responsivity to deployment exposures and chronic unexplained medical symptoms in Gulf War veterans.

PMID: 17049422 [PubMed - as supplied by publisher]

1: Philos Trans R Soc Lond B Biol Sci. 2006 Apr 29;361(1468):681-7. Links

Immunological dysfunction, vaccination and Gulf War illness.

Peakman M,

Skowera A,

Hotopf M.

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One candidate cause of Gulf War illness is vaccination against infectious diseases including medical counter-measures against biological weapons. One influential theory has suggested that such mass-vaccination caused a shift in immune response to a Type 2 cytokine pattern (Th2), which it was suggested was accompanied by a chronic fatigue syndrome-like illness. This article critically appraises this theory. We start by examining epidemiological evidence, which indicates that single vaccines are unlikely to be a substantial cause of Gulf War illness, but that there was a modest relationship with multiple vaccines, which was strongest in those vaccinated while deployed to the Gulf. These relationships may be affected by recall bias. We conclude by examining the results of immunological studies carried out in veterans or in a relevant setting in vitro. The balance of evidence from immunological studies on veterans returning from the War, including those developing multi-symptom illness, is that the immune response has not become polarized towards Th2. In summary, the epidemiological evidence for a multiple vaccine effect on Gulf War-related illness remains a potentially important aetiological lead, but mechanistic studies available at this stage do not identify any immunological basis for it.

PMID: 16687270 [PubMed - indexed for MEDLINE]

4: Hunt SC, Jakupcak M, McFall M, Orsborn M, Felker B, Larson S, Klevens M. Related Articles, Links

[Unable to display image] Re: "Chronic multisymptom illness complex in Gulf War I veterans 10 years later".

Am J Epidemiol. 2006 Oct 1;164(7):708-9; author reply 709-10. Epub 2006 Aug 30. No abstract available.

PMID: 16943267 [PubMed - indexed for MEDLINE]

1: Med Mycol. 2006 Nov;44(7):585-90. Links

Fatigue in coccidioidomycosis. Quantification and correlation with clinical, immunological, and nutritional factors.

Muir Bowers J,

Mourani JP,

Ampel NM.

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While described in the past, the frequency and degree of fatigue associated with symptomatic coccidioidomycosis has never been quantified. Using the Fatigue Severity Scale (FSS), severe fatigue (FSS score = 41) was found in 65% of cases of active coccidioidomycosis compared to 42% in cohort of control subjects with

chronic medical diseases (P=0.024). Fatigue in patients with symptomatic coccidioidomycosis declined significantly over four months (P=0.023). Severe fatigue in patients with symptomatic coccidioidomycosis was significantly associated with low body mass index (BMI; P=0.024) but was not significantly associated with either serum leptin (r2=0.078, P=0.261) or serum TNF-alpha (r2=0.028, P=0.504) concentrations. Severe fatigue is a common condition among patients with active coccidioidomycosis and is associated with a declining BMI.

PMID: 17071551 [PubMed - in process]

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2. URANIUM

Depleted uranium: all the questions about DU and Gulf War syndrome are not yet answered.

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For 15 years, the debate about depleted uranium (DU) and its detrimental effects on the health of veterans of the Gulf War of 1991, on the Iraqi people and military (and subsequently on the people of Kosovo, Afghanistan, and Iraq during the second war) has remained unresolved. Meanwhile, the number of Gulf War veterans who have developed the so-called Gulf War syndrome has risen to about one-third of the 800,000 U.S. forces deployed, and unknown proportions of those involved in the subsequent wars. Uncounted civilians and personnel of other nations that fought in Iraq and other wars since 1991 have also been afflicted. The veterans have suffered from multiple serious physiological disorders and have received little or no official recognition, medical relief, or compensation. We need to take another look at this issue, using a holistic and interactive model for the toxic matrix of exposures,

identifying the major roadblocks to resolving the scientific questions, and finding appropriate medical and political responses. This commentary is such an attempt.

PMID: 16981628 [PubMed - in process]

1: Biol Trace Elem Res. 2006 Summer;111(1-3):185-97. Links

Brain accumulation of depleted uranium in rats following 3- or 6-month treatment with implanted depleted uranium pellets.

Fitsanakis VA,

Erikson KM,

Garcia SJ,

Evje L,

Syversen T,

Aschner M.

Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA.

Depleted uranium (DU) is used to reinforce armor shielding and increase penetrability of military munitions. Although the data are conflicting, DU has been invoked as a potential etiological factor in Gulf War syndrome. We examined regional brain DU accumulation following surgical implantation of metal pellets in male Sprague-Dawley rats for 3 or 6 mo. Prior to surgery, rats were randomly divided into five groups: Nonsurgical control (NS Control); 0 DU

pellets/20 tantalum (Ta) pellets (Sham); 4 DU pellets/16 Ta pellets (Low); 10 DU pellets/10 Ta pellets (Medium); 20 DU pellets/0 Ta pellets (High). Rats were weighed weekly as a measure of general health, with no statistically significant differences observed among groups in either cohort. At the conclusion of the respective studies, animals were perfused with phosphate-buffered saline, pH 7.4, to prevent contamination of brain tissue with DU from blood. Brains were removed and dissected into six regions: cerebellum, brainstem (pons and medulla), midbrain, hippocampus, striatum, and cortex. The uranium content was measured in digested samples as its 238U isotope by high-resolution inductively coupled plasma-mass spectrometry. After 3 mo postimplantation, DU significantly accumulated in all brain regions except the hippocampus in animals receiving the highest dose of DU ($p < 0.05$). By 6 mo, however, significant accumulation was measured only in the cortex, midbrain, and cerebellum ($p < 0.01$). Our data suggest that DU implanted in peripheral tissues can preferentially accumulate in specific brain regions.

PMID: 16943605 [PubMed - indexed for MEDLINE]

1: Inhal Toxicol. 2006 Oct;18(11):885-94. Links

Distribution and genotoxic effects after successive exposure to different uranium oxide particles inhaled by rats.

Monleau M,

De Meo M,

Frelon S,

Paquet F,

Donnadieu-Claraz M,

Dumenil G,

Chazel V.

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In nuclear fuel cycle facilities, workers may inhale airborne uranium compounds that lead to internal contamination, with various exposure scenarios depending on the workplace. These exposures can be chronic, repeated, or acute, and can involve many different compounds. The effect of uranium after multiple scenarios of exposure is unknown. The aim of this study, therefore, was to investigate the genotoxic and biokinetics consequences of exposure to depleted insoluble uranium dioxide (UO2) by repeated or acute inhalation on subsequent acute inhalation of moderately soluble uranium peroxide (UO4) in rats. The results show that UO2 repeated preexposure by inhalation increases the genotoxic effects of UO4 inhalation, assessed by comet assay, in different cell types, when UO4 exposure alone has no effect. At the same time, the study of UO4 bioaccumulation showed that the UO4 biokinetics in the kidneys, gastrointestinal tract, and excreta, but not in the lungs, were slightly modified by previous UO2 exposures. All these results show that both genotoxic and biokinetics effects of uranium may depend on preexposure and that repeated exposure induces a potentiation effect compared with acute exposure.

PMID: 16864406 [PubMed - indexed for MEDLINE]

1: J Toxicol Environ Health A. 2006 Sep;69(17):1613-28. Links

Short-term effects of depleted uranium on immune status in rat intestine.

Dublineau I,

Grison S,

Linard C,

Baudelin C,

Dudoignon N,

Souidi M,

Marquette C,

Paquet F,

Aigueperse J,

Gourmelon P.

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In the event of ingestion, the digestive tract is the first biological system exposed to depleted uranium (DU) intake via the intestinal lumen. However, little research has addressed the biological consequences of a contamination with depleted uranium on intestinal properties such as the barrier function and/or the immune status of this tissue. The aim of this study was to determine if the ingestion of depleted uranium led to changes in the gut immune system of the intestine. The experiments were performed at 1 and 3 d following a per os administration of DU to rats at sublethal dose (204 mg/kg). Several parameters referring to the immune status, such as gene and protein expressions of cytokines and chemokines, and localization and density of immune cell populations, were assessed in the intestine. In addition, the overall toxicity of DU on the small intestine was estimated in this study, with histological appearance, proliferation rate, differentiation pattern, and apoptosis process. Firstly, the results of this study indicated that DU was not toxic for the intestine, as measured by the proliferation, differentiation, and apoptosis processes.

Concerning the immune properties of the intestine, the ingestion of depleted uranium induced some changes in the production of chemokines and in the expression of cytokines. A diminished production of monocyte chemoattractant protein-1 (MCP-1) was noted at 1 day post exposure. At 3 d, the increased gene expression of interferon gamma (IFNgamma) was associated with an enhanced mRNA level of Fas ligand, suggesting an activation of the apoptosis pathway. However, no increased apoptotic cells were observed at 3 d in the contaminated animals. There were no changes in the localization and density of neutrophils, helper T lymphocytes, and cytotoxic T lymphocytes after DU administration. In conclusion, these results suggest that depleted uranium is not toxic for the intestine after acute exposure. Nevertheless, DU seems to modulate the expression and/or production of cytokines (IFNgamma) and chemokines (MCP-1) in the intestine. Further experiments need to be performed to determine if a chronic contamination at low dose leads in the long term to modifications of cytokines/chemokines patterns, and to subsequent changes in immune response of the intestine.

PMID: 16854789 [PubMed - indexed for MEDLINE]

Environ Toxicol. 2006 Aug;21(4):349-54. Links

A search for cellular and molecular mechanisms involved in depleted uranium (DU) toxicity.

Pourahmad J,

Ghashang M,

Ettehadi HA,

Ghalandari R.

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Addition of U(VI) (uranyl acetate) to isolated rat hepatocytes results in rapid glutathione oxidation, reactive oxygen species (ROS) formation, lipid peroxidation, decreased mitochondrial membrane potential, and lysosomal membrane rupture before hepatocyte lysis occurred. Cytotoxicity was prevented by ROS scavengers, antioxidants, and glutamine (ATP generator). Hepatocyte dichlorofluorescein oxidation was inhibited by mannitol (a hydroxyl radical scavenger) or butylated hydroxyanisole and butylated hydroxytoluene (antioxidants). Glutathione depleted hepatocytes were resistant to U(VI) toxicity and much less dichlorofluorescein oxidation occurred. Reduction of U(VI) by glutathione or cysteine in vitro was also accompanied by oxygen uptake and was inhibited by Ca(II) (a U(IV) or U(VI) reduction inhibitor). U(VI)-induced cytotoxicity and ROS formation was also inhibited by Ca(II), which suggests that U(IV) and U(IV) GSH mediate ROS formation in isolated hepatocytes. The U(VI) reductive mechanism required for toxicity has not been investigated. Cytotoxicity was also prevented by cytochrome P450 inhibitors, particularly CYP 2E1 inhibitors, but not inhibitors of DT diaphorase or glutathione reductase. This suggests that P450 reductase and reduced cytochrome P450 contributes to U(VI) reduction to U(IV). In conclusion, U(VI) cytotoxicity is associated with mitochondrial/lysosomal toxicity by the reduced biological metabolites and ROS.

PMID: 16841314 [PubMed - in process]

1: Int J Environ Res Public Health. 2006 Jun;3(2):129-35. Links

The evolution of depleted uranium as an environmental risk factor: lessons from other metals.

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Depleted uranium (DU) is used in both civilian and military applications. Civilian uses are primarily limited to ballast and counterweights in ships and aircraft with limited risk of environmental release. The very nature of the military use of DU releases DU into the environment. DU released into the environment from military use takes the form of large fragments that are chemically unchanged and dust in the form of oxides. DU dust is nearly insoluble, respirable and shows little mobility in the soil. Exposure to DU occurs primarily from inhalation of dust and possible hand to mouth activity. Toxicity of DU is believed to be primarily chemical in nature with radiological activity being a lesser problem. DU has been shown to have a variety of behavioral and neurological effects in experimental animals. DU has been used the Balkans, Afghanistan, and both Iraq wars and there is a high probability of its use in future conflicts. Further, other nations are developing DU weaponry; some of these nations may use DU with a greater radiological risk than those currently in use. The toxicity of DU has been studied mostly as an issue of the health of military personnel. However, many tons of DU have been left in the former theater of war and indigenous populations continue to be exposed to DU, primarily in the form of dust. Little epidemiological data exists concerning the impact of DU on these groups. It may be possible to extrapolate what the effects of DU may be on indigenous groups by examining the data on similar metals. DU has many similarities to lead in its route of exposure, chemistry, metabolic fate, target organs, and effect of experimental animals. Studies should be conducted on indigenous groups using lead as a model when ascertaining if DU has an adverse effect.

PMID: 16823086 [PubMed - in process]

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3. CFS - SEE ARTICLE ON CFS (1.)

4. ANTHRAX VACCINE INFORMATION

by Dee Ann Divis, Senior Science & Technology Editor

Submitted by Denise Nichols, former Chairwoman of Committee on Gulf War Illness

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WASHINGTON, DC, March 11(UPI) - Congress will look into whether the Department of Health and Human Services overstepped its authority when it gave the Department of Defense permission to vaccinate military personnel with a controversial anthrax vaccine despite a court injunction halting the program.

The hearings will be called in the next couple of months by Rep. Christopher Shays, R-Conn., chairman of the House Subcommittee on National Security, Emerging Threats and International Relations. Shays has been asking HHS officials for information on their decision to approve Emergency Use Authorization since it was issued Jan. 14 at the request of the Defense Department.

HHS made its ruling based on the new Bioshield Act, which grants the Secretary of Health and Human Services the right to permit use of a vaccine for an otherwise-unapproved use if there is an emergency or potential emergency. Paul Wolfowitz, the deputy secretary of defense, asked for permission in a Dec. 10 letter saying he he "determined there is a significant potential for a military emergency involving a heightened risk to the United States military forces of an attack with anthrax." That use of Bioshield is beyond the intention of Congress, Shays said.

"We believe HHS acquiescence in the DoD request unjustifiably expands and distorts the scope of emergency use authority envisioned by the Act and strays well beyond the legislative intent of the provision," Shays wrote in a March 9 letter to HHS secretary Michael Leavitt.

The anthrax vaccine, called Anthrax Vaccine Absorbed or AVA, manufactured by Bioport of Lansing, Mich., has been the subject of three lawsuits, a congressional investigation and some 100 courts-martial of personnel refusing the vaccination. Critics of the program say the medication can cause serious, even life-threatening, reactions and is not approved for the prevention of inhalation anthrax--the biodefense application at the center of the DOD vaccination program.

ANTHRAX HEARINGS

DOD and Bioport assert the vaccine is safe, pointing to 18 studies, including one by the Institute of Medicine saying the vaccine is no more dangerous than any other vaccine.

Federal District Court Judge Emmet Sullivan agreed with critics and granted an injunction Oct. 27 against the mandatory program for a second time, pending

new steps by the Food and Drug Administration to finish the proper approval process and clear the vaccine for its specific use against inhalational anthrax.

Though it would still be possible to give soldiers the vaccine with their informed consent under the injunction, DoD sought an alteration of the injunction in light of the HHS ruling.

"When the Bioshield Act first passed the House, Mr. Shays was very concerned about a provision in the original bill that talked about waivers of certain informing requirements for emergencies in the military," said a congressional staff member speaking on condition of anonymity. "We put it in Title 10, some years before, that if you are going to use an (investigational drug) on U.S. forces, that has to be presidentially approved after a process where the secretaries of HHS and DoD say what it means and why they have to do it that way."

After some negotiation, the aide said, the House agreed that members of the military should be allowed to consent to receive either unapproved drugs or drugs that were licensed but used in an unapproved way.

"There was a colloquy on the floor between then chairman (Billy) Tauzin (R-La) and Mr. Shays to the effect that the (Bioshield) provision was too broadly written."

Colloquies are a form of scripted conversation held during a congressional session as a way to enter discussion into the record and often are used to express congressional intent.

The Senate also acknowledged restrictions to waivers, even if the situation involved a new use for an already licensed product.

"You still need to inform those receiving the drug," said the aide.

A spokesman for HHS said the department was drafting response to both letters, but he would not comment on the letters of the possibility of a hearing.

5. ALS -- Amyotrophic lateral sclerosis

From the National Gulf War Resource Center VA inadvertently sent letters to at least 1200 veterans notifying them that they have the terminal illness amyotrophic lateral sclerosis commonly known as ALS

Letter from the VA States: "According to records of the Department of Veterans Affairs (VA), you have a diagnosis of amyotrophic lateral sclerosis (ALS). This letter tells you about VA disability compensation benefits that may be available to you."

This letter was automatically generated and sent to no less then1200 veterans, The VA is still working to get the total number. The 1200 may just be from the West Virginia VARO. The NGWRC is receiving phone calls from many veterans concerned they may have a terminal illness.(

Alabama, West Virginia, Florida, Kentucky, Kansas, Wyoming so far) Many of these veterans went to private clinicians to get a second opinion. This second opinion outside of the VA is very expensive and can range from $1000 to $3000 or more.

The National Gulf War Resource Center requests that the VA set up a hotline for veterans to respond to this letter. It also requests that any outside expenses for testing and travel to and from their primary care clinician be reimbursed by the VA. This is a terminal disease many veterans may believe that they are about to die..

The VA has an obligation to go on television and make public service announcements to prevent veterans from becoming overly alarmed. In addition, each veteran that was notified should be rescreened by the Department of Veterans Affairs for neurological issues that are undiagnosed. While it remains

to be seen how this debacle happened we know what needs to be done right now to prevent further harm.

We expect the VA to rapidly notify by telephone each veteran on the list.

Thousands of Gulf War veterans remain ill and so far, the VA does not have any treatment for their chronic multi-symptom illness. One common factor amongst Gulf War veterans is undiagnosed neurological conditions. These veterans need to be rescreened. If you are a veteran who received this notification, please contact the National Gulf War Resource Center and we will advocate on your behalf.

We at NGWRC are deeply concerned that some veterans already very ill will take this ALS letter as a death sentence and there could be suicides that result from this mistake! We are asking the VA to get out in front of this immediately in the press nationally and explain that there was an error!

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6. DIETHYL-M-TOLUAMIDE (DEET)

1: Toxicol Sci. 2009 Mar;108(1):110-23. Epub 2009 Jan 13. Links

N,N,-diethyl-m-toluamide (DEET) suppresses humoral immunological function in B6C3F1 mice.

Keil DE, McGuinn WD, Dudley AC, EuDaly JG, Gilkeson GS, Peden-Adams MM.

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N,N-diethyl-meta-toluamide (DEET) is a particularly effective broad-spectrum insect repellent used commonly in recreational, occupational and military

environments. Due to its widespread use and suggested link to Gulf War Illness, this study examined the immunotoxicity of DEET. Adult female B6C3F1 mice were injected sc for 14 days with DEET at 0, 7.7, 15.5, 31, or 62 mg/kg/day. Due to differences in the dermal absorption of DEET between mice and humans, this study eliminated this confounding factor by utilizing sc injection and measured circulating blood levels of DEET to assess bioavailability from sc administration. Effects on lymphocyte proliferation, natural killer cell activity, thymus and spleen weight and cellularity, the antibody plaque-forming cell (PFC) response, and thymic and splenic CD4/CD8 lymphocyte subpopulations were assessed 24 h after the last dose. No effect was observed in lymphocyte proliferation, natural killer cell activity, thymic weight, splenic weight, thymic cellularity, or splenic cellularity. Significant decreases were observed in the percentage of splenic CD4-/CD8- and CD4+/CD8- lymphocytes but only at the 62 mg DEET/kg/day treatment level and not in absolute numbers of these cells types. Additionally, significant decreases in the antibody PFC response were observed following treatment with 15.5, 31, or 62 mg DEET/kg/day. Pharmacokinetic (PK) data from the current study indicate 95% bioavailability of the administered dose. Therefore, it is likely that DEET exposure ranges applied in this study are comparable to currently reported occupational usage. Together, the evidence for immunosuppression and available PK data suggest a potential human health risk associated with DEET in the occupational or military environments assuming similar sensitivity between human and rodent responses.

PMID: 19141786 [PubMed - in process]

1: Behav Brain Res. 2009 Feb 11;197(2):301-10. Epub 2008 Aug 29. Links

Repeated stress in combination with pyridostigmine Part I: long-term behavioural consequences.

Lamproglou I, Barbier L, Diserbo M, Fauvelle F, Fauquette W, Amourette C.

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Since their return from the first Persian Gulf War, some veterans have complained of a variety of symptoms that were designated as "Gulf War Illness" (GWI). Among other factors, pyridostigmine, used as a prophylaxis treatment against intoxication by nerve agents, has been proposed by many authors as a cause of late social and/or cognitive dysfunction related to GWI. One of the hypotheses placed to explain these behavioural disorders is that operational stress has modified the side effects of pyridostigmine given to soldiers. In an attempt to establish an experimental model of GWI to evaluate the long-term behavioural effects of pyridostigmine administered in stressful conditions, we have developed a new model of repeated stress based on the pole-climbing avoidance technique. We used it to evaluate the effects of pyridostigmine treatment combined to repeated stress over the months following the end of the treatment. We observed that this stress induces impulsiveness and aggressiveness in adult male rat. Moreover, pyridostigmine treatment administered daily 30 min before each stressful session amplifies these behavioural disorders and induces long-term learning dysfunction and slight but significant decrease in phosphocholine level in hippocampus. This suggests that repeated administration of pyridostigmine combined to pole-climbing avoidance (PCA) stress conditions can induce adverse effects in rat central nervous system.

PMID: 18793677 [PubMed - indexed for MEDLINE]

1: Behav Brain Res. 2009 Feb 11;197(2):292-300. Epub 2008 Aug 29. Links

Repeated stress in combination with pyridostigmine Part II: changes in cerebral gene expression.

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Organophosphates (OP) represent a potential threat in terrorism or during military conflicts. Due to its faculty to protect cholinesterase (ChE) activity against irreversible inactivation by OP, pyridostigmine bromide (PB) was used as a prophylaxis treatment during the first Persian Gulf War. To explain dysfunctions reported by Gulf War Veterans (GWV), it was suggested a potentiation of the operational stress effects by PB given to soldiers. Our companion paper (see part 1 in the same journal issue) describes that PB treatment administered in repeated stress conditions results in long-term perturbations of learning and social behaviour. The present paper examines, in adult male Wistar rats, consequences of the association of repeated stress and PB treatment on gene expression in hypothalamus and hippocampus. PB treatment (1.5 mg/kg/day) was orally administered 30 min before each stress session to inhibit 40% of blood ChE as recommended by NATO. 10 days of stress alone induce a decrease in hypothalamic Il-1alpha expression. Treatment with PB alone increases mineralocorticoid receptor expression in hypothalamus which means that PB may thus modify stress perception by animals. Stressed-PB animals showed increase in hippocampal expression of BDNF, TrkB and CamKIIalpha, three genes implicated in memory development. As a supplement to previous studies showing behavioural and biochemical effects of the association of stress with PB, our data reveal that behavioural effects of this association may be linked with genomic changes in hippocampus. Mechanisms underlying these modifications and their link with memory disturbances reported by GWV remain to be further determined.

PMID: 18796314 [PubMed - indexed for MEDLINE]

1: Autoimmun Rev. 2008 Oct;8(1):52-5. Epub 2008 Aug 24. Links

Chronic fatigue syndrome with autoantibodies--the result of an augmented adjuvant effect of hepatitis-B vaccine and silicone implant.

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BACKGROUND: Chronic fatigue syndrome (CFS) that defines by prolonged fatigue and other manifestations, was recently integrated into a spectrum of central sensitivity syndromes including several diseases as fibromylagia. CFS etiology is multi-factorial commonly triggered by infectious agents. Vaccines, induce an immune response similarly to infections, and may trigger just like infections autoimmune diseases, CFS and fibromyalgia. Furthermore vaccines contain an adjuvant which enhances their immune stimulation. CASE PRESENTATION: A 56-year-old woman was diagnosed with CFS accompanied by fibromyalgia, demyelination and autoantibodies. Her illness begun following the 2nd dose of hepatitis-B vaccine, and was aggravated by the 3rd vaccination. She underwent silicone breast implantation 6 years before vaccination with no adverse events. However, between the 2nd and 3rd vaccination she suffered a breast injury with local inflammation. Upon explanation of her breast implants silicone leak was observed. DISCUSSION: Vaccines have been reported to precede CFS mainly following exposure to multiple vaccinations (e.g. the Gulf war syndrome), or as an adverse response to the vaccine adjuvant (e.g. the macrophagic myofasciitis syndrome). Silicone is considered an adjuvant to the immune system, and may induce "the adjuvant disease". Silicone implant, especially silicone leak relationship with autoimmunity and CFS has been the focus of considerable debates. CONCLUSION: Our patient illness started following hepatitis-B vaccine, suggesting that it was caused or accelerated by vaccination. In parallel to vaccination our patient suffered from breast injury,

which might represent the time of silicone leak. The exposure to the adjuvant, silicone, might have augmented her immune response to the vaccine. To the best of our knowledge this is the first case of combined adverse effect to vaccine and silicone. Vaccine safety in individuals with silicone implants requires further studies.

PMID: 18725327 [PubMed - in process]

1: Med Hypotheses. 2009 Feb;72(2):135-9. Epub 2008 Nov 11. Links

A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome.

Exley C, Swarbrick L, Gherardi RK, Authier FJ.

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Macrophagic myofasciitis and chronic fatigue syndrome are severely disabling conditions which may be caused by adverse reactions to aluminium-containing adjuvants in vaccines. While a little is known of disease aetiology both conditions are characterised by an aberrant immune response, have a number of prominent symptoms in common and are coincident in many individuals. Herein, we have described a case of vaccine-associated chronic fatigue syndrome and macrophagic myofasciitis in an individual demonstrating aluminium overload. This is the first report linking the latter with either of these two conditions and the possibility is considered that the coincident aluminium overload contributed significantly to the severity of these conditions in this individual. This case has highlighted potential dangers associated with aluminium-containing adjuvants and we have elucidated a possible mechanism whereby vaccination involving aluminium-containing adjuvants could trigger the

cascade of immunological events which are associated with autoimmune conditions including chronic fatigue syndrome and macrophagic myofasciitis.

PMID: 19004564 [PubMed - in process]

Biochimie. 2009 Mar 23. [Epub ahead of print] Links

Dna methylation during depleted uranium-induced leukemia.

Miller AC, Stewart M, Rivas R.

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OBJECTIVES: The radioactive heavy metal depleted uranium (DU) is used in kinetic-energy penetrators in military applications. The objective of this study was to determine involvement of DNA methylation in DU-induced leukemia. METHODS: Methylation was measured by direct analysis of 5-methylcytosine content of spleen DNA in DU leukemic mice. RESULTS: Spleen hypomethylation occurred during DU-induced leukemogenesis (chronic internal DU exposure). Aberrant gene transcription was also detected. CONCLUSIONS: Epigenetic mechanisms are implicated in DU-induced leukemia. These data are evidence of aberrant DNA hypomethylation being associated with DU leukemogenesis.

PMID: 19324073 [PubMed - as supplied by publisher]

1: Health Phys. 2009 Apr;96(4):483-92. Links

Acute toxicity of subcutaneously administered depleted uranium and the effects of CBMIDA in the simulated wounds of rats.

Fukuda S, Ikeda M, Nakamura M, Yan X, Xie Y.

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We examined the acute toxicity of depleted uranium (DU) after subcutaneous injection as a simulated wound model (experiment I), and the effects of a chelating agent, catechol-3,6-bis(methyleiminodiacetic acid) (CBMIDA), on the removal and damages caused by uranium by local treatment for wounds in rats (experiment II). Experiment I: To examine the initial behavior and toxicity of uranium of different chemical forms, male Wistar rats were subcutaneously injected with 4 and 16 mg kg-1 DU in a solution of pH 1 and 7. The rats were killed 1, 3, 6, and 24 h after DU injection. The DU (pH 1) injection site on the skin was altered markedly by acid burn, and the chemical action of uranium compared with that of DU (pH 7). After the injection of 4 mg kg-1 DU (pH 1), about 60% of the uranium was retained 1-3 h at the injected sites and then decreased to 16% at 24 h. However, the concentration of uranium in the injected site after 16 mg kg-1 DU (pH 1) injection did not change significantly. Urinary excretion rates of uranium (pH 1) increased in a time-independent manner after the injection. Depositions of uranium in the liver, kidneys and femur were found at 1 h after DU injection, and the results of serum and urinary examinations indicated that severe damage in the organs, including the kidney, was induced. The results of the DU (pH 7) were useful for estimating the chemical toxicity of uranium. Experiment II: The effects of CBMIDA by local treatment for wounds with DU were examined. CBMIDA (480 mg kg-1) was infused into the DU-injected site 0, 10, 30, 60, 120 min, and 24 h after the subcutaneous injection of 4 mg kg-1 DU (pH 1 and 7). The uranium at the injected sites decreased to 4-17% of that at 24 h in the DU (pH 1) group without CBMIDA treatment in experiment I, when it was administered within 120 min after DU injection. In addition, CBMIDA had excellent efficacy in excreting the

uranium in urine and feces and decreasing the concentrations of uranium in the kidneys and femur. However, there were no distinct effects of CBMIDA for DU (pH 7). In conclusion, the results indicated that the subcutaneous injected uranium acutely induced severe damage in the DU-injected sites and organs by chemical toxicity within a very short time after DU intake, despite the chemical forms of uranium used, and the local treatment of CBMIDA for wounds contaminated with DU was effective in decreasing the acute toxicity of uranium if carried out within 120 min after DU administration.

PMID: 19276709 [PubMed - indexed for MEDLINE]

J Toxicol Environ Health A. 2009;72(6):410-27. Links

Two-generation reproductive toxicity study of implanted depleted uranium (DU) in CD rats.

Arfsten DP, Still KR, Wilfong ER, Johnson EW, McInturf SM, Eggers JS, Schaeffer DJ, Bekkedal MY.

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Depleted uranium (DU) munitions and armor plating have been used in several conflicts over the last 17 yr, including the Persian Gulf War and the Iraq War. Because of its effectiveness and availability, DU will continue to be used in military applications into the foreseeable future. There is much controversy over the use of DU in weapons and equipment because of its potential radiological and toxic hazards, and there is concern over the chronic adverse health effects of embedded DU shrapnel in war veterans and bystanders. This study evaluated the effects of long-term implantation of DU on the reproductive

success of F0 generation adults and development and survival of subsequent F1 and F2 generations in a two-generation reproductive toxicity study. F0 generation Sprague-Dawley rats, 8 wk of age, were surgically implanted with 0, 4, 8, 12, or 20 DU pellets (1 x 2 mm). Inert implant control animals were implanted with 12 or 20 tantallum (Ta) pellets. The F0 generation was then mated at 120 d post DU implantation. In the F0 generation, when measured on postimplantation d 27 and 117, uranium was present in the urine of DU-implanted animals in a dose-dependent manner. F0 reproductive success was similar across treatment groups and the maternal retrieval test revealed no changes in maternal behavior. DU implantation exerted no effect on the survival, health, or well-being of the F0 generation. Necropsy results of F0 animals were negative with the exception of a marked inflammatory response surrounding the implanted DU pellets. For the F1 generation, measures of F1 development through postnatal day (PND) 20 were unremarkable and no gross abnormalities were observed in F1 offspring. No uranium was detected in whole-body homogenates of PND 4 or PND 20 pups. Necropsy findings of F1 PND 20 pups were negative and no instances of ribcage malformation were observed in F1 PND 20 pups. Body weight and body weight gain of F1 rats through PND 120 were similar across treatment groups. Eight of 414 F1 animals observed from PND 20 to 120 died of unknown causes; 7 were from litters of DU-implanted F0 mating pairs. F1 mating success at 10 wk of age was an overall 70% compared with 91% for F0 mating pairs. Mating success was similar between F1 animals derived from DU-implanted F0 adults and those derived from F0 implant control adults suggesting that the comparatively low mating success was not due to F1 DU exposure. The gestational index of F1 animals derived from mid-dose F0 mating pairs was found to be lower compared with F1 controls. The average gestation duration of F1 animals derived from high-dose F0 mating pairs was found to be significantly longer than F1 controls. F1 sperm motility analyses did not differ among experimental groups and no gross abnormalities were identified at necropsy among surviving F1 animals at PND 120. Histopathology of kidneys, spleen, thymus, bone marrow, ovaries, and testes of F1 high-dose animals did not differ from F1 controls. F1 high-dose females had significantly higher mean relative liver and heart weights compared

with F1 controls; the biological relevance of this finding could not be determined. For the F2 generation, measures of F2 development through PND 20 were unremarkable and no gross abnormalities were observed in F2 offspring. Necropsy findings of F2 PND 20 pups were negative and no instances of ribcage malformation were observed in F2 PND 20 pups. Body weight and body weight gain of F2 rats through PND 90 were similar across treatment groups. Mean relative heart weights of males derived from high-dose F0 parents were significantly lower compared with F2 controls. Sperm motility and concentration analysis of F2 males at PND 90 were similar across F2 groups. Overall, the consistent absence of positive findings in this study seems to suggest that DU is not a significant reproductive or developmental hazard, particularly when one considers that mid- and high-dose rats were implanted with the equivalent of 0.3 and 0.5 lb of DU in a 70-kg human, respectively. However, the findings that seven of eight F1 adults that died postweaning were from DU-implanted F0 mating pairs, and that mean relative heart weights were elevated in high-dose F1 and F2 pups, suggest conservatism is warranted in characterizing the reproductive and teratogenic hazards of embedded DU until further studies are completed.

PMID: 19199148 [PubMed - indexed for MEDLINE]

Toxicology. 2009 Apr 5;258(1):1-9. Epub 2008 Dec 31. Links

Different pattern of brain pro-/anti-oxidant activity between depleted and enriched uranium in chronically exposed rats.

Lestaevel P, Romero E, Dhieux B, Ben Soussan H, Berradi H, Dublineau I, Voisin P, Gourmelon P.

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Uranium is not only a heavy metal but also an alpha particle emitter. The main toxicity of uranium is expected to be due to chemiotoxicity rather than to radiotoxicity. Some studies have demonstrated that uranium induced some neurological disturbances, but without clear explanations. A possible mechanism of this neurotoxicity could be the oxidative stress induced by reactive oxygen species imbalance. The aim of the present study was to determine whether a chronic ingestion of uranium induced anti-oxidative defence mechanisms in the brain of rats. Rats received depleted (DU) or 4% enriched (EU) uranyl nitrate in the drinking water at 2mg(-1)kg(-1)day(-1) for 9 months. Cerebral cortex analyses were made by measuring mRNA and protein levels and enzymatic activities. Lipid peroxidation, an oxidative stress marker, was significantly enhanced after EU exposure, but not after DU. The gene expression or activity of the main antioxidant enzymes, i.e. superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), increased significantly after chronic exposure to DU. On the contrary, oral EU administration induced a decrease of these antioxidant enzymes. The NO-ergic pathway was almost not perturbed by DU or EU exposure. Finally, DU exposure increased significantly the transporters (Divalent-Metal-Transporter1; DMT1), the storage molecule (ferritin) and the ferroxidase enzyme (ceruloplasmin), but not EU. These results illustrate that oxidative stress plays a key role in the mechanism of uranium neurotoxicity. They showed that chronic exposure to DU, but not EU, seems to induce an increase of several antioxidant agents in order to counteract the oxidative stress. Finally, these results demonstrate the importance of the double toxicity, chemical and radiological, of uranium.

PMID: 19154773 [PubMed - in process]

Med Sci Monit. 2009 Mar;15(3):RA75-90. Links

Current opinion on the science of organophosphate pesticides and toxic stress: a systematic review.

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The aim of this article is to provide a brief review of the current status of our knowledge related to organophosphates (OPs) and oxidative stress. For this purpose, we performed a systematic review on the literatures using Pubmed and Scopus databases without date limitation. A total of 127 articles including 112 experimental and 15 human studies were found relevant and reviewed. Data were categorized according to experimental and clinical studies. Occurrence of cell membrane lipid peroxidation, alteration in the levels of total antioxidant capacity, total thiol molecules, and protective effects of natural and synthetic antioxidants against OP-induced histopathological and biochemical alterations are the most important evidences for involvement of oxidative stress in OP-induced toxicity. It is concluded that evaluation of blood oxidative stress parameters can be useful for monitoring exposed people. Supplementing of people in exposure to OPs with potent antioxidants such as vitamin E and C is recommended. Much human studies with higher sample size and better exclusion of biasing factors are still needed.

PMID: 19247260 [PubMed - in process]

7. PARKINSON'S DISEASE - Epidemological Study

Scott Dodd, Environmental journalist

Posted: February 4, 2010 11:13 AM

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The evidence that environmental factors play a role in Parkinson's Disease is growing.

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The largest-ever epidemiological study of the ailment, published online in the journal Neuroepidemiology and reported yesterday by Yale Environment 360, shows that the incidence of the illness is extremely high in many parts of the Northeast and Midwest.

"These are the two regions of the country most involved in metal processing and agriculture," says Dr. Allison Wright Willis, the paper's lead author and an assistant professor of neurology at Washington University School of Medicine in St. Louis, "and chemicals used in these fields are the strongest potential environmental risk factors for Parkinson's disease that we've identified so far."

The study was based on data from 36 million Medicare patients aged 65 and older and found numerous areas in the Northeast and Midwest where 14 percent or more of the population suffers from the neurodegenerative condition. Parkinson's causes tremors, stiffness, and mood and behavioral changes.

Many regions of the West, as well as Alaska, had extremely low rates of the disease, the researchers found.

The study is yet more evidence of the link between Parkinson's and pesticides, which was reported by science writer Robin Marantz Henig in OnEarth magazine last summer. Henig acknowledges that it's tough to prove a cause-and-effect relationship between neurotoxins and the disease ("there will probably never be a smoking gun," she writes) but cites a wealth of population studies and other scientific evidence that have produced a steadily mounting consensus about such a connection.

A January 2009 consensus statement from CHE, in collaboration with the Parkinson's Action Network, a patient advocacy group, found that there was "limited suggestive evidence of an association" between pesticides and Parkinson's, and between farming or agricultural work and Parkinson's. This followed by just a few months the publication of Environmental Threats to Healthy Aging, a report co-authored by the Science and Environmental Health Network, a consortium of advocacy groups based in Ames, Iowa; it included a summary of 31 population studies that have looked at the possible connection between pesticide exposure and Parkinson's. Twenty-four of those studies, according to the report, found a positive association, and in 12 cases the association was statistically significant. In some studies, the group found, there was as much as a sevenfold greater risk of Parkinson's in people exposed to pesticides. In addition, in April 2009, scientists at the University of California, Los Angeles (UCLA), published a provocative study connecting the disease not only to occupational pesticide exposure but also to living in homes or going to schools that were close to a pesticide-treated field.

"Taken together," Henig writes, "30-plus years of research add up to an increasingly persuasive conclusion: exposure to pesticides and other toxins increases the risk of Parkinson's disease, and we are only now beginning to wrestle with the true scope of the damage."

Now the Washington University School of Medicine study can be added to that pile of evidence. According to Willis, its lead author, genetic factors explain only a small percent of Parkinson's cases. Environmental factors -- including prolonged exposure to herbicides and insecticides used in farming, as well as metals such as copper, manganese, and lead -- appear to be more common contributors to developing the disease.

Read more about the evidence for a link between Parkinson's and pesticides here.

Map: The largest U.S. study of the epidemiology of Parkinson's disease shows the highest prevelance (13,800 cases or more per 100,000 residents ages 65 and older) in red. Lower prevalence rates are progressively indicated by orange, yellow, light green and green. Neuroepidemiology/S. Karger AG

--END RELEVANT RESEARCH SECTION--

A WORD FROM THE NV&GWVC: ***The NV&GWVC would like to express their sincere "thank you" to former Chairwoman of the Gulf War Illness Committee, Denise Nichols, RN MAJ. USAF RET., for the outstanding research and investigations that have gone into her work for Gulf War Illness.***