Heavy Metal Toxicity

ABSTRACTS

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Treatment of mercury and lead poisonings with dimercaptosuccinic acid (DMSA) and sodium dimmercapto-propanesulfonate (DMPS).

Aaseth J, Jacobsen D, Andersen O, Wickstron E. Analyst 1995 Mar;120:853ff

SUMMARY: The organic mercury species with greatest toxicity are methylmercury compounds, which have a high affinity for the brain and nervous system. DMSA is shown to cross the blood brain barrier and remove mercury from that organ. DMPS is much less effective. DMPS is also 3 times more toxic than DMSA, based on LD-50. Animal studies show DMSA to be almost 3 times more effective than DMPS in removing brain mercury, as tabulated below. DMSA has the added advantage that it is taken by mouth in capsule form. DMPS is usually given by injection. STUDY OF MERCURY TOXIC MICE: Brain mercury before treatment averaged 2.3 nmol/g; brain mercury after DMPS treatment = 1.6 nmol.g; brain mercury after DMSA treatment = 0.6 nmol/g. CONCLUSION: DMSA may now be considered as the treatment of first choice in cases of acute or subacute lead poisoning and in methylmercury poisoning. All experimental and clinical experiences show a low toxicity for this drug.

Chelation therapy. AHA recommendation.

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Anderton, R.M. May 2001 American Dental Association, Chicago, IL, U.S.A.

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No abstract available.

Management of the poisoned/overdosed patient.

Anon. (no authors given). Continuing Education No. 430-000-99-026-H01. U.S. Pharmacist 2001 Jobson, New York, NY, U.S.A.

No abstract available.

Protective role of DL-alpha-lipoic acid against mercury-induced neural lipid peroxidation.

Anuradha B, Varalakshmi P. Department of Medical Biochemistry, Dr. AL Mudaliar Post Graduate Institute of Basic Medical Sciences, Madras University, Taramani, Madras, 600 113, India. Pharmacol Res 1999 Jan;39(1):67-80

Experimental neurotoxicity in rat models was induced by an intramuscular injection of mercuric chloride. dl-alpha-lipoic acid was administered as an antidote in three protocols of experimental design. Two protocols of short-term exposure of mercury was designed, one with prophylactic therapy and the other with curative therapy of lipoic acid. The third protocol was with prophylactic therapy of lipoic acid on long-term exposure of mercury. Enhanced lipid peroxidation, depleted non-enzymic and perturbed enzymic antioxidant status were observed in cerebral cortex, cerebellum and sciatic nerves of the toxic groups. The ameliorating effect of lipoic acid and its therapeutic efficacy during various modes of therapy, on the antioxidant status was established in the nervous tissues. Copyright 1999 The Italian Pharmacological Society.

Case-control studies of liver, gallbladder and pancreatic cancer and metalworking fluid exposure in the automobile industry.

Bardin JA, Eisen EE, Wegman DH, Kriebel D, Woskie SR, Gore RJ. Paper presented to the 128th Annual Meeting of the American Public Health Association, November 14, 2000 American Public Health Association, Washington, D.C., U.S.A.

No abstract available.

Poisoning.

Beers MH, Berkow MD. 1999 The Merck Manual of Diagnosis and Therapy. Section 23. Chapter 307. Merck & Co., Whitehouse Station, NJ, U.S.A.

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Lactoferrin: the bioactive peptide that fights disease.

Brink W. Life Extension Magazine 2000 Oct; 6(10): 20-6 (http://www.lef.org/magazine/mag2000/oct2000_report_lactoferrin.html) Life Extension Foundation, Ft. Lauderdale, FL, U.S.A.

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Characterizing risk at metal finishing facilities.

Brown DJ. May 1998 Report EPA/600/R-97/111. U.S. Environmental Protection Agency, Washington, D.C., U.S.A.

Facility-based risk characterization for workers and surrounding communities is a high priority issue for stakeholders in the Environmental Protection Agency's Common Sense Initiative Metal Finishing Sector. Platers, environmental groups, community groups, labor, and regulators all need and want to know what emissions are coming out and in what amounts from metal finishing operations. They also want to know what health risks those emissions create for workers and the surrounding communities. A process is described herein that includes a problem formulation phase to identify the types and forms of information that are wanted by the different stakeholders and a risk assessment phase to quantify the health risks associated with facility emissions. A screening level risk assessment is performed in which toxicity information and exposure data are used to show how a facility-based risk assessment could be performed for a typical electroplating operation. Information needs for a more refined assessment are presented. A single iteration of the problem formulation and risk assessment processes may lead directly to a risk management

decision or the steps may be modified and repeated, taking into account input from stakeholders obtained during the risk communication process. Uncertainties associated with toxicity information and exposure scenarios will present challenges for providing simple (but not simplistic) methods of risk assessment that can be applied by facility operators, community groups, and other stakeholders. This type of risk characterization is not only desired but possible to carry out for a variety of exposure scenarios.

Roles of vitamin C in radiation-induced DNA damage in presence and absence of copper.

Cai L, Koropatnick J, Cherian MG. Department of Pathology, University of Western Ontario, London, Ontario, Canada N6A 5C1. Chem Biol Interact 2001 Jul 31;137(1):75-88

Exposure to either ionizing radiation or certain transition metals results in generation of reactive oxygen species that induce DNA damage, mutation, and cancer. Vitamin C (a reactive oxygen scavenger) is considered to be a dietary radioprotective agent. However, it has been reported to be genotoxic in the presence of certain transition metals, including copper. In order to explore the capacity of vitamin C to protect DNA from radiation-induced damage, and the influence of the presence of copper on this protection, we investigated vitamin C-mediated protection against radiation-induced damage to calf thymus DNA in vitro in the presence or absence of copper(II). Vitamin C (0.08-8.00 mM, pH 7.0) significantly reduced DNA damage induced by gamma-irradiation (30-150 Gy) by 30-50%, similar to the protective effect of glutathione. However, vitamin C plus copper (50 microM) significantly enhanced gamma-radiation-induced DNA damage. Low levels of added copper (5 microM), or chelation of copper with 1-N-benzyltriethylenetetraine tetrahydrochloride (BzTrien) and bathocuprinedisulfonic acid (BCSA), abolished the enhanced damage without diminishing the protective effect of vitamin C. These results indicate that vitamin C can act as: (1) an antioxidant to protect DNA damage from ionizing radiation; and (2) a reducing agent in the presence of copper to induce DNA damage. These effects are important in assessing the role of vitamin C, in the presence of mineral supplements or radioprotective therapeutic agents, particularly in patients with abnormally high tissue copper levels.

A study on the effect of garlic to the heavy metal poisoning of rat.

Cha CW. Department of Preventive Medicine, College of Medicine, Korea University, Seoul. J Korean Med Sci 1987 Dec;2(4):213-24

When garlic (Allium sativum) was administered to rat per os simultaneously with cadmium, methylmercury and phenylmercury to detect the protective effect against the heavy metal poisoning, accumulation of heavy metals in liver, kidneys, bone and testes were decreased, and histopathological damages and the inhibition of serum alkaline phosphatase activities by heavy metals were reduced. Such effect of garlic was not shown in the 1.7% garlic treated group and most remarkable in the 6.7% garlic treated group. The protective effect of garlic was superior to those of 2,3 dimercapto-1-propanol (BAL) and D-penicillamine (PEN), and nearly similar to those of 2,3-dimercaptosuccinic acid (DMSA) and N-acetyl-DL-penicillamine (APEN), the current remedies, while garlic was not effective as a curative agent for heavy metal poisoning. The excretion of cadmium was enhanced, more through feces than urine by garlic but the effect to the urinary excretion of cadmium was not significant comparing with DMSA or APEN when cadmium was ip injected in the first 3 days during the 12 days of oral administration of DMSA, APEN or garlic.

In vitro effect of arsenical compounds on glutathione-related enzymes.

Chouchane S, Snow ET. Nelson Institute of Environmental Medicine, New York University School of Medicine, 57 Old Forge Road, Tuxedo, NY 10987, U.S.A. Chem Res Toxicol 2001 May;14(5):517-22

The mechanism of arsenic toxicity is believed to be due to the ability of arsenite (As(III)) to bind protein thiols. Glutathione (GSH) is the most abundant cellular thiol, and both GSH and GSH-related enzymes are important antioxidants that play an important role in the detoxification of arsenic and other carcinogens. The effect of arsenic on the activity of a variety of enzymes that use GSH has been determined using purified preparations of glutathione reductase (GR) from yeast and bovine glutathione peroxidase (GPx) and equine glutathione S-transferase (GST). The effect on enzyme activity of increasing concentrations (from 1 microM to 100 mM) of commercial sodium arsenite (As(III)) and sodium arsenate (As(V)) and a prepared arsenic(III)-glutathione complex [As(III)(GS)(3)] and methylarsenous diiodide (CH(3)As(III)) has been examined. GR, GPx, and GST are not sensitive to As(V) (IC(50) > 50 mM), and none of the enzymes are inhibited or activated by physiologically relevant concentrations of As(III), As(III)(GS)(3), or CH(3)As(III), although CH(3)As(III) is the most potent inhibitor (0.3 mM < IC(50) < 1.5 mM). GPx is the most sensitive to arsenic treatment and GST the least. Our results do not implicate a direct interaction of As with the glutathione-related enzymes, GR, GPx, and GST, in the mechanism of arsenic toxicity. CH(3)As(III) is the most effective inhibitor, but it is unclear whether this product of arsenic metabolism is produced at a sufficiently high concentration in critical target tissues to play a major role in either arsenic toxicity or carcinogenesis.

Mercury: an element of mystery.

Clarkson TW. N Engl J Med 1990;323:1137-9

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The American Medical Association Encyclopedia of Medicine.

Clayman CB. 1989 Random House, New York, NY, U.S.A.

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Oral administration of rutoside can ameliorate inflammatory bowel disease in rats.

Cruz T, Galvez J, Ocete MA, Crespo ME, Sanchez de Medina L-H F, Zarzuelo A. Department of Pharmacology, School of Pharmacy, University of Granada, Spain. Life Sci 1998;62(7):687-95

Rutoside, a flavonoid with antioxidant properties, was tested for acute and chronic antiinflammatory activity in trinitrobenzenesulfonic acid-induced rat colitis. Pretreatment with 10 or 25 mg/kg of rutoside by the oral route reduced colonic damage at 2 days. Several mechanisms can be involved in this activity, and one of these may be related to its ability in preventing glutathione depletion of colitic animals, and this could result in mucosal protection against oxidative insult. When rutoside was tested for 1 and 2 weeks after colitis induction, it was able to promote colonic healing. The chronic effect of the flavonoid was also related with its ability to increase colonic glutathione levels and thus reduce the tissue damage derived from intestinal oxidative stress which characterizes inflammatory colitis.

Effects of lead on rat kidney and liver: GST expression and oxidative stress.

Daggett DA, Oberley TD, Nelson SA, Wright LS, Kornguth SE, Siegel FL. The Environmental Toxicology Center, University of Wisconsin, Madison, WI 53705, U.S.A. Toxicology 1998 Jul 17;128(3):191-206

The effect of acute exposure to lead acetate on the expression of glutathione S-transferase (GST) subunits and the levels of reduced and oxidized glutathione (GSH) and malondialdehyde (MDA) in rat kidney and liver was determined. The purpose of this study was to determine if GSH depletion and/or oxidative stress were responsible for changes in the expression of some or all GSTs that followed lead exposure. In kidney, all GST subunits increased following injection of lead. The level of kidney GSH was not changed at either 0.5 or 1 h after lead exposure, but increased 3, 6, 12 and 24 h after a single injection of lead. MDA levels (a marker of lipid peroxidation) did not change in kidney following lead injection. Immunohistochemical markers of oxidative stress and nitric oxide production were also unchanged by lead administration. Therefore, we conclude that the increases in GST levels in kidney following lead exposure were not dependent on oxidative stress. In liver, lead injection caused GSH depletion (61% of control 12 h after lead treatment) and increased MDA production (2.5-fold increase 6 h after lead exposure), while GSTA1, GSTA2, GSTM1 and GSTM2 did not increase. Analysis of the effects of lead on GST mRNA and GST cellular localization were performed by Northern blot and immunohistochemical techniques. Immunoperoxidase light microscopy and immunogold electron microscopy revealed that the increase in kidney GSTM1 and GSTP1 occurred in nuclei, cytoplasm and microvilli of proximal tubules. Northern blot analysis of GSTA2 and GSTP1 mRNAs showed that their increase following lead exposure was inhibited by actinomycin D, suggesting transcriptional induction. This study demonstrates that acute lead exposure causes dramatic changes in the subcellular distribution and expression of rat kidney GSTs, and that these changes are not a result of oxidative stress.

Mechanisms of N-acetylcysteine in the prevention of DNA damage and cancer, with special reference to smoking-related end-points.

De Flora S, Izzotti A, D'Agostini F, Balansky RM. Department of Health Sciences, Section of Hygiene and Preventive Medicine, University of Genoa, Via A. Pastore 1, I-16132 Genoa, Italy. sdf@unige.it Carcinogenesis 2001 Jul;22(7):999-1013

Although smoking cessation is the primary goal for the control of cancer and other smoking-related diseases, chemoprevention provides a complementary approach applicable to high risk individuals such as current smokers and ex-smokers. The thiol N-acetylcysteine (NAC) works per se in the extracellular environment, and is a precursor of intracellular cysteine and glutathione (GSH). Almost 40 years of experience in the prophylaxis and therapy of a variety of clinical conditions, mostly involving GSH depletion and alterations of the redox status, have established the safety of this drug, even at very high doses and for long-term treatments. A number of studies performed since 1984 have indicated that NAC has the potential to prevent cancer and other mutation-related diseases. N-Acetylcysteine has an impressive array of mechanisms and protective effects towards DNA damage and carcinogenesis, which are related to its nucleophilicity, antioxidant activity, modulation of metabolism, effects in mitochondria, decrease of the biologically effective dose of carcinogens, modulation of DNA repair, inhibition of genotoxicity and cell transformation, modulation of gene expression and signal transduction pathways, regulation of cell survival and apoptosis, anti-inflammatory activity, anti-angiogenetic activity, immunological effects, inhibition of progression to malignancy, influence on cell cycle progression, inhibition of pre-neoplastic and neoplastic lesions, inhibition of invasion and metastasis, and protection towards adverse effects of other chemopreventive agents or chemotherapeutical agents. These mechanisms are herein reviewed and commented on with special reference to smoking-related end-points, as evaluated in in vitro test systems, experimental animals

and clinical trials. It is important that all protective effects of NAC were observed under a range of conditions produced by a variety of treatments or imbalances of homeostasis. However, our recent data show that, at least in mouse lung, under physiological conditions NAC does not alter per se the expression of multiple genes detected by cDNA array technology. On the whole, there is overwhelming evidence that NAC has the ability to modulate a variety of DNA damage- and cancer-related end-points.

The effect of dietary quercetin and rutin on AOM-induced acute colonic epithelial abnormalities in mice fed a high-fat diet.

Deschner EE, Ruperto JF, Wong GY, Newmark HL. Laboratory of Digestive Tract Carcinogenesis, Sloan-Kettering Institute, New York, NY, U.S.A. Nutr Cancer 1993;20(3):199-204

Dietary quercetin (QU) and rutin (RU), phenolic flavonoids found in many fruits and vegetables, when fed to mice on a low-fat diet successfully modified the response to azoxymethanol (AOM) by initially inhibiting hyperproliferation and the formation of foci of dysplasia (FADs) and ultimately reducing tumor incidence (Carcinogenesis 12, 1193-1196, 1991). In this study, we tested the efficacy of QU and RU when a high-fat diet was presented. An AIN 76A diet made with 20% corn oil (CO) was supplemented with QU (0.5%, 2.0%, or 5.0%) and RU (2.0% or 4.0%). These five diets, as well as a 5.0% and a 20.0% CO diet, were fed to a group of CF1 female mice for nine weeks. Both QU and RU showed nonsignificant dose-related trends toward normalization of the AOM-induced upward extension of S phase cells. Examination of 500 microns of serially sectioned distal colon revealed that 29% of mice fed the 20% CO control diet were free of FADs. Among the mice fed QU, regardless of dose, > 80% were free of FADs. When the three groups fed QU were pooled and compared with the control 20% CO-fed mice, the degree of protection was significant ($p < 0.01$). Mice fed RU expressed a level of protection that bordered on the significant ($p < 0.08$). These data suggest that, regardless of the fat content of the diet, QU and RU are capable of modifying or inhibiting events in the development of chemically induced colonic neoplasia.

Modification of clastogenicity of lead and aluminium in mouse bone marrow cells by dietary ingestion of Phyllanthus emblica fruit extract.

Dhir H, Roy AK, Sharma A, Talukder G. Department of Botany, University of Calcutta, India. Mutat Res 1990 Jul;241(3):305-12

Extract of Phyllanthus emblica fruit and ascorbic acid were evaluated separately for protection against clastogenicity induced by lead (Pb) and aluminium (Al) salts on mouse bone marrow chromosomes. Oral administration of Phyllanthus fruit extract (PFE) for 7 days before exposure to both metals by intraperitoneal injection increased the frequency of cell division and reduced the frequency of chromosome breaks significantly. Comparable doses of synthetic ascorbic acid (AA) were less effective and could protect against the effects of Al and only a low dose of Pb (10 mg/kg body weight). AA administered before treatment in mice given higher doses of Pb (40 mg/kg body weight) enhanced the frequency of chromosome breaks, giving a synergistic effect. The higher protection afforded by PFE may be due to the combined action of all ingredients, rather than to AA alone.

Relative efficiency of Phyllanthus emblica fruit extract and ascorbic acid in modifying lead and aluminium-induced sister-chromatid exchanges in mouse bone marrow.

Dhir H, Roy AK, Sharma A. Department of Botany, University of Calcutta, India. Environ Mol Mutagen 1993;21(3):229-36

The identification of desmutagens and bioantimutagens in plants has prompted the search for additional plant extracts capable of modifying adverse cellular effects of environmental toxicants. The protective action of crude extracts of Phyllanthus emblica fruits (PFE) against lead (Pb) and aluminium (Al)-induced sister chromatid exchanges (SCEs) was studied in bone marrow cells of Mus musculus. The modifying effect of the crude extract was compared with that of comparable amounts of synthetic ascorbic acid (AA), a major component of the fruits. Oral administration of PFE or AA for 7 consecutive days before exposure of mice to the metals by intraperitoneal injections reduced the frequencies of SCEs induced by both metals. PFE afforded a more pronounced protective effect than AA in counteracting the genotoxicity induced by both Al and Pb: This difference was significant with Pb. The higher protection afforded by PFE may be attributed to the interaction of AA with other natural ingredients present in the crude fruit extract.

Heavy metal poisoning.

Dr. Joseph F. Smith Medical Library (no authors given). November 2001 Dr. Joseph F. Smith Medical Library, Wassau, WI, U.S.A.

No abstract available.

Heavy metal poisoning.

Dupler D. 2001 Gale Encyclopedia of Alternative Medicine, Gale Group, Farmington Hills, MI, U.S.A.

No abstract available.

Study of the effect of the administration of Cd(II), cysteine, methionine, and Cd(II) together with cysteine or methionine on the conversion of xanthine dehydrogenase into xanthine oxidase.

Esteves AC, Felcman J. Department of Chemistry, Pontificia Universidade Catolica de Rio de Janeiro, Rio de Janeiro, Brazil. Biol Trace Elem Res 2000 Jul;76(1):19-30

Cadmium is known as to be a potent pulmonary carcinogen to human beings and to induce prostate tumor. The sequestration of cadmium, an extremely toxic element to living cells, which is performed by biological ligands such as amino acids, peptides, proteins or enzymes is important to minimize its participation in such deleterious processes. The synthesis of metallothionein is induced by a wide range of metals, in which cadmium is a particularly potent inducer. This protein is usually associated with cadmium exposure in man. Because metallothioneins may act as a detoxification agent for cadmium and chelation involves sulfur donor atoms, we administered only cadmium, cysteine, or methionine to rats and also each of these S-amino acids together with cadmium and measured the production of superoxide radicals derived from the conversion of xanthine dehydrogenase to xanthine oxidase. It could be seen in this work that the presence of cadmium enhances this conversion. However, its inoculation with cysteine or methionine almost completely diminishes this effect and this can be the result of the fact that these amino acids complex Cd(II). Thus, these compounds can be a model of the action of metallothionein, removing cadmium from circulation and preventing its deleterious effect.

Increased inorganic mercury in spinal motor neurons following chelating agents.

Ewan KB, Pamphlett R. Department of Pathology (Neuropathology Division), University of Sydney, Australia. Neurotoxicology 1996 Summer;17(2):343-9

Heavy metal toxicity has been implicated in the pathogenesis of motor neuron diseases. In an attempt to assess the efficacy of chelating agents to remove mercury from motor neurons, we quantitated the effect of the chelating agents meso-2,3-dimercaptosuccinic acid (DMSA) and 2,3- dimercaptopropane -1-sulphonate (DMPS) on the burden of inorganic mercury in mouse spinal motor neurons. Mice were injected intraperitoneally with 1.0 mg HgCl2/kg body weight and one week later with either 4,400 mg/kg DMPS, 3,600 mg/kg DMSA or 5% NaHCO3 (control) over 4 weeks. Mercury deposits in motor neurons of 50 micron frozen sections of lumbar spinal cord were visualised with an autometallographic technique. Optical sections of silver-enhanced deposits were acquired using a confocal microscope in reflective mode and the volume of the deposits within the perikaryon was estimated. Mercury deposits occupied significantly more volume in motor neurons after both DMPS (7.4%, SD +/- 0.7%) and DMSA (8.0% +/- SD 0.7%) treatment than in controls (4.3%, SD +/- 1.7%). The higher levels of neuronal inorganic mercury may be due to increased entry of mercury into motor axons across the neuromuscular junction as a result of chelator-induced elevated circulating mercury.

DMPS.

FDA (no authors given). 1999 (http://www.fda.gov/cder/fdama/pclist.txt). Food and Drug Administration, Washington, D.C., U.S.A.

Toxicity, heavy metals.

Ferner DJ. eMed.J 2001 May 25;2(5):1

No abstract available.

2,3-Dimercaptosuccinic acid treatment of heavy metal poisoning in humans.

Fournier L, Thomas G, Garnier R, Buisine A, Houze P, Pradier F, Dally S. Department of Clinical Toxicology, Fernand Widal Hospital, Paris, France. Med Toxicol Adverse Drug Exp 1988 Nov-Dec;3(6):499-504

14 patients with heavy metal poisoning received 2,3-dimercaptosuccinic acid (DMSA). 12 subjects were given 30 mg/kg/day for 5 days; 1 subject was started on a lower dose because of a history of atopy; another subject was treated for 15 days because of very high initial blood lead concentrations. In the 9 subjects who had lead poisoning, DMSA decreased blood lead concentrations by 35 to 81%, and induced a 4.5- to 16.9-fold increase in mean daily urinary excretion of the metal. In the acutely arsenic-poisoned case, the plasma arsenic concentration on day 7 was half the pretreatment value, while no clear decrease was observed in a chronically exposed subject. In 3 mercury cases, DMSA increased daily mercury urinary excretion 1.5-, 2.8- and 8.4-fold, respectively, while blood mercury concentrations remained below detection limits. No serious side effects were observed and 3 weeks after administration of the drug the clinical condition of all subjects was either stable or improved. These results indicate the efficacy of DMSA for lead poisoning in humans and provide a rationale for further investigating its usefulness in mercury and arsenic poisoning cases.

Rutoside as mucosal protective in acetic acid-induced rat colitis.

Galvez J, Cruz T, Crespo E, Ocete MA, Lorente MD, Sanchez de Medina F, Zarzuelo A. Department of Pharmacology, School of Pharmacy, University of Granada, Spain. Planta Med 1997 Oct;63(5):409-14

The effect of the flavonoid rutoside on acetic acid-induced rat colitis was studied. Rats were pretreated orally with different doses of the flavonoid (10, 25, and 100 mg/kg) 48, 24, and 1 hour prior to colitis induction and examined for colonic damage 24 hours later. Colonic inflammation was characterized by gross and microscopical injury, bowel wall thickening, abolition of fluid absorption, glutathione depletion, enhanced leukotriene B4 synthesis, and increased levels of myeloperoxidase and alkaline phosphatase activities. Rutoside treatment (25 and 100 mg/kg) reduced histologic injury and prevented the increase in alkaline phosphatase activity, but it had no effect on myeloperoxidase levels or leukotriene B4 synthesis. In addition, glutathione depletion was effectively counteracted at the dose of 25 mg/kg, whereas fluid absorption was achieved at the highest dose assayed. It is concluded that rutoside has an acute anti-inflammatory activity in this model which may be related to a putative direct protective effect on intestinal cells, mainly enterocytes, in which the antioxidative properties of the flavonoid may play a role.

[Influence of chewing gum consumption and dental contact of amalgam fillings to different metal restorations on urine mercury content.][Article in German]

Gebel T, Dunkelberg H.

Abteilung fur Allgemeine Hygiene und Umweltmedizin, Zentrum Umwelt- und Arbeitsmedizin, Universitat Gottingen. Zentralbl Hyg Umweltmed 1996 Nov;199(1):69-75

It had been shown previously by various authors that contact of amalgam fillings to metal fillings of different type can increase the electrochemically caused amalgam corrosion in vitro thus leading to an elevated release of mercury. So it was recommended to renounce of a dental contact of amalgam to metal fillings of other type. One aim of the present study was to evaluate possible influences of this contact in vivo on the urinary mercury contents in human volunteers. Neither proximal nor occlusal contacts had any influence on the urinary mercury excretion in comparison to a reference group with similar amalgam status. Furthermore, the influence of gum chewing on urinary mercury levels was taken into account. It could be shown that the consumption of chewing gum resulted in a significantly higher mean urinary mercury content in probands with amalgam fillings in comparison to people with similar amalgam status (gum chewers: 1.36 Hg/24 h vs. non-chewers 0.70 microgram Hg/24 h). Thus, gum chewing has to be considered as important parameter of influence on the urinary mercury levels of people with amalgam fillings.

Depletion of iron and ascorbate in rodents diminishes lung injury after silica.

Ghio AJ, Kennedy TP, Crissman KM, Richards JH, Hatch GE. National Health and Environmental Effects Research Laboratory, Environmental Protection Agency, Research Triangle Park, NC 27711, U.S.A. Exp Lung Res 1998 Mar-Apr;24(2):219-32

Exposures of the lung to iron chelates can be associated with an injury. The catalysis of oxygen-based free radicals is postulated to participate in this injury. Such oxidant generation by mineral oxide particles can be dependent on availability of both iron and a reductant. We tested the study hypothesis that lung injury after silica is associated with the availability of both iron and ascorbate in the host by depleting this metal and reductant in the lungs of rats and guinea pigs, respectively. Rats were fed either a normal diet or a diet deficient of iron. After 30 days, animals were instilled with either saline or 1.0 mg Minusil-5 silica. Relative to saline, silica significantly increased neutrophils and lavage protein. Iron depletion significantly diminished both the cellular influx and injury but only at 1 week after silica exposure. Guinea pigs were provided either a normal diet supplemented with 1,000 ppm vitamin C or a diet deficient in ascorbate. After 14 days, the guinea pigs were instilled with either saline or 1.0 mg silica. Silica exposure significantly increased neutrophils and lavage protein. Ascorbate depletion significantly diminished the influx of inflammatory cells and injury at both 1 day and 1 week after silica exposure. We conclude that host concentrations of both iron and ascorbate can affect lung injury after silica exposure.

Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network.

Girodon F, Galan P, Monget AL, Boutron-Ruault MC, Brunet-Lecomte P, Preziosi P, Arnaud J, Manuguerra JC, Herchberg S. Scientific and Technical Institute for Foods and Nutrition, Conservatiore National des Arts et Mettiers, Paris, France. Arch Intern Med 1999 Apr 12;159(7):748-54

BACKGROUND: Antioxidant supplementation is thought to improve immunity and thereby reduce infectious morbidity. However, few large trials in elderly people have been conducted that include end points for clinical variables. OBJECTIVE: To determine the effects of long-term daily supplementation with trace elements (zinc sulfate and selenium sulfide) or vitamins (beta carotene,

ascorbic acid, and vitamin E) on immunity and the incidence of infections in institutionalized elderly people. METHODS: This randomized, double-blind, placebo-controlled intervention study included 725 institutionalized elderly patients (>65 years) from 25 geriatric centers in France. Patients received an oral daily supplement of nutritional doses of trace elements (zinc and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) or a placebo within a 2 x 2 factorial design for 2 years. MAIN OUTCOME MEASURES: Delayed-type hypersensitivity skin response, humoral response to influenza vaccine, and infectious morbidity and mortality. RESULTS: Correction of specific nutrient deficiencies was observed after 6 months of supplementation and was maintained for the first year, during which there was no effect of any treatment on delayed-type hypersensitivity skin response. Antibody titers after influenza vaccine were higher in groups that received trace elements alone or associated with vitamins, whereas the vitamin group had significantly lower antibody titers (P<.05). The number of patients without respiratory tract infections during the study was higher in groups that received trace elements (P = .06). Supplementation with neither trace elements nor vitamins significantly reduced the incidence of urogenital infections. Survival analysis for the 2 years did not show any differences between the 4 groups. CONCLUSIONS: Low-dose supplementation of zinc and selenium provides significant improvement in elderly patients by increasing the humoral response after vaccination and could have considerable public health importance by reducing morbidity from respiratory tract infections.

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Glanze WD. 1996 C.V. Mosby, St. Louis, MO, U.S.A.

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The enigma of arsenic carcinogenesis: role of metabolism.

Goering PL, Aposhian HV, Mass MJ, Cebrian M, Beck BD, Waalkes MP. Division of Life Sciences, Center for Devices and Radiological Health, Food and Drug Administration, Rockville, MD 20852, U.S.A. plg@cdrh.fda.gov Toxicol Sci 1999 May;49(1):5-14

Inorganic arsenic is considered a high-priority hazard, particularly because of its potential to be a human carcinogen. In exposed human populations, arsenic is associated with tumors of the lung, skin, bladder, and liver. While it is known to be a human carcinogen, carcinogenesis in laboratory animals by this metalloid has never been convincingly demonstrated. Therefore, no animal models exist for studying molecular mechanisms of arsenic carcinogenesis. The apparent human sensitivity, combined with our incomplete understanding about mechanisms of carcinogenic action, create important public health concerns and challenges in risk assessment, which could be met by understanding the role of metabolism in arsenic toxicity and carcinogenesis. This symposium summary covers three critical major areas involving arsenic metabolism: its biodiversity, the role of arsenic metabolism in molecular mechanisms of carcinogenesis, and the impact of arsenic metabolism on human risk assessment. In mammals, arsenic is metabolized to mono- and dimethylated species by methyltransferase enzymes in reactions that require S-adenosyl-methionine (SAM) as the methyl donating cofactor. A remarkable species diversity in arsenic methyltransferase activity may account for the wide variability in sensitivity of humans and animals to arsenic toxicity. Arsenic interferes with DNA methyltransferases, resulting in inactivation of tumor suppressor genes through DNA hypermethylation. Other studies suggest that arsenic-induced malignant transformation is linked to DNA hypomethylation subsequent to depletion of SAM, which results in aberrant gene activation, including oncogenes. Urinary profiles of arsenic metabolites may be a valuable tool for assessing human susceptibility to arsenic carcinogenesis. While controversial, the idea is that unique arsenic metabolic properties may explain the apparent non-linear threshold response for arsenic carcinogenesis in humans. In order to address these outstanding issues, further efforts are required to identify an appropriate animal model to elucidate carcinogenic mechanisms of action, and to define dose-response relationships.

Effects of silymarin MZ-80 on hepatic oxidative stress in rats with biliary obstruction.

Gonzalez-Correa JA, de la Cruz JP, Gordillo J, Urena I, Redondo L, Sanchez de la Cuesta F. Department of Pharmacology and Therapeutics, School of Medicine, University of Malaga, Spain. Pharmacology 2002 Jan;64(1):18-27

This study was designed to evaluate the effects of three pharmaceutical forms of silymarin (silymarin MZ-80, silybinin-beta-cyclodextrin, and silybinin) on the liver oxidative status in vitro and after oral administration to rats with extrahepatic biliary obstruction (EBO) and sham-operated animals. We evaluated thiobarbituric acid-reactive substances (TBARS), glutathione (GSH + GSSG) and their related enzyme activities (GSH peroxidase, GSSG reductase and GSH transferase). All three compounds inhibited the in vitro production of TBARS (IC(50) 56-533 micromol/l). These compounds, mainly silymarin MZ-80, also increased GSH peroxidase and GSH transferase activities. In EBO rats we found increases in TBARS production which was inhibited by 50-70% after treatment. Glutathione was reduced by 55% and elevated by silymarin MZ-80. GSH transferase increased in the group given silymarin MZ-80. We conclude that all three derivatives of silymarin show a clear ability to reduce lipid peroxidation in the liver. Silymarin MZ-80 was the only compound that enhanced the glutathione antioxidant system. Copyright 2002 S. Karger AG, Basel.

Toxic effects of metals: mercury.

Goyer RA. 1996 Casarett and Doull's Toxicology: The Basic Science of Poisons, Fifth Edition. McGraw-Hill, New York, NY, U.S.A.

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Role of S-adenosyl-L-methionine in potentiating cadmium mobilization by diethylenetriamine penta acetic acid in mice.

Gubrelay U, Mathur R, Kannan GM, Flora SJ. School of Studies in Zoology, Jiwaji University, Gwalior, India. Cytobios 2001;104 (406):99-105

The beneficial effects of S-adenosyl-L-methionine (SAM) in potentiating the obilization of cadmium by cadmium trisodium diethylenetriamine penta acetic acid (DTPA) from the major target organs and restoration of depleted tissue glutathione (GSH), zinc and copper concentration, were determined in cadmium-exposed mice. The results indicated a significant depletion of cadmium concentration from the blood in DTPA plus SAM treated animals compared with DTPA or SAM alone treated groups. The treatment with SAM alone was also effective in correcting the zinc and GSH concentrations. The results indicated few beneficial effects of concomitant SAM administration during chelation of cadmium with DTPA. **Antioxidant role of alpha-lipoic acid in lead toxicity.** Gurer H, Ozgunes H, Oztezcan S, Ercal N. Department of Chemistry, University of Missouri-Rolla, Rolla, MO 65409-0010, U.S.A. Free Radic Biol Med 1999 Jul;27(1-2):75-81

The assumption of oxidative stress as a mechanism in lead toxicity suggests that antioxidants might play a role in the treatment of lead poisoning. The present study was designed to investigate the efficacy of lipoic acid (LA) in rebalancing the increased prooxidant/antioxidant ratio in lead-exposed Chinese hamster ovary (CHO) cells and Fischer 344 rats. Furthermore, LA's ability to decrease lead levels in the blood and tissues of lead-treated rats was examined. LA administration resulted in a significant improvement in the thiol capacity of cells via increasing glutathione levels and reducing malondialdehyde levels in the lead-exposed cells and animals, indicating a strong antioxidant shift on lead-induced oxidative stress. Furthermore, administration of LA after lead treatment significantly decreased catalase and red blood cell glucose-6-phosphate dehydrogenase activity. In vitro administration of LA to cultures of CHO cells significantly increased cell survival that was inhibited by lead treatment in a concentration-dependent manner. Administration of LA was not effective in decreasing blood or tissue lead levels compared to a well-known chelator (succimer) that was able to reduce them to control levels. Hence, LA seems to be a good candidate for therapeutic intervention of lead poisoning, in combination with a chelator, rather than as a sole agent.

Uptake of uranium by various cell fractions of Chlorella regularis.

Horikoshi T, Nakajima A, Sakaguchi T. Radioisotopes 1979 Aug;28(8):485-8

To know what kinds of the cell components of Chlorella regularis are concerned with uranium binding, uptake of uranium by various cell fractions was examined. The uptake value (microgramU/mg starting dry cells) of the hot water-treated cells was almost the same as that of the starting dry Chlorella cells, showing that the cell components extracted with hot water were not so concerned with uranium binding. The cell components extracted with dilute alkali seemed to play an important role in uranium binding, and those extracted with chloroform-methanol seemed to be partly concerned with uranium binding. The cellulose fraction of the cells was scarcely concerned with uranium binding. In the dry cells, 34% of uranium taken up existed in the cell walls. However, in the living cells, 85% existed in the cell walls. The above results showed that the dry or the hot water-treated cells are the most convenient for uranium recovery from the aqueous systems.

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Huang K-C. 1993 CRC Press, Boca Raton, FL, U.S.A.

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International Occupational Safety and Health Information Centre. September 1999 Basics of Chemical Safety, Chapter 7. International Labour Organization, Geneva, Switzerland.

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Impact of nocturnal bruxism on mercury uptake from dental amalgams.

Isacsson G, Barregard L, Selden A, Bodin L. Orofacial Pain Clinic, Postgraduate Dental Education Centre, Orebro County Council, Sweden. goran.isacsson@pain.se.astra.com Eur J Oral Sci 1997 Jun;105(3):251-7

The mercury (Hg) release from dental amalgam fillings increases by mechanical stimulation. The aim of this study was to investigate the possible impact of nocturnal bruxism on Hg exposure from dental amalgams and to evaluate the effect of an occlusal appliance. 88 female patients from an orofacial pain clinic with a complete maxillary and mandibular dentition, a normal frontal vertical overbite with cuspid guidance, and at least 4 occlusal amalgam fillings in contact with antagonists in intercuspidal position, were examined with the Bruxcore bruxism monitoring device to measure the level of on-going nocturnal bruxism. Based on the degree of abrasion recorded, the subjects were divided into a group defined as bruxists, (n = 29), another group defined as non-bruxists, (n = 32), serving as controls, the intermediate group being discarded. The Hg exposure was assessed from the Hg concentration in plasma and urine, corrected for the creatinine content. In a regression model with bruxism as the only explanatory variable, no significant effect of bruxism was found, but when the number of amalgam fillings, chewing gum use, and other background variables were taken into account, there was a limited impact of bruxism on Hg in plasma. The nocturnal use of an occlusal appliance did not, however, significantly change the Hg levels. This study indicates that mechanical wear on amalgams from nocturnal bruxism may increase the Hg uptake, but the magnitude of this effect seems to be less than from the use of chewing gum.

General methods for treating poisoning.

James D. 2001 University of Alberta, Alberta, Canada.

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Clinical toxicology.

Klein-Schwartz W, Oderda GM. 2000 Textbook of Therapeutics: Drug and Disease Management, Seventh Edition, p. 51. Williams & Wilkins, Baltimore, MD, U.S.A.

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Protective effect of natural flavonoids on rat peritoneal macrophages injury caused by asbestos fibers.

Kostyuk VA, Potapovich AI, Speransky SD, Maslova GT. Laboratory of Bioenergetics, Byelorussian State University, Minsk, Belarus. Free Radic Biol Med 1996;21(4):487-93

Exposure of macrophages to asbestos fibers resulted in enhancement of the production of oxygen radicals, determined by a lucigenin enhanced chemiluminescence (LEC) assay, a formation of thiobarbituric acid reactive substances (TBARS), a LDH release into the incubation mixture, and a rapid lysis of the cells. Rutin (Rut) and quercetin (Qr) were effective in inhibiting LEC, TBARS formation, and reducing peritoneal macrophages injury caused by asbestos. The concentrations pre-treatment of antioxidants that were required to prevent the injury of peritoneal macrophages caused by asbestos by 50% (IC50) were 90 microM and 290 microM for Qr and Rut, respectively. Both flavonoids were found to be oxidized during exposure of peritoneal macrophages to asbestos and the oxidation was SOD sensitive. The efficacy of flavonoids as antioxidant agents as well as superoxide ion scavengers was also evaluated using appropriate model systems, and both quercetin and rutin were found to be effective in scavenging O2.-. These findings indicate that flavonoids are able to prevent the respiratory burst in rat peritoneal macrophages exposed to asbestos at the stage of activated oxygen species generation, mainly as superoxide scavengers. On the basis of this study it was concluded that natural flavonoids quercetin and rutin would be promising drug candidates for a prophylactic asbestos-induced disease.

Antiradical and chelating effects in flavonoid protection against silica-induced cell injury.

Kostyuk VA, Potapovich AI. Laboratory of Bioenergetics, Byelorussian State University, Scorina St. 4, Minsk, 220050, Belarus. kostyuk@bio.bsu.unibel.by Arch Biochem Biophys 1998 Jul 1;355(1):43-8

Quercetin, dihydroquercetin, and rutin are capable of scavenging superoxide anion (rate constants of the reaction with superoxide at pH 10 were 1.7 x 10(5), 1.5 x 10(5), and 0.5 x 10(5) M-1 s-1, respectively). At the same time rutin and quercetin but not dihydroquercetin are iron ion chelators. These substances were used to elucidate the role of radical scavenging and iron chelating in flavonoid protection against asbestos-induced oxidative cellular injury. Exposure of rat peritoneal macrophages to chrysotile asbestos fibers resulted in "frustrated" phagocytosis, cell injury, and a LDH release. Quercetin, dihydroquercetin, and rutin were effective in protecting the phagocytic cells against injury caused by asbestos. Moreover, these flavonoids exhibited cellular

protection in the same order of effectiveness as that observed for the quenching of superoxide: quercetin > dihydroquercetin > rutin. Exposure of human red blood cells to asbestos fibers also caused progressive cell injury and lysis. Quercetin and rutin protected the red cells (quercetin > rutin), whereas dihydroquercetin was ineffective in preventing asbestos-induced hemolysis. The protective ability of quercetin and rutin may be related to their iron-chelating activity. Due to this these flavonoids can be located on asbestos surface in sites of initiation of free radical reactions and their antiradical moieties can scavenge reactive oxygen species immediately after the appearance. Thus, both antiradical and chelating effects appear to be involved in the flavonoid protection against silica-induced cell injury. Copyright 1998 Academic Press.

Trace elements that act as antioxidants in parenteral micronutrition.

Leung FY. Can J Nutr Biochem 1998;9(6):304-7

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Role of the Multidrug Resistance Protein 1 in protection from heavy metal oxyanions: investigations in vitro and in MRP1-deficient mice.

Lorico A, Bertola A, Baum C, Fodstad O, Rappa G. Department of Tumor Biology, Norwegian Radium Hospital, Montebello, 0310, Norway. aureliol@labmed.uio.no Biochem Biophys Res Commun 2002 Mar 1;291(3):617-22

The Multidrug Resistance Protein 1 (MRP1) is a membrane pump that mediates the efflux of a wide variety of xenobiotics, including arsenical and antimonial compounds, as demonstrated by the study of MRP1-transfected cell lines. We have previously shown that mrp1(-/-) cells are hypersensitive to sodium arsenite, sodium arsenate, and antimony potassium tartrate. We now report that the retroviral vector-mediated overexpression of MRP1 and of the two subunits of gamma-GCS (heavy and light) resulted in higher intracellular glutathione levels and in a greater level of resistance to sodium arsenite and antimony potassium tartrate, compared to the overexpression of MRP1 and gamma-GCS heavy alone. These observations further demonstrate that glutathione is an important component of MRP1-mediated cellular resistance to arsenite and antimony. However, the constitutive expression of MRP1 did not protect mice from the lethality of sodium arsenite and antimony potassium tartrate nor reduced the tissue accumulation of arsenic in mice injected i.p. with sodium arsenite. It is conceivable that, in vivo, other pump(s) effectively vicariate for MRP1-mediated transport of heavy metal oxyanions.

Cutaneous mercury granuloma. A clinicopathologic study and review of the literature.

Lupton GP, Kao GF, Johnson FB, Graham JH, Helwig EB. J Am Acad Dermatol 1985 Feb;12(2 Pt 1):296-303

Cutaneous mercury granulomas are rarely encountered. Clinically they pose difficulty in diagnosis when there is no clear history of penetrating injury by objects containing metallic mercury. Histologic, chemical, and scanning electron microscopic studies of such cutaneous lesions were performed on four cases from the Armed Forces Institute of Pathology files. Reported cases from the literature were reviewed. Metallic mercury in tissue sections appears as dark, opaque globules, usually spherical in shape and of varying sizes and numbers. A zone of collagen necrosis often surrounds the mercury globules. A granulomatous foreign body-giant cell reaction and a mixed inflammatory cellular infiltrate composed of neutrophils, lymphocytes, histiocytes, plasma cells, and occasional eosinophils are usually present. Epidermal and dermal necrosis, with or without ulceration or pseudoepitheliomatous hyperplasia, is also a common finding. The gold lysis test and energy-dispersive x-ray analysis confirmed the presence of metallic mercury in the tissue. Following cutaneous injury from mercury, systemic toxicity may develop and death may even occur. An approach to clinical management is discussed.

Effects on levels of glutathione and some related enzymes in tissues after an acute arsenic exposure in rats and their relationship to dietary protein deficiency.

Maiti S, Chatterjee AK. University Grants Commission, New Delhi 110002, India. maitism@rediffmail.com Arch Toxicol 2001 Nov;75 (9):531-7

Arsenic is a potent toxin, carcinogen and modulator of antioxidant defense system. In this study, male rats of Wistar strain, maintained on either 18% or 6% protein (casein) diet, received an acute i.p. exposure to sodium arsenite (As3+) at its LD50 dose (15.86 mg/kg body weight). One hour after the arsenic exposure, glutathione (GSH) concentration was significantly depleted and

lipid peroxidation was increased. A relationship between any two of tissue arsenic concentrations, GSH levels and lipid peroxidation values was observed only for liver when the proportional changes of respective parameters in either of the dietary groups of animals were compared. This suggests that, in liver, arsenic metabolism appears dependant upon the GSH concentration. Acute arsenic exposure significantly increased the glutathione peroxidase (GPx) activity in liver of both dietary groups and in kidney of only the 18% protein-fed group of animals. The glutathione-S-transferase (GST) activity significantly decreased in liver of the 18% protein-fed animals while GST increased in kidney of both the 18% and the 6% protein-fed groups. No significant change in glutathione reductase (GR) or glucose-6-phosphate dehydrogenase (G6PDH) activity was observed. In the present investigation, liver as a whole seems to be more affected in terms of GSH level and GST activity. The mode of responses of GPx and GR activities as well as the unaltered G6PDH activity might result in arsenic-induced GSH depletion and increase in lipid peroxidation. The animals of the 6% protein-fed group, appeared to be affected less in terms of tissue arsenic concentration, lipid peroxidation, GSH level and GST activity.

Toxicity, lead.

Marcus S. eMed. J. 2001 Jun 4; 2(6):7

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B.A.L.™

Micromedex (no authors given). 1999 Thompson/Micromedex, Greenwood Village, CO, U.S.A.

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The effects of glutathione and vitamin E on iron toxicity in isolated rat hepatocytes.

Milchak LM, Douglas Bricker J. Department of Pharmacology-Toxicology, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, U.S.A. Toxicol Lett 2002 Feb 7;126(3):169-77

This study examined the acute toxicity of ferrous sulfate on rat hepatocyte suspensions, the correlation between lipid peroxidation and cell death, and the roles of glutathione and vitamin E in protecting against iron toxicity. Incubation with ferrous sulfate for 2 h produced lipid peroxidation, but did not decrease cell viability in the hepatocytes. When diethyl maleate (DEM) was added to deplete cellular glutathione concentrations, ferrous sulfate treatment (2.0-5.0 mM) did cause cell death and lipid peroxidation developed more extensively, suggesting that iron-mediated hepatotoxicity is influenced by glutathione content. Reduced glutathione (GSH), N-acetylcysteine (NAC) and alpha-tocopherol (vitamin E), alone and in combination, were added to hepatocyte suspensions in an attempt to protect cells against iron-induced damage. In iron-DEM-treated cells, GSH and NAC treatment increased viability by 43 and 36%, respectively, but only the combination of the two agents reduced lipid peroxidation (53% decrease). Vitamin E treatment reduced lipid peroxidation by 39% and also increased cell viability by 12%. The greatest protection against iron-induced lipid peroxidation occurred with the combination of GSH, NAC and vitamin E, which reduced lipid peroxidation by 94% in iron-treated cells, and by 98% in iron-DEM-treated cells. However, this combination did not prevent iron-induced cell death, although it did increase viability by 18%. These esults suggest that iron-induced cell death may not be dependent upon lipid peroxidation, at least in short-term exposures. The results also suggest an interaction between GSH and vitamin E in protecting against lipid peroxidation.

Protective effects of DL-alpha-lipoic acid on cadmium-induced deterioration of rat hepatocytes.

Muller L. Institute of Toxicology, University of Dusseldorf, F.R.G. Toxicology 1989 Oct 2;58(2):175-85

The suitability of DL-alpha-lipoic acid (LA) to serve as an antidote in cadmium (Cd) toxicity in rat hepatocytes was investigated. Isolated hepatocytes were exposed to 200 and 450 microM Cd in the presence of 0.2, 1.0 and 5.0 mM LA, respectively. After 30 min of incubation various criteria of cell viability were monitored. Lipoic acid markedly diminished Cd uptake. Concomitantly, Cd-induced membrane injury, as reflected by the leakage of aspartate aminotransferase and sorbitol dehydrogenase (SDH) was decreased. Moreover, LA protected against intracellular toxic responses to Cd, such as a decrease in cellular SDH activity, a

decrease in cellular acid soluble thiols, especially in total glutathione, a decrease in cellular urea and an increase in thiobarbituric acid (TBA) reactants, as a measure of lipid peroxidation. Most protective effects were seen in hepatocytes challenged with the lower Cd concentration and coincubated with 5 mM LA. In contrast, at 450 microM Cd even the highest LA concentration applied either did only reverse Cd-effects incompletely (SDH-response, TBA-reactants) or did not protect at all (Cd uptake, enzyme leakage, loss of glutathione). The data indicate that DL-alpha-lipoic acid serves as a protective tool against Cd-induced membrane damage and cell dysfunction in hepatocytes. This stands as long as Cd exposure is low enough to permit interaction with LA prior to interaction with cell structures.

Studies on the efficacy of lipoate and dihydrolipoate in the alteration of cadmium 2+ toxicity in isolated hepatocytes.

Muller L, Menzel H. Institute of Toxicology, University of Dusseldorf, F.R.G. Biochim Biophys Acta 1990 May 22;1052(3):386-91

Lipoate (thioctic acid) is presently used in therapy of a variety of diseases such as liver and neurological disorders. However, nothing is known about the efficacy of lipoate and its reduced form dihydrolipoate in acute cadmium (Cd2+) toxicity which involves severe liver disturbances. Therefore, we investigated the effects of these redox compounds on Cd2(+)-induced injuries in isolated rat hepatocytes. The cells were coincubated with 150 microM Cd2+ and either 1.5-6.0 mM lipoate or 17-89 microM dihydrolipoate for up to 90 min and Cd2+ uptake as well as viability criteria were monitored. Both exposure regimens diminished Cd2+ uptake in correspondence to time and concentration. They also ameliorated Cd2(+)-induced cell deterioration as reflected by the decrease in Cd2(+)-induced membrane damage (leakage of aspartate aminotransferase), by the lessening of the Cd2(+)-stimulated lipid peroxidation (TBA-reactants) and by the increase in Cd2(+)-depleted cellular glutathione (GSH + 2 GSSG). Half-maximal protection was achieved at molar ratios of 9.9 to 19 (lipoate vs. Cd2+) and 0.25 to 0.74 (dihydrolipoate vs. Cd2+), indicating a 19.5 to 50.6 lower protective efficacy of lipoate as compared to dihydrolipoate. Lipoate induced an increase in extracellular acid-soluble thiols different from glutathione. It is suggested that dihydrolipoate primarily protects cells by extracellular chelation of Cd2+, whereas intracellular reduction of lipoate to the dihydro-compound followed by complexation of both intra- and extracellular Cd2+ contributes to the amelioration provided by lipoate.

Prolonged pretreatment with alpha-lipoic acid protects cultured neurons against hypoxic, glutamate-, or iron-induced injury.

Muller U, Krieglstein J. Institut fur Pharmakologie und Toxikologie, Philipps-Universitat, Marburg, Germany. J Cereb Blood Flow Metab 1995 Jul;15(4):624-30

The antioxidant dihydrolipoic acid has been shown to reduce hypoxic and excitotoxic neuronal damage in vitro. In the present study, we tested whether pretreatment with alpha-lipoic acid, which presumably allows endogenous formation of dihydrolipoic acid, can protect cultured neurons against injury caused by cyanide, glutamate, or iron ions, using the trypan blue exclusion method to determine neuronal damage. One hour of preincubation with dihydrolipoic acid (1 microM), but not with alpha-lipoic acid, reduced damage of neurons from chick embryo telencephalon caused by 1 mM sodium cyanide or iron ions. alpha-lipoic acid (1 microM) reduced cyanide-induced neuronal damage when added 24 h before hypoxia, and pretreatment with alpha-lipoic acid for > 24 h enhanced this neuroprotective effect. Both the R- and the S-enantiomer of alpha-lipoic acid exerted a similar neuroprotective effect. Pretreatment with alpha-lipoic acid (1 microM) from the day of plating onward prevented the degeneration of chick embryo telencephalic neurons that had been exposed to Fe2+/Fe3+. alpha-lipoic acid (1 microM) added to the culture medium the day of plating also reduced neuronal injury induced by 1 mM L-glutamate in rat hippocampal cultures, whereas 30 min of preincubation with alpha-lipoic acid failed to attenuate glutamate-induced neuronal damage. Our results indicate that neuroprotection by prolonged pretreatment with alpha-lipoic acid is probably due to the radical scavenger properties of endogenously formed dihydrolipoic acid.

Poisoning first aid.

National Medical Library (no authors given). 2001 Medical Encyclopedia (http://www.nlm.nih.gov/medlineplus/ency/article/000003.htm) National Institutes of Health, Bethesda, MD, U.S.A.

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Mercury amalgam toxicity.

O'Brien J. Life Extension Magazine 2001 May. 7(5):43-51 (http://www.lef.org/magazine/mag2001/may2001_report_mercury_1.html) Life Extension Foundation, Ft. Lauderdale, FL, U.S.A.

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Role of mercury (Hg) in resistant infections & effective treatment of Chlamydia trachomatis and Herpes family viral infections (and potential treatment for cancer) by removing localized Hg deposits with Chinese parsley and delivering

effective antibiotics using various drug uptake enhancement methods.

Omura Y, Beckman SL. Heart Disease Research Foundation, New York, NY U.S.A. Acupunct Electrother Res 1995 Aug-Dec;20(3-4):195-229

The authors found that antibiotics used to treat various infections often were ineffective in the presence of abnormal localized deposits of heavy metals like Hg and Pb, which were often observed to co-exist with Chlamydia trachomatis, Herpes Simplex Types I & II, Cytomegalovirus(CMV), and other micro-organisms. Our earlier research revealed that despite rigorous treatment with antibiotics together with various drug uptake enhancement techniques, subjects who had been treated for Chlamydia trachomatis infections, seemingly successfully with disappearance of their symptoms, were often experiencing recurrences within several months after completion of their treatment despite taking precautions against reinfection. Careful examination of the entire body of these symptom-free patients with the Bi-Digital O-Ring Test revealed that the Chlamydia trachomatis had retreated to 3 approximately 5 hiding places with localized increase in uric acid levels: 1) sublingual caruncle, 2) a small round area in the right and/or left axillae, 3) the genitals (Corona Glandis area of the Glans Penis at the Fossa Navicularis of the urethra in the male, and near the orifice of the urethra in the female), 4) Insulin-like Growth Factor positive horizontal lines, particularly above and below the knees, 5) the maxillary, ethmoid and frontal sinuses and the horizontal lines at the base of the nostrils (particularly small areas where Insulin-like Growth Factors exist). We found that all these areas contain Insulin-like Growth Factors I & II which are reduced in the presence of infection. Even when drug uptake of antibiotics was selectively increased in these 3 approximately 5 areas by various drug uptake enhancement methods developed by the 1st author, still the infection persisted. In the spring of 1995, use of Chinese parsley for successful elimination of Hg deposits existing in various organs of the first author as the result of the decay of radioactive Thallium 201 injected for cardiac SPECT, was accidentally discovered after eating Vietnamese soup, which happened to contain Chinese parsley, also called cilantro. We also found Chinese parsley accelerates the excretion of Hg, Pb, and A1 from the body though the urine. Our subjects were given a course of antibiotics (Doxycycline for Chlamydia trachomatis infection) or anti-viral agents (EPA with DHA for Herpes Family Viruses) together with Chinese parsley. Since these vegetable/herbs were eaten, the amount of effective substance absorbed varied and some people did not like the taste of these relatively large amounts of either cooked or raw parsley or its juice, but together with effective antibiotics delivered by drug uptake enhancement methods to the infected areas, the substances worked synergistically, rapidly reducing the generalized symptoms and infection. The micro-organisms retreated to the 3 approximately 5 areas listed above where, with continued treatment, they were significantly reduced, but not completely eliminated. Because of these problems, a pharmaceutical company was asked to produce a Chinese parsley table containing a controlled amount in a highly absorbable form. When 11 subjects were treated with Doxycycline for Chlamydia trachomatis infection, or anti-viral agents (EPA with DHA) for Herpes Family Viruses, drug uptake enhancement methods to selectively increase delivery of the drugs to the affected areas, and Chinese parsley tablets to remove the heavy metal deposits, the last traces of the infections and clinical symptoms disappeared completely. Therefore we hypothesized that the infectious micro-organisms mentioned above, somehow utilize the Hg or Pb to protect themselves from what would otherwise be effective antibiotics, and/or that heavy metal deposits in some way make antibiotics ineffective. Since the micro-organisms retreat to areas in which Insulin-like Growth Factors I & II normally exist, they may be utilizing them for their own growth and multiplication.

ABSTRACTS

Omura Y., 1996. Significant mercury deposits in internal organs following the removal of dental amalgam, & development of pre-cancer on the gingiva and the sides of the tongue and their represented organs as a result of inadvertent exposure to strong curing light (used to solidify synthetic dental filling material) & effective treatment: a clinical case report, along with organ representation areas for each tooth.
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Significant mercury deposits in internal organs following the removal of dental amalgam, & development of pre-cancer on the gingiva and the sides of the tongue and their represented organs as a result of inadvertent exposure to strong curing light (used to solidify synthetic dental filling material) & effective treatment: a clinical case report, along with organ representation areas for each tooth.

Omura Y, Shimotsuura Y, Fukuoka A, Fukuoka H, Nomoto T. Heart Disease Research Foundation, New York, NY, U.S.A.
Acupunct Electrother Res 1996 Apr-Jun;21(2):133-60

Because of the reduced effectiveness of antibiotics against bacteria (e.g., Chlamydia trachomatis, alpha-Streptococcus, Borrelia burgdorferi, etc.) and viruses (e.g., Herpes Family Viruses) in the presence of mercury, as well as the fact that the 1st author has found that mercury exists in cancer and pre-cancer cell nuclei, the presence of dental amalgam (which contains about 50% mercury) in the human mouth is considered to be a potential hazard for the individual's health. In order to solve this problem, 3 amalgam fillings were removed from the teeth of the subject of this case study. In order to fill the newly created empty spaces in the teeth where the amalgams had formerly existed, a synthetic dental-filling substance was introduced and to solidify the synthetic substance, curing light (wavelength range reportedly between 400-520 nm) was radiated onto the substance in order to accelerate the solidifying process by photo-polymerization. In spite of considerable care not to inhale mercury vapor or swallow minute particles of dental amalgam during the process of removing it by drilling, mercury entered the body of the subject. Precautions such as the use of a rubber dam and strong air suction, as well as frequent water suctioning and washing of the mouth were insufficient. Significant deposits of mercury, previously non-existent, were found in the lungs, kidneys, endocrine organs, liver, and heart with abnormal low-voltage ECGs (similar to those recorded 1-3 weeks after i.v. injection of radioisotope Thallium-201 for Cardiac SPECT) in all the limb leads and V1 (but almost normal ECGs in the precordial leads V2-V6) the day after the procedures were performed. Enhanced mercury evaporation by increased temperature and microscopic amalgam particles created by drilling may have contributed to mercury entering the lungs and G.I. system and then the blood circulation, creating abnormal deposits of mercury in the organs named above. Such mercury contamination may then contribute to intractable infections or pre-cancer. However, these mercury deposits, which commonly occur in such cases, were successfully eliminated by the oral intake of 100 mg tablet of Chinese parsley (Cilantro) 4 times a day (for average weight adults) with a number of drug-uptake enhancement methods developed by the 1st author, including different stimulation methods on the accurate organ representation areas of the hands (which have been mapped using the Bi-Digital O-Ring Test), without injections of chelating agents. Ingestion of Chinese parsley, accompanied by drug-uptake enhancement methods, was initiated before the amalgam removal procedure and continued for about 2 to 3 weeks afterwards, and ECGs became almost normal. During the use of strong bluish curing light to create a photo-polymerization reaction to solidify the synthetic filling material, the adjacent gingiva and the side of the tongue were inadvertently exposed. This exposure to the strong bluish light was found to produce pre-cancerous conditions in the gingiva, the exposed areas of the tongue, as well as in the corresponding organs represented on those areas of the tongue, and abnormally increased enzyme levels in the liver. These abnormalities were also successfully reversed by the oral intake of a mixture of EPA with DHA and Chinese parsley, augmented by one of the non-invasive drug-uptake enhancement methods previously described by the 1st author, repeated 4 times each day for 2 weeks.

Symptomatic treatment of brain tumor patients with sodium selenite, oxygen, and other supportive measures.

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Biol Trace Elem Res 1998 Apr-May;62(1-2):1-6

Patients (16 women and 16 men) with brain tumors previously treated conservatively by surgery, radiation, and/or chemotherapy with typical symptoms of increased intracranial pressure were consecutively enrolled to test the effects of pharmacological dosages of sodium selenite (selenase) in conjunction with other supportive therapies (biological response modifiers, detoxification, chemotherapy, immunotherapy, oxygen therapy). The rationale for the use of sodium selenite was that the whole-blood selenium levels were subnormal in 70% of the patients on admission. Patients also frequently presented abnormal levels of other minerals, especially lowered sodium and elevated potassium levels, which appears to be characteristic of brain tumor patients. Sodium selenite was administered by infusion at dosages of 1000 microg Se in physiological saline/d for 4-8 wk. In 76% of the patients, a definite, and in 24% a slight improvement of the general condition and a decrease in symptoms, such as nausea, emesis, headache, vertigo, unsteady gait, speech disorders, and Jacksonian seizures, were observed. In all treated patients, improvements of erythrocyte, hemoglobin, and thrombocyte counts were observed. Additional beneficial effects were noted in the patients receiving the oxygen therapy. It is concluded that the sodium selenite can be employed with oxygen therapy and other supportive measures in the management of brain tumor patients.

S-adenosyl-L-methionine a counter to lead intoxication?

Paredes SR, Kozicki PA, Batlle AM.

Comp Biochem Physiol B 1985;82(4):751-7

The effect of S-adenosyl-L-methionine (SAM) administration to both acute and chronic lead exposed mice was investigated. SAM was given s.c. at different doses and for different time intervals. The best results were obtained using 20 mg SAM/kg applied daily over a period of 20-22 days. Results obtained in both acute and chronic lead poisoning were quite similar. GSH concentration in blood and liver, reduced in intoxicated animals was increased after SAM administration reaching normal values. Blood, liver and kidney lead content notably increased at the beginning of SAM treatment and decreased rapidly in the group receiving SAM, attaining values near control levels in 2 weeks. A significant recovery of blood, liver, kidney, spleen and brain delta-aminolevulic acid dehydratase (ALA-D) initially reduced in poisoned animals, was clearly produced after SAM administration. A clear and direct correlation between the recovery of both ALA-D activity and GSH levels and the decreased concentration of lead in tissues was observed, reinforcing our proposal that enhancement of thiol content as a result of SAM administration would facilitate the detoxification process and lead removal, consequently reversing the inactivation of the enzyme. We conclude that SAM therapy is beneficial in the treatment of lead intoxication.

Prevention by rutin of gastric lesions induced by ethanol in rats: role of endogenous prostaglandins.

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Gen Pharmacol 1994 May;25(3):575-80

1. This study was designed to demonstrate the cytoprotective effect of Rutin against ethanol-induced gastric injury in rats and to determine whether this cytoprotective effect is mediated by endogenous prostaglandins. 100 and 200 mg/kg of Rutin given orally 1 hr before administration of 1 ml of 100% ethanol significantly ($p < 0.01$) reduced the area of macroscopic lesions induced by ethanol (84.16 +/- 23.01 and 54.75 +/- 16.05 respectively) when compared to distilled water (305.60 +/- 67.20). However, it did not induce changes in the amount and total proteins and hexosamines content of gastric mucus. 2. Pretreatment with indomethacin, 10 mg/kg s.c. 30 min before Rutin administration, slightly but not significantly reduced the cytoprotective effect. 3. The levels of PGE2 present in the mucous material were not significantly modified with administration of Rutin (100 mg/kg). 4. These results show that Rutin has a cytoprotective effect against ethanol injury in the rat, but this property does not appear to be mediated by endogenous prostaglandins.

Antioxidant activity of silybin in vivo during long-term iron overload in rats.

Pietrangelo A, Borella F, Casalgrandi G, Montosi G, Ceccarelli D, Gallesi D, Giovannini F, Gasparetto A, Masini A. Dipartimento di Medicina Interna, University of Modena, Italy.

Gastroenterology 1995 Dec;109(6):1941-9

BACKGROUND & AIMS: Hepatic iron toxicity may be mediated by free radical species and lipid peroxidation of biological membranes. The antioxidant property of silybin, a main constituent of natural flavonoids, was investigated in vivo during experimental

iron overload. METHODS: Rats were fed a 2.5% carbonyl-iron diet and 100 mg.kg body wt-1.day-1 silybin for 4 months and were assayed for accumulation of hepatic lipid peroxidation by-products by immunocytochemistry, mitochondrial energy-dependent functions, and mitochondrial malondialdehyde content. RESULTS: Iron overload caused a dramatic accumulation of malondialdehyde-protein adducts into iron-filled periportal hepatocytes that was decreased appreciably by silybin treatment. The same beneficial effect of silybin was found on the iron-induced accumulation of malondialdehyde in mitochondria. As to the liver functional efficiency, mitochondrial energy wasting and tissue adenosine triphosphate depletion induced by iron overload were successfully counteracted by silybin. CONCLUSIONS: Oral administration of silybin protects against iron-induced hepatic toxicity in vivo. This effect seems to be caused by the prominent antioxidant activity of this compound.

Antioxidant therapy in the prevention of organ dysfunction syndrome and infectious complications after trauma: early results of a prospective randomized study.

Porter JM, Ivatury RR, Azimuddin K, Swami R. The Lincoln Medical Center, Bronx, New York, U.S.A.

Am Surg 1999 May;65(5):478-83; erratum, Am Surg 1999 Sep;65(9):902

Reactive oxygen species have been implicated in the etiology of multiorgan dysfunction syndrome and infectious complications in trauma patients by either direct cellular toxicity and/or the activation of intracellular signaling pathways. Studies have shown that the antioxidant defenses of the body are decreased in trauma patients; these include glutathione, for which N-acetylcysteine is a precursor, and selenium, which is a cofactor for glutathione. Eighteen trauma patients were prospectively randomized to a control or antioxidant group where they received N-acetylcysteine, selenium, and vitamins C and E for 7 days. As compared with the controls, the antioxidant group showed fewer infectious complications (8 versus 18) and fewer organs dysfunctioning (0 versus 9). There were no deaths in either group. We conclude that these preliminary data may support a role for the use of this antioxidant mixture to decrease the incidence of multiorgan dysfunction syndrome and infectious complications in the severely injured patient. This remains to be confirmed in larger trials.

MSM: the multi-purpose compound.

Prater G. Life Extension Magazine 1999 Sep;5(9):71-2 (http://www.lef.org/magazine/mag99/sep99-products.htm) Life Extension Foundation, Ft. Lauderdale, FL. U.S.A.

No abstract available.

Vitamin E and heart disease: basic science to clinical intervention trials.

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Free Radic Biol Med 2000 Jan 1;28(1):141-64

A review is presented of studies on the effects of vitamin E on heart disease, studies encompassing basic science, animal studies, epidemiological and observational studies, and four intervention trials. The in vitro, cellular, and animal studies, which are impressive both in quantity and quality, leave no doubt that vitamin E, the most important fat-soluble antioxidant, protects animals against a variety of types of oxidative stress. The hypothesis that links vitamin E to the prevention of cardiovascular disease (CVD) postulates that the oxidation of unsaturated lipids in the low-density lipoprotein (LDL) particle initiates a complex sequence of events that leads to the development of atherosclerotic plaque. This hypothesis is supported by numerous studies in vitro, in animals, and in humans. There is some evidence that the ex vivo oxidizability of a subject's LDL is predictive of future heart events. This background in basic science and observational studies, coupled with the safety of vitamin E, led to the initiation of clinical intervention trials. The three trials that have been reported in detail are, on balance, supportive of the proposal that supplemental vitamin E can reduce the risk for heart disease, and the fourth trial, which has just been reported, showed small, but not statistically significant, benefits. Subgroup analyses of cohorts from the older three trials, as well as evidence from smaller trials, indicate that vitamin E provides protection against a number of medical conditions, including some that are indicative of atherosclerosis (such as intermittent claudication). Vitamin E supplementation also produces an improvement in the immune system and protection against diseases other than cardiovascular disease (such as prostate cancer). Vitamin E at the supplemental levels being used in the current trials, 100 to 800 IU/d, is safe, and there is little likelihood that increased risk will be found for those taking supplements. About one half of American cardiologists take supplemental vitamin E, about the same number as take aspirin. In fact, one study suggests that aspirin plus vitamin E is more effective than aspirin alone. There are a substantial number of trials involving vitamin E that are in progress. However, it is possible, or even likely, that each condition for which vitamin E provides benefit will have a unique dose-effect curve. Furthermore, different antioxidants appear to act synergistically, so supplementation with vitamin E might be more effective if combined with other micronutrients. It will be extremely difficult to do trials that adequately probe the dose-effect curve for vitamin E for each condition that it might affect, or to do studies of all the possible combinations of other micronutrients that might act with vitamin E to improve its effectiveness. Therefore, the scientific community must recognize that there never will be a time when the science is "complete." At some point, the weight of the scientific evidence must be judged adequate; although some may

regard it as early to that judgement now, clearly we are very close. In view of the very low risk of reasonable supplementation with vitamin E, and the difficulty in obtaining more than about 30 IU/day from a balanced diet, some supplementation appears prudent now.

Cysteine metabolism and metal toxicity.

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Altern Med Rev 1998 Aug;3(4):262-70

Chronic, low level exposure to toxic metals is an increasing global problem. The symptoms associated with the slow accumulation of toxic metals are multiple and rather nondescript, and overt expression of toxic effects may not appear until later in life. The sulfhydryl-reactive metals (mercury, cadmium, lead, arsenic) are particularly insidious and can affect a vast array of biochemical and nutritional processes. The primary mechanisms by which the sulfhydryl-reactive metals elicit their toxic effects are summarized. The pro-oxidative effects of the metals are compounded by the fact that the metals also inhibit antioxidative enzymes and deplete intracellular glutathione. The metals also have the potential to disrupt the metabolism and biological activities of many proteins due to their high affinity for free sulfhydryl groups. Cysteine has a pivotal role in inducible, endogenous detoxication mechanisms in the body, and metal exposure taxes cysteine status. The protective effects of glutathione and the metallothioneins are discussed in detail. Basic research pertaining to the transport of toxic metals into the brain is summarized, and a case is made for the use of hydrolyzed whey protein to support metal detoxification and neurological function. Metal exposure also affects essential element status, which can further decrease antioxidation and detoxification processes. Early detection and treatment of metal burden is important for successful detoxification, and optimization of nutritional status is paramount to the prevention and treatment of metal toxicity.

The effects of glutathione depletion on reproductive success in oysters, Crassostrea virginica.

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Mar Environ Res 2000 Jul-Dec;50(1-5):207-11

Glutathione (GSH) is a ubiquitous tripeptide that functions as a very important modulator of cellular homeostasis, including detoxification of metals and oxyradicals. Therefore, depletion of GSH may predispose organisms to pollutant stress. Reproductively active oysters (Crassostrea virginica) were exposed to buthionine sulfoximine in the laboratory to deplete gonadal GSH. The effects of metal exposures (Cd and Cu) on fertilization and developmental assays were evaluated using gametes from control and GSH-depleted adults. Fertilization success was not affected by GSH status, i.e. the fertilization rates of gametes derived from GSH-depleted adults were the same or slightly higher. However, GSH depletion did increase the susceptibility of developing embryos to metal toxicity, i.e. adverse effects on embryonic development were observed at lower metal concentrations with gametes derived from GSH-depleted adults. These effects may be related to diminished removal of free radicals or increased availability of metals. Whereas sperm penetration of embryonic membranes and fertilization success may be facilitated by free radicals, the persistence of free radicals during subsequent developmental periods may adversely affect differentiation and normal development. GSH probably also plays an important role in scavenging toxic metals and reducing metal interactions with essential developmental processes. These results suggest that parental depletion of GSH may increase the susceptibility of embryos to metal toxicity.

Metal toxicity in children.

Roberts JR. June 1999 Training Manual on Pediatric Environmental Health: Putting It into Practice. (http://www.cehn.org/cehn/trainingmanual/pdf/manual-full.pdf) Children's Environmental Health Network, Emeryville, CA, U.S.A.

No abstract available.

Long-term use of nicotine chewing gum and mercury exposure from dental amalgam fillings.

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J Dent Res 1996 Jan;75(1):594-8

In experimental studies, chewing gum has been shown to increase the release rate of mercury vapor from dental amalgam fillings. The aim of the present study was to investigate the influence of long-term frequent chewing on mercury levels in plasma and urine. Mercury levels in plasma (P-Hg) and urine (U-Hg), and urinary cotinine were examined in 18 subjects who regularly used nicotine

chewing gum, and in 19 referents. Age and number of amalgam surfaces were similar in the two groups. Total mercury concentrations in plasma and urine were determined by means of cold vapor atomic absorption spectrometry. Urinary cotinine was determined by gas chromatography-mass spectrometry. The chewers had been using 10 (median) pieces of gum per day for the past 27 (median) months. P-Hg and U-Hg levels were significantly higher in the chewers (27 nmol/L and 6.5 nmol/mmol creatinine) than in the referents (4.9 nmol/L and 1.2 nmol/mmol creatinine). In both groups, significant correlations were found between P-Hg or U-Hg on the one hand and the number of amalgam surfaces on the other. In the chewers, no correlations were found between P-Hg or U-Hg and chewing time per day or cotinine in urine. Cotinine in urine increased with the number of pieces of chewing gum used. The impact of excessive chewing on mercury levels was considerable.

Alzheimer's disease, dental amalgam and mercury.

Saxe SR, Wekstein MW, Kryscio RJ, Henry RG, Cornett CR, Snowdon DA, Grant FT, Schmitt FA, Donegan SJ, Wekstein DR, Ehmann WD, Markesbery WR. Geriatric Oral Health Program, College of Dentistry, University of Kentucky, Lexington, KY, U.S.A.

J Am Dent Assoc 1999 Feb;130(2):191-9

BACKGROUND: Mercury, or Hg, is a neurotoxin that has been speculated to play a role in the pathogenesis of Alzheimer's disease, or AD. Dental amalgam releases low levels of Hg vapor and is a potential source of Hg for a large segment of the adult population. METHODS: The authors studied 68 subjects with AD and 33 control subjects without AD to determine Hg levels in multiple brain regions at autopsy and to ascertain the subjects' dental amalgam status and history. The subjects were from central Kentucky and Elm Grove, Wis. The authors conducted dental amalgam assessments during the lives of the majority of subjects and in some subjects at the time of autopsy only. The authors also determined three dental amalgam index scores--Event (placement, repair or removal of amalgam), Location and Time In Mouth--in addition to the numbers of and surface area of occlusal amalgam restorations. The authors determined Hg levels in multiple brain regions and performed full neuropathologic evaluations to confirm the normal status of the brain or the presence of AD. RESULTS: The authors found no significant association of AD with the number, surface area or history of having dental amalgam restorations. They also found no statistically significant differences in brain Hg level between subjects with AD and control subjects. CONCLUSIONS: Hg in dental amalgam restorations does not appear to be a neurotoxic factor in the pathogenesis of AD. The authors found that brain Hg levels are not associated with dental amalgam, either from existing amalgam restorations or according to subjects' dental amalgam restoration history. CLINICAL IMPLICATIONS: Dental amalgam restorations, regardless of number, occlusal surface area or time, do not relate to brain Hg levels.

Effect of selenium on the side effect profile of adjuvant chemotherapy/radiotherapy in patients with breast carcinoma. Design for a clinical study.] [Article in German]

Schumacher K.

Med Klin 1999 Oct 15;94 Suppl 3:45-8

Selenium is a very important component of the antioxidative protective mechanism which belongs to every cell. By chemotherapy and radiotherapy a strong increase of free oxygen radicals is induced leading to damage also of normal tissue. This phenomenon is registered as adverse drug reactions. Since, in addition, tumor patients frequently have low selenium blood levels the application of higher doses of selenium in connection with chemo- and radiotherapy will induce the toxicity of the treatment without lowering the efficiency. Within the presented prospective randomized placebo-controlled double-blind phase-III study we intend to answer the question whether the application of higher doses of sodium selenite will reduce the toxicity of chemotherapy and radiotherapy. Primary targets of the study are therefore the evaluation of toxicity according to CTC-criteria and of life quality.

Dependence of cadmium-metallothionein nephrotoxicity on glutathione.

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J Toxicol Environ Health A 1999 Jun 11;57(3):211-22

Acute cadmium-metallothionein (CdMT) injection is frequently used as a model to study the mechanism of chronic Cd-induced nephrotoxicity. The purpose of this study was to investigate the relationship between glutathione (GSH) status and the ability of CdMT, either administered as a bolus dose or infused over a 24-h period by an osmotic minipump, to cause nephrotoxicity. GSH levels were modulated by pretreatment with either buthionine sulfoximine (BSO) or GSH. BSO enhanced while GSH suppressed acute CdMT nephrotoxicity. An infused dose of CdMT (150 microg Cd/kg) that was well tolerated when delivered over a 24-h period became nephrotoxic when GSH synthesis was inhibited by BSO. With depletion of GSH, as little as 0.4 microg Cd/g renal cortex was sufficient to cause nephrotoxicity after an acute dose of CdMT. While BSO had no effect on renal Cd accumulation, pretreatment with GSH reduced renal cortical Cd accumulation by 36%. CdMT nephrotoxicity was enhanced by depleting renal GSH, but without increasing renal Cd accumulation, which suggests that intracellular GSH is directly involved in protection against

CdMT nephrotoxicity. Reduced Cd accumulation in the renal cortex following GSH pretreatment suggests an additional extracellular mechanism of GSH protection. It is concluded that GSH status is an important determinant of CdMT nephrotoxicity, with low GSH levels enhancing and high GSH levels reducing its toxicity, and that the mechanism appears to involve both intracellular and extracellular sites.

Protection against chronic cadmium toxicity by glycine.

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A Japanese drug containing glycine, glycyrrhizin, and cysteine (Stronger Neo-Minophagen C) has been reported to protect against chronic cadmium (Cd) toxicity. The present study was conducted to evaluate which of the three constituents of this drug was the main antagonist for Cd toxicity and whether the mechanism of protection involved antioxidant action. Adult female Sprague-Dawley rats were injected sc with 5 micromol CdCl2/kg per day, five times per week, for 15 weeks. Four groups of Cd-injected animals received co-treatments with either 10 mg glycyrrhizin/kg, 100 mg glycine/kg, 5 mg cysteine/kg, or with a mixture of all three compounds, five times per week, starting from week 7. An additional Cd-injected group was co-treated with vitamin E (100 mg/kg, five times per week, starting from week 7) as a positive control. Only those animals that received vitamin E, Minophagen mixture, or glycine were protected against Cd-induced hepatotoxicity as well as nephrotoxicity. All three co-treatments suppressed Cd-induced hepatic and renal lipid peroxidation. We conclude that the reported beneficial effects of Stronger Neo-Minophagen C are due to glycine, which appears to protect against chronic Cd toxicity by reducing oxidative stress.

Glutathione status and cadmium neurotoxicity: studies in discrete brain regions of growing rats.

Shukla GS, Srivastava RS, Chandra SV. Industrial Toxicology Research Centre, Lucknow, India.

Fundam Appl Toxicol 1988 Aug;11(2):229-35

Intraperitoneal administration of cadmium (Cd2+, 0.4 mg/kg) daily for 30 days to rats was found to decrease the contents of reduced glutathione (GSH) and increase oxidized glutathione (GSSG) in various brain regions. These changes resulted in a significant decline in the GSH/GSSG ratio in different brain regions, except for the hippocampus and midbrain. In addition, the activities of glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (GPDH) were also significantly inhibited in different brain regions. Measurement of regional Cd levels revealed that Cd administration significantly increased the levels in all brain regions except for the hippocampus, which could be the reason for not finding any change in any of the biochemical parameters studied in this region. The observed changes in the regional GSH/GSSG ratios could be the result of inhibition in GR activity, as this enzyme catalyzes an irreversible conversion of GSH to GSSG and is responsible for higher cellular GSH levels. GR uses NADPH in its reaction; therefore, the inhibition of GPDH may further aggravate the situation because of the short supply of NADPH. The alterations in the regional "glutathione status" may affect various related metabolic processes, including those required for detoxification of lipid peroxides which have recently been suggested to play a role in the mechanism of Cd neurotoxicity.

Effect of chronic cadmium exposure on glutathione S-transferase and glutathione peroxidase activities in rhesus monkey: the role of selenium. Sidhu M, Sharma M, Bhatia M, Awasthi YC, Nath R. Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Toxicology 1993 Oct 25;83(1-3):203-13

The effect of cadmium (Cd) on the activity of glutathione S-transferase (GST) and glutathione peroxidase (GSH-Px) which play an important role in the detoxification of xenobiotics, was studied in the liver, kidney, heart and lung of Rhesus monkeys. Furthermore, the role of selenium (Se) in the modulation of Cd toxicity with respect to GST and GSH-Px was also evaluated. Cadmium exposure (5 mg Cd/kg body wt./day as CdCl2 for 10 weeks) to monkeys resulted in decreased GSH-Px activity in all four organs present in the order liver > kidney > heart > lung. Cadmium administration also resulted in a significant decrease in total GST activity present in the order liver > heart > kidney > lung, whereas a significant increase in the pi class GST activity was observed greatest in the heart followed by lung, kidney and liver. Oral administration of Se (0.5 mg Se/kg body wt./day as Na2SeO3 for 10 weeks) caused a significant increase in GSH-Px activity in the order liver > heart > kidney > lung. Selenium administration caused an increase in total GST activity in liver and lung but a decrease in kidney and heart. Simultaneous administration of Cd and Se resulted in an increase in total GST activity (except in lung) including the pi class activity as well as GSH-Px activity in all four tissues under study. Thus, the mechanism by which selenium decreases Cd toxicity in Rhesus monkeys, seems to rely on the protection of the enzyme systems GST and GSH-Px in the four organs, possibly by forming non-toxic cadmium selenide.

Activities of silymarin and its flavonolignans upon low density lipoprotein oxidizability in vitro.

Skottova N, Krecman V, Simanek V. Institute of Medical Chemistry, Medical Faculty, Palacky University, Hnevotinska 3, 775 15 Olomouc, Czech Republic.

Phytother Res 1999 Sep;13(6):535-7

Silymarin, a standardized extract from Silybum marianum, inhibited in vitro the copper- nduced oxidation of human LDL in a concentration-dependent manner. Silybin, a main flavonolignan of silymarin, appeared to be responsible for this LDL antioxidant effect. Silychristin and silydianin, other flavonolignans of silymarin, acted rather as pro- oxidants, but with regard to their content in silymarin, it did not contribute significantly to the reduction of the total LDL antioxidant capacity of silymarin. Copyright 1999 John Wiley & Sons, Ltd.

Case report of metallic mercury injury.

Smith SR, Jaffe DM, Skinner MA. Department of Pediatric Emergency Medicine, St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, MO 63110-1077, U.S.A.

Pediatr Emerg Care 1997 Apr;13(2):114-6

OBJECTIVE: Injury and poisoning from metallic mercury has become a rare event. Review of the literature and a case report of pediatric metallic mercury injury are presented. DESIGN: A case report. SETTING: The Emergency Department at St. Louis Children's Hospital. PATIENTS OR PARTICIPANTS: A 15-year-old boy. INTERVENTIONS: None. MAIN OUTCOME MEASURES: None. RESULTS: The 15-year-old boy fell on a broken mercury thermometer. A subcutaneous abscess formed on his left forearm during the next five days. He had no signs or symptoms of mercury toxicity. His wound was debrided in the operating room and healed completely after several months. CONCLUSIONS: This case shows elemental mercury from a thermometer as a potential, if unusual, source of mercury toxicity.

Carcinogen binding to various types of dietary fiber.

Smith-Barbaro P, Hanson D, Reddy BS.

J Natl Cancer Inst 1981 Aug;67(2):495-7

The percent of the carcinogen 1,2-dimethylhydrazine (DMH) bound to a variety of fibers, such as wheat bran, corn bran, citrus pulp, citrus pectin, and alfalfa, was examined at pH values ranging from 1 to 12. The percent of DMH bound to wheat bran increased from 4% at PH 1 to 55% at pH 2 to 77% at pH 12. A sharp rise in carcinogen binding to corn bran occurred between pH 5% of the DMH was bound and pH 8 where 51% of the DMH was bound. The percent of DMH bound to dehydrated citrus pulp also increased as the pH increased with 10% binding observed at pH 1 and with 57% binding observed at pH 12. Between pH 2 and pH 7, the percent of DMH bound to pectin decreased from 60 to 11%. As the pH became more basic, the percent of DMH bound to pectin increased to 42% at pH 12. The sharpest rise in the percent of DMH bound to alfalfa meal occurred between pH 10.5 and pH 12.0. Results from this experiment showed that the affinity to various types of dietary fibers for the colon carcinogen DMH was differentially affected by pH. These results suggested that the protective effect of certain types of dietary fiber against chemically induced colon cancer my in part be attributed to enhanced carcinogen binding by dietary fiber in the colon.

Stimulatory effect of Silibinin on the DNA synthesis in partially hepatectomized rat livers: non-response in hepatoma and other malign cell lines.

Sonnenbichler J, Goldberg M, Hane L, Madubunyi I, Vogl S, Zetl I.

Biochem Pharmacol 1986 Feb 1;35(3):538-41

No abstract available.

Stimulatory effects of silibinin and silicristin from the milk thistle Silybum marianum on kidney cells.

Sonnenbichler J, Scalera F, Sonnenbichler I, Weyhenmeyer R. Max Planck Institute for Biochemistry, Martinsried, Germany.

J Pharmacol Exp Ther 1999 Sep;290(3):1375-83

The biochemical influence of flavonolignans from the milk thistle Silybum marianum has been tested on kidney cells of African green monkeys. Two nonmalignant cell lines were selected, with the focus of the work on the fibroblast-like Vero line. Proliferation rate,

biosynthesis of protein and DNA, and the activity of the enzyme lactate dehydrogenase (as a measure of the cellular metabolic activity) were chosen as parameters for the effect of the flavonolignans. Silibinin and silicristin show remarkable stimulatory effects on these parameters, mainly in Vero cells; however, isosilibinin and silidianin proved to be inactive. In vitro experiments with kidney cells damaged by paracetamol, cisplatin, and vincristin demonstrated that administration of silibinin before or after the chemical-induced injury can lessen or avoid the nephrotoxic effects. The results warrant in vivo evaluations of the flavonolignan derivatives.

[Evaluation of the antiradical protector effect of multifermented milk serum with reiterated dosage in rats.] [Article in French]

Stella V, Postaire E. Direction Scientifique, Pharmacie Centrale des Hopitaux, Paris.

C R Seances Soc Biol Fil 1995;189(6):1191-7

Epidemiological and experimental studies suggest that dietary milk products may exert an inhibitory effect on the development of several types of tumors. Some recent experiments in rodents indicate that the antitumor activity of the dairy product is in the protein fraction and more specifically in the whey protein component of milk. It has been demonstrated that whey protein diets result in increased glutathione (GSH) concentration in a number of tissues, and that some of the beneficial effects of whey protein intake are abrogated by inhibition of GSH synthesis. Whey protein is particularly rich in substrates for GSH synthesis. It has been suggested that whey protein may be exerting its effect on carcinogenesis and VIH infection by enhancing GSH concentration. Lactoferrin, one of the proteins contained in whey has aise been studied in this way. It has been suggested that lactoferrin binding may play an important role in maintaining, optimal mononuclear phagocyte function, thus protecting adjacent tissue against phagocyte derived radicals. Moreover it has been demonstrated by one of us that the level of plasma lactoferrin were decreased in HIV-1 infected patients in relation to the progression of the disease. The aim of the present study is to evaluate in rat the reactive oxygen species, scavenger activities (ROSSA) of red blood cells (RBCs) with a multifermented whey (SK 344), by repeated doses during 16 days. This study has permitted to demonstrate in vivo that the SK 344 has an excellent ROSSA corresponding to a limitation of the lipoperoxidation of RBCs membranes by singlet oxygen and nitric oxide. We can conclude that whey protein, lactoferrin and multifermented whey are good candidates as dietary inhibitors of the oxidative stress and should be considered as potential medicinal foods in various pathologies as HIV infection and cancer.

Restoration of the cellular thiol status of peritoneal macrophages from CAPD patients by the flavonoids silibinin and silymarin.

Tager M, Dietzmann J, Thiel U, Hinrich Neumann K, Ansorge S. Institute of Immunology, Otto-von-Guericke University, Leipziger Str. 44 D-39120 Magdeburg, Germany. michael.tager@medizin.uni-magdeburg.de

Free Radic Res 2001 Feb;34(2):137-51

During continuous ambulatory peritoneal dialysis (CAPD) the peritoneal immune ells, mainly macrophages, are highly compromised by multiple factors including oxidative stress, resulting in a loss of functional activity. One reason for the increase of inflammatory reactions could be an imbalance in the thiol-disulfide status. Here, the possible protective effects of the antioxidant flavonoid complex silymarin and its major component silibinin on the cellular thiol status were investigated. Peritoneal macrophages from dialysis fluid of 30 CAPD patients were treated with silymarin or silibinin up to 35 days. A time-dependent increase of intracellular thiols was observed with a nearly linear increment up to 2.5-fold after 96 hours, reaching a maximum of 3.5-fold after 20 days of culture. Surface-located thiols were also elevated. The stabilization of the cellular thiol status was followed by an improvement of phagocytosis and the degree of maturation as well as significant changes in the synthesis of IL-6 and IL-1ra. Furthermore, the treatment of peritoneal macrophages with flavonoids in combination with cysteine donors resulted in a shortened and more efficient time course of thiol normalization as well as in a further increased phagocytosis. In addition, GSH-depletion in thiol-deficient media simulating CAPD procedures led to intracellular thiol deficiency similar to the in vivo situation. It is concluded that treatment with milk thistle extracts silymarin and silibinin alone or, more effectively in combination with cysteine donors, provide a benefit for peritoneal macrophages of CAPD-patients due to a normalization and activation of the cellular thiol status followed by a restoration of specific functional capabilities.

Preventive effect of vitamin E in cadmium intoxication.

Tandon SK, Singh S, Dhawan M. Industrial Toxicology Research Centre, Lucknow, India.

Biomed Environ Sci 1992 Mar;5(1):39-45

The influence of vitamin E on cadmium intoxication was investigated in rats. The exposure to cadmium (1 mg/kg, Cd as CdCl2.2H2O, intraperitoneally for 7 days) decreased the activity of hepatic and renal glutamic oxalacetic and glutamic pyruvic transaminases (GOT, GPT) and alkaline phosphatase (ALP) accompanied by increase in the levels of serum GOT and GPT and urinary protein. Simultaneous administration of vitamin E (5 mg/kg, intramuscularly for 7 days) reduced these Cd induced

biochemical alterations. The accumulation of Cd in blood, liver and kidney also decreased significantly upon co-exposure to vitamin E. The antioxidant property of vitamin E seems to be responsible for the observed protection of Cd intoxication. **Nephrotoxicity of cadmium-metallothionein: protection by zinc and role of glutathione.**

Tang W, Sadovic S, Shaikh ZA. College of Pharmacy, University of Rhode Island, Kingston, RI 02881, U.S.A.

Toxicol Appl Pharmacol 1998 Aug;151(2):276-82

Chronic cadmium (Cd) exposure can cause renal proximal tubular dysfunction resulting from the release of Cd metallothionein (CdMT) from the liver and its accumulation and degradation in the renal tubular epithelial cells. Pretreatment with zinc (Zn) can protect against acute CdMT nephrotoxicity. While induction of MT by Zn plays a part in Zn protection, other factors, such as glutathione (GSH), may also be involved because protection is offered even in MT-null mice. The present study was designed to investigate the involvement of GSH in Zn protection against acute CdMT nephrotoxicity. The study was carried out in MT-null mice to remove the induction of MT by Zn as a confounding variable. Three approaches were used to modulate renal cortex GSH levels: buthionine sulfoximine (BSO) was administered to inhibit GSH synthesis, and GSH and Zn were administered to increase the GSH levels. Both GSH and Zn were effective in protecting against CdMT nephrotoxicity. Elevation in renal cortex GSH levels, however, was not essential for Zn protection, as a low dose of Zn that caused no significant increase in renal GSH also protected against CdMT. On the other hand, maintenance of normal GSH status was essential for Zn protection, as inhibition of GSH synthesis abolished this protection. Both GSH and Zn reduced the accumulation of Cd as well as MT in the renal cortex, with Zn causing greater reduction in Cd accumulation than that of MT. The relative intracellular distribution of Cd was unaltered. These results suggest that in MT-null mice Zn protects against CdMT nephrotoxicity by possibly displacing some of the Cd from CdMT as well as reducing the uptake of CdMT, and that this protection requires the maintenance of normal GSH status. Copyright 1998 Academic Press.

Association of glutathione S-transferase isozyme-specific induction and lipid peroxidation in two inbred strains of mice subjected to chronic dietary iron overload.

Tjalkens RB, Valerio LG Jr, Awasthi YC, Petersen DR. Department of Pharmaceutical Sciences, University of Colorado Health Sciences Center, Denver, CO 80262, U.S.A.

Toxicol Appl Pharmacol 1998 Jul;151(1):174-81

The alpha-class glutathione S-transferases are proposed to play a prominent role in catalyzing the conjugation of glutathione with electrophilic aldehydic products of lipid peroxidation. The effect of iron-induced lipid peroxidation on induction of glutathione S-transferase (GST) isozymes A1 and A4 in the livers of male C57/BL6Ibg and DBA/J2Ibg mice was studied. C57 and DBA mice were fed for 4 months on a diet supplemented with iron as ferrocene and then were assessed for liver injury, hepatic iron loading, indices of lipid peroxidation, GST activity, and induction of GST isozymes A1 and A4. Iron-treated animals displayed a loss in body weight from pair-fed controls and had large increases in hepatic non-heme iron with concomitant liver injury, as measured by serum alanine aminotransferase. Hepatic lipid hydroperoxides, a direct measure of oxidized membrane lipids, were significantly increased only in C57 mice, but hepatic concentrations of reduced glutathione (GSH) were significantly increased in both inbred strains. Total GST activity toward 1-chloro-2,4-dinitrobenzene was significantly increased in C57 mice but not in DBA. Western blot studies using polyclonal antibodies specific for GST A1 and A4 revealed significant increases of 1.5-2.0-fold in these GST isoforms in both inbred strains. These results in a unique murine model for hepatic iron overload further support recent in vivo studies (Khan et al., Toxicol. Appl. Pharmacol., 131, 63-72, 1995) that have associated induction of GST A4 with protection against oxidative stress-induced lipid peroxidation. The observed increases in lipid hydroperoxides, hepatic GSH, GST activity, and GST A1 and A4 protein strongly support the hypothesis that induction of GST A1 and A4 represents an important protective event in the detoxification of electrophilic products of lipid peroxidation. Copyright 1998 Academic Press.

ToxFAQs™ for Aluminum. CAS 7429-90-5.

Agency for Toxic Substances and Disease Registry. June 1999 Division of Toxicology, 1600 Clifton Road NE, Mailstop E-29, Atlanta, GA 30333, U.S.A.

HIGHLIGHTS: Everyone is exposed to low levels of aluminum from food, air, and water. Exposure to high levels of aluminum may result in respiratory problems. Aluminum has been found in at least 427 of the 1,467 National Priorities List sites identified by the Environmental Protection Agency (EPA).

ToxFAQs™ for Arsenic. CAS 7440-38-2.

Agency for Toxic Substances and Disease Registry. July 2001 Division of Toxicology, 1600 Clifton Road NE, Mailstop E-29, Atlanta, GA 30333, U.S.A.

HIGHLIGHTS: Exposure to higher than average levels of arsenic occurs mostly in the workplace, near hazardous waste sites, or in areas with high natural levels. At high levels, inorganic arsenic can cause death. Exposure to lower levels for a long time can cause a discoloration of the skin and the appearance of small corns or warts. Arsenic has been found at 1,014 of the 1,598 National Priority List sites identified by the Environmental Protection Agency (EPA).

ToxFAQs™ for Cadmium. CAS 7440-43-9.

Agency for Toxic Substances and Disease Registry. June 1999 Division of Toxicology, 1600 Clifton Road NE, Mailstop E-29, Atlanta, GA 30333, U.S.A.

HIGHLIGHTS: Exposure to cadmium happens mostly in the workplace where cadmium products are made. The general population is exposed from breathing cigarette smoke or eating cadmium contaminated foods. Cadmium damages the lungs, can cause kidney disease, and may irritate the digestive tract. This substance has been found in at least 776 of the 1,467 National Priorities List sites identified by the Environmental Protection Agency (EPA).

ToxFAQs™ for Lead. CAS 7439-92-1.

Agency for Toxic Substances and Disease Registry. June 1999 Division of Toxicology, 1600 Clifton Road NE, Mailstop E-29, Atlanta, GA 30333, U.S.A.

HIGHLIGHTS: Exposure to lead can happen from breathing workplace air or dust, eating contaminated foods, or drinking contaminated water. Children can be exposed from eating lead-based paint chips or playing in contaminated soil. Lead can damage the nervous system, kidneys, and reproductive system. Lead has been found in at least 1,026 of 1,467 National Priorities List sites identified by the Environmental Protection Agency (EPA).

ToxFAQs™ for Mercury. CAS 7439-97-6.

Agency for Toxic Substances and Disease Registry. April 1999 Division of Toxicology, 1600 Clifton Road NE, Mailstop E-29, Atlanta, GA 30333, U.S.A.

HIGHLIGHTS: Exposure to mercury occurs from breathing contaminated air, ingesting contaminated water and food, and having dental and medical treatments. Mercury, at high levels, may damage the brain, kidneys, and developing fetus. This chemical has been found in at least 714 of 1,467 National Priorities List sites identified by the Environmental Protection Agency.

Effects of some thiol chelators on enzymatic activities in blood, liver and kidneys of acute arsenic (III) exposed mice.

Tripathi N, Flora SJ. Division of Pharmacology and Toxicology, Defence Research and Development Establishment, Gwalior, India. Biomed Environ Sci 1998 Mar;11(1):38-45

The effects of meso 2, 3-dimercaptosuccinic acid (DMSA), sodium 2, 3-dimercaptopropane 1-sulfonate (DMPS) and S-adenosyl L-methionine (SAM) on the enzymatic activities of mice were studied. The mice were given intraperitoneal (i.p.) injections of these chelating agents (1 mmol/kg) and 3 h later the activity of delta-aminolevulinic acid dehydratase (ALAD) in the blood, and aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (gamma-GT), alkaline phosphatase (ALP) in the liver and kidney were determined. The activity of blood ALAD was significantly increased by the administration of DMSA and SAM while DMPS had only a moderate effect. The activities of other hepatic enzymes changed little when the mice were treated with these chelating agents, except for a significant reduction in hepatic ALP activity following DMPS administration. Arsenic (III) administration markedly increased the activities of ALT and ALP in the liver and kidneys. The changes in the enzymatic activities by treatment with arsenic were prevented by injection of DMSA, DMPS and SAM, DMSA being the most effective. These results indicate that DMSA, DMPS and SAM were not toxic to the liver or kidneys of mice and that treatment with DMSA is more effective than DMPS or SAM in protecting mice from acute hepatic or renal toxicity caused by arsenic.

Serum selenium and glutathione-peroxidase activities and their interaction with toxic metals in dialysis and renal transplantation patients.

Turan B, Delilbasi E, Dalay N, Sert S, Afrasyap L, Sayal A. Department of Biophysics, Faculty of Medicine, Ankara University, Turkiye. Biol Trace Elem Res 1992 Apr-Jun;33:95-102

Selenium, aluminum, cadmium, and magnesium concentrations and glutathione-peroxidase activities in sera of 35 healthy individuals, 30 renal transplants, and 30 hemodialysis patients were measured. Serum selenium, aluminum, and cadmium concentrations in both groups of patients were higher than the controls (p less than 0.001), whereas the serum glutathione-peroxidase levels were lower (p less than 0.001). According to our results, it can be concluded that the patients receiving

hemodialysis are subjected to more toxic elements than the transplantation patients. These findings imply that dietary selenium supplement may be suggested in renal failure for the detoxification of elements, such as cadmium and mercury. The essential trace element selenium takes part not only in the direct protection of endothelial cells against the accumulation of aggressive oxygen species, but also in the prevention of the toxic effects of cadmium or in the modulation of the active calcium transport.

Deferoxamine (Systemic).

USNLM/NIH (no authors given). 2001 Drug Information (http://www.nlm.nih.gov/medlineplus/druginfo). U.S. National Laboratory of Medicine/National Institutes of Health, Bethesda, MD, U.S.A. (http://www.nlm.nih.gov/medlineplus/druginfo)

No abstract available.

DMSA (Succimer Systemic).

USNLM/NIH (no authors given). 2001 Drug Information (http://www.nlm.nih.gov/medlineplus/druginfo). U.S. National Laboratory of Medicine/National Institutes of Health, Bethesda, MD, U.S.A. (http://www.nlm.nih.gov/medlineplus/druginfo)

No abstract available.

EDTA (Edetate Disodium Systemic).

USNLM/NIH (no authors given). 2001 Drug Information (http://www.nlm.nih.gov/medlineplus/druginfo). U.S. National Laboratory of Medicine/National Institutes of Health, Bethesda, MD, U.S.A. (http://www.nlm.nih.gov/medlineplus/druginfo)

No abstract available.

Penicillamine (Systemic).

USNLM/NIH (no authors given). 2001 Drug Information (http://www.nlm.nih.gov/medlineplus/druginfo). U.S. National Laboratory of Medicine/National Institutes of Health, Bethesda, MD, U.S.A.

Biochemical bases of the pharmacological action of the flavonoid silymarin and of its structural isomer silibinin.

Valenzuela A, Garrido A. Unidad de Bioquimica Farmacologica y Lipidos, Universidad de Chile, Santiago. Biol Res 1994;27(2):105-12

The flavonoid silymarin and one its structural components, silibinin, have been well characterized as hepato-protective substances. However, little is known about the biochemical mechanisms of action of these substances. This review deals with recent investigations to elucidate the molecular action of the flavonoid. Three levels of action have been proposed for silymarin in experimental animals: a) as an antioxidant, by scavenging prooxidant free radicals and by increasing the intracellular concentration of the tripeptide glutathione; b) regulatory action of the cellular membrane permeability and increase of its stability against xenobiotic injury; c) at the nuclear expression, by increasing the synthesis of ribosomal RNA by stimulating DNA polymerase I and by exerting a steroid-like regulatory action on DNA transcription. The specific hepatoprotective action of silibinin against the toxicity of ethanol, phenylhydrazine and acetaminophen is also discussed. It is suggested that the biochemical effects observed for the flavonoid in experimental models may settle the basis for understanding the pharmacological action of silymarin and silibinin.

Induction of lesions of selenium-vitamin E deficiency in ducklings fed silver, copper, cobalt, tellurium, cadmium, or zinc: protection by selenium or vitamin E supplements.

Van Vleet JF, Boon GD, Ferrans VJ. Am J Vet Res 1981 Jul;42(7):1206-17

In 3 experiments, 684 newly hatched White Pekin ducklings were fed (for 15 to 28 days) a commercial starter mash that was adequate in selenium and vitamin E (Se-E) content, either alone or with supplements of Ag (3,000 mg/kg of feed, as acetate), Cu (1,500 mg/kg, as sulfate), Co (200 or 500 mg/kg, as chloride), Te (500 mg/kg, as tetrachloride), Cd (100 or 500 mg/kg, as sulfate), Zn (3,000 or 6,000 mg/kg, as sulfate), or V (100 mg/kg, as vanadate). The ducklings fed Ag, Cu, Co, Te, Cd, and Zn frequently developed lesions characteristic of Se-E deficiency, such as necrosis of skeletal and cardiac muscle and of smooth muscle of the gizzard and intestine. Complete protection from the muscle lesions produced by Cu, Co, Te, Cd, and Zn supplements was provided by vitamin E (200 IU of alpha-tocopherol acetate/kg) and Se (2 mg/kg, as selenite). Ducklings fed Ag were protected by supplements of vitamin E and partial protection was achieved by Se addition. The birds fed excessive Zn developed pancreatic necrosis and fibrosis that was not prevented by supplements of Se or vitamin E. Terminally, blood glutathione peroxidase activity was low and hepatic Se concentration was increased in the ducklings fed Ag. However, neither blood glutathione peroxidase activity

nor hepatic Se concentrations were consistently abnormal in ducklings fed other trace elements, although lesions of Se-E deficiency were often present in these animals.

Lead induced disorders in hematopoietic and drug metabolizing enzyme system and their protection by ascorbic acid supplementation.

Vij AG, Satija NK, Flora SJ. Defence Institute of Physiology and Allied Sciences, Timarpur, Delhi, India. Biomed Environ Sci 1998 Mar;11(1):7-14

Effect of vitamin C supplementation in restoring lead induced alterations in hematopoietic system and drug metabolizing enzymes were investigated in male rats. Intraperitoneal administration of 20 mg/kg lead produced a significant inhibition of heme synthesis in blood and liver and drug metabolism in liver. Toxic insult by lead also resulted into a marked decline in tissue thiols and vitamin C levels. Oral supplementation of vitamin C (100 mg/kg for 3 days) completely restored blood delta aminolevulinic acid dehydratase, uroporphyrinogen I synthetase and a few drug metabolizing enzymes. Level of vitamin C and sulfhydryl contents too recovered to a great extent. A marked reduction in blood and liver lead concentration occurred on vitamin C supplementation although renal lead contents were marginally reduced in lead exposed animals. The results, thus, indicate a significant protective action of vitamin C against toxic effects of lead on heme synthesis and drug metabolism.

Vitamin A supplementation: implications for morbidity and mortality in children.

Villamor E, Fawzi WW. Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA 02115, U.S.A. J Infect Dis 2000 Sep;182 Suppl 1:S122-33

Vitamin A deficiency impairs epithelial integrity and systemic immunity and increases the incidence and severity of infections during childhood. However, findings from vitamin A supplementation trials are not consistent. Supplementation has resulted in significant reductions in mortality in several (but not all) large community-based trials among apparently healthy children. In hospital-based studies, vitamin A supplements have been consistently found to reduce the severity of measles infection, but no effect on nonmeasles respiratory infections has been observed. In some cases, the supplements were associated with an apparently increased risk of lower respiratory infection. Vitamin A supplements also reduced the severity of diarrhea in most (but not all) trials. Potential explanations for the differences in efficacy across trials are reviewed. While vitamin A supplementation is effective in reducing total mortality and complications from measles infections, it is likely to be more effective in populations suffering from nutritional deficiencies.

Maternal-fetal distribution of mercury (203Hg) released from dental amalgam fillings.

Vimy MJ, Takahashi Y, Lorscheider FL. Department of Medicine, Faculty of Medicine, University of Calgary, Alberta, Canada. Am J Physiol 1990 Apr;258(4 Pt 2):R939-45

In humans, the continuous release of Hg vapor from dental amalgam tooth restorations is markedly increased for prolonged periods after chewing. The present study establishes a time-course distribution for amalgam Hg in body tissues of adult and fetal sheep. Under general anesthesia, five pregnant ewes had twelve occlusal amalgam fillings containing radioactive 203Hg placed in teeth at 112 days gestation. Blood, amniotic fluid, feces, and urine specimens were collected at 1- to 3-day intervals for 16 days. From days 16-140 after amalgam placement (16-41 days for fetal lambs), tissue specimens were analyzed for radioactivity, and total Hg concentrations were calculated. Results demonstrate that Hg from dental amalgam will appear in maternal and fetal blood and amniotic fluid within 2 days after placement of amalgam tooth restorations. Excretion of some of this Hg will also commence within 2 days. All tissues examined displayed Hg accumulation. Highest concentrations of Hg from amalgam in the adult occurred in kidney and liver, whereas in the fetus the highest amalgam Hg concentrations appeared in liver and pituitary gland. The placenta progressively concentrated Hg as gestation advanced to term, and milk concentration of amalgam Hg postpartum provides a potential source of Hg exposure to the newborn. It is concluded that accumulation of amalgam Hg progresses in maternal and fetal tissues to a steady state with advancing gestation and is maintained. Dental amalgam usage as a tooth restorative material in pregnant women and children should be reconsidered.

Silymarin: a review of its clinical properties in the management of hepatic disorders.

Wellington K, Jarvis B. Adis International Limited, Auckland, New Zealand. demail@adis.co.nz BioDrugs 2001;15(7):465-89

The mechanisms of action of silymarin involve different biochemical events, such as the stimulation of the synthetic rate of ribosomal RNA (rRNA) species through stimulation of polymerase I and rRNA transcription, protecting the cell membrane from radical-induced damage and blockage of the uptake of toxins such as alpha-amanitin. Studies in patients with liver disease have shown that silymarin increases superoxide dismutase (SOD) activity of lymphocytes and erythrocytes, as well as the expression of SOD in lymphocytes. Silymarin has also been shown to increase patient serum levels of glutathione and glutathione peroxidase. Silybin 20 to 48 mg/kg/day has shown promise as a clinical antidote to acute Amanita (deathcap mushroom) poisoning. Primary

efficacy data from 3 trials which examined the therapeutic potential of silymarin in patients with cirrhosis, and included patient survival as an end-point, demonstrated that silymarin had no significant beneficial effect on patient mortality. However, upon subanalysis, silymarin 420 mg/day had a significantly beneficial effect on patient survival rate (compared with patients receiving placebo) in 1 randomised, double-blind trial in patients with alcoholic cirrhosis. Silymarin 420 mg/day was also shown to improve indices of liver function [AST, ALT, gamma-glutamyl transferase and bilirubin] in patients with liver disease of various aetiology, including those exposed to toxic levels of toluene or xylene; however, it was largely ineffective in patients with viral hepatitis. Reports of adverse events while receiving silymarin therapy are rare. However, there have been accounts of nausea, epigastric discomfort, arthralgia, pruritus, headache and urticaria. Silymarin has also been reported to have possibly caused a mild laxative effect. CONCLUSION: The antioxidant properties of silymarin (a mixture of at least 4 closely related flavonolignans, 60 to 70% of which is a mixture of 2 diastereomers of silybin) have been demonstrated in vitro and in animal and human studies. However, studies evaluating relevant health outcomes associated with these properties are lacking. Although silymarin has low oral absorption, oral dosages of 420 mg/day have shown some therapeutic potential, with good tolerability, in the treatment of alcoholic cirrhosis. Moreover, silybin 20 to 48 mg/kg/day has shown promise as an antidote for acute mushroom poisoning by Amanita phalloides; however, further studies paying attention to the amount of ingested mushroom and time elapsed before administration of treatment are needed to clarify its role in this indication. Studies in patients with the early onset of liver disease may demonstrate the liver regeneration properties that silymarin is promoted as possessing.

Chelation therapy: conventional treatments.

Wentz PW. (LabCorp., Burlington, NC). May 2000 Advance Magazines for Administrators of the Laboratory (http://www.advanceforal.com/common/editorial/editorial/aspx). Merion Publications, King of Prussia, PA

Maternal low level lead and pregnancy outcomes.

West WL, Knight EM, Edwards CH, Manning M, Spurlock B, James H, Johnson AA, Oyemade UJ, Cole OJ, Westney OE, et al. Department of Pharmacology, College of Medicine, Howard University, Washington, D.C. 20059.

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We examined the relationship between the concentrations of blood lead and pregnancy outcomes in a subset of 349 African American women who enrolled in the program project, "Nutrition, Other Factors, and the Outcome of Pregnancy." Vitamin-mineral supplement users had significantly higher serum levels of ascorbic acid and vitamin E. Also, in supplement users, there were significantly lower mean concentrations of maternal blood lead. Inverse correlations were found between maternal levels of lead and the antioxidant vitamins, vitamin E and ascorbic acid. In addition, significant Pearson's correlations were observed between maternal blood lead levels and the following variables: positive correlations with calcium, phosphorus, mean corpuscular volume; inverse correlations with gestational age, Ponderal Index, infant orientation, and hematologic values. In the total subset, the three trimester sample means for maternal blood lead concentrations were not significantly different for mothers of infants who weighed less than 2500 g (low birth weight) and those who were delivered infants who weighed 2500 g or more. Clinically, nutrition may play a role in the reduction of potentially adverse effects from lead during pregnancy, i.e. protection of the fetus against lead toxicity and/or free radical damage through the antioxidant actions of vitamin E and ascorbic acid. Even when maternal blood lead levels are within the so-called "safe" range, maternal/use of a vitamin supplement supplying vitamin E and ascorbic acid during pregnancy may offer protection.

Aluminum.

WHO (no authors given). 1998 Guidelines for Drinking-Water Quality, Second Edition, Health Criteria and Other Supporting Information, pp. 3-13 (http://www.who.into/water_sanitation_health/GDWQ/Chemicals/aluminfull.html). World Health Organization, Geneva.

No health-based guideline value for aluminium was recommended in the second edition of the WHO Guidelines for drinking-water quality. It was concluded that although further studies were needed, the balance of epidemiological and physiological evidence did not support a causal role for aluminium in Alzheimer disease. An aluminium concentration of 0.2 mg/litre in drinking-water provided a compromise between the practical use of aluminium salts in water treatment and discoloration of distributed water. The Coordinating Committee for the updating of the WHO Guidelines recommended that a health criteria document be prepared for aluminium, based on the IPCS Environmental Health Criteria monograph that was finalized in 1995.

[Mercury concentration in the mouth mucosa of patients with amalgam fillings.] [Article in German]

Willershausen-Zonnchen B, Zimmermann M, Defregger A, Schramel P, Hamm G. Poliklinik fur Zahnerhaltung und Parodontologie, Universitat Munchen. Dtsch Med Wochenschr 1992 Nov 13;117(46):1743-7

Mercury concentrations were measured in specimens of oral mucosa taken during oral surgery from 90 patients (53 men, 37

women, mean age 42 +/- 16 years); 30 of the patients had no amalgam fillings. All the mucosal specimens extended for at least 2-3 mm from the epithelium of the gingival margin and were clinically and radiologically normal. Thirteen patients without metallic fillings of any kind had mercury concentrations of 118.4 +/- 83.7 ng/g tissue, and in 17 patients with precious metal fillings but no amalgam the mean mercury concentrations were 144 +/- 290 ng/g tissue. Seventeen patients with 1-3 amalgam fillings had an average of 1975 +/- 4300 ng/g tissue and in 26 patients with 3-6 amalgam fillings the average concentration was 1158 +/- 2500 ng/g tissue. In 17 patients with more than six amalgam fillings the mean mercury concentration was 2302 +/- 5600 ng/g tissue. Although these results demonstrate a considerable degree of transfer of mercury from the amalgam fillings to the oral mucosa, it had not resulted in any clinically detectable mucosal lesions.

Effects of lead on glutathione S-transferase expression in rat kidney: a dose-response study.

Wright LS, Kornguth SE, Oberley TD, Siegel FL. Waisman Center, University of Wisconsin, Madison, WI 53705, U.S.A. Toxicol Sci 1998 Dec;46(2):254-9

Glutathione S-transferases (GST, EC 2.5.1.18) are a family of phase II detoxification enzymes involved in the conjugation of glutathione to a highly diverse group of compounds. The purpose of this study was to evaluate the dose-response effects of lead acetate administration on the expression of rat kidney GST. Sprague-Dawley rats were injected with doses of lead acetate ranging from 0.11 to 114 mg/kg (0.3 to 300 mumol/kg) for three consecutive days and sacrificed 24 h later. Kidney GST activity, GST isoform HPLC profiles, blood lead analysis, and electron microscopy were performed. A dose of 1.1 mg/kg lead acetate resulted in a blood lead level of 26 micrograms/dl and produced a significant increase in GST activity which continued to increase with dose up to 38 mg/kg. Morphological changes were detected at 3.8 mg/kg and increasing severity of cellular damage paralleled dose, blood lead levels, and changes in body weight. Individual GST isoforms exhibited different thresholds and maxima; rGSTP1 and rGSTM1 had thresholds of 1.1 and 3.8 mg/kg, respectively, very similar rates of increase with dose, and a maximum yield that was 450% above control at a dose of 38 mg/kg for both enzymes. rGSTA1 and rGSTA3 showed similar thresholds (1.1 mg/kg) and maximal fold increase (275%) but varied in the relative response to each dose. These results indicate that renal GST increases occur at lead levels which are environmentally significant, that these changes precede cellular damage, and suggest that GST may serve as a tissue biomarker of lead exposure.

Metabolic methylation is a possible genotoxicity-enhancing process of inorganic arsenics.

Yamanaka K, Hayashi H, Tachikawa M, Kato K, Hasegawa A, Oku N, Okada S. Department of Biochemical Toxicology, Nihon University College of Pharmacy, Chiba, Japan. Mutat Res 1997 Nov 27;394(1-3):95-101

To elucidate if the metabolic methylation participates in the induction of inorganic arsenic-responsible genetic damage, arsenite (ARS) and its methylated metabolites, methanearsonic acid (MMAA) and dimethylarsinic acid (DMAA), were comparatively assayed for the induction of DNA damage by determining DNA repair synthesis using polymerization inhibitors such as aphidicolin (aph) and hydroxyurea (HU). When human alveolar epithelial type II (L-132) cells in culture were exposed to either one of these three arsenic compounds, DNA single-strand breaks resulting from the inhibition of repair polymerization were remarkably produced by exposure to DMAA at 5 to 100 microM, while not by that to ARS and MMAA even at 100 microM. Furthermore, a bromodeoxyuridine (BrdrU)-photolysis assay indicated that the induction of DNA repair synthesis was observed only in the case of exposure to DMAA. When L-132 cells were exposed to 100 microM MMAA in the presence of 10 mM S-adenosyl-L-methionine (SAM), which is a well-known methyl-group donor in metabolic methylation of arsenics, DNA repair synthesis was induced along with an increase in the amount of dimethylarsenic in the cells. These results indicate that metabolic methylation of inorganic arsenics to dimethylarsenics is predominantly involved in the induction of DNA damage.

Mercury use in espiritismo: a survey of botanicas.

Zayas LH, Ozuah PO. Am J Public Health 1996 Jan;86(1):111-2

No abstract available.

taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.