



The American Academy of Clinical Toxicology

Uniting scientists and clinicians in the advancement of research, education, prevention and treatment of diseases caused by chemicals, drugs and other toxins.

HERBS & DIETARY SUPPLEMENTS SPECIAL INTEREST GROUP ABSTRACTING SERVICE

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1. Knudsen K, Jonsson U, Abrahamsson J. Twenty-three deaths with gamma-hydroxybutyrate overdose in western Sweden between 2000 and 2007. *Acta Anaesthesiol Scand.* 2010;54(8):987-92.

BACKGROUND: gamma-Hydroxybutyrate (GHB) is a drug of abuse with a status as being safe. In spite of a reputation of low toxicity, a huge number of deaths associated with this drug have been recorded during recent years in Sweden. It is unclear whether coingestion with other drugs or ethanol causes death in GHB overdoses or whether GHB itself is the main cause of death. OBJECTIVES: The aim of this study was to analyze the cause of death in GHB-related fatalities seen in our region. METHODS: All cases of deaths with GHB during the year 2000-2007 in the region of western Sweden were studied retrospectively. The cases were classified as either GHB poisonings without any, with a minor or a major influence of other drugs on the cause of death. RESULTS: Twenty-three cases were diagnosed as deaths due to GHB overdose. Ninety-one percent coingested other substances. Ninety-one percent of the decedents were male. Age varied between 16 and 46, with the median age at 25 years. Forty-three percent of the cases were classified as GHB poisonings without any or a minor influence of other drugs on the cause of death. Thirty percent also ingested ethanol. Two patients (9%) were only intoxicated with GHB. CONCLUSIONS: Intoxication with GHB carries some mortality. Combining GHB with ethanol does not explain the many deaths in our region, nor do extremely high plasma concentrations of GHB. The intake of opioids increases the toxicity of GHB. The drug itself has such biological activities that an overdose is dangerous and may lead to death.
2. Shiyovich A, Sztarkier I, Neshet L. Toxic hepatitis induced by *Gymnema sylvestris*, a natural remedy for type 2 diabetes mellitus. *Am J Med Sci.* 2010;340(6):514-7.

Toxic hepatitis or drug-induced liver injury (DILI) encompasses a spectrum of conditions ranging from mild biochemical abnormalities to acute liver failure. Recent studies report that 35% to 48% of patients with diabetes use some form of complementary and alternative medical therapy. Moreover, >800 plants have been traditionally used for the treatment of diabetes. Despite this widespread use, only few were supported by rigorous clinical evidence. *Gymnema sylvestris*, also known as gurmar (sugar destroyer in Hindi), is a plant considered to be with potent antidiabetic effects and, hence, widely used in folk, ayurvedic and homeopathic systems in medicine. The authors were unable to find previous reports associating *G sylvestris* to liver injury. Herein, the authors report a case of DILI in a patient who

was treated with *G. sylvestre* for diabetes mellitus and review the literature to suggest possible mechanisms that led to this acute condition.

3. Teschke R. Kava hepatotoxicity--a clinical review. *Ann Hepatol.* 2010;9(3):251-65. This review critically analyzes the clinical data of patients with suspected kava hepatotoxicity and suggests recommendations for minimizing risk. Kava is a plant (*Piper methysticum*) of the pepper family Piperaceae, and its rhizome is used for traditional aqueous extracts in the South Pacific Islands and for commercial ethanolic and acetonic medicinal products as anxiolytic herbs in Western countries. A regulatory ban for ethanolic and acetonic kava extracts was issued in 2002 for Germany on the basis of reports connecting liver disease with the use of kava, but the regulatory causality assessment was a matter of international discussions. Based on one positive reexposure test with the kava drug, it was indeed confirmed that kava is potentially hepatotoxic. In subsequent studies using a structured, quantitative and hepatotoxicity specific causality assessment method in 14 patients with liver disease described worldwide, causality for kava +/- comedicated drugs and dietary supplements including herbal ones was highly probable (n = 1), probable (n = 4) or possible (n = 9) regarding aqueous extracts (n = 3), ethanolic extracts (n = 5), acetonic extracts (n = 4), and mixtures containing kava (n = 2). Risk factors included overdose, prolonged treatment, and comedication with synthetic drugs and dietary supplements comprising herbal ones in most of the 14 patients. Hepatotoxicity occurred independently of the used solvent, suggesting poor kava raw material quality as additional causative factor. In conclusion, in a few individuals kava may be hepatotoxic due to overdose, prolonged treatment, comedication, and probably triggered by an unacceptable quality of the kava raw material; standardization is now required, minimizing thereby hepatotoxic risks.
4. Alkahtani S, Sammons H, Choonara I. Epidemics of acute renal failure in children (diethylene glycol toxicity). *Arch Dis Child.* 2010;95(12):1062-4. Acute renal failure in children can have a variety of causes. There have been several epidemics of acute renal failure affecting predominantly young children where the cause has been diethylene glycol (DEG) poisoning. These children have presented with gastrointestinal bleeding, seizures and liver failure as well as renal failure. The poisoning has been the result of either contamination of the medicinal products by DEG or the deliberate illegal use of DEG as a solvent. More than 300 children worldwide have died from DEG poisoning. Health professionals need to be aware of the clinical presentation of DEG poisoning as prompt action is likely to save lives by the removal of the contaminated/illegal medicine from pharmacies and shops in the affected area.
5. Pestka JJ. Deoxynivalenol: mechanisms of action, human exposure, and toxicological relevance. *Arch Toxicol.* 2010;84(9):663-79. The trichothecene mycotoxin deoxynivalenol (DON) is produced in wheat, barley and corn following infestation by the fungus *Fusarium* in the field and during storage. Colloquially known as "vomitoxin" because of its emetic effects in pigs, DON has been associated with human gastroenteritis. Since DON is commonly detected in cereal foods, there are significant questions regarding the risks of acute poisoning and chronic effects posed to persons ingesting this trichothecene. A

further challenge is how to best manage perceived risks without rendering critical food staples unavailable to an ever-expanding world population. In experimental animal models, acute DON poisoning causes emesis, whereas chronic low-dose exposure elicits anorexia, growth retardation, immunotoxicity as well as impaired reproduction and development resulting from maternal toxicity. Pathophysiologic effects associated with DON include altered neuroendocrine signaling, proinflammatory gene induction, disruption of the growth hormone axis, and altered gut integrity. At the cellular level, DON induces ribotoxic stress thereby disrupting macromolecule synthesis, cell signaling, differentiation, proliferation, and death. There is a need to better understand the mechanistic linkages between these early dose-dependent molecular effects and relevant pathological sequelae. Epidemiological studies are needed to determine if relationships exist between consumption of high DON levels and incidence of both gastroenteritis and potential chronic diseases. From the perspective of human health translation, a particularly exciting development is the availability of biomarkers of exposure (e.g. DON glucuronide) and effect (e.g. IGF1) now make it possible to study the relationship between DON consumption and growth retardation in susceptible human populations such as children and vegetarians. Ultimately, a fusion of basic and translational research is needed to validate or refine existing risk assessments and regulatory standards for this common mycotoxin.

6. Choi EH, Park JH, Kim MK, Chun HS. Alleviation of doxorubicin-induced toxicities by anthocyanin-rich bilberry (*Vaccinium myrtillus* L.) extract in rats and mice. *Biofactors*. 2010;36(4):319-27.
The objective of this study was to investigate the effects of anthocyanin-rich bilberry extract (BE) with highly antioxidative potential against doxorubicin (Dox)-induced toxicity in rat and mouse models. Sprague-Dawley rats treated with Dox (15 mg/kg intraperitoneally) showed marked body weight loss, increased abdominal ascites and serum glutamate oxaloacetate transaminase (GOT) level, serum and cardiac lipid peroxidation, myocardial histopathological damage, and depletion of cardiac glutathione (GSH). Dietary supplementation with 1% BE significantly reduced serum lipid peroxidation and increased cardiac creatine phosphokinase activity and total GSH level compared with the levels in the Dox control rats ($P < 0.05$). Serum GOT and cardiac lipid peroxide levels did not change significantly after BE treatment. Morphologic examination revealed that Dox-induced myocardial damage was also significantly suppressed in rats fed with the 1% BE diet. Oral administration of 500 mg/kg of BE for 10 days to mice treated with Dox (10 mg/kg) partially restored the Dox-induced changes by increasing red blood cell and bone marrow cell counts, and hemoglobin level. Although the protective effects of BE were insufficient to completely counteract the toxic effects of Dox, these results suggest that BE supplementation provides moderate protection against Dox-induced cardiac and hematopoietic damage.
7. Christie SN, Giammarco R, Gawel M, Mackie G, Gladstone J, Becker WJ. Botulinum toxin type A and acute drug costs in migraine with triptan overuse. *Can J Neurol Sci*. 2010;37(5):588-94.
BACKGROUND: Patients with chronic migraine and medication overuse are significant consumers of health care resources. OBJECTIVE: To determine whether

botulinum toxin type A prophylaxis reduces the cost of acute migraine medications in patients with chronic migraine and triptan overuse. **METHODS:** In this multicenter, open-label study, patients with chronic migraine (≥ 15 headache days/month) who were triptan overusers (triptan intake ≥ 10 days/month for ≥ 3 months) received botulinum toxin type A (95-130 U) at baseline and month three. Headache (HA) frequency and medication use were assessed with patient diaries, and headache-related disability by means of the MIDAS and Headache Impact Test-6 questionnaires. **RESULTS:** Of 53 patients enrolled (mean age \pm standard deviation, 46.5 years \pm 8.4; 47 [88.7%] females), 48 (90.6%) completed the study at month six. Based on headache diaries, significant ($P \leq 0.0002$) decreases from baseline were observed for days per month with headache/migraine, days with any acute headache medication use, days with triptan use, and triptan doses taken per month. A significant ($P < 0.0001$) increase from baseline in headache-free days per month was also observed. Prescription medication costs for acute headache medications decreased significantly, including significant reductions in triptan costs (mean reduction of -C\$106.32 \pm 122.87/month during botulinum toxin type A prophylaxis; $P < 0.0001$). At baseline, 78% of patients had severe disability (MIDAS score) and 86.8% had severe impact due to headache (HIT-6 scores); at month six, this decreased to 60% and 68%, respectively. **CONCLUSIONS:** Botulinum toxin type A prophylactic therapy markedly decreased costs related to acute headache medication use in patients with chronic migraine and triptan overuse.

8. Zhao M, Wang Y, Huo C, Liu J, Li C, Zhang X, et al. Lead detoxification activity and ADMET hepatotoxicity of N-(α -L-arabino-furanos-1-yl)-L-cysteine. *Chem Res Toxicol.* 2010;23(7):1282-5.
N-(α -L-Arabinofuranos-1-yl)-L-cysteine was stereoselectively prepared from L-arabinose and L-cysteine. Its in vivo detoxification action was evaluated on lead loaded mice at the doses of 0.1, 0.2, and 0.4 mmol/kg. The results show that lead accumulation in the livers, kidneys, brains, and femurs of the treated mice could be efficiently decreased by N-(α -L-arabinofuranos-1-yl)-L-cysteine, even at the dose of 0.1 mmol/kg. Compared with the lead detoxification efficacy, 0.4 mmol/kg of N-(α -L-arabinofuranos-1-yl)-L-cysteine did not affect the essential metals in the treated mice, such as Fe, Cu, Zn, and Ca. In the apparent permeability coefficient test, the values of $P(\text{app})(A \rightarrow B)$, $P(\text{app})(B \rightarrow A)$, and $P(\text{app})(A \rightarrow B)/P(\text{app})(B \rightarrow A)$ indicated that N-(α -L-arabinofuranos-1-yl)-L-cysteine was transported actively across the Caco-2 cell monolayer. Silico molecular modeling results predicted that N-(α -L-arabinofuranos-1-yl)-L-cysteine had no hepatotoxicity.
9. Xu H, Chen KJ. Herb-drug interaction: an emerging issue of integrative medicine. *Chin J Integr Med.* 2010;16(3):195-6.
10. Bronstein AC, Spyker DA, Cantilena LR, Jr., Green JL, Rumack BH, Giffin SL. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila).* 2010;48(10):979-1178.
BACKGROUND: This is the 27th Annual Report of the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS). As of 1 July 2009, 60 of the nation's 60 US poison centers (PCs) uploaded case data

automatically. The upload time was 19.9 [9.7, 58.7] (median [25%, 75%]) minutes, creating a near real-time national exposure and information database and surveillance system. **METHODOLOGY:** We analyzed the case data tabulating specific indices from NPDS. The methodology was similar to that of previous years. Where changes were introduced, the differences are identified. Poison center cases with medical outcomes of death were evaluated by a team of 29 medical and clinical toxicologist reviewers using an ordinal scale of 1-6 to determine Relative Contribution to Fatality (RCF) of the exposure to the death. **RESULTS:** In 2009, 4,280,391 calls were captured by NPDS: 2,479,355 closed human exposures, 116,408 animal exposures, 1,677,403 information calls, 6,882 human confirmed nonexposures, and 343 animal confirmed nonexposures. The top 5 substance classes most frequently involved in all human exposures were analgesics (11.7%), cosmetics/personal care products (7.7%), household cleaning substances (7.4%), sedatives/hypnotics/antipsychotics (5.8%), and foreign bodies/toys/miscellaneous (4.3%). Analgesic exposures as a class increased the most rapidly (12,494 calls per year) over the last decade. The top 5 most common exposures in children age 5 or less were cosmetics/personal care products (13.0%), analgesics (9.7%), household cleaning substances (9.3%), foreign bodies/toys/miscellaneous (7.0%), and topical preparations (6.8%). Drug identification requests comprised 63.0% of all information calls. NPDS documented 1,544 human exposures resulting in death with 1,158 human fatalities judged related with an RCF of 1-Undoubtedly responsible, 2-Probably responsible, or 3-Contributory. **CONCLUSIONS:** Unintentional and intentional exposures continue to be a significant cause of morbidity and mortality in the US. The near real-time, always current status of NPDS represents a national public health resource to collect and monitor US exposure cases and information calls. The continuing mission of NPDS is to provide a nationwide infrastructure for public health surveillance for all types of exposures, public health event identification, resilience response and situational awareness tracking. NPDS is a model system for the nation and global public health.

11. Gilotta I, Brvar M. Accidental poisoning with *Veratrum album* mistaken for wild garlic (*Allium ursinum*). *Clin Toxicol (Phila)*. 2010;48(9):949-52.

INTRODUCTION: *Veratrum album* (white or false hellebore) is a poisonous plant containing steroidal alkaloids that cause nausea, vomiting, headache, visual disturbances, paresthesia, dizziness, bradycardia, atrioventricular block, hypotension, and syncope. It is regularly mistaken for *Gentiana lutea* (yellow gentian). We report accidental poisoning with *V. album* mistaken for *Allium ursinum* (wild garlic), a wild plant used in soups and salads in Central Europe. **CASE SERIES:** Four adults (24-45 years) accidentally ingested *V. album* mistaken for *A. ursinum* in self-prepared salads and soups. Within 15-30 min of ingestion they developed nausea, vomiting, and abdominal pain. At the same time dizziness, tingling, dimmed and jumping vision, transient blindness, and confusion appeared. On arrival at the ED, all patients had sinus bradycardia and hypotension. Following treatment the patients were discharged well 24-48 h after ingestion. **CONCLUSION:** In patients presenting with gastrointestinal, neurological, and cardiovascular symptoms a history of wild plant ingestion suggests possible poisoning with *V. album* mistaken for wild garlic.

12. Consolini AE, Ragone MI. Patterns of self-medication with medicinal plants and related adverse events--a South American survey. *Curr Drug Saf.* 2010;5(4):333-41. Medicinal plants are useful as a natural therapy to treat minor illnesses, as gastrointestinal disorders or as topic antiinflammatories. Also, they have been increasingly used as a coadjuvant in cronic diseases as hypertension, diabetes or hyperlipidemias. Nevertheless, many of the plants have active principles which are contraindicated or need precaution in certain illnesses as coagulation disorders or in certain states as pregnancy or breastfeeding. In this review we had compiled the side-effects, precautions and interactions with other medicines of many plants which are used in self-medication in our region. A previous population study gave us information on the consumption of medicinal plants in 73 pharmacies of the Buenos Aires province, in Argentina. During a period of one year, there were 37102 self-medicated plants, while only 1532 were prescribed by the physician. Among the most frequently self-medicated plants are *Malva sylvestris* L., *Matricaria chamomile* L, and *Quassia amara*. Among the most frequently prescribed are also "malva" and "chamomile", *Tilia cordata* Mill. and *Valeriana officinalis*. Based in the most consumed medicinal plants in our region, we reviewed the risks of such plants and the precautions that should be taken for a rational use. Also, we detected 15 adverse-reactions reported by the pharmacists through a pharmaceutical vigilance program, which are described and analyzed here. The results of the study and other reports suggest that adverse reactions of herbal medicines could be avoided if preventing self-medication, and taking into consideration possible contraindications and interactions.

13. Li BQ, Dong X, Yang GQ, Fang SH, Gao JY, Zhang JX, et al. Role of chlorogenic acid in the toxicity induced by Chinese herbal injections. *Drug Chem Toxicol.* 2010;33(4):415-20. Adverse reactions induced by Chinese herbal injections have been frequently reported. However, the precise causes of these adverse reactions are not yet fully understood. The aim of the present study was to determine the role of chlorogenic acid (a ubiquitous component of Chinese herbs) in the toxicity of Chinese herbal injections. Beagle dogs were given chlorogenic acid, Yuxingcao injection, or Qingkailing injection (the latter two both containing chlorogenic acid) by intravenous (i.v.) injection, once a day for 7 or 9 days. The systemic toxicity was evaluated. An additional ultrastructural observation on liver and kidney was performed. Anaphylactoid reactions were obvious in dogs treated with Yuxingcao injection. Varying degrees of ultrastructural changes in liver and kidney were observed in the treated dogs, especially in dogs treated with Chinese herbal injections. Our study has led to the view that chlorogenic acid is not an allergen when administrated by i.v. injection, but liver and kidney injury induced by Chinese herbal injections can be partly attributed to chlorogenic acid.

14. Leung AY. Tradition- and science-based quality control of Chinese medicines--introducing the Phyto-True system. *J AOAC Int.* 2010;93(5):1355-66. The current QC practice of quantifying presumed active chemicals or arbitrarily selected chemical markers is of doubtful value in assessing multicomponent complex traditional Chinese medicines (CMs) and often leads to an inconsistent or irreproducible research and clinical outcome. Consequently, the first and most

important step in the QC of CMs (or other botanical medicines) whose exact active chemical components are unknown is to use analytical techniques that can comprehensively define the totality of the components/attributes making up their identity and quality. One of the most versatile techniques is HPTLC. Using HPTLC, along with other simple techniques such as FTIR spectroscopy and UV-Vis spectroscopy combined with complementary gene expression profiling, we have been able to correctly identify CM materials, detect adulterants, and differentiate closely related materials and botanical species. Our research has resulted in the introduction of the concept and specimens of Phyto-True Reference Material (PTRM), aka Representative Botanical Reference/Research Material (RBRM), now commercially available, and a novel patent-pending technology (Phyto-True system) that can serve as a starting point for the meaningful QC of traditional CMs so far not possible for these complex materials. Examples will be highlighted to demonstrate this new concept.

15. Zamani J, Aslani A. Cardiac findings in acute yellow oleander poisoning. *J Cardiovasc Dis Res.* 2010;1(1):27-8.
BACKGROUND: #ENTITYSTARTX02014; The Yellow Oleander is an ornamental tree that is common throughout the tropics. Ingestion of its seeds results in a clinical picture similar to digoxin toxicity. OBJECTIVES: #ENTITYSTARTX02014; The aim of this study was to evaluate cardiac findings in acute Yellow Oleander poisoning. METHODS AND MATERIALS: #ENTITYSTARTX02014; A total of 21 patients with history of Yellow Oleander ingestion were enrolled in this study. RESULTS: #ENTITYSTARTX02014; All symptomatic patients had conduction defects affecting the sinus node, theatrio-ventricular node or both. Patients showing cardiac arrhythmias that required specific management had significantly higher serum potassium concentrations. CONCLUSION: #ENTITYSTARTX02014; Most of the symptomatic patients had conduction defects affecting sinus or atrio-ventricular nodes but few had atrial or ventricular arrhythmias typical of digoxin poisoning.
16. Vilke GM, Douglas DJ, Shipp H, Stepanski B, Smith A, Ray LU, et al. Pediatric Poisonings in Children Younger than Five Years Responded to by Paramedics. *J Emerg Med.* 2011.
BACKGROUND: Treatment of poisonings in children has been well studied, but few data are available on the various causes of the poisoning episodes in the pediatric population. OBJECTIVES: To describe the incidence and demographics of accidental poisonings incurred by children<5 years old in the County of San Diego, California who accessed paramedics through the 9-1-1 system. METHODS: Eight years of prehospital records for children<5 years of age were searched for poisoning cases. Detailed narrative information was abstracted to determine the circumstances surrounding the incident. RESULTS: There were more than 40,000 paramedic transport calls for patients 5 years and younger over the study period; 996 (2.5%) of these calls had the chief complaint of poisoning. Of the calls classified as poisonings, 38% involved a 1-year-old and 35% involved a 2-year-old. Fifty-six percent of these poisonings involved either prescription or over-the-counter medications. An additional 16% were due to household cleaners. Eighty-eight percent of all calls were classified as mild in acuity, with 13% of poisoning calls for children under a year of age classified as moderate or acute; 50% of moderate or

acute poisoning calls were to children 2 years of age. July and March were the months with the highest incidence of poisoning calls. The fewest calls were received on Saturdays and Sundays. CONCLUSIONS: Children 1 year of age had the highest incidence of unintentional poisonings. Among all age groups, medications were the number one cause of unintentional poisonings. Other unintentional poisonings could be prevented if hazardous materials were out of reach of children; many of the cases in this study happened in front of the parent with the parent watching.

17. Oerther SE. Plant Poisonings: Common Plants that Contain Cardiac Glycosides. *J Emerg Nurs.* 2011;37(1):102-3.
18. Kamendi HW, Brott DA, Chen Y, Litwin DC, Lengel DJ, Fonck C, et al. Combining radio telemetry and automated blood sampling: a novel approach for integrative pharmacology and toxicology studies. *J Pharmacol Toxicol Methods.* 2010;62(1):30-9.
INTRODUCTION: A novel automated blood sampling and telemetry (ABST) system was developed to integrate pharmacokinetic (PK), pharmacodynamic (PD) and toxicology studies. The goals of this investigation were to determine: 1) optimal feeding conditions and minimal acclimation times for recording PD parameters (blood pressure, heart rate, and temperature) after animals arrived on-site; 2) stress hormone levels in ABST-housed rats; 3) the feasibility of simultaneously recording cardiovascular parameters with electroencephalogram (EEG); 4) the equivalence of renal endpoints from ABST-housed rats with those in the metabolic cage, and 5) the cardiovascular responses to baclofen. METHODS: Body weight, blood pressure, temperature, stress biomarkers, urine chemistries, renal biomarkers and responses to vehicle or baclofen (10mg/kg) were compared in awake and freely moving rats housed in the ABST system, home cage (HC) or metabolic cage. RESULTS: Fasted rats lost 5+/-1% and 7+/-1% body weight when housed in ABST and metabolic cages, respectively. Weight loss was reversed by supplementing regular diet with hydration and nutritional supplements. Based on PD parameters, the minimum acclimation time required for both ABST and HC rats was 3days. The feasibility of simultaneously measuring multiple parameters, such as EEG with cardiovascular parameters in ABST was demonstrated. Renal function and biomarkers in rats continuously housed in the ABST and metabolic cages were equivalent ($p>0.05$) on days 1, 3, and 7. Baclofen-induced quantitatively and qualitatively similar ($p>0.05$) PK, mean arterial pressure, heart rate and temperature in ABST- and HC-housed rats. DISCUSSION: These studies demonstrate for the first time that drug-induced PD responses can be recorded simultaneously with time-matched pharmacokinetic, biochemical and metabolic parameters in the same animal. The ABST system has the added advantage of blood sampling without the need for satellite PK animals. ABST is a useful and novel tool for establishing efficacy and safety margins using an in vivo integrative pharmacology approach.
19. Teschke R, Schulze J. Risk of kava hepatotoxicity and the FDA consumer advisory. *JAMA.* 2010;304(19):2174-5.
20. May ML, Corkeron MA, Stretton M. Infant botulism in Australia: availability of human

botulinum antitoxin for treatment. *Med J Aust.* 2010;193(10):614-5.

We report the first Australian case of treatment of infant botulism with a human botulinum antitoxin developed in the United States by the California Department of Public Health. Our patient's clinical improvement was rapid, and although the product is expensive, cost-analysis supports the economical viability of its use. In future cases of suspected infant botulism, we recommend that Australian clinicians promptly obtain and administer this antitoxin to their patient.

21. Lead Poisoning of a Child Associated with Use of a Cambodian Amulet --- New York City, 2009. *MMWR Morb Mortal Wkly Rep.* 2011;60(3):69-71.

Lead poisoning in children is a preventable public health problem that can adversely affect the developing nervous system and result in learning and behavior problems. The most common source of exposure for lead-poisoned children aged <6 years in the United States is lead-based paint. However, nonpaint sources have been identified increasingly as the cause of lead poisoning, particularly in immigrant communities. This report describes a case of lead poisoning in a child aged 1 year that was investigated by the New York City Department of Health and Mental Hygiene's (NYC DOHMH) Lead Poisoning Prevention Program in 2009. The likely source of exposure was an amulet made in Cambodia with leaded beads that was worn by the child. Health-care providers and public health workers should consider traditional customs when seeking sources of lead exposure in Southeast Asian populations. Health-care providers should ask parents about their use of amulets, especially those in Southeast Asian families and those with children found to have elevated blood lead levels (BLLs). Educational efforts are needed to inform Southeast Asian immigrants that amulets can be a source of lead poisoning.

22. Ge H, Wang YF, Xu J, Gu Q, Liu HB, Xiao PG, et al. Anti-influenza agents from Traditional Chinese Medicine. *Nat Prod Rep.* 2010;27(12):1758-80.

23. Mathangi DC, Shyamala R, Vijayashree R, Rao KR, Ruckmani A, Vijayaraghavan R, et al. Effect of Alpha-Ketoglutarate on Neurobehavioral, Neurochemical and Oxidative Changes Caused by Sub-Chronic Cyanide Poisoning in Rats. *Neurochem Res.* 2010.

Recent studies revealed that alpha-ketoglutarate (A-KG) alone or with sodium thiosulfate (STS) provide significant protection against acute and sub-acute cyanide poisoning in rodents. This study addresses the protective effect of A-KG and/or STS in sub-chronic (90 days) cyanide poisoning. Wistar rats were divided into seven groups (n = 10): Control animals, potassium cyanide (KCN) A-KG, STS, KCN + A-KG, KCN + STS and KCN + A-KG + STS. Spontaneous motor activity and motor coordination were recorded every 15th day. Lipid peroxidation (LPO), reduced glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) in blood, brain, liver and kidney, and glutamate, aspartate and dopamine in discrete regions of brain were measured following 90 days exposure. Cyanide significantly decreased motor coordination, accompanied by increase in LPO (blood, brain and liver) and dopamine (corpus striatum and cerebral cortex) levels, and depletion in GSH (blood, brain and liver), GPx (brain and liver), SOD (brain and liver), and CAT (blood and brain) levels. Although treatment of A-KG and STS alone significantly blunted the toxicity of KCN, concomitant use of both

afforded the maximum protection. This study shows a promising role of A-KG and STS as treatment regime for long term cyanide exposure.

24. Costa LG, Giordano G, Faustman EM. Domoic acid as a developmental neurotoxin. *Neurotoxicology*. 2010;31(5):409-23.
Domoic acid (DomA) is an excitatory amino acid which can accumulate in shellfish and finfish under certain environmental conditions. DomA is a potent neurotoxin. In humans and in non-human primates, oral exposure to a few mg/kg DomA elicits gastrointestinal effects, while slightly higher doses cause neurological symptoms, seizures, memory impairment, and limbic system degeneration. In rodents, which appear to be less sensitive than humans or non-human primates, oral doses cause behavioral abnormalities (e.g. hindlimb scratching), followed by seizures and hippocampal degeneration. Similar effects are also seen in other species (from sea lions to zebrafish), indicating that DomA exerts similar neurotoxic effects across species. The neurotoxicity of DomA is ascribed to its ability to interact and activate the AMPA/KA receptors, a subfamily of receptors for the neuroexcitatory neurotransmitter glutamate. Studies exploring the neurotoxic effects of DomA on the developing nervous system indicate that DomA elicits similar behavioral, biochemical and morphological effects as in adult animals. However, most importantly, developmental neurotoxicity is seen at doses of DomA that are one to two orders of magnitude lower than those exerting neurotoxicity in adults. This difference may be due to toxicokinetic and/or toxicodynamic differences. Estimated safe doses may be exceeded in adults by high consumption of shellfish contaminated with DomA at the current limit of 20 microg/g. Given the potential higher susceptibility of the young to DomA neurotoxicity, additional studies investigating exposure to, and effects of this neurotoxin during brain development are warranted.
25. Michiels EA, Mazor SS. Toddler with seizures due to ingesting camphor at an Indian celebration. *Pediatr Emerg Care*. 2010;26(8):574-5.
We report a 3-year-old girl who presented to the emergency department with seizures. Earlier in the evening, the patient was with her parents at an Indian celebration where she vomited once and then became hyperactive. Fifteen minutes later, she became unresponsive and had an episode characterized by eye blinking, teeth grinding, and posturing that lasted 2 to 3 minutes. To our knowledge, this is the first report of seizure after ingestion of ceremonial camphor tablets at an Indian ceremony. Given the inadequate packaging and use of many grams of camphor at these ceremonies, the pediatric population specifically is at risk for camphor toxicity from this source. Health care professionals should be aware of this unique and culturally specific source of potential camphor toxicity.
26. El-Ashmawy IM, Gad SB, Salama OM. Grape seed extract prevents azathioprine toxicity in rats. *Phytother Res*. 2010;24(11):1710-5.
Azathioprine (Aza) is an important drug commonly used in the therapy of autoimmune system disorders. It induces hepatotoxicity and hazard effects that restrict its use. The effects of administration of grape seed extract and folic acid on Aza toxicity by gavage (simultaneously) daily for 4 weeks were studied by determining the changes in some hematological parameters and liver histology. The

glutathione level (GSH) and lipid peroxidation content as malondialdehyde (MDA) in the liver tissue were measured. The repeated intake of Aza (25 mg/kg body weight) induced anemia characterized by decreased erythrocyte and leukocyte counts and reticulocyte and hematocrit percentages, while the prothrombin time was significantly increased. Moreover, Aza caused a significant decrease in phagocytic activity and lymphocyte percentage. Aza induced hepatic damage as indicated by pronounced changes in the histological structure, a significant increase in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), and MDA content in the liver tissue. Meanwhile, the GSH activity was significantly decreased. Co-treatment with grape seed extract and Aza minimized the previously mentioned hazard effects of Aza and significantly protected the hepatic tissue by ameliorating the antioxidant activity. Folic acid administration, simultaneously, with Aza only improved the anemia. It may be concluded that grape seed extract is a useful herbal remedy, especially for controlling oxidative damages and is considered as a potent protective agent against Aza hepatotoxicity.

27. Hoi CP, Ho YP, Baum L, Chow AH. Neuroprotective effect of honokiol and magnolol, compounds from *Magnolia officinalis*, on beta-amyloid-induced toxicity in PC12 cells. *Phytother Res.* 2010;24(10):1538-42.
Amyloid beta peptide (Abeta) induced toxicity is a well-established pathway of neuronal cell death which might play a role in Alzheimer's disease. In this regard, the toxic effect of Abeta on a cultured Abeta-sensitive neuronal cell line was used as a primary screening tool for potential anti-Alzheimer's therapeutic agents. The effects of nine pure compounds (vitamin E, alpha-asarone, salidroside, baicalin, magnolol, gastrodin, bilobalide, honokiol and beta-asarone) from selected Chinese herbs on neuronal cell death induced by Abeta in NGF-differentiated PC12 cells were examined. Only two of the studied compounds, honokiol and magnolol, significantly decreased Abeta-induced cell death. Further experiments indicated that their neuroprotective effects are possibly mediated through reduced ROS production as well as suppression of intracellular calcium elevation and inhibition of caspase-3 activity. The results provide for the first time a scientific rationale for the clinical use of honokiol and magnolol in the treatment of Alzheimer's disease.
28. Koyashiki GA, Paoliello MM, Tchounwou PB. Lead levels in human milk and children's health risk: a systematic review. *Rev Environ Health.* 2010;25(3):243-53.
Lead (Pb), a naturally-occurring element and industrially-produced metal, is highly toxic to children, causing intellectual and behavioral deficits, hyperactivity, fine motor function deficits, decreased intelligence quotient, alteration of hand-eye coordination, and problems in reaction time. Children's exposure to Pb occurs mainly through ingestion of contaminated food, water and soil. Few discussions have been held on the magnitude and potential risk associated with exposure from the consumption of breast milk. Hence, this research was designed to systematically review the scientific literature on published epidemiologic studies, with an emphasis on the study designs and analytical procedures used for Pb assessment in breast milk. From a total of 112 selected articles published since the 1980s, 11 met the inclusion criteria. A review of the data indicated that Pb levels varied from 0.15 to 6.1 microg L(-1) in mature milk samples, from 0.48 to 14.6

microg L(-1) in colostrum samples, and were non-detectable in some samples. The milk/blood ratio, which estimates the mean efficiency transfer of lead from blood to milk, varied between 0.01 and 0.48. The heterogeneity of methods revealed by our assessment of published studies underscores the need for harmonization of study designs and sample collection and analysis protocols to reflect specific exposure scenarios. Human milk seems to be one of the relevant biological matrices for use as a biomarker for assessing children's health risk to Pb poisoning.

29. Martinez SM, Bradford BU, Soldatow VY, Kosyk O, Sandot A, Witek R, et al. Evaluation of an in vitro toxicogenetic mouse model for hepatotoxicity. *Toxicol Appl Pharmacol.* 2010;249(3):208-16.
Numerous studies support the fact that a genetically diverse mouse population may be useful as an animal model to understand and predict toxicity in humans. We hypothesized that cultures of hepatocytes obtained from a large panel of inbred mouse strains can produce data indicative of inter-individual differences in in vivo responses to hepato-toxicants. In order to test this hypothesis and establish whether in vitro studies using cultured hepatocytes from genetically distinct mouse strains are feasible, we aimed to determine whether viable cells may be isolated from different mouse inbred strains, evaluate the reproducibility of cell yield, viability and functionality over subsequent isolations, and assess the utility of the model for toxicity screening. Hepatocytes were isolated from 15 strains of mice (A/J, B6C3F1, BALB/cJ, C3H/HeJ, C57BL/6J, CAST/EiJ, DBA/2J, FVB/NJ, BALB/cByJ, AKR/J, MRL/MpJ, NOD/LtJ, NZW/LacJ, PWD/PhJ and WSB/EiJ males) and cultured for up to 7 days in traditional 2-dimensional culture. Cells from B6C3F1, C57BL/6J, and NOD/LtJ strains were treated with acetaminophen, WY-14,643 or rifampin and concentration-response effects on viability and function were established. Our data suggest that high yield and viability can be achieved across a panel of strains. Cell function and expression of key liver-specific genes of hepatocytes isolated from different strains and cultured under standardized conditions are comparable. Strain-specific responses to toxicant exposure have been observed in cultured hepatocytes and these experiments open new opportunities for further developments of in vitro models of hepatotoxicity in a genetically diverse population.
30. Chan TY. Vegetable-borne nitrate and nitrite and the risk of methaemoglobinaemia. *Toxicol Lett.* 2011;200(1-2):107-8.
High levels of nitrate in vegetables are frequently reported. The potential hazard of vegetable-borne nitrate is from its conversion to methaemoglobin-producing nitrite before and/or after ingestion. Methaemoglobin cannot bind oxygen and produces a leftward shift in oxygen-dissociation curve, causing hypoxaemia. Infants under 3 months old are particularly susceptible to methaemoglobinaemia. Older infants and children are also at risk. Adults are not thought to be at risk of vegetable-borne nitrate or nitrite induced methaemoglobinaemia. This view should now change if the high nitrate levels in some vegetables and the effects of storage and food processing on its conversion to nitrite are taken into consideration. In fresh, undamaged vegetables, the nitrite concentrations are usually very low. Under adverse post-harvest storage conditions, nitrite concentrations in vegetables increase as a result of bacterial contamination and endogenous nitrate reductase action. Nitrite accumulation in vegetables is inhibited under frozen storage because

endogenous nitrate reductase is inactivated. Pureeing releases endogenous nitrate reductase, increasing nitrite concentrations in vegetables. Oral reduction of nitrate is the most important source of nitrite. In order to maximise the health benefits from eating vegetables, measures should be taken to reduce the nitrate and nitrite exposures while maintaining the recommended vegetable intake. Excessive use of nitrogen fertilizers should be avoided so as to reduce nitrate build up in soil or vegetables. Vegetables must be stored and processed properly to prevent bacteria contamination. Removal of stem and midrib results in a decrease of nitrate content in lettuce and spinach. Peeling of potatoes and beetroot decreases the nitrate content. Nitrate levels in some vegetables can decrease after cooking in water or blanching. Home prepared infant food containing vegetables should be avoided until the infant is 3 months or older.

31. Latha P, Chaitanya D, Rukkumani R. Protective effect of *Phyllanthus niruri* on alcohol and heated sunflower oil induced hyperlipidemia in Wistar rats. *Toxicol Mech Methods*. 2010;20(8):498-503.
The relationship between chronic alcohol consumption and various hepatic lesions are grouped under the term alcoholic liver disease. This is an extremely common disease with a high mortality. Alcoholics, along with alcohol, consume high fat diet and are susceptible to permanent liver damage. The current treatment modalities are inadequate and the need for effective treatment without side-effects is increasing. The present work tested the protective role of *Phyllanthus niruri* aqueous leaf extract on alcohol and heated sunflower oil-induced hyperlipidemia. Male albino rats of Wistar strain were used for this study. This study analyzed the variation in lipid profiles; cholesterol, triglycerides, phospholipids, and free fatty acids in liver, histopathological changes, and the activities of liver marker enzymes in the plasma. The liver damage was apparent with the increase in the activities of AST and ALT in the rats treated with alcohol + heated sunflower oil (DeltaPUFA). Treatment with *P.niruri* protected the liver from damage, and prevented the release of the liver markers enzymes. The levels of cholesterol, triglycerides, and free fatty acids were increased significantly in the alcohol + DeltaPUFA group. Administration of *P.niruri* extract effectively reduced their levels. The phospholipid levels, which were decreased in the liver of the alcohol + DeltaPUFA group, were positively modulated by treatment with *P.niruri*. The histopathological observations were also in correlation with the biochemical parameters. From the results obtained, one could conclude that the *P.niruri* leaf extract effectively protects the system against alcohol and DeltaPUFA-induced hyperlipidemia and has a definite anti-hyperlipidemic potential.
32. Ren R, Wang T, Jiang N, Liu T, Du Y, Li C, et al. Protective effects of Danshensu on liver injury induced by omethoate in rats. *Toxicol Mech Methods*. 2010;20(8):510-4.
This study was to evaluate the protective effects of Danshensu on liver injury induced by omethoate in Sprague Dawley rats. The acute omethoate poisoning model was established by administrating subcutaneously with omethoate at a single dose of 60 mg/kg. Danshensu treatment markedly inhibited the increases of aspartate aminotransferase, alanine aminotransferase, cyclooxygenase-2, tumor necrosis factor-alpha, thromboxane B(2), and thromboxane B(2)/6-keto-PGF1alpha

ratio induced by omethoate. The histopathological examination further confirmed that administration with Danshensu ameliorated liver injury. The results demonstrated that Danshensu possesses protective action on hepatic injury induced by omethoate and the pharmacological mechanism was related to the anti-inflammatory effect and circulation improvement of Danshensu, at least in part.

33. Li Q, Hickman M. Toxicokinetic and toxicodynamic (TK/TD) evaluation to determine and predict the neurotoxicity of artemisinins. *Toxicology*. 2011;279(1-3):1-9. Studies with laboratory animals have demonstrated fatal neurotoxicity that is associated with administration of artemether (AM) and arteether (AE) intramuscularly or arteminic acid (AL) orally. Toxicokinetic studies showed oil-soluble artemisinins form a depot at the intramuscular injection sites, which is associated with fascia inflammation in muscles. Oral administration of AL induces a gastrointestinal toxicity that is linked with delayed gastric emptying. These effects suggest that the exposure time of artemisinins was extended due to drug accumulation in blood, and this in turn resulted in neurotoxicity. In the present report, the drug exposure time with a neurotoxic outcome (neurotoxic exposure time) was evaluated as a predictor of neurotoxicity in vivo. The neurotoxic exposure time represents a total time spent above a lowest observed neurotoxic effect levels (LONEL) in plasma. The dose of AE required to induce minimal neurotoxicity requires a 2-3 fold longer exposure time in rhesus monkeys (179.5 h) than in rats (67.1 h) and dogs (103.7 h) by using a daily dose of 6-12.5 mg/kg for 7-28 days, indicating that the safe dosing duration in monkeys should be longer than 7 days under the exposure. The neurotoxic exposure time of artemisinins could be longer in humans as the comparison of monkeys to humans is likely more relevant than from rodents or dogs. Oral AL required much longer exposure times (8-fold) than intramuscular AE to induce neurotoxicity, suggesting that water-soluble artemisinins appear to be much safer than oil-soluble artemisinins. Due to lower doses (2-4 mg/kg) used with current artemisinins and the more rare use of AE in treating humans the exposure time is much shorter in humans. Therefore, the current regimen of 3-5 days dosing duration should be quite safe. These findings support a recently published WHO guide for malaria treatment with artemisinin regimens, such as artemisinin-based combination therapies and injectable artesunate, to avoid neurotoxicity.
34. Ralston NV, Raymond LJ. Dietary selenium's protective effects against methylmercury toxicity. *Toxicology*. 2010;278(1):112-23. Dietary selenium (Se) status is inversely related to vulnerability to methylmercury (MeHg) toxicity. Mercury exposures that are uniformly neurotoxic and lethal among animals fed low dietary Se are far less serious among those with normal Se intakes and are without observable consequences in those fed Se-enriched diets. Although these effects have been known since 1967, they have only lately become well understood. Recent studies have shown that Se-enriched diets not only prevent MeHg toxicity, but can also rapidly reverse some of its most severe symptoms. It is now understood that MeHg is a highly specific, irreversible inhibitor of Se-dependent enzymes (selenoenzymes). Selenoenzymes are required to prevent and reverse oxidative damage throughout the body, particularly in the brain and neuroendocrine tissues. Inhibition of selenoenzyme activities in these vulnerable

tissues appears to be the proximal cause of the pathological effects known to accompany MeHg toxicity. Because Hg's binding affinities for Se are up to a million times higher than for sulfur, its second-best binding partner, MeHg inexorably sequesters Se, directly impairing selenoenzyme activities and their synthesis. This may explain why studies of maternal populations exposed to foods that contain Hg in molar excess of Se, such as shark or pilot whale meats, have found adverse child outcomes, but studies of populations exposed to MeHg by eating Se-rich ocean fish observe improved child IQs instead of harm. However, since the Se contents of freshwater fish are dependent on local soil Se status, fish with high MeHg from regions with poor Se availability may be cause for concern. Further studies of these relationships are needed to assist regulatory agencies in protecting and improving child health.

35. Tubaro A, Durando P, Del Favero G, Ansaldi F, Icardi G, Deeds JR, et al. Case Definitions for Human Poisonings Postulated to Palytoxins Exposure. *Toxicol.* 2011.

A series of case reports and anecdotal references describe the adverse effects on human health ascribed to the marine toxin palytoxin (PLTX) after different exposure routes. They include poisonings after oral intake of contaminated seafood, but also inhalation and cutaneous/systemic exposures after direct contact with aerosolized seawater during *Ostreopsis* blooms and/or through maintaining aquaria containing cnidarian zoanthids. The symptoms commonly recorded during PLTX intoxication are general malaise and weakness, associated with myalgia, respiratory effects, impairment of the neuromuscular apparatus and abnormalities in cardiac function. Systemic symptoms are often recorded together with local damages whose intensity varies according to the route and length of exposure. Gastrointestinal malaise or respiratory distress is common for oral and inhalational exposure, respectively. In addition, irritant properties of PLTX probably account for the inflammatory reactions typical of cutaneous and inhalational contact. Unfortunately, the toxin identification and/or quantification are often incomplete or missing and cases of poisoning are indirectly ascribed to PLTXs, according only to symptoms, anamnesis and environmental/epidemiological investigations (i.e. zoanthid handling or ingestion of particular seafood). Based on the available literature, we suggest a "case definition of PLTX poisonings" according to the main exposure routes, and, we propose the main symptoms to be checked, as well as, hemato-clinical analysis to be carried out. We also suggest the performance of specific analyses both on biological specimens of patients, as well as, on the contaminated materials responsible for the poisoning. A standardized protocol for data collection could provide a more rapid and reliable diagnosis of palytoxin-poisoning, but also the collection of necessary data for the risk assessment for this family of toxins.